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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF BIOTECHNOLOGY

UNIT – I– CANCER BIOLOGY – SBB1605

CANCER: A HISTORIC PERSPECTIVE

Since the earliest medical records were kept, cancer as a disease has been described in the history of medicine. The earliest known descriptions of cancer appear in seven papyri, discovered and deciphered late in the 19th century. They provided the first direct knowledge of Egyptian medical practice. Two of them, known as the "Edwin Smith" and "George Ebers" papyri, contain descriptions of cancer written around 1600 B.C., and are believed to date from sources as early as 2500 B.C. The Smith papyrus describes surgery, while the Ebers' papyrus outlines pharmacological, mechanical, and magical treatments.

Based on the information recorded on papyri and hieroglyphic inscriptions, ancient Egyptians were able to distinguish benign tumors from malignant tumors. They were also able to use different treatments, including surgery, and other various modes of medicine.

Following the decline of Egypt, the next chapters of medical and scientific history were written in Greece and Rome. The great doctors Hippocrates and Galen dominated medical thought for 1500 years. They lifted medicine out of the realms of magic, superstition, and religion. Hippocrates and Galen defined disease as a natural process, and based treatment on observation and experience. Cancers were identified, with warnings against treatment of the more severe forms. Hippocrates is credited with naming "cancer" as "karkinoma" (carcinoma) because a tumor looked like a "crab" ("karkinoma" is Greek for "crab") in that there is a central body to a tumor and the tumor extension appeared as the legs of the "crab".

After the fall of Rome, Constantinople became the intellectual storehouse of civilization. From there, in Arabic translations, classic Greek and Roman texts made their way back through Europe. The ancient teachings of Galen continued to inspire physicians in Constantinople, Cairo, Alexandria, Athens, and Antioch in a time when magic spells and myths dominated the West. Cancer continued to be explained as the result of an excess of black bile, curable only in its earliest stages.

In the modern world, science and surgery advanced as physicians returned to direct observation of the human body. However, the theory that cancer was caused by an excess of black bile continued to prevail in the 16th century. Cancer was considered incurable, although a wide variety of pastes containing arsenic were formulated to treat its manifestations. In the 17th century, the old theory of disease based on bodily humors was discarded when Gaspare Aselli

discovered the vessels of the lymphatic system and suggested abnormalities of lymph as the primary cause of cancer.

Rejecting the 17th-century theory about the cause of cancer was the French physician Claude Gendron. He concluded that cancer arises locally as a hard, growing mass, untreatable with drugs, and must be removed with all its "filaments."

Two 18th-century French scientists, physician Jean Astruc and chemist Bernard Peyrilhe, conducted experiments to confirm or disprove hypotheses related to cancer. Their efforts, however absurd they seem in retrospect, established experimental oncology, the science of seeking better diagnosis, treatments and understanding of the causes of cancer. During this period, environmental cancers were reported, and hospitals specializing in cancer care were opened.

In the late 19th century, the development of better microscopes not only helped document and define disease-causing organisms, but also made possible the examination of cells and cellular activity. Study of cancer tissues and tumors revealed that cancercells were markedly different in appearance than normal cells of surrounding tissue or the cells from which they originated. Researchers began to focus on questions such as the origin of cells and the relationship of disease to the behavior of a cell. It was the invention of the microscope that revealed the cancer cell itself.

The early 20th century saw great strides made in understanding the structures, functions and chemistry of living organisms. Cancer research in cell culture, chemical carcinogens, diagnostic techniques and chemotherapy firmly established oncology as science. Researchers pursued different theories of the origin of cancer, subjecting their hypotheses to systematic experimentation. A viral cause of cancer in chickens was documented in 1911, and both chemical and physical carcinogens were conclusively identified. Chromosomal abnormalities were also investigated as possible causes of cancer.

In 1913, a need to combat rising public fear and ignorance concerning cancer led to two significant events: the publication of the first known article on cancer's warning signs in a popular woman's magazine, and formation of a nationwide organization dedicated to public education on cancer. Cancer, as a disease, was brought into the light of day.

In 1937, the U.S. Congress made the conquest of cancer a national goal with a unanimous vote to pass the National Cancer Institute Act. This Act created the National Cancer Institute, which was expected to break new theoretical ground by conducting its own research, promoting research in other institutions and coordinating cancer-related projects and activities. In 1971, President Richard M. Nixon signed the National Cancer Act, launching a National Cancer Program administered by the National Cancer Institute. Key events in the United States' national cancer policy legislative history, from 1937 to 1999 are available here.

Since its establishment, fundamental biomedical research supported by the National Cancer Institute has advanced the understanding of cancer. Using tools of molecular biology and molecular genetics, scientists are making great leaps in the discovery and mapping of links between chromosomes, the genes within, and cancer. In addition to traditional cancer therapies, potential solutions to the prevention and cure of cancer seem limited only by the imagination.

REVIEW: CANCER: A HISTORIC PERSPECTIVE

Here is what we have learned from *Cancer: A Historic Perspective*:

- Ancient Egyptians first recorded cancer as a disease. From papyrus manuscripts and hieroglyphic inscriptions we learned that some 4500 years ago, attempts were already made by Egyptians to understand cancer and to treat the cancer patients, using surgery and magical treatments.
- In Greece and Rome, and throughout the Middle Ages, cancer was continuously regarded as a disease caused by an excess of black bile. While surgeries were carried out to treat cancer, doctors believed that the disease was curable only in its earliest stages and best left alone.
- In the 16th century, the theory that cancer was caused by an excess of black bile continued to prevail.
- During the 17th century, the old theory of disease based on bodily humors was discarded when Gaspare Aselli discovered the vessels of the lymphatic system and suggested abnormalities of lymph as the primary cause of cancer.
- Observations on environmental cancers were made in the 18th century. People started research on the connection between certain environments and cancer incidence

patterns. With the first systematic experiments in cancer, oncology was born as a medical discipline.

- In the late 19th century, study of cancer tissues and tumors revealed that cancer cells were markedly different in appearance than normal cells of surrounding tissue.
- In the early 20th century, cancer research in cell culture, chemical carcinogens, diagnostic techniques and chemotherapy firmly established oncology as an experimental science.
- In 1937, the U.S. Congress passed the National Cancer Institute Act with a unanimous vote, creating the National Cancer Institute.
- In 1971, President Richard Nixon signed the National Cancer Act, launching a National Cancer Program administered by the National Cancer Institute.

WHAT IS CANCER?

There are many texts and references that attempt to define cancer. The simplest definition is from the American Cancer Society (ACS). According to the ACS, cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death.

Characteristics of Cancer

Abnormality

Cells are the structural units of all living things. Each of us has trillions of cells, as does a growing tree. Cells make it possible for us to carry out all kinds of functions of life: the beating of the heart, breathing, digesting food, thinking, walking, and so on. However, all of these functions can only be carried out by normal healthy cells. Some cells stop functioning or behaving as they should, serving no useful purpose in the body at all, and become cancerous cells.

Uncontrollability

The most fundamental characteristic of cells is their ability to reproduce themselves. They do this simply by dividing: one cell becomes two, the two become four, and so on. The division of normal and healthy cells occurs in a regulated and systematic fashion. In most parts of the body, the cells continually divide and form new cells to supply the material for growth or to replace worn-out or injured cells. For example, when you cut your finger, certain cells divide rapidly until the tissue is healed and the skin is repaired. They will then go back to their normal rate of division. In contrast, cancer cells divide in a haphazard manner. The result is that they typically pile up into a non-structured mass or tumor.

Invasiveness

Sometimes tumors do not stay harmlessly in one place. They destroy the part of the body in which they originate and then spread to other parts where they start new growth and cause more destruction. This characteristic distinguishes cancer from benign growths, which remain in the part of the body in which they start. Although benign tumors may grow quite large and press on neighboring structures, they do not spread to other parts of the body. Frequently, they are completely enclosed in a protective capsule of tissue and they typically do not pose danger to human life like malignant tumors (cancer) do.

A Group of Diseases

Although cancer is often referred to as a single condition, it actually consists of more than 100 different diseases. These diseases are characterized by uncontrolled growth and spread of abnormal cells. Cancer can arise in many sites and behave differently depending on its organ of origin. Breast cancer, for example, has different characteristics than those of lung cancer. It is important to understand that cancer originating in one body organ takes its characteristics with it even if it spreads to another part of the body. For example, metastatic breast cancer in the lungs continues to behave like breast cancer when viewed under a microscope, and it continues to look like a cancer that originated in the breast.

Cancer Terms: Cancer, Neoplasia, Tumor, Neoplasm

The word cancer comes from the Latin (originally Greek) derived term for crab, because of the way a cancer adheres to any part that it seizes upon in an obstinate manner like the crab.

Hippocrates first described cancer as having a central body with the tendency to reach out and spread like "the arms of a crab." Besides the popular, generic term "cancer" used by most people, there is another more technical term: neoplasia. Neoplasia (neo = new, plasia = tissue or cells) or neoplasm literally means new tissue in Greek. This indicates that cancers are actually new growths of cells in the body.

Another term for cancer is "malignant tumor." Tumor literally means "swelling" or "mass." In this case, it refers to a mass of non-structured new cells, which have no known purpose in the physiological function of the body.

There are two general types of tumors: benign (non-cancerous) tumors and malignant (cancerous) tumors. A benign tumor is composed of cells that will not invade other unrelated tissues or organs of the body, although it may continue to grow in size abnormally. A malignant tumor is composed of cells that invade the basement membrane and invade or spread to other parts of the body. This occurs either by direct extension to neighboring organs and/or tissues or by metastasizing to distant sites by means of the vascular system (the blood stream), the lymphatic system, or by seeding or implantation of cancer cells in body cavities.

Terms such as "mass" and "lump" are used to describe any overgrowth of tissue. However, these terms may not necessarily mean that such growths contain cancer cells.

Types of Abnormal Cell Growth

In addition to neoplasia, there are several other terms referring to abnormal cell growth. These include the following:

Hyperplasia refers to an abnormal increase in the number of cells, which are in a normal component of that tissue and are arranged in a normal fashion with subsequent enlargement of the affected part. One example is thyroid hyperplasia, an enlargement of the thyroid gland caused by an abnormal rapid growth of the epithelial cells lining the follicles. Another example is: Guitar strumming leads to hyperplasia of the cells on the thumb (a callus is formed). The callus on the thumb is a hyperplastic growth.

Hypertrophy refers to an abnormal increase in the size of each cell, for example, the increase in cell size of cardiac muscle.

Metaplasia refers to the replacement of one mature cell type with another mature cell type: for example, squamous metaplasia of the respiratory columnar epithelium — as evidenced by the metaplastic cough of a smoker.

Dysplasia refers to the replacement of one mature cell type with a less mature cell type: for example, dysplasia of the cervix epithelium.

Hyperplasia, metaplasia, and dysplasia are reversible because they are results of a stimulus. Neoplasia is irreversible because it is autonomous.

Tumor Terminology Generalizations

Names of benign tumors usually end with "oma" regardless of their cell type. For example, a benign glandular tumor (epithelium tissue) is called adenoma and a benign bone tumor is called osteoma, while a malignant glandular tumor is called adenocarcinoma and a malignant bone tumor is called osteosarcoma.

In addition to benign tumors, there are in situ tumors and invasive tumors. In situ tumors do not invade the basement membrane, whereas invasive tumors do invade the basement membrane.

CELL BIOLOGY OF CANCER

The cell is the fundamental unit of life. It is the smallest structure of the body capable of performing all of the processes that define life. Each of the organs in the body, such as the lung, breast, colon, and brain, consists of specialized cells that carry out the organ's functions such as the transportation of oxygen, digestion of nutrients, excretion of waste materials, locomotion, reproduction, thinking, etc.

To assure the proper performance of each organ, worn out or injured cells must be replaced, and particular types of cells must increase in response to environmental changes. For example, the bone marrow increases its production of oxygen-carrying red blood cells sevenfold or greater in response to bleeding or high altitude. Certain white blood cells are produced more rapidly during an infection. Similarly, the liver or endocrine organs frequently respond to injury by regenerating damaged cells.

As stated in the previous section, reproduction of cells is a process of cell division. The division of normal cells is a highly regulated process. The cell growth, inheritance and containment is controlled by its DNA (deoxyribonucleic acid).

DNA is a highly complex molecule manufactured in the cell nucleus and serves as the cell's "brain." DNA is the blueprint for everything the cell does. In a human cell, the DNA is arranged in 46 distinct sections called chromosomes. They are arranged in pairs, 23 chromosomes from each biological parent.

Together, the 46 chromosomes contain more than 100,000 genes. A gene is a segment of DNA that determines the structure of a protein, which is needed for development and growth as well as carrying out vital chemical functions in the body. Like the chromosomes, genes are arranged in pairs — one gene from the mother and one from the father.

Each gene occupies a specific location on a chromosome. Through a number of biochemical steps, each gene tells a cell to make a different protein. Some genes instruct the cell to manufacture structural proteins, which serve as building blocks. Other genes tell the cell to produce hormones, growth factors or cytokines, which exit the cell and communicate with other cells. Still other genes tell the cell to produce regulatory proteins that control the function of other proteins or tell other genes when to turn "on" or "off." When a gene is turned on, it manufactures another complex molecule called ribonucleic acid (RNA), which contains all the information the cell needs to make new proteins.

Cells divide only when they receive the proper signals from growth factors that circulate in the bloodstream or from a cell they directly contact. For example, if a person loses blood, a growth factor called erythropoietin, which is produced in the kidneys, circulates in the bloodstream and tells the bone marrow to manufacture more blood cells.

When a cell receives the message to divide, it goes through the cell cycle, which includes several phases for the division to be completed. Checkpoints along each step of the process make sure that everything goes the way it should.

Many processes are involved in cell reproduction and all these processes have to take place correctly for a cell to divide properly. If anything goes wrong during this complicated process, a cell may become cancerous.

A cancer cell is a cell that grows out of control. Unlike normal cells, cancer cells ignore signals to stop dividing, to specialize, or to die and be shed. Growing in an uncontrollable manner and unable to recognize its own natural boundary, the cancer cells may spread to areas of the body where they do not belong.

In a cancer cell, several genes change (mutate) and the cell becomes defective. There are two general types of gene mutations. One type, dominant mutation, is caused by an abnormality in one gene in a pair. An example is a mutated gene that produces a defective protein that causes the growth-factor receptor on a cell's surface to be constantly "on" when, in fact, no growth factor is present. The result is that the cell receives a constant message to divide. This dominant "gain of function gene" is often called an oncogene (onco = cancer).

The second general type of mutation, recessive mutation, is characterized by both genes in the pair being damaged. For example, a normal gene called p53 produces a protein that turns "off" the cell cycle and thus helps to control cell growth. The primary function of the p53 gene is to repair or destroy defective cells, thereby controlling potential cancerous cells. This type of gene is called an anti-oncogene or tumor suppressor gene. If only one p53 gene in the pair is mutated, the other gene will still be able to control the cell cycle. However, if both genes are mutated, the "off" switch is lost, and the cell division is no longer under control.

Abnormal cell division can occur either when active oncogenes are expressed or when tumor suppressor genes are lost. In fact, for a cell to become malignant, numerous mutations are necessary. In some cases, both types of mutations — dominant and recessive — may occur.

A gene mutation may allow an already abnormal cell to invade the normal tissue where the cancer started or to travel in the bloodstream (metastasize) to remote parts of the body, where it continues to divide.

A normal cell can become damaged in different ways. A cell can become abnormal when part of a gene is lost (deleted), when part of a chromosome is rearranged and ends up in the wrong place (translocation), or when an extremely small defect occurs in the DNA, which results in an abnormal DNA "blueprint" and production of a defective protein occurs.

Abnormal cell division can also be caused by viruses. In this case, genes may be normal, but the protein may not function normally because the cell contains a cancer-producing virus.

How a specific cancer cell behaves depends on which processes are not functioning properly. Some cancer cells simply divide and produce more cancer cells, and the tumor mass stays where it began. Other cancer cells are able to invade normal tissue, enter the bloodstream, and metastasize to a remote site in the body.

In summary, cancer cells have defects in normal cellular functions that allow them to divide, invade the surrounding tissue, and spread by way of vascular and/or lymphatic systems. These defects are the result of gene mutations sometimes caused by infectious viruses.

CELL CYCLE

Cell division is the process by which cells reproduce (mitosis). The cell cycle is a series of changes the cell goes through from the time it is first formed until it divides into two daughter cells. It starts at mitosis (M-phase) and ends with mitosis. In between are the G-1, S, and G-2 phases. The duration of S, M and G-2 are relatively constant in different tissues.

Between the M-phase and the S-phase is a gap (G-l) where production of RNA, proteins, and enzymes needed for DNA synthesis occurs. The duration of G-1 varies and determines the length of the cell cycle.

The S-phase is when DNA synthesis occurs.

Between the S-phase and M-phase is a second gap (G-2). Cells are thought to prepare for mitosis in G-2 when specialized proteins and RNA are produced. G-0 is a dormant phase.

The four phases of mitosis are:

1. Prophase
    a. Centrosomes separate and migrate to opposite poles.
    b. Centrioles separate.
    c. Chromatin is transformed into chromosomes composed of pairs of filaments called chromatids (each is a complete genetic copy of its chromosome).
    d. The nuclear membrane disappears.
2. Metaphase
    a. Paired chromosomes become lined up between the centrioles.
3. Anaphase

    a. Chromatids are pulled toward the centrioles. One chromatid from each pair goes to each daughter cell.

4. Telophase (divided into parts I and II)
    a. Telophase I
        i. Chromosomes become more polarized and transformed into thread-like structures.
        ii. A nuclear membrane forms around each set of chromosomes forming a new nucleus with a nucleolus.
        iii. The centrioles duplicate.
    b. Telophase II
        i. Actual dividing of the cell occurs (cytokinesis).
        ii. Cytoplasm splits and two daughter cells are formed.

CANCER RISK FACTORS

The search for cause(s) of cancer has been going on for centuries. Early researchers said that cancer was a natural result of aging. As cells degenerated, it was believed that some simply became malignant. Others said cancer was hereditary, and investigations into genetics began. Then some began to consider chemical links while still others questioned whether viruses or bacteria were at fault. Finally, the "irritation" theory became popular,and researchers began trying to identify irritants — such as tobacco and coal tar — that would cause cancer in laboratory animals. Ultimately, though, cancer experts were forced to confront the fact that although all these factors might be involved, none of them invariably ***cause*** cancer. Not every animal or person exposed to an irritant or a particular chemical in the laboratory developed cancer, nor did all elderly people or everyone with a family history of cancer get it. As a result, scientists had to abandon the theory that cancer had a single cause.

However, despite the fact that there is yet no absolute agreement among the cancer research community in terms of what actually ***causes*** cancer, scientists are certain that many factors can be linked to cancer. These factors, including many other possible causes of cancer suggested by cancer researchers, are believed to be "cancer risk factors." These risk factors include eating habits, lifestyle, living or working environments, genetics, and many others. Following are some major cancer risk factors identified by researchers with the support of scientific statistics:

- Smoking
- Diet
- Genetics
- Occupation and Environment
- Infectious Agents

Smoking

Cigarette smoking alone is directly related to at least one-third of all cancer deaths annually in the United States. Cigarette smoking is the most significant cause of lung cancer and the leading cause of lung cancer death in both men and women. Smoking is also responsible for most cancers of the larynx, oral cavity, and esophagus. In addition, it is highly associated with the development of, and deaths from, bladder, kidney, pancreatic, and cervical cancers.

Tobacco smoke contains thousands of chemical agents, including 60 substances that are known to cause cancer (carcinogens).

The health risks with cigarette smoking are not limited to smokers. Exposure to environmental tobacco smoke significantly increases a nonsmoker's risk of developing lung cancer. Environmental tobacco smoke is the smoke that nonsmokers are exposed to when they share air space with someone who is smoking.

Diet

The lifestyle factor that has received the most attention in recent years is diet. Evidence suggests that about one-third of the cancer deaths each year that occur in the United States are related to dietary factors. These include types of food, preparation methods, portion size, variety, and overall caloric balance.

A high-fat diet has been associated with an increased risk for cancer of the prostate, endometrium, and colon and rectum. It is believed that a high-fat diet is a cancer promoter, with numerous theories to explain the effects of excess fat. For instance, excess fat seems to be involved in the production of free radicals, which play a role in many types of cancer. A high-fat diet also increases the flow of bile acids into the intestine, which can promote colon cancer.

Study results suggest that certain food additives, as well as preparation methods, can either cause or promote cancer. Even some so-called natural methods of preserving foods are not considered safe. For example, pickled, cured, and smoked products appear to promote stomach cancer, possibly due to nitrites used in curing as well as to other compounds produced during smoking and pickling. The decrease in gastric cancer incidence is largely due to modern refrigeration and a reduction in pickled, cured, and smoked food products.

Genetics

By definition, cancer is really a disease of genes. Genes are very small molecules in our cells, which determine almost everything in our body. Genes that control the genetics and heredity of each cell are strung like beads on a necklace along the cell's DNA in the cell nucleus. In a benign or malignant tumor, several of the genes regulating these processes

are abnormal (mutated). Abnormal genes may be inherited or damaged by carcinogens, viruses, errors in cell division, and as yet unknown factors.

A number of the most common cancers, including breast, colon, ovarian, and uterine cancer, recur generation after generation in some families. In addition, certain genetic factors may predispose those affected to specific cancers. A few rare cancers, such as the eye cancer, retinoblastoma, and a type of colon cancer, have been linked to specific genes that can be tracked within a family.

Although it is helpful to know the role that our genetic heritage may play as a possible cause of cancer, scientists believe that environmental influences and our behaviors may outweigh the risks inherent in our family tree.

Occupation and Environment

Scientists have long been aware of the linkage between one's health conditions and one's occupation and environment.

People who have direct contact to carcinogenic agents in the workplace are at the highest risk for developing cancer. For example, a recent study suggests that people with brain cancer are more likely to have worked in certain occupations than similarly aged people without brain cancer. Many cancer-causing chemicals have been identified and many of them are banned from manufacture in the United States.

More recently, investigators have identified a link between the environment and skin cancer. The environmental factor is something we depend on for our life: sunlight. Scientists have found that ultraviolet light causes mutations of genes, producing a carcinogenic effect. Now, we not only know that tumors may appear years after the damaging effects of sunlight, but also the risks from exposure to ultraviolet light are greater for light-skinned people. Statistics show that in the U.S. alone about a million new cases of skin cancer (basal and squamous cell carcinomas) occur annually, rivaling the incidence of all other types of cancer combined.

The common body surfaces that are exposed to carcinogens are the skin, nasal passages, and lung. The primary internal body surface that has contact with carcinogens is the urinary bladder.

Infectious Agents

Because viruses can invade and alter cells' genetic material, viral infections are implicated in some cancers. The Epstein-Barr virus, for example, is associated with Burkitt lymphoma, a tumor found mainly among children in Africa. The hepatitis B virus is responsible for much of the liver cancer around the world. The highest rates of hepatitis B infection in the world is in China, Taiwan, Japan, and Thailand with equally high rates of liver cancer in these countries. The human papilloma virus that causes genital warts has been shown to play an important causative role in cervical cancer. The human T-cell leukemia virus, a close relative of the virus that causes acquired immunodeficiency syndrome (AIDS), is associated with a cancer known as Kaposisarcoma and some types of Non-Hodgkin lymphomas.

Cancer risk factors are not limited to those listed above. There are still other risk factors such as ethanol use, use of certain medications, hormones, and reproductive and sexual behavior. With further scientific research, more cancer risk factors will be identified in the future.

In summary, cancer is caused by both external (chemical, radiation, and viruses) and internal (hormones, immune conditions, and inherited mutations) factors. Causal factors may act together, or in sequence, to initiate or promote carcinogenesis.

Review: What Is Cancer?

Here is what we have learned from *What Is Cancer?*:

- The American Cancer Society defines cancer as "a group of diseases characterized by uncontrollable growth and spread of abnormal cells. If the spread is not controlled, it can result in death."
- Cancer does not refer to a single disease. Rather, it consists of more than 100 different diseases.
- A few cancer-related terms are introduced: cancer, neoplasia, tumor, neoplasm, and growth. Neoplasia, a synonym of cancer, is often used by medical professionals. Neoplasm is a synonym for tumor, which literally means "new growth." Several other terms referring to abnormal cell growth which are not cancer include: hyperplasia, metaplasia, and dysplasia.

- Cell biology of cancer defines the differences between normal cells and cancer cells. Normal, healthy cells carry out specific functions of the body and the cells' growth is controlled by a complicated biochemical mechanism of the body. Cancer cells grow in an uncontrollable manner and are unable to recognize their own natural boundaries due to faulty gene mutations in the cancer cells.
- Although scientists have not yet pinpointed an exact cause for cancer, many factors have been identified that are likely to cause development of cancer in the body. These factors are called "cancer risk factors" and include smoking, diet, genetics, occupation, environment, and infectious agents.

Categories of Cancer

Cancers are named according to the organ in which they originate. Even if a cancer metastasizes to another part of the body, it keeps its original name. Cancer names such as breast cancer, brain cancer, lung cancer, skin cancer are examples. However, cancer names may also be based on the type of tissue affected. This section will introduce you to some basics regarding the derivation of tissues in the context of embryology, which is the study of the development of an organism.

Derivation of Cells

Human beings begin life as a single, newly fertilized cell. Like every cell that contains a nucleus, the fertilized cell holds all the instructions for its growth and development. The characteristics common to all living cells include the ability to reproduce, exchange gases, move, react to external stimuli, and create or utilize energy to perform their tasks.

Shortly after the ovum or egg is fertilized, it divides to form two cells. These two cells then divide to form a total of four, which again divide to form eight and continues on. This group of cells continues dividing; after nine days it attaches to the wall of the uterus and becomes an embryo.

About two weeks after conception, the cells of the embryo continue to divide, changing their shape and structure. This process is known as differentiation. The cells arrange into distinct layers called germ layers: an outer ectoderm and inner endoderm (entoderm). A third embryonic layer, the mesoderm, develops between the ectoderm and the endoderm. All the organs of the body develop or differentiate in an orderly fashion from these three primary germ layers.

Derivation of Tissues

Cells that are similar in structure tend to group themselves together and form tissues. A tissue, then, is composed of a group of cells that are similar in structure and perform one or more common functions. Some tissues contain intercellular material which is very important in the performance of a particular function belonging to that tissue.

The body tissues and organs develop from the three primary germ layers that form during the growth process of the human embryo.

The tissues derived from the ectoderm are: some epithelial tissue (epidermis or outer layer of the skin, the lining for all hollow organs which have cavities open to a surface covered by epidermis), modified epidermal tissue (fingernails and toenails, hair, glands of the skin), all nerve tissue, salivary glands, and mucous glands of the nose and mouth.

In fact, epithelial tissue can be derived from either the ectoderm or endoderm. The epithelial tissue derived from the endoderm includes the epithelial lining of the digestive tract, except at the open ends, and the epithelial lining of all hollow structures formed as outpockets in the digestive tract. This includes:

- The parenchyma of the liver including communicating or connecting ducts
- The lining of the pharynx and respiratory tract (except the nose). This includes the lungs and the passageways leading from the pharynx to the lungs
- The epithelium of the bladder and urethra
- Glands that form secretions in the digestive tract

Epithelial tissue derived from ectoderm is generally squamous epithelium; epithelial tissue derived from endoderm is essentially glandular epithelium.

There are a variety of body tissues derived from the third or middle primary germ layer known as the mesoderm. These body tissues include:

- Muscles
- Fibrous tissue
- Bone and cartilage
- Fat or adipose tissue
- Blood and lymph vessels
- Blood cells

In the early embryo the first cavity that develops is the coelomic cavity; this is derived from mesoderm. Parts of the urinary and genital systems are derived as outpouchings of the coelomic cavity. Later this coelomic cavity divides into the pleural cavity and the pericardial cavity. The linings of these cavities are composed of a single layer of cells called mesothelium. A few epithelial cells are of mesodermal origin, e.g. endometrium of the uterus, vaginal epithelium, and mucosa of the bladder.

Endothelium derived from mesoderm lines the blood and lymphatic vessels and the walls of the heart. In the capillaries where the endothelium is covered only by a basement membrane, diffusion takes place. It is surrounded elsewhere by supportive layers of connective tissue and smooth muscle. This is necessary because the endothelium is so thin that diffusion would occur otherwise. Many authorities classify this endothelium as connective tissue.

CANCER CLASSIFICATION

Cancers are classified in two ways: by the type of tissue in which the cancer originates (histological type) and by primary site, or the location in the body where the cancer first developed. This section introduces you to the first method: cancer classification based on histological type. The international standard for the classification and nomenclature of histologies is the International Classification of Diseases for Oncology, Third Edition (ICD-O-3).

From a histological standpoint there are hundreds of different cancers, which are grouped into six major categories:

- Carcinoma
- Sarcoma
- Myeloma
- Leukemia
- Lymphoma
- Mixed Types

Carcinoma

Carcinoma refers to a malignant neoplasm of epithelial origin or cancer of the internal or external lining of the body. Carcinomas, malignancies of epithelial tissue, account for 80 to 90 percent of all cancer cases.

Epithelial tissue is found throughout the body. It is present in the skin, as well as the covering and lining of organs and internal passageways, such as the gastrointestinal tract.

Carcinomas are divided into two major subtypes: adenocarcinoma, which develops in an organ or gland, and squamous cell carcinoma, which originates in the squamous epithelium.

Adenocarcinomas generally occur in mucus membranes and are first seen as a thickened plaque-like white mucosa. They often spread easily through the soft tissue where they occur. Squamous cell carcinomas occur in many areas of the body.

Most carcinomas affect organs or glands capable of secretion, such as the breasts, which produce milk, or the lungs, which secrete mucus, or colon or prostate or bladder.

Sarcoma

Sarcoma refers to cancer that originates in supportive and connective tissues such as bones, tendons, cartilage, muscle, and fat. Generally occurring in young adults, the most common sarcoma often develops as a painful mass on the bone. Sarcoma tumors usually resemble the tissue in which they grow.

Examples of sarcomas are:

- Osteosarcoma or osteogenic sarcoma (bone)
- Chondrosarcoma (cartilage)
- Leiomyosarcoma (smooth muscle)
- Rhabdomyosarcoma (skeletal muscle)
- Mesothelial sarcoma or mesothelioma (membranous lining of body cavities)
- Fibrosarcoma (fibrous tissue)
- Angiosarcoma or hemangioendothelioma (blood vessels)
- Liposarcoma (adipose tissue)
- Glioma or astrocytoma (neurogenic connective tissue found in the brain)
- Myxosarcoma (primitive embryonic connective tissue)
- Mesenchymous or mixed mesodermal tumor (mixed connective tissue types)

Myeloma

Myeloma is cancer that originates in the plasma cells of bone marrow. The plasma cells produce some of the proteins found in blood.

Leukemia

Leukemias ("liquid cancers" or "blood cancers") are cancers of the bone marrow (the site of blood cell production). The word leukemia means "white blood" in Greek. The disease is often associated with the overproduction of immature white blood cells. These immature white blood cells do not perform as well as they should, therefore the patient is often prone to infection. Leukemia also affects red blood cells and can cause poor blood clotting and fatigue due to anemia. Examples of leukemia include:

- Myelogenous or granulocytic leukemia (malignancy of the myeloid and granulocytic white blood cell series)
- Lymphatic, lymphocytic, or lymphoblastic leukemia (malignancy of the lymphoid and lymphocytic blood cell series)
- Polycythemia vera or erythremia (malignancy of various blood cell products, but with red cells predominating)

Lymphoma

Lymphomas develop in the glands or nodes of the lymphatic system, a network of vessels, nodes, and organs (specifically the spleen, tonsils, and thymus) that purify bodily fluids and produce infection-fighting white blood cells, or lymphocytes. Unlike the leukemias which are sometimes called "liquid cancers," lymphomas are "solid cancers." Lymphomas may also occur in specific organs such as the stomach, breast or brain. These lymphomas are referred to as extranodal lymphomas. The lymphomas are subclassified into two categories: Hodgkin lymphoma and Non-Hodgkin lymphoma. The presence of Reed-Sternberg cells in Hodgkin lymphoma diagnostically distinguishes Hodgkin lymphoma from Non-Hodgkin lymphoma.

Mixed Types

The type components may be within one category or from different categories. Some examples are:

- adenosquamous carcinoma
- mixed mesodermal tumor
- carcinosarcoma

- teratocarcinoma

In the next section, you will be provided with a comprehensive list of tissue types and the tumors that arise from them.

TUMOR LIST

Different body tissue types give rise to different tumors, both benign and malignant. The following tables show the different kinds of tumors each of the following tissue types are vulnerable to:

- Connective Tissue
- Endothelium and Mesothelium
- Blood and Lymphoid Cells
- Muscle
- Epithelial Tissues
- Neural
- APUD System (APUD - Amine Precursor Uptake and Decarboxylation)
- Other Neural Crest-Derived Cells
- Tumors
- Gonadal Tumors

Table 1.1:Connective Tissue

Tissue	Benign Tumors	Malignant Tumors
Adult fibrous tissue	Fibroma	Fibrosarcoma
Embryonic (myxomatous) fibrous tissue	Myxoma	Myxosarcoma
Fat	Lipoma	Liposarcoma

Cartilage	Chondroma	Chondrosarcoma
Bone	Osteoma	Osteosarcoma
Notochord	—	Chordoma
Connective tissue, probably fibrous	Fibrous histiocytoma	Malignant fibrous histiocytoma

Table 1.2: Endothelium and Mesothelium

Tissue	Benign Tumors	Malignant Tumors
Blood vessels	Hemangioma, hemangiopericytoma	Hemangiosarcoma, angiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Mesothelium	—	Mesothelioma

Blood and Lymphoid Cells

Tissue	Benign Tumors	Malignant Tumors
Hematopoietic cells	"Preleukemias", "myeloproliferative disorders"	Leukemia, of various types; aleukemic leukemia
Lymphoid tissue	Plasmacytosis	Plasmacytoma; multiple myeloma; Hodgkin lymphoma and Non-Hodgkin lymphoma

Tissue	Benign Tumors	Malignant Tumors
Smooth muscle	Leiomyoma	Leiomyosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarcoma

Table:1.3: Epithelial Tissues

Tissue	Benign Tumors	Malignant Tumors
Stratified squamous	Papilloma Seborrheic keratosis and some skin adnexal tumors	Squamous cell carcinoma; epidermoid carcinoma and some malignant skin adnexal tumors
Glandular epithelium 1. Liver 2. Kidney 3. Bile duct	Adenoma Hepatic adenoma Renal tubular adenoma Bile duct adenoma	Adenocarcinoma Hepatoma: hepatocellular carcinoma Renal cell carcinoma; hypernephroma Cholangiocarcinoma
Transitional epithelium	Transitional cell papilloma	Transitional cell carcinoma
Placenta	Hydatidiform mole	Choriocarcinoma

Tissue	Benign Tumors	Malignant Tumors
Pituitary	Basophilic adenoma Eosinophilic adenoma Chromophobe adenoma	— — —
Parathyroid	Parathyroid adenoma	Parathyroid carcinoma
Thyroid (C cells)	C cell hyperplasia	Medullary carcinoma of thyroid
Bronchial lining (Kultschitzky cells)	—	Bronchial carcinooid; oat cell carcinoma
Adrenalmedulla Pheochromocytoma	Pheochromocytoma	Malignant Pheochromocytoma
Pancreas	Islet celladenoma; Insulinoma; gastrinoma	Islet cell carcinoma
Stomach and intestines	Carcinoid	Malignant carcinoid
Carotid body and chemo-receptor system	Chemodectoma; paraganglioma	Malignantcarcinoid Malignant paraganglioma
Testis	—	Seminoma; embryonal cell carcinoma

Table 1.4 :table

APUD System (APUD - Amine Precursor Uptake and Decarboxylation)

The APUD system is a recently defined series of cells which have endocrine functions in that they secrete one of a variety of small amine or polypeptide hormones. The stored forms of these hormones located in the cytoplasm are small, dense-core membrane-bound granules visible by electron microscopy. Some of these cells appear to be derived from neural crest cells which migrate into a variety of organs. APUD system tissues give rise to the benign and malignant tumors outlined in Table G.

Other Neural Crest-Derived Cells

Tissue	Benign Tumors	Malignant Tumors
Pigment-producing cells in skin, eyes, and occasional other sites	Nevus	Melanoma
Schwann cells of peripheral nervous system	Schwannoma, or neurilemmoma	Malignant schwannoma
Merkel cells in squamous epithelium (unknown function)	—	Merkel cell neoplasm (similar to oat cell)

Table 1.4:Tumors

Tissue	Benign Tumors	Malignant Tumors

Breast	Fibroadenoma	Cystosarcoma phylloides
Renal anlage	—	Wilms tumor

Gonadal Tumors

Terminology for Gonadal tumors or tumors of the ovary and testis is somewhat more confusing. One general class of tumors arises from multi-potential cells that give rise to tumors containing a variety of tissue types, often within the same tumor. These "germ cell" tumors include seminoma (dysgerminoma in women), choriocarcinoma, embryonal carcinoma, endodermal sinus tumor, and teratocarcinoma. Although all of these tumors are most common in the ovaries or testes, they also occur in extragonadal sites.

Another group of Gonadal tumors arises from the connective tissue stroma. In males, these include Sertoli-Leydig cell tumors (homologous tumors in females may be arrhenoblastoma, although most pathologists use "Sertoli-Leydig cell"), and in females, granulose-theca cell tumors, hilar cell tumors, and lipid cell tumors. Although all of these tumors technically arise from the connective tissues, they are given separate names because of the specialized nature and function of the Gonadal stromal cells.

A number of epithelial tumors occur in the ovary. It will be easy to distinguish benign from malignant tumors because they are named in exactly the same way as other epithelial lesions. However, in some lesions, the pathologist may call a tumor "borderline" or "of low malignant potential." These terms are applied to a group of potentially malignant lesions that metastasize much less frequently than the carcinomas.

Cancer Types by Site

Medical professionals frequently refer to cancers based on their histological type. However, the general public is more familiar with cancer names based on their primary sites. The most common sites in which cancer develops include:

- Skin
- Lungs
- Female Breasts
- Prostate
- Colon and Rectum
- Cervix and Uterus

Compared with those based on histological type, cancers named after the primary site may not be as accurate. Take lung cancer for example; the name does not specify the type of tissue involved. It simply indicates where the cancer is located. In fact, depending on how the cells look under a microscope, there are two major types of lung cancer: non-small cell lung cancer and small cell lung cancer. Non-small cell lung cancer can be further divided into various types named for the type of cells in which the cancer develops, typically: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma.

However, it's important to know that cancer can be classified either by the cell type or its primary site. Saying that a woman has uterine carcinoma or uterine cancer is the same thing as saying that she has cancer (or carcinoma) of the uterus.

Following are some examples of common types of cancers named for their primary site.

Skin

There are three primary types of skin cancer: basal cell, squamous cell, and melanoma. These cancers are derived from the epidermal layers with the same names. Melanomas are derived from the melanocytes, or pigment cells, in the deepest level of the epidermis.

Basal cell and squamous cell cancers usually occur on parts of the body exposed to the sun, such as the face, ears, and extremities. These cancers are highly curable, especially if detected

and treated early. Melanomas, which form dark moles that spread over the surface of the skin, are more lethal because they metastasize very quickly.

Lung

Lung cancer is very difficult to detect at an early stage because the symptoms often do not appear until the disease has advanced. The symptoms include persistent cough, sputum streaked with blood, chest pain, and repeated attacks of pneumonia or bronchitis.

Female Breast

It has been estimated that in the U.S., about 1 in 8 women will eventually develop breast cancer in her lifetime. Most breast cancers are ductal carcinomas. Women most likely to develop the disease are those over the age of 50; those who have already had cancer in one breast; those whose mother or sister had breast cancer; those who never had children; and those who had their first child after the age of 30. Other risk factors include obesity, a high-fat diet, early menarche (age menstruation begins) and late menopause (age menstruation ceases).

Monthly breast self-examination is recommended as a way to detect breast cancer early. Most of the lumps found in the breasts are not cancerous, but women should see their physicians to find out for sure. The American Cancer Society also recommends periodic mammograms (or breast X-rays) for all women over the age of 40 as well as physical examinations of the breast by a physician for all women over the age of 20, even if they have no symptoms of breast cancer.

Prostate

Cancer of the prostate is found mainly in older men. As men age, the prostate may enlarge and block the urethra or bladder. This may cause difficulty in urination or interfere with sexual functions. This condition is called benign prostatic hypertrophy (BPH). Although BPH is not cancerous, surgery may be needed to correct it. The symptoms of BPH, or of other problems in the prostate, may be similar to symptoms for prostate cancer.

Individuals should consult a physician if any of the following symptoms appear: weak or interrupted flow of urine; urinating often (especially at night); difficulty urinating; pain or

burning during urination; blood in the urine; or nagging pain in the back, hips, or pelvis. Often there are no symptoms of early cancer of the prostate.

Colon and Rectum

Of the cancers that affect the large intestine, about 70 percent occur in the colon and about 30 percent in the rectum. These cancers are the third most common cancers overall. Symptoms include blood in the stool, which can be tested for by a simple fecal occult blood test, or a change in bowel habits, such as severe constipation or diarrhea.

Uterus (Corpus Uteri)

The uterus is the sac in a woman's pelvis which allows a baby to develop from a fertilized egg and protects it until birth.

Cancer of the uterus is the most common gynecologic malignancy. This cancer occurs infrequently in women under 40 years of age. It occurs most frequently after the age of 60. The presenting symptom is usually abnormal uterine bleeding. An endometrial biopsy or D&C is often performed to confirm the diagnosis.

Currently, there has been little insight into the exact causes for uterine cancer. However, 10-25 percent of malignancies occur in women who received pelvic radiation five to 25 years earlier for benign bleeding. As in other cancers of its type, risk factors for uterine cancer include diabetes, hypertension, obesity, and improper estrogen levels.

In addition to cancer types named after the primary site discussed above, there are many other examples such as brain cancer, testicular cancer, bladder cancer, and so on.

Review: Categories of Cancer

Here is what we have learned from *Categories of Cancer*:

- Cancers can be classified based either on histological type or their primary site (the location where the cancer originated).
- Derivation of cells and tissues starts with cell differentiation, which refers to the process of cells becoming arranged into three distinct germ layers: an outer ectoderm, an inner endoderm, and a mesoderm in between.

- All of the organs of the body develop or differentiate from these three primary germ layers.
- Tissue is composed of a group of cells that are similar in structure and perform one or more common functions.
- Five major categories of cancer, based on their histological characteristics, are: carcinoma; sarcoma; myeloma; leukemia; and lymphoma. In addition, there are also some mixed types.
- The most common sites in which cancer develops include the skin, lungs, female breasts, prostate, colon and rectum, and uterus.

Cancer Diagnosis

The diagnosis of cancer entails an attempt to accurately identify the anatomical site of origin of the malignancy and the type of cells involved. Cancer can arise in any organ or tissue in the body except fingernails, hair, and teeth.

The site refers to the location of the cancer within the body. The body part in which cancer first develops is known as the primary site. A cancer's primary site may determine how the tumor will behave; whether and where it may spread (metastasize) and what symptoms it is most likely to cause. The most common sites in which cancer develops include the skin, lungs, female breasts, prostate, colon and rectum, and corpus uteri.

Secondary site refers to the body part where metastasized cancer cells grow and form secondary tumors. A cancer is always described in terms of the primary site, even if it has spread to another part of the body. For instance, advanced breast cancer that has spread to the lymph nodes under the arm and to the bone and lungs is always considered breast cancer (and the spread to the lymph nodes, bones, and lungs describe the stage of the cancer).

As is the case with other medical conditions, there are many signs and symptoms that may indicate the presence of cancer. These may be observed directly, through imaging technologies, or confirmed by lab tests. However, these signs and symptoms of cancer may resemble those of other conditions. For example, weight loss and abdominal pain can be caused by stomach cancer or an ulcer. Pink or reddish urine can be caused by kidney cancer or a kidney infection. A positive fecal occult blood test can indicate a variety of intestinal problems. A biopsy (removal of tissue for microscopic evaluation) is preferred to establish, or rule out, a diagnosis of cancer.

Tissue samples can be easily retrieved from a tumor near the body's surface. If the mass is inaccessible, an imaging exam that enables a tumor to be located precisely and visualized may be ordered before the biopsy is performed.

The histological type is determined by microscopic examination of suspected tissue that has been excised by biopsy or surgical resection. If the histological type is different from what is usually found in the tissue being examined, it can mean the cancer has spread to that area from some primary site. Metastasis can occur by direct extension, via the blood stream or the lymphatic system, or by seeding or implantation of cancer cells.

A biopsy, together with advanced imaging technologies, may not only confirm the presence of cancer, but may also pinpoint the primary site and secondary site(s).

It is also important to identify the cell type(s). Various histological types have different growth rates and dissimilar prognoses. More than one histological type of cell may be found in the same site. For example, a tumor whose primary site is skin can be a basal cell carcinoma, a squamous cell carcinoma, or a melanoma.

Once cancer has been confirmed, the pathologist tries to determine how closely the cancer cells resemble healthy, mature cells. Such cells are said to be differentiated. Cancer cells that do not look like their healthy counterparts are called undifferentiated, or, because they often look like very immature cells, primitive. The pathologist assigns a pathological grade to a tumor according to how aggressive the tissue looks under the microscope. Tumor grades can be expressed in words or by a number. One set of terms consists of well differentiated (grade 1), moderately differentiated (grade 2), poorly differentiated (grade 3), or undifferentiated (grade 4). When tumors are graded by number (1 through 4), a grade-1 tumor has a better natural history than a grade-4 tumor does.

Cancers are further classified according to stage. Staging describes how far a cancer has progressed based on the size of the primary tumor and whether and/or where it has spread. Go to the Summary Staging and Summary Stage 2000 training module for more details on cancer staging.

In summary, a biopsy is the preferred method to confirm the diagnosis of cancer. Biopsies can provide information about histological type, classification, grade, potential aggressiveness and other information that may help determine the best treatment. More information regarding cancer treatment is provided in the Cancer Treatment training module.

Review: Cancer Diagnosis

Here is what we have learned from *Cancer Diagnosis*:

- A biopsy (removal of tissue for microscopic evaluation) is preferred to establish, or rule out, a diagnosis of cancer.
- Usually, a biopsy, together with advanced imaging technologies, can not only confirm the presence of cancer, but also pinpoint the primary site and secondary site(s) of the

cancer, if any. A cancer's primary site may determine how the tumor will behave; whether and where it may spread, or metastasize; and what symptoms it is most likely to cause. A secondary site refers to the body part where metastasized cancer cells grow and form secondary tumors.

- Once a cancer has been confirmed, the pathologist often assigns a pathological grade to a tumor according to how malignant the tissue looks under the microscope. Cancers are further classified according to stage.

Cancer Facts & the War on Cancer

Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death. The following facts will help us understand the importance of the "War on Cancer."

More than 1.2 million Americans develop cancer each year. A new cancer is diagnosed every 30 seconds in the United States. Since 1990, nearly 15 million new cancer cases have been diagnosed. These estimates do not include carcinoma in situ (non-invasive cancer) of any site except urinary bladder and do not include the basal and squamous cell skin cancers.

Lung and prostate cancer are the top cancer killers for men in the United States. Lung and breast cancer are the top cancer killers for women in the United States. One in two men in the U.S. will be diagnosed with cancer at some time during his lifetime. One in three women in the US will be diagnosed with cancer at some time during her lifetime.

Cancer is the second leading cause of death after heart disease in the United States. It is the primary cause of death in women between the ages of 35 and 74. About 8,000 American children will be diagnosed with cancer this year. Cancer is the chief cause of death in children between the ages of 1 and 14.

If current trends continue, cancer is expected to be the leading cause of death in the United States by the year 2010. One in five persons in the US will die from cancer. Every three minutes, two people in the US die from cancer.

Based on estimates of the National Institutes of Health, overall costs for cancer in the year 2000 was $180.2 billion: $60 billion for direct medical costs (total of all health expenditures); $15 billion for indirect morbidity costs (cost of lost productivity due to illness); and $105.2 billion

for indirect mortality costs (cost of lost productivity due to premature death). Cancer-related costs account for about 10 percent of the total amount spent on disease treatment in the United States. Cancer is a major national burden.

In 1970, the American people knew what they wanted -- a cure for the second-leading cause of death. President Nixon heard the voice of the people and the concerns of the medical profession. In his January 1971 State of the Union address, President Nixon made a special request for an additional $100 million to be added to the NCI budget for cancer research. In October 1971 he converted the Army's Fort Detrick, Maryland, biological warfare facility to a cancer research center. The resulting Frederick Cancer Research and Development Center eventually became an internationally recognized laboratory for cancer and AIDS research. However, President Nixon took a much bigger step when he signed the National Cancer Act into law on December 23, 1971, declaring, "I hope in the years ahead we will look back on this action today as the most significant action taken during my Administration."

After more than three decades, the "War on Cancer," declared by President Nixon in 1971 with the enactment of the National Cancer Act, is still going on in this country. The Question is: "Are we winning the war?"

Unfortunately, there is no simple answer to the question. The good news is that since Nixon's initiative, there have been incredible advances in cancer detection, prevention, and treatment. Since the mid 1990s, the cancer death rate has been decreasing steadily. As one cancer experts puts it: "It's just amazing those who are making it and are living, whereas 10 years ago these same people would not have lived." A diagnosis of cancer once was the virtual equivalent of a death sentence. Today, nearly half of all cancer patients can expect to live for five or more years after the diagnosis of cancer.

However, scientists are still not able to pinpoint a "cause" for cancer. Instead, cancer researchers now believe that cancer can be triggered by many factors, such as our genetics, diet and occupation. We know that our chances of developing cancer can be significantly reduced if we choose to live a healthy lifestyle, not smoke and avoid certain foods.

Finally, while a "cure" for cancer has not yet been found, scientists are more confident than ever that further breakthroughs in cancer detection and therapy are not far away, allowing us to effectively control the disease.

Review: The War on Cancer

To illustrate how important the "War On Cancer" is in this country, some sobering facts about cancer are provided in *The War On Cancer*:

- More than 1.2 million Americans develop cancer each year.
- Since 1990, nearly 15 million new cancer cases have been diagnosed in the U.S.
- Cancer is the second leading cause of death after heart disease in the United States, but it is the major cause of death in women between the ages of 35 and 74. One in two men in the U.S. will be diagnosed with cancer at some time during his lifetime.
- Cancer is the chief cause of death in children between the ages of 1 and 14.
- Cancer-related costs account for about 10 percent of the total amount of money spent on disease treatment in the United States.

New Global Cancer Data: GLOBOCAN 2018

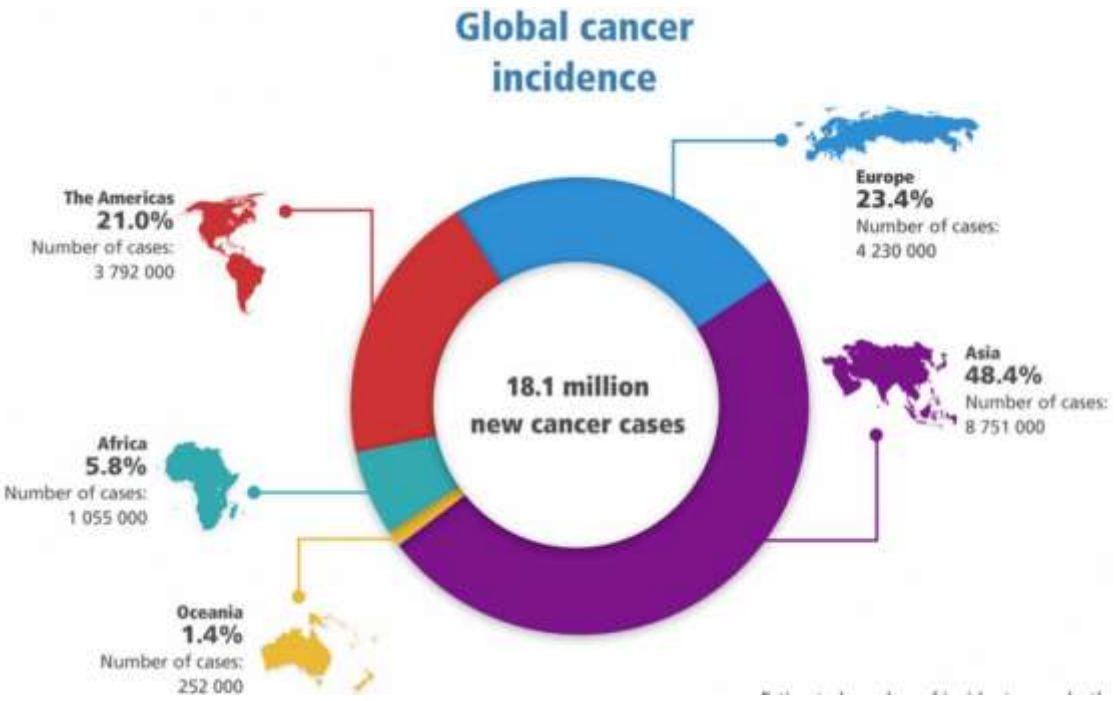


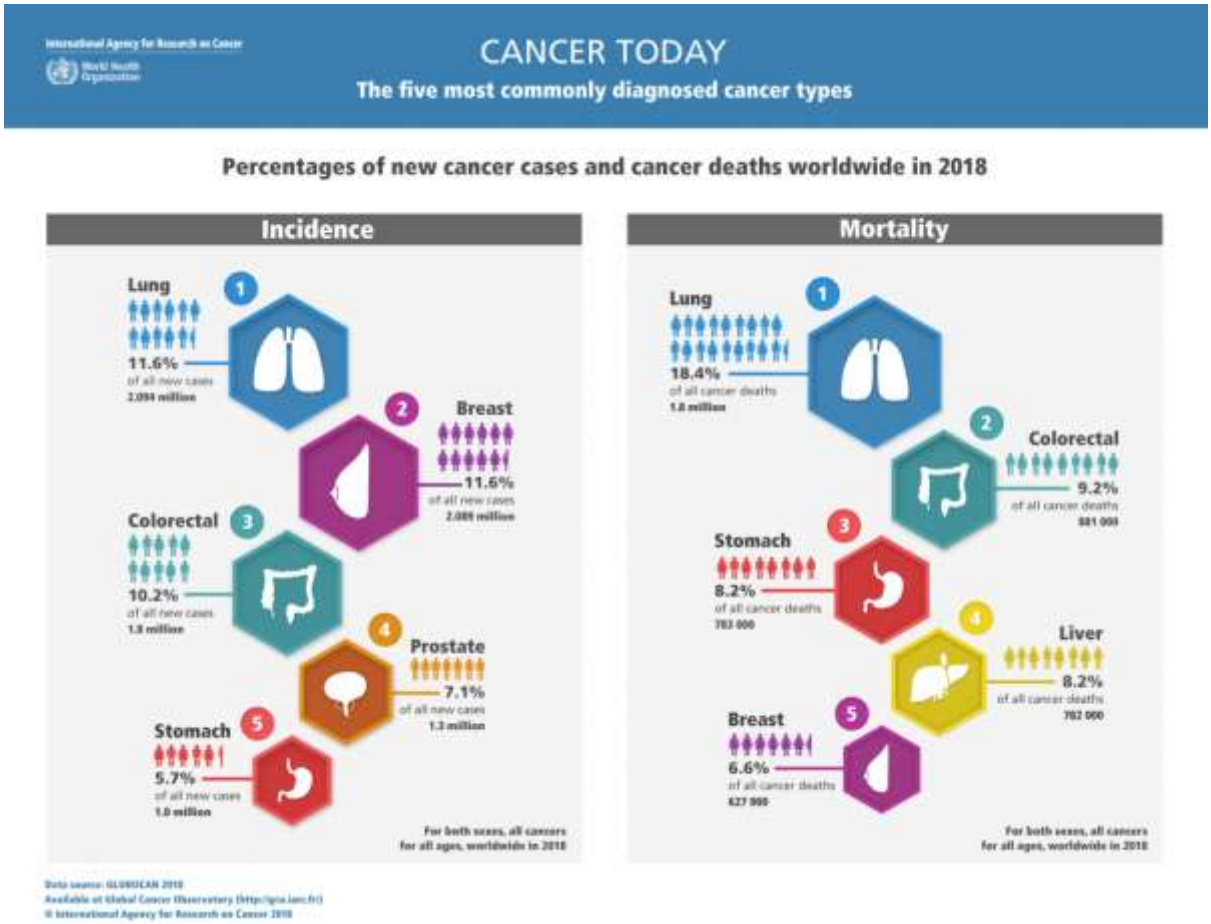
Figure 1.1: New global cancer data suggests that the global cancer burden has risen to 18.1 million cases and 9.6 million cancer deaths.

The International Agency for Research on Cancer (IARC) estimate that one-in-five men and one-in-six women worldwide will develop cancer over the course of their lifetime, and that one-in-eight men and one-in-eleven women will die from their disease. A number of factors appear to be driving this increase, particularly a growing and ageing global population and an increase in exposure to cancer risk factors linked to social and economic development. For rapidly-growing economies, the data suggests a shift from poverty- or infection-related cancers to those associated with lifestyles more typical in industrialised countries.

There are some indications that scaled-up prevention efforts are starting to reduce cancer incidence rates, for example lower lung cancer incidence in men in Northern Europe and North America, or in cervical cancer across most regions except Sub-Saharan Africa compared to 2012 data.

However countries are facing an overall increase in the absolute number of cancer cases. Asia accounts for nearly half of the new cancer cases and more than half of cancer deaths. Estimated suggest that Asia and Africa have a higher proportion of cancer deaths (7.3% and 57.3% respectively) compared with their incidence (5.8% and 48.4% respectively). IARC suggests this trend is likely due to the higher frequency of cancer types associated with poorer prognosis, along with limited access to timely diagnosis and treatment. The 2018 data also suggests that countries with high Human Development Index (HDI) have 2-3 times higher cancer incidence than those with low or medium HDI. The leading cancers globally have also changed compared to 2012 data.

Figure 1.2: cancer in global level



Clear call for action

It is clear that cancer is an urgent global challenge and Governments must take meaures to scale up prevention, early detection and diagnosis, treatment, and care services. The global cancer community has an important role to play in holding Governments accountable to their commitments and advocating for accelerated and evidence-based action nationally.

One of the key concerns raised by IARC is that lung cancer is the leading cause of death globally and its prevalence is rising amongst women, surpassing breast cancers in 28 countries.

> *"Best practice measures embedded in the WHO Framework Convention on Tobacco Control have effectively reduced active smoking and prevented involuntary exposure to tobacco smoke in many countries," said Dr Freddie Bray, Head of the Section of Cancer Surveillance at IARC. "However, given that the tobacco epidemic is at different stages in different regions and in men and women, the results highlight the need for continue to put in place targeted and effective tobacco control policies in every country in the world."*

UICC is commited to working closely with out members to advocate for comprehensive cancer control, driven by the 2017 cancer resolution to deliver sustainable action. Dr Cary Adam's, CEO of UICC, suggested that:

> *"GLOBOCAN 2018 shows that we don't have time to waste in driving governments to step up cancer control efforts. We know what works, we know it is cost effective, we know it is feasible in every country. My ask to the global cancer community is to join our call to our Heads of Government to lead and take responsibility for this. We have Governments attending the HLM on NCDs; let's use the opportunity we have to start changing things now."*

UICC launched the '**Treatment for All**' campaign to help reduce premature mortality from cancer and promote equitable access to treatment and care. Find out more at the webpage above and learn how it can support your work nationally.

What is GLOBOCAN?

GLOBOCAN 2018 is an online database providing estimates of incidence and mortality in 185 countries for 36 types of cancer, and for all cancer sites combined. The data is part of IARC's Global Cancer Observatory, and is available online at **Cancer Today(link is external)** with user-friendly facilities to produce maps and explore visualisations.

An analysis of these results, published on 12th September in *CA: A Cancer Journal for Clinicians*, highlights the large geographical diversity in cancer occurrence and the variations in the magnitude and profile of the disease between and within world regions.

These estimates are based on the most recent data available at IARC and on information publicly available online. GLOBOCAN 2018 has been developed using a number of methods that are dependent on the availability and the accuracy of the data. National sources are used where possible, and in their absence local data and statistical modelling are used. IARC coordinates the Global Initiative for Cancer Registry Development(link is external), an international partnership that supports better estimation, as well as the collection and use of local data, to prioritise and evaluate national cancer control efforts.

CANCER IN INDIA (WWW. http://cancerindia.org.in/cancer-statistics/)

Cancer Statistics

- One woman dies of cervical cancer every 8 minutes in India [1].
- For every 2 women newly diagnosed with breast cancer, one woman dies of it in India [2-4].
- Mortality due to tobacco use in India is estimated at upwards of 3500 persons every day [5].
- Tobacco (smoked and smokeless) use accounted for 3,17,928 deaths (approx) in men and women in 2018.

Cancer Statistics in India [7]

- Estimated number of people living with the disease: around 2.25 million
- Every year, new cancer patients registered: Over 11,57,294 lakh
- Cancer-related deaths: 7,84,821

Risk of developing cancer before the age of 75 years

Male: 9.81%

Female: 9.42%

Total deaths due to cancer in 2018 [7]

- Total: 7,84,821
- Men: 4,13,519

Women: 3,71,302

Risk of dying from cancer before the age of 75 years is 7.34% in males and 6.28% in females.

Cancers of oral cavity and lungs account for over 25% of cancer deaths in males and cancer of breast and oral cavity account for 25% cancers in females [9]**.**

Table 1.6: The top five cancers in men and women account for 47.2% of all cancers; these cancers can be prevented, screened for and/or detected early and treated at an early stage [10]**. This could significantly reduce the death rate from these cancers.**

	MEN	WOMEN
1	LIP,ORAL CAVITY	BREAST
2	LUNG	LIP, ORAL
3	STOMACH	CERVIX
4	COLORECTAL	LUNG
5	ESOPHAGUS	GASTRIC

Breast Cancer

Breast cancer is the most common cancer in women in India and accounts for 14% of all cancers in women [2,3].

Globocan 2018 data:

- **New cases registered**: 1,62,468
- **Deaths**: 87,090

The incidence rates in India begin to rise in the early thirties and peak at ages 50-64 years [9].

Overall, 1 in 28 women is likely to develop breast cancer during her lifetime.

In urban areas, 1 in 22 women is likely to develop breast cancer during her lifetime as compared to rural areas where 1 in 60 women develops breast cancer in her lifetime [15].

Cervical Cancer

Cervical cancer is the second most common cancer in India in women accounting for 22.86% of all cancer cases in women and 12% of all cancer cases in both men and women [11].

Globocan 2018 data [2,3]:

- **New cases registered**: 96,922
- **Deaths**: 60,078

Median age: 38 years (age 21–67 years).

Rural women are at higher risk of developing cervical cancer as compared to their urban counterparts [12].

Cervical cancer is less common in Muslim than in Hindu women [8].

Cervical cancer is the third largest cause of cancer mortality in India accounting for nearly 10% of all cancer related deaths in the country [13].

Survival rate

The relative five year survival averages to 48.7% [14].

Length of survival depends on the cancer stage at the time of detection.

The survival chance of a person becomes better if the cervical cancer is detected and treated at earlier stages. Therefore it is important to avail of cervical cancer screening.

Oral Cancer

Oral cancer is the most common cancer in India amongst men (16.1 % of all cancers),

Globocan 2018 data:

- **New cases registered**: 92,011

Oral cancer is the second most common cancer in India amongst women (10.4 % of all cancers),

Globocan 2018 data:

- **New cases registered**: 1,19,992

Globocan 2018 data:

- **Total number of deaths in men and women together** : 72,616

Around 80-90% of oral cancers are directly attributable to tobacco use [16].

The mean age of oral cancer is 50 years [17].

The incident rate for oral cancer among females is significantly higher than males.

Survival rate (5-year) [18]

Patients with early stage oral cancer: 82%
Patients with advanced stages: 27%

- According to GLOBOCAN 2018 data, in 2018 there were 11,57,294 new cancer cases in India in both men and women, 7,84,821 deaths and 22,58,208 people living with cancer (within 5 years of diagnosis)
- Top 5 cancers that affect Indian population are Breast,Oral, Cervical, Gastric and lung cancers.

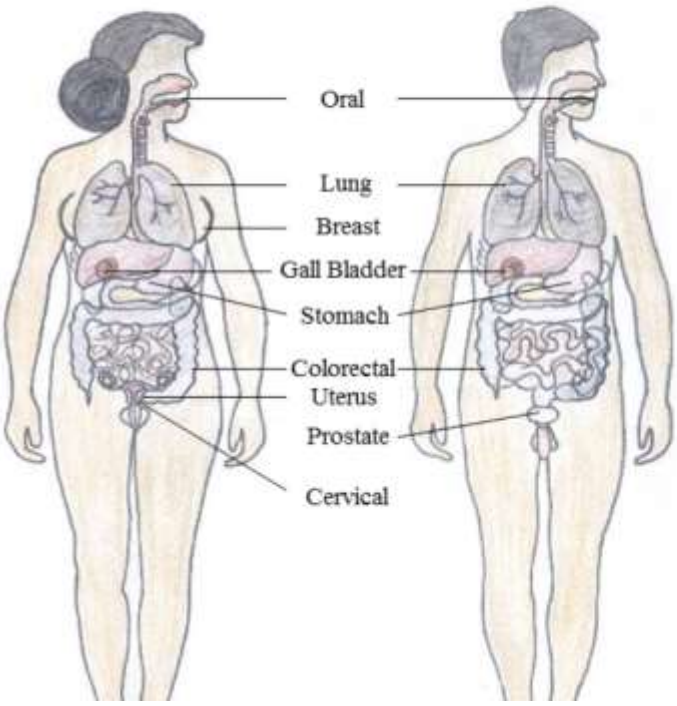


Figure 1.3: parts of the body most commonly affected by cancer

CANCER CLASSIFICATION

Cancers may be classified by their primary site of origin or by their histological or tissue types.

Classification by site of origin

By primary site of origin, cancers may be of specific types like breast cancer, lung cancer, prostate cancer, liver cancer renal cell carcinoma (kidney cancer), oral cancer, brain cancer etc.

Classification by tissue types

The international standard for the classification and nomenclature of histologies is the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). This classification is based on the ICD-O-3.

Based on tissue types cancers may be classified into six major categories:

1. Carcinoma

This type of cancer originates from the epithelial layer of cells that form the lining of external parts of the body or the internal linings of organs within the body.

Carcinomas, malignancies of epithelial tissue, account for 80 to 90 percent of all cancer cases since epithelial tissues are most abundantly found in the body from being present in the skin to the covering and lining of organs and internal passageways, such as the gastrointestinal tract.

Carcinomas usually affect organs or glands capable of secretion including breast, lungs, bladder, colon and prostate.

Carcinomas are of two types – adenocarcinoma and squamous cell carcinoma. Adenocarcinoma develops in an organ or gland and squamous cell carcinoma originates in squamous epithelium. Adenocarcinomas may affect mucus membranes and are first seen as a thickened plaque-like white mucosa. These are rapidly spreading cancers.

2. Sarcoma

These cancers originate in connective and supportive tissues including muscles, bones, cartilage and fat. Bone cancer is one of the sarcomas termed osteosarcoma. It affects the young most commonly. Sarcomas appear like the tissue in which they grow.

Other examples include chondrosarcoma (of the cartilage), leiomyosarcoma (smooth muscles), rhabdomyosarcoma (skeletal muscles), Mesothelial sarcoma or mesothelioma (membranous lining of body cavities), Fibrosarcoma (fibrous tissue), Angiosarcoma or hemangioendothelioma (blood vessels), Liposarcoma (adipose or fatty tissue), Glioma or astrocytoma (neurogenic connective tissue found in the brain), Myxosarcoma (primitive embryonic connective tissue) and Mesenchymous or mixed mesodermal tumor (mixed connective tissue types).

3. Myeloma

These originate in the plasma cells of bone marrow. Plasma cells are capable of producing various antibodies in response to infections. Myeloma is a type of blood cancer.

4. Leukemia

This a group of cancers that are grouped within blood cancers. These cancers affect the bone marrow which is the site for blood cell production. When cancerous, the bone marrow begins to produce excessive immature white blood cells that fail to perform their usual actions and the

Types of leukemia include:

- Acute myelocytic leukemia (AML) – these are malignancy of the myeloid and granulocytic white blood cell series seen in childhood.
- Chronic myelocytic leukemia (CML) – this is seen in adulthood.
- Acute Lymphatic, lymphocytic, or lymphoblastic leukemia (ALL) – these are malignancy of the lymphoid and lymphocytic blood cell series seen in childhood and young adults.
- Chronic Lymphatic, lymphocytic, or lymphoblastic leukemia (CLL) – this is seen in the elderly.
- Polycythemia vera or erythremia – this is cancer of various blood cell products with a predominance of red blood cells.

5. Lymphoma

These are cancers of the lymphatic system. Unlike the leukemias, which affect the blood and are called “liquid cancers”, lymphomas are “solid cancers”. These may affect lymph nodes at specific sites like stomach, brain, intestines etc. These lymphomas are referred to as extranodal lymphomas.

Lymphomas may be of two types – Hodgkin’s lymphoma and Non-Hodgkin’s lymphomas. In Hodgkin lymphoma there is characteristic presence of Reed-Sternberg cells in the tissue samples which are not present in Non-Hodgkin lymphoma.

6. Mixed types

These have two or more components of the cancer. Some of the examples include mixed mesodermal tumor, carcinosarcoma, adenosquamous carcinoma and teratocarcinoma. Blastomas are another type that involves embryonic tissues.

Classification by grade

Cancers can also be classified according to grade. The abnormality of the cells with respect to surrounding normal tissues determines the grade of the cancer. Increasing abnormality increases the grade, from 1–4.

Cells that are well differentiated closely resemble normal specialized cells and belong to low grade tumors. Cells that are undifferentiated are highly abnormal with respect to surrounding tissues. These are high grade tumors.

- Grade 1 – well differentiated cells with slight abnormality
- Grade 2 – cells are moderately differentiated and slightly more abnormal
- Grade 3 – cells are poorly differentiated and very abnormal
- Grade 4 – cells are immature and primitive and undifferentiated

Classification by stage

Cancers are also classified individually according to their stage. There are several types of staging methods. The most commonly used method uses classification in terms of tumor size

(T), the degree of regional spread or node involvement (N), and distant metastasis (M). This is called the TNM staging.

For example, T0 signifies no evidence of tumor, T 1 to 4 signifies increasing tumor size and involvement and Tis signifies carcinoma in situ or limited to surface cells. Similarly N0 signifies no nodal involvement and N 1 to 4 signifies increasing degrees of lymph node involvement. Nx signifies that node involvement cannot be assessed. Metastasis is further classified into two – M0 signifies no evidence of distant spread while M1 signifies evidence of distant spread.

Stages may be divided according to the TNM staging classification. Stage 0 indicates cancer being in situ or limited to surface cells while stage I indicates cancer being limited to the tissue of origin. Stage II indicates limited local spread, Stage II indicates extensive local and regional spread while stage IV is advanced cancer with distant spread and metastasis.

A

Acute Lymphoblastic Leukemia (ALL)

Acute Myeloid Leukemia (AML)

Adolescents, Cancer in

Adrenocortical Carcinoma

AIDS-Related Cancers

Kaposi Sarcoma (Soft Tissue Sarcoma)

AIDS-Related Lymphoma (Lymphoma)

Primary CNS Lymphoma (Lymphoma)

Anal Cancer

Appendix Cancer - see Gastrointestinal Carcinoid Tumors

Astrocytomas, Childhood (Brain Cancer)

Atypical Teratoid/Rhabdoid Tumor, Childhood, Central Nervous System (Brain Cancer)

B

Basal Cell Carcinoma of the Skin - see Skin Cancer

Bile Duct Cancer

Bladder Cancer

Bone Cancer (includes Ewing Sarcoma and Osteosarcoma and Malignant Fibrous Histiocytoma)

Brain Tumors

Breast Cancer

Bronchial Tumors (Lung Cancer)

Burkitt Lymphoma - see Non-Hodgkin Lymphoma

C

Carcinoid Tumor (Gastrointestinal)

Carcinoma of Unknown Primary

Cardiac (Heart) Tumors, Childhood

Central Nervous System

Atypical Teratoid/Rhabdoid Tumor, Childhood (Brain Cancer)

Medulloblastoma and Other CNS Embryonal Tumors, Childhood (Brain Cancer)

Germ Cell Tumor, Childhood (Brain Cancer)

Primary CNS Lymphoma

Cervical Cancer

Childhood Cancers

Cancers of Childhood, Rare

Cholangiocarcinoma - see Bile Duct Cancer

Chordoma, Childhood (Bone Cancer)

Chronic Lymphocytic Leukemia (CLL)

Chronic Myelogenous Leukemia (CML)

Chronic Myeloproliferative Neoplasms

Colorectal Cancer

Craniopharyngioma, Childhood (Brain Cancer)

Cutaneous T-Cell Lymphoma - see Lymphoma (Mycosis Fungoides and Sézary Syndrome)

D

Ductal Carcinoma In Situ (DCIS) - see Breast Cancer

E

Embryonal Tumors, Medulloblastoma and Other Central Nervous System, Childhood (Brain Cancer)

Endometrial Cancer (Uterine Cancer)

Ependymoma, Childhood (Brain Cancer)

Esophageal Cancer

Esthesioneuroblastoma (Head and Neck Cancer)

Ewing Sarcoma (Bone Cancer)

Extracranial Germ Cell Tumor, Childhood

Extragonadal Germ Cell Tumor

Eye Cancer

Intraocular Melanoma

Retinoblastoma

F

Fallopian Tube Cancer

Fibrous Histiocytoma of Bone, Malignant, and Osteosarcoma

G

Gallbladder Cancer

Gastric (Stomach) Cancer

Gastrointestinal Carcinoid Tumor

Gastrointestinal Stromal Tumors (GIST) (Soft Tissue Sarcoma)

Germ Cell Tumors

Childhood Central Nervous System Germ Cell Tumors (Brain Cancer)

Childhood Extracranial Germ Cell Tumors

Extragonadal Germ Cell Tumors

Ovarian Germ Cell Tumors

Testicular Cancer

Gestational Trophoblastic Disease

H

Hairy Cell Leukemia

Head and Neck Cancer

Heart Tumors, Childhood

Hepatocellular (Liver) Cancer

Histiocytosis, Langerhans Cell

Hodgkin Lymphoma

Hypopharyngeal Cancer (Head and Neck Cancer)

I

Intraocular Melanoma

Islet Cell Tumors, Pancreatic Neuroendocrine Tumors

K

Kaposi Sarcoma (Soft Tissue Sarcoma)

Kidney (Renal Cell) Cancer

L

Langerhans Cell Histiocytosis

Laryngeal Cancer (Head and Neck Cancer)

Leukemia

Lip and Oral Cavity Cancer (Head and Neck Cancer)

Liver Cancer

Lung Cancer (Non-Small Cell, Small Cell, Pleuropulmonary Blastoma, and Tracheobronchial Tumor)

Lymphoma

M

Male Breast Cancer

Malignant Fibrous Histiocytoma of Bone and Osteosarcoma

Melanoma

Melanoma, Intraocular (Eye)

Merkel Cell Carcinoma (Skin Cancer)

Mesothelioma, Malignant

Metastatic Cancer

Metastatic Squamous Neck Cancer with Occult Primary (Head and Neck Cancer)

Midline Tract Carcinoma With NUT Gene Changes

Mouth Cancer (Head and Neck Cancer)

Multiple Endocrine Neoplasia Syndromes

Multiple Myeloma/Plasma Cell Neoplasms

Mycosis Fungoides (Lymphoma)

Myelodysplastic Syndromes, Myelodysplastic/Myeloproliferative Neoplasms

Myelogenous Leukemia, Chronic (CML)

Myeloid Leukemia, Acute (AML)

Myeloproliferative Neoplasms, Chronic

N

Nasal Cavity and Paranasal Sinus Cancer (Head and Neck Cancer)

Nasopharyngeal Cancer (Head and Neck Cancer)

Neuroblastoma

Non-Hodgkin Lymphoma

Non-Small Cell Lung Cancer

O

Oral Cancer, Lip and Oral Cavity Cancer and Oropharyngeal Cancer (Head and Neck Cancer)

Osteosarcoma and Malignant Fibrous Histiocytoma of Bone

Ovarian Cancer

P

Pancreatic Cancer

Pancreatic Neuroendocrine Tumors (Islet Cell Tumors)

Papillomatosis (Childhood Laryngeal)

Paraganglioma

Paranasal Sinus and Nasal Cavity Cancer (Head and Neck Cancer)

Parathyroid Cancer

Penile Cancer

Pharyngeal Cancer (Head and Neck Cancer)

Pheochromocytoma

Pituitary Tumor

Plasma Cell Neoplasm/Multiple Myeloma

Pleuropulmonary Blastoma (Lung Cancer)

Pregnancy and Breast Cancer

Primary Central Nervous System (CNS) Lymphoma

Primary Peritoneal Cancer

Prostate Cancer

R

Rare Cancers of Childhood

Rectal Cancer

Recurrent Cancer

Renal Cell (Kidney) Cancer

Retinoblastoma

Rhabdomyosarcoma, Childhood (Soft Tissue Sarcoma)

S

Salivary Gland Cancer (Head and Neck Cancer)

Sarcoma

Childhood Rhabdomyosarcoma (Soft Tissue Sarcoma)

Childhood Vascular Tumors (Soft Tissue Sarcoma)

Ewing Sarcoma (Bone Cancer)

Kaposi Sarcoma (Soft Tissue Sarcoma)

Osteosarcoma (Bone Cancer)

Soft Tissue Sarcoma

Uterine Sarcoma

Sézary Syndrome (Lymphoma)

Skin Cancer

Small Cell Lung Cancer

Small Intestine Cancer

Soft Tissue Sarcoma

Squamous Cell Carcinoma of the Skin - see Skin Cancer

Squamous Neck Cancer with Occult Primary, Metastatic (Head and Neck Cancer)

Stomach (Gastric) Cancer

T

T-Cell Lymphoma, Cutaneous - see Lymphoma (Mycosis Fungoides and Sèzary Syndrome)

Testicular Cancer

Throat Cancer (Head and Neck Cancer)

Nasopharyngeal Cancer

Oropharyngeal Cancer

Hypopharyngeal Cancer

Thymoma and Thymic Carcinoma

Thyroid Cancer

Tracheobronchial Tumors (Lung Cancer)

Transitional Cell Cancer of the Renal Pelvis and Ureter (Kidney (Renal Cell) Cancer)

U

Unknown Primary, Carcinoma of

Ureter and Renal Pelvis, Transitional Cell Cancer (Kidney (Renal Cell) Cancer

Urethral Cancer

Uterine Cancer, Endometrial

Uterine Sarcoma

V

Vaginal Cancer

Vascular Tumors (Soft Tissue Sarcoma)

Vulvar Cancer

W

Wilms Tumor and Other Childhood Kidney Tumors

Y

Young Adults, Cancer in

CANCER CAUSES

Tobacco smoke at a concert. Pollution from the factory around the corner. Radiation from a routine X-ray. When it comes to environmental factors that raise the risk of cancer, it may seem like avoiding exposure is as impossible as avoiding the air you breathe. In reality, though, you have more control than you think. Experts say you can lower your cancer risk simply by making strategic lifestyle changes or taking conscious measures to reduce your exposure. Environmental risk factors account for at least two-thirds of all cancer cases in the United States, so knowing more about what to look out for, and what to avoid, may go a long way in protecting your health.

Cancer develops when changes, or mutations, in a cell's DNA cause the cell to grow out of control. Sometimes, the mutations are caused by chemicals and other toxic substances in the environment—classified as carcinogens because of their cancer-causing potential. While such chemicals are toxic, they don't always cause cancer. Your risk for developing the disease depends on several factors—including how long and how often you're exposed, your genetic makeup, your diet and lifestyle, your overall health, and your age and gender.

The International Agency for Research on Cancer (IARC) and the U.S. National Toxicology Program (NTP) group carcinogens into categories based on how likely they are to cause cancer. While most people think environmental cancer risks are strictly external toxins like air and water pollution and chemicals like radon, the IARC, NTP and others also count lifestyle factors

like nutrition and tobacco use and natural exposures like ultraviolet light in the mix. Known environmental risk factors include:

Tobacco

The most significant environmental risk factor for cancer is tobacco, whether they're using products like cigarettes, pipes, cigars, chewing tobacco, snuff or vaping, or being exposed to secondhand smoke. In fact, tobacco accounts for 80 percent to 90 percent of all cases of lung cancer, which is the second most common cancer in both men and women.

To reduce your risk of lung cancer, avoid tobacco altogether—don't start the habit, and if you have, quit as soon as possible, and steer clear of secondhand smoke.

" I think it's safe to say that any tobacco use will increase your risk of getting cancer." - *Jeffrey Hoag, MD, MS, FCCP - Vice Chair of the Department of Medicine at CTCA*

Alcohol

Research has found that the more alcohol someone drinks—especially regular use over time—the higher the risk of cancer. For example, people who have three-and-a-half drinks or more a day are two to three times more likely to develop head and neck cancer than those who don't drink. Alcohol consumption also has been linked to liver, esophageal, colorectal and breast cancers.

Alcohol increases cancer risk by damaging cell DNA and proteins, as well as the body's ability to break down nutrients, and by increasing estrogen levels. People who use both alcohol and tobacco have much higher risks of developing head and neck cancer than those who use alcohol or tobacco alone.

Obesity

Obesity is linked to 13 types of cancer, including two of the most common—breast and prostate—but only a little more than half of Americans are aware that it's a risk factor for cancer. In fact, physical inactivity and obesity together account for 25 percent to 30 percent of colorectal, breast, uterine, kidney and esophageal cancers, which are among the most common types. "Obesity has become so important in the field of oncology today that maintaining an

appropriate weight is one of the most important ways you can protect yourself from cancer," says Anthony Perre, MD, Chief of the Division of Outpatient Medicine at Cancer Treatment Centers of America® (CTCA).

To help avoid obesity-related cancers, experts recommend you lose excess weight through diet and exercise, if possible, and with the help of behavioral and dietary counseling, if necessary.

Ultraviolet radiation

Ultraviolet (UV) rays from the sun, sunlamps or tanning beds may damage cell DNA and lead to melanoma or other forms of skin cancer. Skin cancer is the most common form of cancer, affecting more than 3.5 million Americans each year, and melanoma accounts for the most skin cancer deaths. And its incidence is on the rise. In fact, if melanoma rates continue to increase at the same pace, 112,000 new cases of the disease will be diagnosed in 2030.

To reduce your risk, limit your exposure to UV rays—both from the sun and indoor tanning—and wear sunscreen and protective clothing when outdoors.

Asbestos

Asbestos occurs in rock and soil, and is often found in building construction materials for insulation. The mineral fiber increases the risk of lung cancer, mesothelioma, laryngeal cancer and ovarian cancer. Asbestos exposure accounts for the largest percentage of occupational cancer risks, with the highest risk among affected workers who also smoke. The Occupational Safety and Health Administration regulates asbestos levels in workplaces, but because the fiber is present in the air, water and soil, avoiding asbestos is nearly impossible. Most people who are exposed to the fiber don't develop disease, but the greater the exposure, the greater the risk.

If you are planning to remodel your home, which may disturb building materials, or if your home contains damaged materials, such as crumbling drywall or insulation, you may consider hiring someone to inspect it for asbestos-containing materials. If your home does contain asbestos, an inspector can give you recommendations for correction or prevention. And make sure to wear a mask and other protective gear while doing any of your own remodeling.

Viruses

Certain viruses are linked to several types of cancer. Human papillomavirus (HPV), for instance, is responsible for almost all cervical cancers. But in November, a study published in *The Annals of Internal Medicine* journal found that HPV-related head and neck cancers in men (7.8 per 100,000) are even more prevalent than HPV-related cervical cancers in women (7.4 per 100,000). The Centers for Disease Control and Prevention recommends that 11- and 12-year-old boys and girls receive two doses of the HPV vaccine six months apart, and that young men and women ages 15 to 26 receive three doses.

Chronic infection with hepatitis B or hepatitis C virus is the most common risk factor for liver cancer. Both viruses are spread by sharing contaminated needles, unprotected sex and childbirth. Also, the Epstein-Barr virus, which causes mononucleosis, is linked to some types of lymphoma. Currently, there are no vaccines for hepatitis C or Epstein-Barr, but there is a vaccine for hepatitis B.

Ionizing radiation

Ionizing radiation is thought to cause about 1 percent of all cancers. It comes from cosmic rays that enter the Earth's atmosphere, the radioactive gas radon—found naturally at low levels in soil—and from certain medical procedures, such as X-rays and radiation therapy. When cancer treatments increase your risk of developing another cancer later in life, the decision-making process often involves weighing the risks against the benefits, says Glynis Vashi, MD, Intake Physician and Chief of Medicine at our hospital near Chicago. "It takes years for a cancer to develop," she says. "So you do what you have to do at the time, and then you take as many preventive steps as possible to improve the chance that you won't develop another cancer in the future."

As medicine continues to evolve, scientists may discover more environmental substances that we should avoid, or at least limit in use. Today, some possible but unproven risk factors include fluoride in water, radiation from power lines and electrical devices, chemicals in certain hair dyes and cosmetics, lead, the mineral talc in talcum powder, diesel exhaust and the chemical BPA in some plastics. "My advice is to avoid or limit even these unproven risk factors now, especially if doing so doesn't affect your quality of life," Dr. Perre says.

The significance of environmental risk factors is underscored in cancer rate disparities throughout the world and how those rates fluctuate when people move from place to place. For

example, people who live in Asia tend to have low rates of prostate and breast cancer and high rates of stomach cancer, but when they emigrate to the United States—where prostate and breast cancers are prevalent—their prostate and breast cancer rates rise over time.

Still, if everyone took all the known precautions in reducing environmental exposure to cancer-causing substances, some would still develop the disease—because environmental risk is only part of cancer's story. For example, one man may smoke for 30 years and never develop lung cancer, while another who only smoked in college may develop the disease years later. "Many people believe that if they're exposed to a carcinogen, they'll get cancer," Dr. Vashi says. "But you always have to question why, out of two people in the same environment, one will develop cancer and one will not. That is when you realize that there is something at play beyond the environment. It's the interplay between the environment and what's going on within us."

Understanding the relationship between the environment and genetics is vital to lowering your cancer risk, Dr. Vashi says. "It's education, education, education," she says. "Every doctor should help his or her patient realize that a poor diet, excessive alcohol consumption and certain medications may affect chemical levels in the body that break down cancer-causing substances, for instance. It's imperative that we help our patients learn how to decrease their environmental risks for cancer." Researchers today are working to identify the unique combinations of gene alterations and environmental exposures that explain why one person develops cancer and another does not.

At the end of the day, you have the power to reduce potential exposures to substances in the environment, Dr. Hoag says. "I think the take-home point I would want to convey is that there may be a lot in your environment you can't control, but the more you learn about what's there, the more you learn about what you can control."

CELL CYCLE CHECKPOINTS

The length of the cell cycle is highly variable, even within the cells of a single organism. In humans, the frequency of cell turnover ranges from a few hours in early embryonic development, to an average of two to five days for epithelial cells, and to an entire human lifetime spent in G_0 by specialized cells, such as cortical neurons or cardiac muscle cells. There is also variation in the time that a cell spends in each phase of the cell cycle. When fast-dividing mammalian cells are grown in culture (outside the body under optimal growing conditions), the length of the cycle is about 24 hours. In rapidly dividing human cells with a 24-hour cell cycle, the G_1 phase lasts approximately nine hours, the S phase lasts 10 hours, the G_2 phase lasts about four and one-half hours, and the M phase lasts approximately one-half hour. In early embryos of fruit flies, the cell cycle is completed in about eight minutes. The timing of events in the cell cycle is controlled by mechanisms that are both internal and external to the cell.

Regulation of the Cell Cycle by External Events

Both the initiation and inhibition of cell division are triggered by events external to the cell when it is about to begin the replication process. An event may be as simple as the death of a nearby cell or as sweeping as the release of growth-promoting hormones, such as human growth hormone (HGH). A lack of HGH can inhibit cell division, resulting in dwarfism, whereas too much HGH can result in gigantism. Crowding of cells can also inhibit cell division. Another factor that can initiate cell division is the size of the cell; as a cell grows, it becomes inefficient due to its decreasing surface-to-volume ratio. The solution to this problem is to divide.

Whatever the source of the message, the cell receives the signal, and a series of events within the cell allows it to proceed into interphase. Moving forward from this initiation point, every parameter required during each cell cycle phase must be met or the cycle cannot progress.

Regulation at Internal Checkpoints

It is essential that the daughter cells produced be exact duplicates of the parent cell. Mistakes in the duplication or distribution of the chromosomes lead to mutations that may be passed forward to every new cell produced from an abnormal cell. To prevent a compromised cell from continuing to divide, there are internal control mechanisms that operate at three main cell

cycle checkpoints. A checkpoint is one of several points in the eukaryotic cell cycle at which the progression of a cell to the next stage in the cycle can be halted until conditions are favorable. These checkpoints occur near the end of G_1, at the G_2/M transition, and during metaphase (Figure 1).

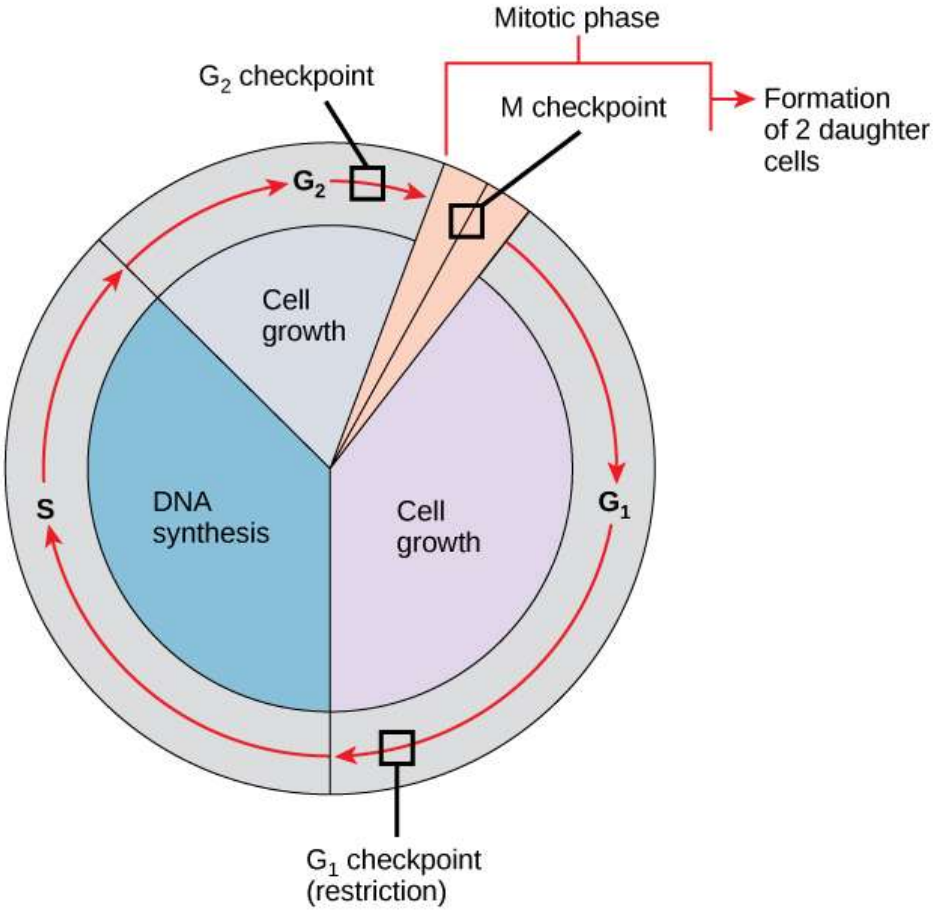


Figure 1.4: The cell cycle is controlled at three checkpoints. The integrity of the DNA is assessed at the G_1 checkpoint. Proper chromosome duplication is assessed at the G_2 checkpoint. Attachment of each kinetochore to a spindle fiber is assessed at the M checkpoint.

The G_1 Checkpoint

The G_1 checkpoint determines whether all conditions are favorable for cell division to proceed. The G_1 checkpoint, also called the restriction point (in yeast), is a point at which the cell irreversibly commits to the cell division process. External influences, such as growth factors, play a large role in carrying the cell past the G_1 checkpoint. In addition to adequate reserves and cell size, there is a check for genomic DNA damage at the G_1 checkpoint. A cell that does not meet all the requirements will not be allowed to progress into the S phase. The cell can halt

the cycle and attempt to remedy the problematic condition, or the cell can advance into G_0 and await further signals when conditions improve.

The G_2 Checkpoint

The G_2 checkpoint bars entry into the mitotic phase if certain conditions are not met. As at the G_1 checkpoint, cell size and protein reserves are assessed. However, the most important role of the G_2 checkpoint is to ensure that all of the chromosomes have been replicated and that the replicated DNA is not damaged. If the checkpoint mechanisms detect problems with the DNA, the cell cycle is halted, and the cell attempts to either complete DNA replication or repair the damaged DNA.

The M Checkpoint

The M checkpoint occurs near the end of the metaphase stage of karyokinesis. The M checkpoint is also known as the spindle checkpoint, because it determines whether all the sister chromatids are correctly attached to the spindle microtubules. Because the separation of the sister chromatids during anaphase is an irreversible step, the cycle will not proceed until the kinetochores of each pair of sister chromatids are firmly anchored to at least two spindle fibers arising from opposite poles of the cell.

Regulator Molecules of the Cell Cycle

In addition to the internally controlled checkpoints, there are two groups of intracellular molecules that regulate the cell cycle. These regulatory molecules either promote progress of the cell to the next phase (positive regulation) or halt the cycle (negative regulation). Regulator molecules may act individually, or they can influence the activity or production of other regulatory proteins. Therefore, the failure of a single regulator may have almost no effect on the cell cycle, especially if more than one mechanism controls the same event. Conversely, the effect of a deficient or non-functioning regulator can be wide-ranging and possibly fatal to the cell if multiple processes are affected.

Positive Regulation of the Cell Cycle

Two groups of proteins, called cyclins and cyclin-dependent kinases (Cdks), are responsible for the progress of the cell through the various checkpoints. The levels of the four cyclin proteins fluctuate throughout the cell cycle in a predictable pattern (Figure 2). Increases in the concentration of cyclin proteins are triggered by both external and internal signals. After the cell moves to the next stage of the cell cycle, the cyclins that were active in the previous stage are degraded.

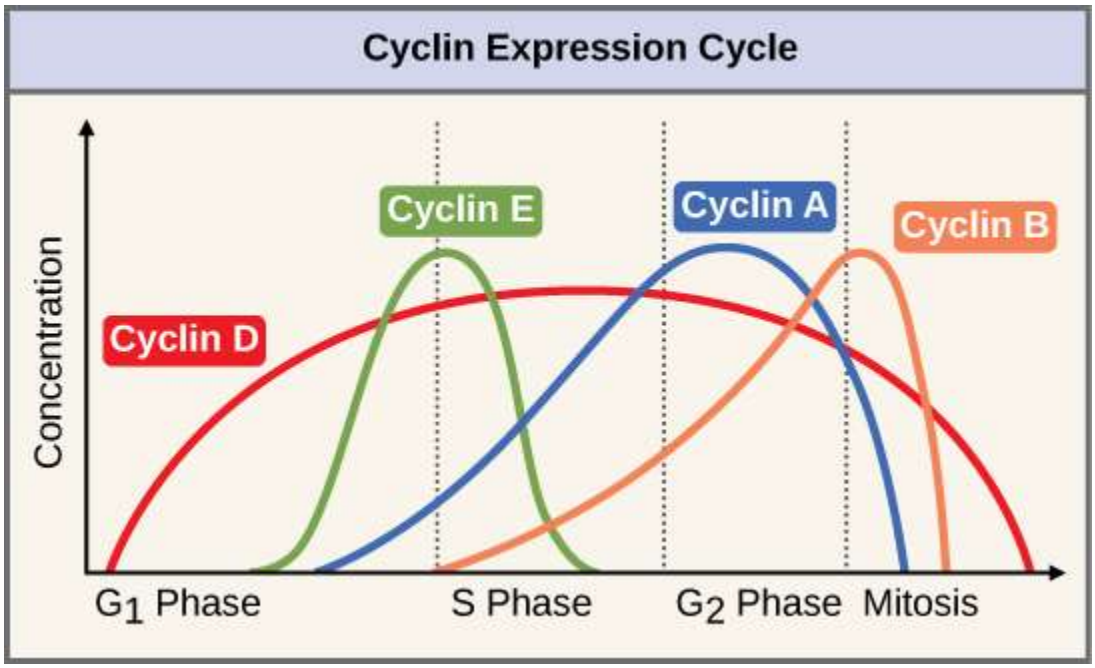


Figure 1.5: The concentrations of cyclin proteins change throughout the cell cycle. There is a direct correlation between cyclin accumulation and the three major cell cycle checkpoints. Also note the sharp decline of cyclin levels following each checkpoint (the transition between phases of the cell cycle), as cyclin is degraded by cytoplasmic enzymes. (credit: modification of work by "WikiMiMa"/Wikimedia Commons)

Cyclins regulate the cell cycle only when they are tightly bound to Cdks. To be fully active, the Cdk/cyclin complex must also be phosphorylated in specific locations. Like all kinases, Cdks are enzymes (kinases) that phosphorylate other proteins. Phosphorylation activates the protein by changing its shape. The proteins phosphorylated by Cdks are involved in advancing the cell to the next phase (Figure 3). The levels of Cdk proteins are relatively stable throughout the cell cycle; however, the concentrations of cyclin fluctuate and determine when Cdk/cyclin

complexes form. The different cyclins and Cdks bind at specific points in the cell cycle and thus regulate different checkpoints.

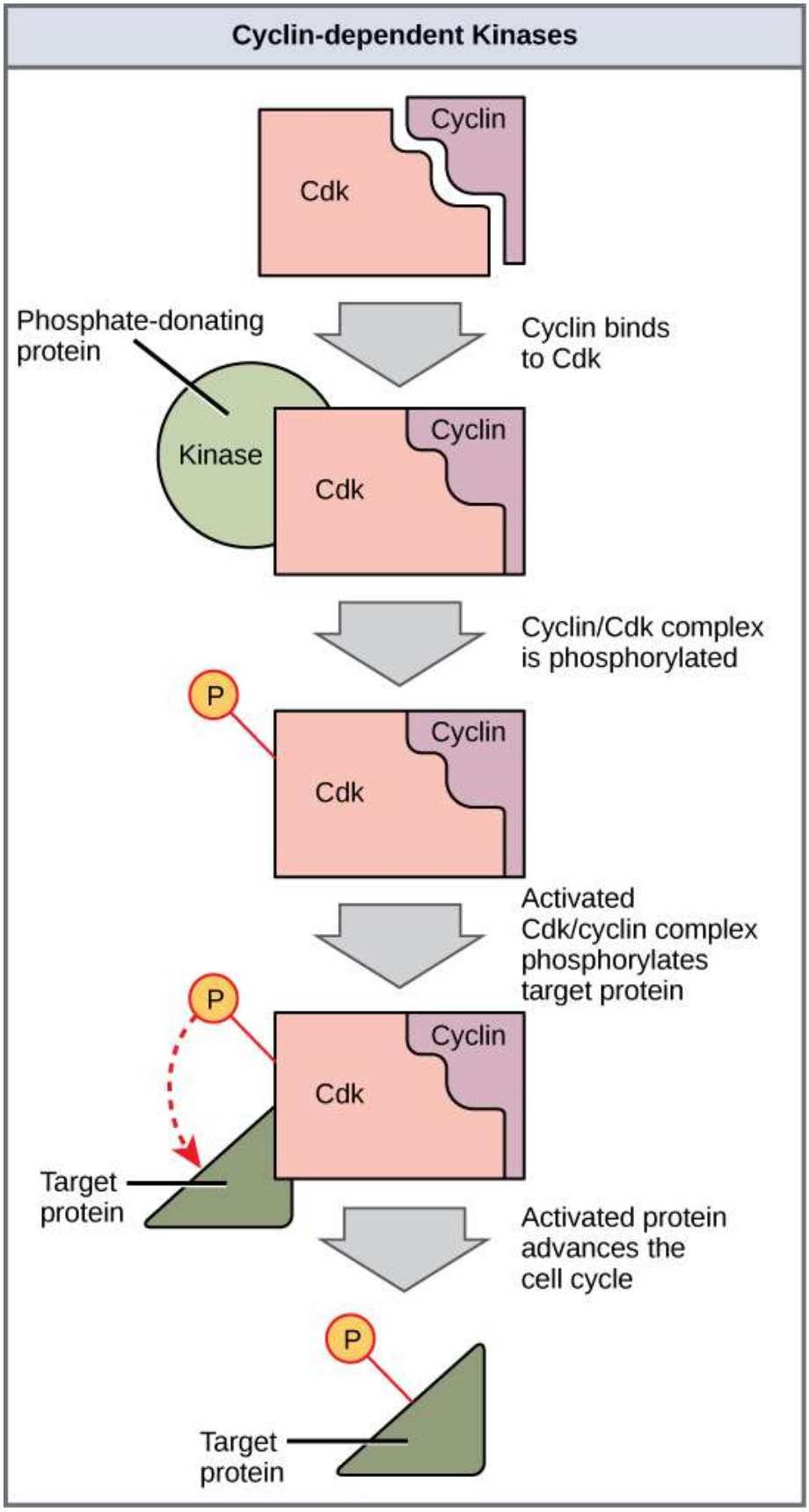


Figure 1:6. Cyclin-dependent kinases (Cdks) are protein kinases that, when fully activated, can phosphorylate and thus activate other proteins that advance the cell cycle past a checkpoint. To become fully activated, a Cdk must bind to a cyclin protein and then be phosphorylated by another kinase.

Since the cyclic fluctuations of cyclin levels are based on the timing of the cell cycle and not on specific events, regulation of the cell cycle usually occurs by either the Cdk molecules alone or the Cdk/cyclin complexes. Without a specific concentration of fully activated cyclin/Cdk complexes, the cell cycle cannot proceed through the checkpoints.

Although the cyclins are the main regulatory molecules that determine the forward momentum of the cell cycle, there are several other mechanisms that fine-tune the progress of the cycle with negative, rather than positive, effects. These mechanisms essentially block the progression of the cell cycle until problematic conditions are resolved. Molecules that prevent the full activation of Cdks are called Cdk inhibitors. Many of these inhibitor molecules directly or indirectly monitor a particular cell cycle event. The block placed on Cdks by inhibitor molecules will not be removed until the specific event that the inhibitor monitors is completed.

Negative Regulation of the Cell Cycle

The second group of cell cycle regulatory molecules are negative regulators. Negative regulators halt the cell cycle. Remember that in positive regulation, active molecules cause the cycle to progress.

The best understood negative regulatory molecules are retinoblastoma protein (Rb), p53, and p21. Retinoblastoma proteins are a group of tumor-suppressor proteins common in many cells. The 53 and 21 designations refer to the functional molecular masses of the proteins (p) in kilodaltons. Much of what is known about cell cycle regulation comes from research conducted with cells that have lost regulatory control. All three of these regulatory proteins were discovered to be damaged or non-functional in cells that had begun to replicate uncontrollably (became cancerous). In each case, the main cause of the unchecked progress through the cell cycle was a faulty copy of the regulatory protein.

Rb, p53, and p21 act primarily at the G_1 checkpoint. p53 is a multi-functional protein that has a major impact on the commitment of a cell to division because it acts when there is damaged

DNA in cells that are undergoing the preparatory processes during G_1. If damaged DNA is detected, p53 halts the cell cycle and recruits enzymes to repair the DNA. If the DNA cannot be repaired, p53 can trigger apoptosis, or cell suicide, to prevent the duplication of damaged chromosomes. As p53 levels rise, the production of p21 is triggered. p21 enforces the halt in the cycle dictated by p53 by binding to and inhibiting the activity of the Cdk/cyclin complexes. As a cell is exposed to more stress, higher levels of p53 and p21 accumulate, making it less likely that the cell will move into the S phase.

Rb exerts its regulatory influence on other positive regulator proteins. Chiefly, Rb monitors cell size. In the active, dephosphorylated state, Rb binds to proteins called transcription factors, most commonly, E2F (Figure 4). Transcription factors "turn on" specific genes, allowing the production of proteins encoded by that gene. When Rb is bound to E2F, production of proteins necessary for the G_1/S transition is blocked. As the cell increases in size, Rb is slowly phosphorylated until it becomes inactivated. Rb releases E2F, which can now turn on the gene that produces the transition protein, and this particular block is removed. For the cell to move past each of the checkpoints, all positive regulators must be "turned on," and all negative regulators must be "turned off."

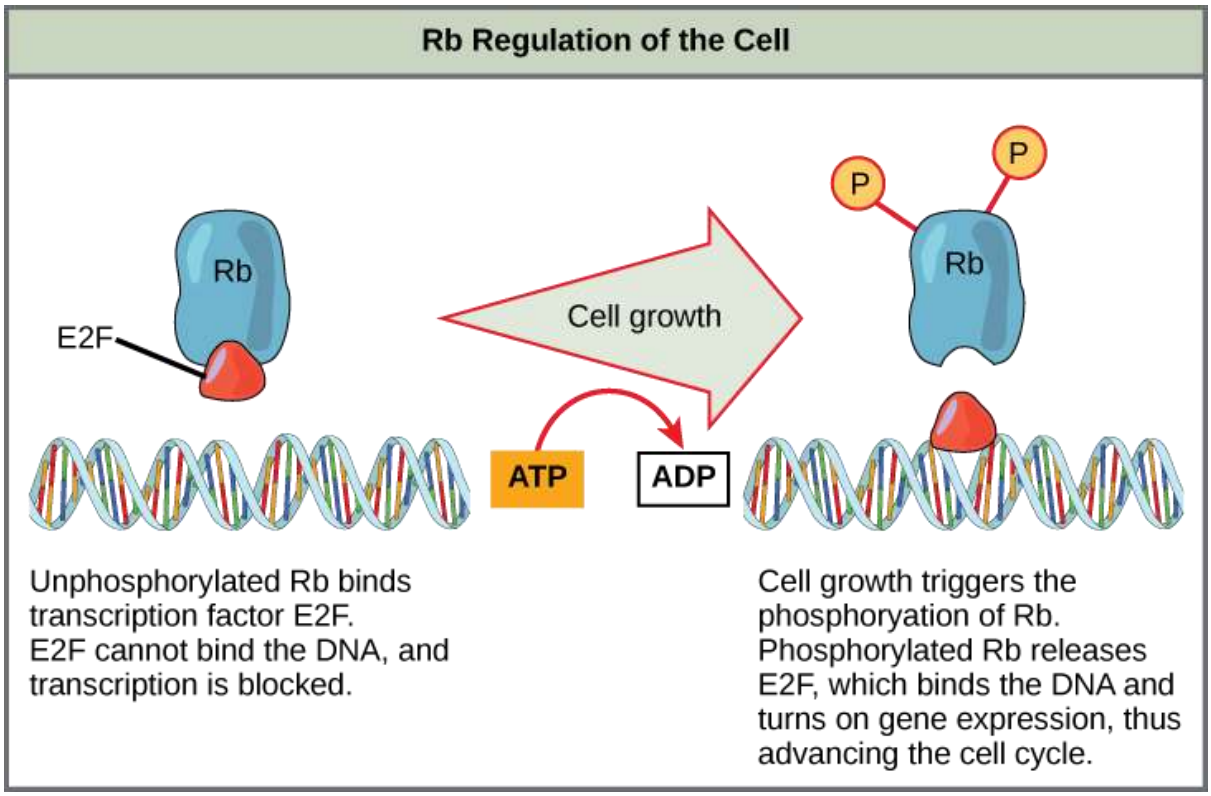


Figure 1:7. Rb halts the cell cycle and releases its hold in response to cell growth.

Cancer and the Cell Cycle

Cancer comprises many different diseases caused by a common mechanism: uncontrolled cell growth. Despite the redundancy and overlapping levels of cell cycle control, errors do occur. One of the critical processes monitored by the cell cycle checkpoint surveillance mechanism is the proper replication of DNA during the S phase. Even when all of the cell cycle controls are fully functional, a small percentage of replication errors (mutations) will be passed on to the daughter cells. If changes to the DNA nucleotide sequence occur within a coding portion of a gene and are not corrected, a gene mutation results. All cancers start when a gene mutation gives rise to a faulty protein that plays a key role in cell reproduction. The change in the cell that results from the malformed protein may be minor: perhaps a slight delay in the binding of Cdk to cyclin or an Rb protein that detaches from its target DNA while still phosphorylated. Even minor mistakes, however, may allow subsequent mistakes to occur more readily. Over and over, small uncorrected errors are passed from the parent cell to the daughter cells and amplified as each generation produces more non-functional proteins from uncorrected DNA damage. Eventually, the pace of the cell cycle speeds up as the effectiveness of the control and repair mechanisms decreases. Uncontrolled growth of the mutated cells outpaces the growth of normal cells in the area, and a tumor (~*oma*) can result.

Proto-oncogenes

The genes that code for the positive cell cycle regulators are called **proto-oncogenes**. Proto-oncogenes are normal genes that, when mutated in certain ways, become **oncogenes**, genes that cause a cell to become cancerous. Consider what might happen to the cell cycle in a cell with a recently acquired oncogene. In most instances, the alteration of the DNA sequence will result in a less functional (or non-functional) protein. The result is detrimental to the cell and will likely prevent the cell from completing the cell cycle; however, the organism is not harmed because the mutation will not be carried forward. If a cell cannot reproduce, the mutation is not propagated and the damage is minimal. Occasionally, however, a gene mutation causes a change that increases the activity of a positive regulator. For example, a mutation that allows Cdk to be activated without being partnered with cyclin could push the cell cycle past a

checkpoint before all of the required conditions are met. If the resulting daughter cells are too damaged to undergo further cell divisions, the mutation would not be propagated and no harm would come to the organism. However, if the atypical daughter cells are able to undergo further cell divisions, subsequent generations of cells will probably accumulate even more mutations, some possibly in additional genes that regulate the cell cycle.

The Cdk gene in the above example is only one of many genes that are considered proto-oncogenes. In addition to the cell cycle regulatory proteins, any protein that influences the cycle can be altered in such a way as to override cell cycle checkpoints. An oncogene is any gene that, when altered, leads to an increase in the rate of cell cycle progression.

Tumor Suppressor Genes

Like proto-oncogenes, many of the negative cell cycle regulatory proteins were discovered in cells that had become cancerous. **Tumor suppressor genes** are segments of DNA that code for negative regulator proteins, the type of regulators that, when activated, can prevent the cell from undergoing uncontrolled division. The collective function of the best-understood tumor suppressor gene proteins, Rb, p53, and p21, is to put up a roadblock to cell cycle progression until certain events are completed. A cell that carries a mutated form of a negative regulator might not be able to halt the cell cycle if there is a problem. Tumor suppressors are similar to brakes in a vehicle: malfunctioning brakes can contribute to a car crash.

Mutated p53 genes have been identified in more than one-half of all human tumor cells. This discovery is not surprising in light of the multiple roles that the p53 protein plays at the G_1 checkpoint. A cell with a faulty p53 may fail to detect errors present in the genomic DNA (Figure 5). Even if a partially functional p53 does identify the mutations, it may no longer be able to signal the necessary DNA repair enzymes. Either way, damaged DNA will remain uncorrected. At this point, a functional p53 will deem the cell unsalvageable and trigger programmed cell death (apoptosis). The damaged version of p53 found in cancer cells, however, cannot trigger apoptosis.

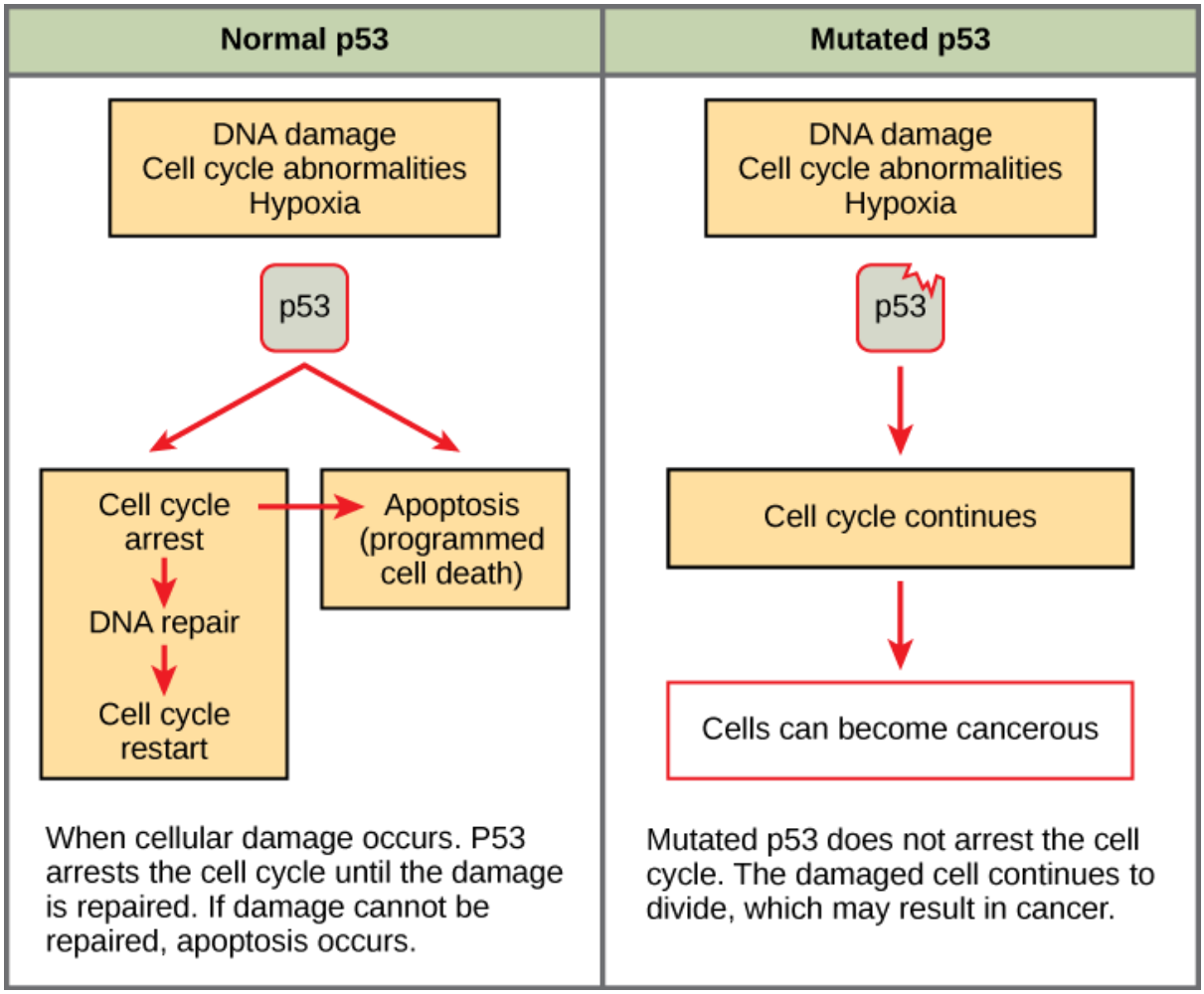


Figure 1.8: The role of normal p53 is to monitor DNA and the supply of oxygen (hypoxia is a condition of reduced oxygen supply). If damage is detected, p53 triggers repair mechanisms. If repairs are unsuccessful, p53 signals apoptosis. A cell with an abnormal p53 protein cannot repair damaged DNA and thus cannot signal apoptosis. Cells with abnormal p53 can become cancerous. (credit: modification of work by Thierry Soussi)

The loss of p53 function has other repercussions for the cell cycle. Mutated p53 might lose its ability to trigger p21 production. Without adequate levels of p21, there is no effective block on Cdk activation. Essentially, without a fully functional p53, the G_1 checkpoint is severely compromised and the cell proceeds directly from G_1 to S regardless of internal and external conditions. At the completion of this shortened cell cycle, two daughter cells are produced that have inherited the mutated p53 gene. Given the non-optimal conditions under which the parent cell reproduced, it is likely that the daughter cells will have acquired other mutations in addition to the faulty tumor suppressor gene. Cells such as these daughter cells quickly accumulate both oncogenes and non-functional tumor suppressor genes. Again, the result is tumor growth.

This video reviews the ways that cancer is a by-product of broken DNA replication:

In Summary: Cell Cycle Checkpoints

Each step of the cell cycle is monitored by internal controls called checkpoints. There are three major checkpoints in the cell cycle: one near the end of G_1, a second at the G_2/M transition, and the third during metaphase. Positive regulator molecules allow the cell cycle to advance to the next stage. Negative regulator molecules monitor cellular conditions and can halt the cycle until specific requirements are met.

Cancer is the result of unchecked cell division caused by a breakdown of the mechanisms that regulate the cell cycle. The loss of control begins with a change in the DNA sequence of a gene that codes for one of the regulatory molecules. Faulty instructions lead to a protein that does not function as it should. Any disruption of the monitoring system can allow other mistakes to be passed on to the daughter cells. Each successive cell division will give rise to daughter cells with even more accumulated damage. Eventually, all checkpoints become nonfunctional, and rapidly reproducing cells crowd out normal cells, resulting in a tumor or leukemia (blood cancer).

CELL SIGNALING PATHWAY (Richard Sever[1] and Joan S. Brugge, ,Cold Spring Harb Perspect Med. 2015 Apr; 5(4): a006098.

Signal Transduction in Cancer

1. INTRODUCTION

The development of cancer involves successive genetic and epigenetic alterations that allow cells to escape homeostatic controls that ordinarily suppress inappropriate proliferation and inhibit the survival of aberrantly proliferating cells outside their normal niches. Most cancers arise in epithelial cells, manifesting as carcinomas in organs such as the lung, skin, breast, liver, and pancreas. Sarcomas, in contrast, arise from mesenchymal tissues, occurring in fibroblasts, myocytes, adipocytes, and osteoblasts. Nonepithelial tumors can also develop in cells of the nervous system (e.g., gliomas, neuroblastomas, and medulloblastomas) and hematopoietic tissues (leukemia and lymphoma).

In solid tumors, these alterations typically promote progression from a relatively benign group of proliferating cells (hyperplasias) to a mass of cells with abnormal morphology, cytological appearance, and cellular organization. After a tumor expands, the tumor core loses access to oxygen and nutrients, often leading to the growth of new blood vessels (angiogenesis), which restores access to nutrients and oxygen. Subsequently, tumor cells can develop the ability to invade the tissue beyond their normal boundaries, enter the circulation, and seed new tumors at other locations (metastasis), the defining feature of malignancy (Fig. 1). This linear sequence of events is clearly an oversimplification of complex cancer-associated events that proceed in distinct ways in individual tumors and between tumor sites; however, it provides a useful framework in which to highlight the critical role of dysregulated signaling in processes associated with the initiation and progression of cancer.

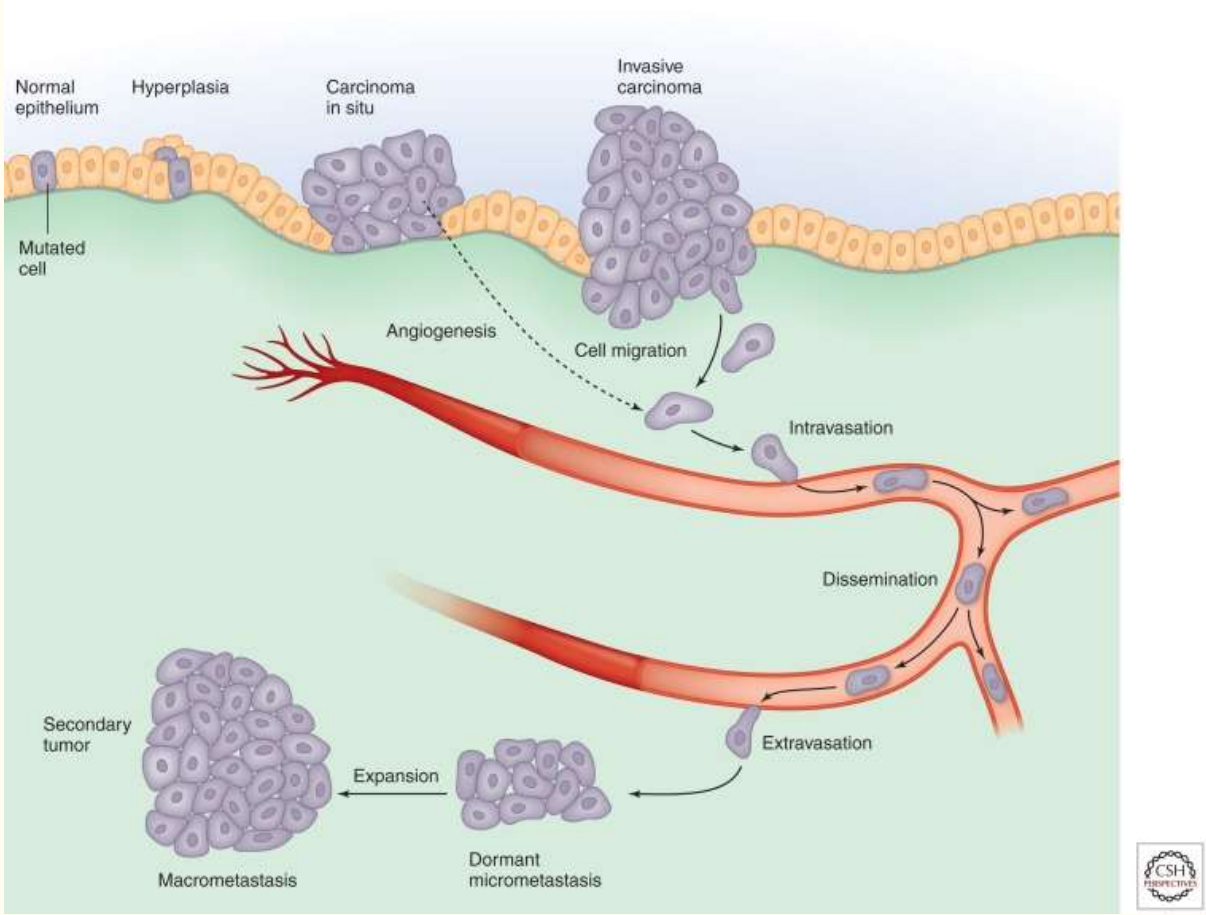


Figure 1.9:Cancer progression.

The root cause of cancer is usually genetic or epigenetic alterations in the tumor cells (see below). Progression of the cancer, however, is associated with a complex interplay between the tumor cells and surrounding non-neoplastic cells and the extracellular matrix (ECM). Moreover, the tumor cells develop several well-defined features (Hanahan and Weinberg 2000; Solimini et al. 2007). In addition to increased cell proliferation, these include resistance to apoptosis and other forms of cell death, metabolic changes, genetic instability, induction of angiogenesis, and increased migratory capacity. Dysregulation of cellular signal transduction pathways underlies most of these characteristics.

Here, we describe how tumor cells co-opt signaling pathways to allow them to proliferate, survive, and invade other tissues. To cover all of the signaling molecules involved and their myriad contributions to cancer would require an entire textbook (Weinberg 2013). We therefore focus primarily on two pathways—Ras-ERK (Morrison 2012) and PI3K-Akt signaling (Hemmings and Restuccia 2012)—that play central roles in multiple processes

associated with cancer, while highlighting the involvement of some other key signaling molecules.

2. MUTATIONS AS THE CAUSE OF CANCER

Most tumors arise as a consequence of genetic alterations to cellular genes, which may be inherited or arise spontaneously—for example, as a result of DNA damage induced by environmental carcinogens or mutations arising from replication errors. These alterations confer a selective advantage to the cells, which together with changes in the microenvironment, promote tumor growth and progression. Some are gain-of-function mutations, producing so-called oncogenes that drive tumor formation. Others inactivate tumor suppressor genes that normally ensure that cells do not proliferate inappropriately or survive outside their normal niche.

Tumors can possess tens to hundreds or even thousands of mutations, but many of these are merely so-called "passengers." Typically only two to eight are the "driver mutations" that cause progression of the cancer (Vogelstein et al. 2013). These may be point mutations (such as G12V Ras), deletions (as seen with PTEN), inversions, or amplifications (as seen with Myc). Large-scale rearrangements also occur—for example, the *BCR-ABL* fusions involving chromosomes 9 and 22, which are associated with several leukemias and generate an oncogenic version of the tyrosine kinase Abl. Loss of heterozygosity due to gene conversion or mitotic recombination between normal and mutant parental alleles is another source of genetic alterations that drive cancer. This often affects tumor suppressors such as the retinoblastoma protein (pRB) and p53 (encoded by the *TP53* gene in humans).

Changes in the methylation state of promoters of genes that impact cancer can also play an important role in oncogenesis (Sandoval and Esteller 2012; Suva et al. 2013). Indeed, epigenetic silencing is more common than mutational silencing for some genes—for example, the cyclin-dependent kinase (CDK) inhibitor (CKI) p16 (also known as CDKN2A or INK4a) and the mismatch repair (MMR) enzyme MLH1. Silencing of MMR enzymes can lead to additional genetic changes because it affects proteins that prevent errors by repairing DNA. Conversely, several mutations associated with cancer affect epigenetic regulators that influence multiple cellular programs—for example, DNMT1 and TET1, which control DNA methylation, and the histone-modifying enzymes EZH2, SETD2, and KDM6A are deleted or mutated in cancer (Delhommeau et al. 2009; Ley et al. 2010; Wu et al. 2012). Interestingly, mutations in the metabolic enzymes isocitrate dehydrogenase (IDH) 1 and IDH2 may promote

cancer by generating an “oncometabolite” not present in normal cells that inhibits certain chromatin-modifying enzymes (see below) (Ward and Thompson 2012a).

Finally, in a minority of cancers, infectious agents are the triggers. A few human cancers are triggered by viruses that encode genes that promote tumorigenesis through activation of oncogene pathways or inactivation of tumor suppressors. The human papilloma virus, which is associated with cervical and head and neck cancers, encodes a protein, E6, that promotes degradation of p53, while another viral protein, E7, inactivates pRB and CKIs, among other effects (Munger and Howley 2002). In hepatocellular carcinoma caused by hepatitis B virus, by contrast, it is not clear whether viral proteins themselves are oncogenic, viral integration promotes expression of nearby cellular oncogenes, or cancer is simply a consequence of persistent liver injury and inflammation (Seeger et al. 2013). Epstein–Barr virus (also known as human herpesvirus 4) produces a protein called LMP1 that acts as a constitutively active tumor necrosis factor (TNF) receptor, engaging a plethora of signaling pathways, including NF-κB, JNK/p38, PI3K, and ERK (Morris et al. 2009). An extreme case of a transmissible cancer is that affecting the Tasmanian devil. All tumors are derived from a founder tumor and are transmitted as allografts from devil to devil during intraspecies facial biting (Murchison et al. 2012; Hamede et al. 2013).

2.1. Cancer-Causing Mutations Affect Signaling Pathways

We can connect the genetic alterations in cancer cells with signaling pathways that control processes associated with tumorigenesis and place these in the context of distortions of wider signaling networks that fuel cancer progression. In each case, the result is dysregulated signaling that is not subject to the normal control mechanisms.

Oncogenic mutations can cause the affected genes to be overexpressed (e.g., gene amplification) or produce mutated proteins whose activity is dysregulated (e.g., point mutations, truncations, and fusions). Examples include proteins involved in signaling pathways that are commonly activated in many physiological responses, such as growth factor receptor tyrosine kinases (RTKs; e.g., the epidermal growth factor receptor, EGFR), small GTPases (e.g., Ras), serine/threonine kinases (e.g., Raf and Akt), cytoplasmic tyrosine kinases (e.g., Src and Abl), lipid kinases (e.g., phosphoinositide 3-kinases, PI3Ks), as well as nuclear receptors (e.g., the estrogen receptor, ER). Components of developmental signaling pathways, such as Wnt, Hedgehog (Hh), Hippo, and Notch can also be affected, as can downstream nuclear

targets of signaling pathways—for example, transcription factors (e.g., Myc and NF-κB), chromatin remodelers (e.g., EZH2), and cell cycle effectors (e.g., cyclins).

Alternatively, deletions and other mutations can inactivate negative regulators that normally function as tumor suppressors. Indeed, one of the most commonly mutated genes in cancer is the tumor suppressor p53, the so-called "guardian of the genome." p53 is a critical hub that controls cell proliferation and stress signals such as apoptosis and DNA damage responses (see below). pRB and CKIs such as p16 are other tumor suppressors whose mutation deregulates the cell cycle. Many tumor suppressors function as negative regulators of cytoplasmic signaling—for example, the adenomatous polyposis coli protein (APC) is a negative regulator of the Wnt pathway, and the lipid phosphatase PTEN is a negative regulator of the PI3K-Akt pathway.

It is worth noting that hyperactivated oncogene pathways can also induce a state of irreversible cell cycle arrest termed senescence (Gorgoulis and Halazonetis 2010; Vargas et al. 2012). This is believed to represent a fail-safe mechanism to inhibit proliferation caused by aberrant activation of oncoproteins in normal cells and is accompanied by changes in cellular structure, chromatin organization, DNA damage, cytokine secretion, and gene expression. Oncogenic transformation requires alterations that abrogate senescence, such as loss of p53 or PTEN.

2.1.1. The PI3K-Akt and Ras-ERK Pathways as Examples of Oncogenic Signaling Pathways

Many of the genes commonly mutated in cancer encode components or targets of the PI3K-Akt and Ras-ERK pathways (Fig. 2). Ordinarily these pathways are transiently activated in response to growth factor or cytokine signaling and ligand occupancy of integrin adhesion receptors, but genetic alterations can lead to constitutive signaling even in the absence of growth factors. The PI3K-Akt pathway can be activated through amplification or activating mutations affecting several PI3K-Akt-pathway proteins—the type I PI3K isoform PIK3CA (p110a), Akt, and the adaptor protein PIK3R1—or through deletion or inactivating mutations in the phosphatases that hydrolyze PI3K products such as phosphatidylinositol 3,4,5-trisphosphate (p1p3)—the PTEN and INPP4B tumor suppressors. Further downstream, mutations in the tumor suppressors TSC1 and TSC2 hyperactivate signaling by mTORC1 (Laplante and Sabatini 2012), an important target of PI3K-Akt signaling. Similarly, the Ras-ERK pathway is activated by mutations in Ras, or its downstream target Raf, that cause constitutive activation of these proteins or by inactivation of GTPase-activating proteins (GAPs), such as NF1 (Cichowski and Jacks 2001), DAB2IP (Min et al. 2010), and RASAL2

(McLaughlin et al. 2013), that stimulate the hydrolysis of GTP bound to Ras, which leads to its inactivation. The transcription factor Myc is an important downstream target of Ras-ERK signaling and many other pathways. It is frequently amplified or overexpressed in cancer; interestingly, Myc can not only bind to promoter regions of genes but also enhance transcriptional elongation of polymerase II, thus extending its effects beyond genes with Myc-binding sites in their promoters. Myc can thus serve as a universal amplifier of expressed genes rather than merely binding to promoters and initiating transcription de novo (Rahl et al. 2010; Lin et al. 2012; Nie et al. 2012).

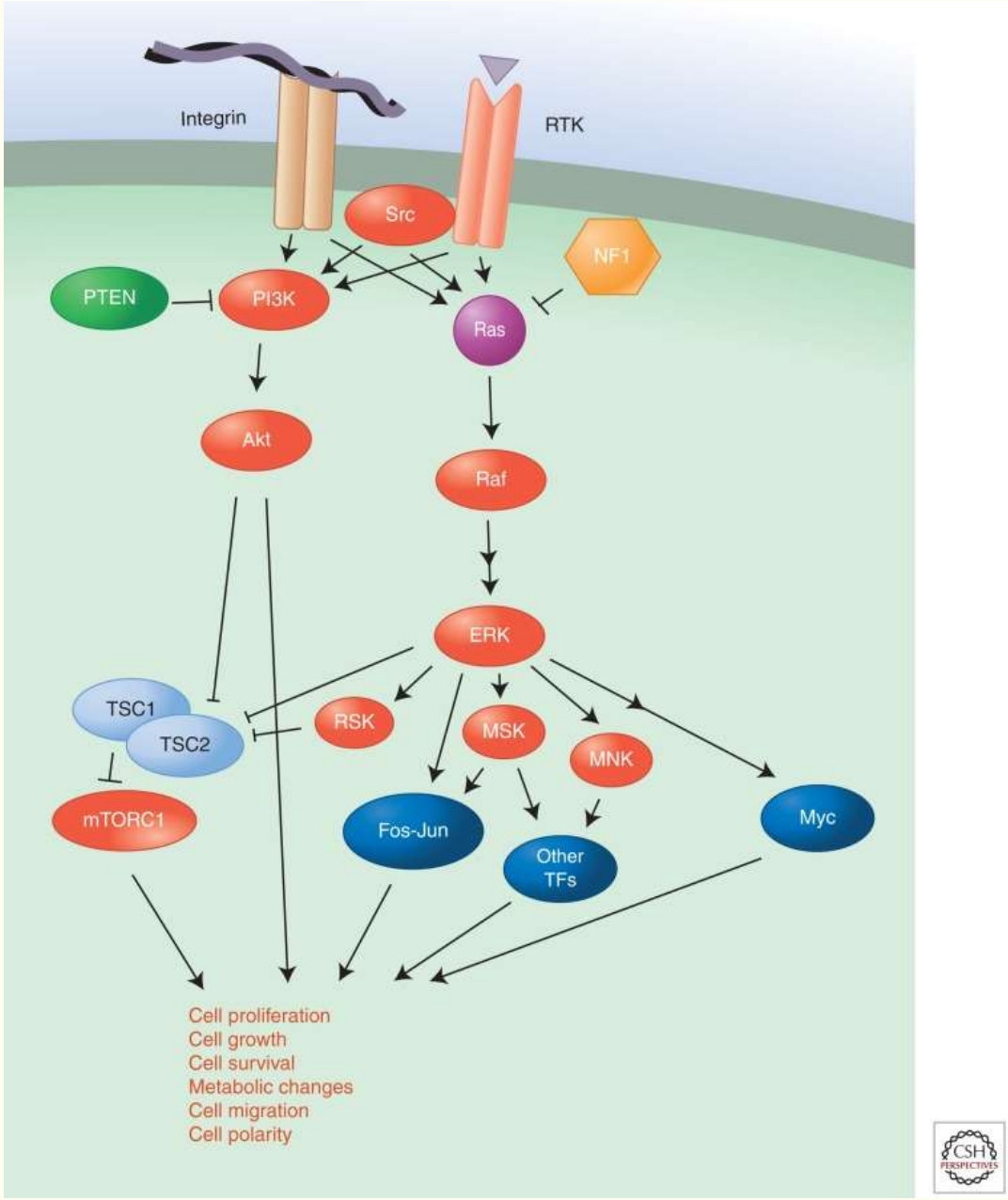


Figure 1.9:The Ras-ERK and PI3K pathways.

Oncogenic mutations, amplification, or gene fusions involving upstream tyrosine kinases lead to constitutive signaling through both the Ras-ERK and PI3K-Akt pathways. RTKs including EGFR, ErbB2, fibroblast growth factor receptor (FGFR), and platelet-derived growth factor receptor (PDGFR) are mutated or amplified in a variety of cancers. Similarly, oncogenic mutations in G-protein-coupled receptors (GPCRs) can also activate these pathways.

Finally, it is important to recognize that deregulated synthesis of growth factors themselves plays an important role in many cancers. Inappropriate synthesis of growth factors by cells expressing the appropriate receptor can generate an autocrine loop driving signaling. This can also be achieved through cleavage and release of anchored soluble growth factors by surface ADAM proteases, which are activated downstream from oncogenic signaling pathways (Turner et al. 2009). Alternatively, the growth factor may be synthesized by a neighboring cell (paracrine stimulation). In both cases, signaling via the Ras-ERK and PI3K-Akt pathways may be increased.

Go to:

3. DYSREGULATION OF CELLULAR PROCESSES BY ONCOGENIC SIGNALING

How, then, does dysregulation of cellular signaling drive cancer progression and produce the characteristic features of tumor cells mentioned above? Below we discuss the role of signal transduction in cancer-associated processes, surveying the major signals involved and focusing on Ras-ERK and PI3K-Akt signaling to illustrate how their targets influence the behavior of the tumor cells.

Go to:

4. CELL PROLIFERATION

Excessive cell proliferation is a feature of most cancers. Limited availability of growth factors or nutrients, contact inhibition, and other feedback mechanisms ensure that the pathways that regulate proliferation (see Fig. 3) are normally tightly controlled. As outlined above, however, mutations in proto-oncogenes and tumor suppressors or inappropriate synthesis of ligands/receptors can hyperactivate these pathways, leading to activation of the cell cycle machinery. Note that signaling targets that represent critical components of cell cycle control mechanisms can also undergo genetic alterations in cancer; for example, the genes encoding

cyclin D, cyclin E, and CDK4 are amplified in certain cancers and the G1 restriction point inhibitor pRB and p16 can be deleted or mutated as well.

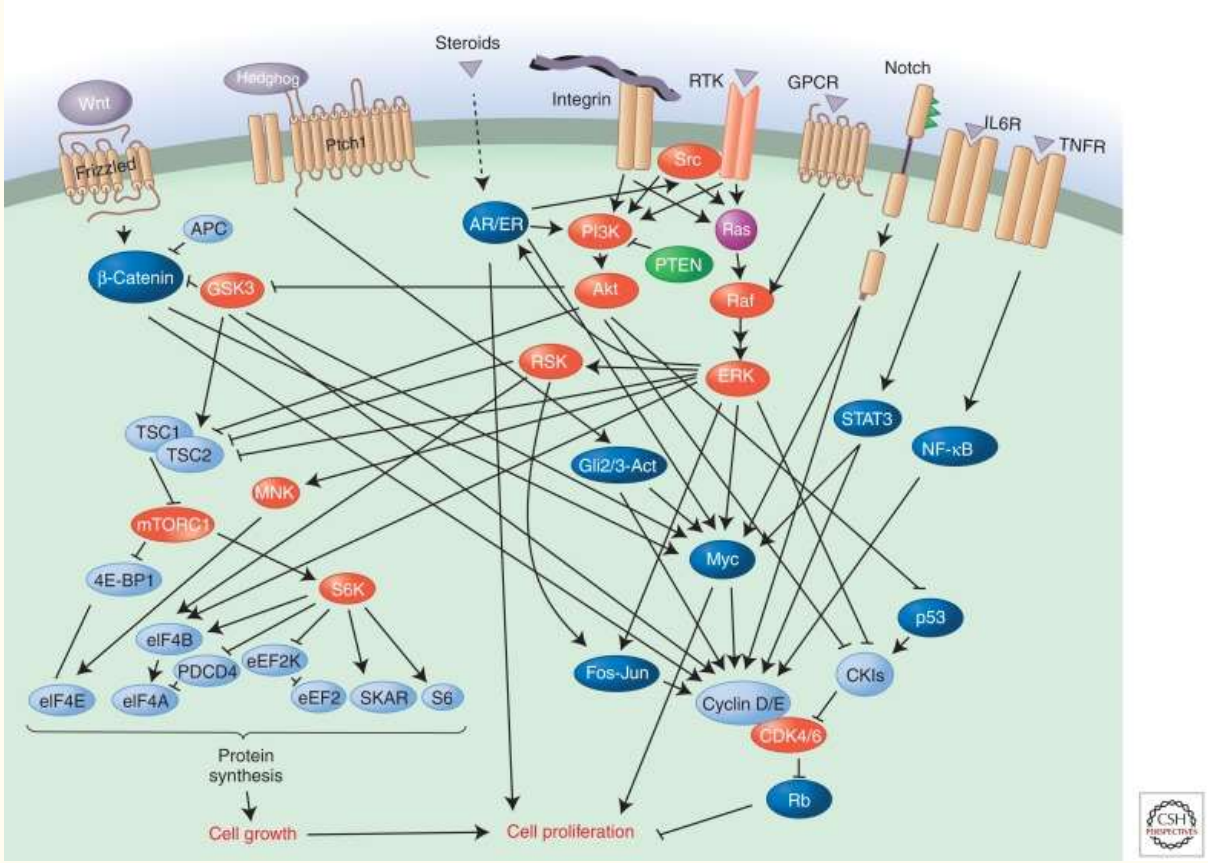


Figure 1.10:Regulation of cell proliferation by the Ras-ERK and PI3K-Akt pathways.

The Ras-ERK and PI3K-Akt pathways are important regulators of normal cell proliferation and thus their constitutive hyperactivation can lead to excessive proliferation. One important target of the Ras-ERK pathway is Myc, which is phosphorylated by ERK; this leads to its stabilization by suppression of ubiquitylation (Sears et al. 2000). Myc stimulates cell proliferation by inducing numerous genes that promote cell proliferation, including those encoding G_1/S cyclins, CDKs, and the E2F-family transcription factors that drive the cell cycle (Duronio and Xiong 2013). In addition, it represses expression of various cell cycle inhibitors (e.g., CKIs), blocks the activity of transcription factors that promote differentiation (see below), induces genes that enhance translation, and shifts cells to anabolic metabolism. ERK also phosphorylates numerous other transcription factors important for cell proliferation. Elk1, for example, in combination with the SRF transcription factor, induces the immediate early gene *FOS*, whose product is also stabilized by ERK phosphorylation (Murphy et al.

2002). *FOS*, also an oncogene, encodes a component of the transcription factor AP1, which regulates many genes involved in cell proliferation.

Multiple kinases in the ribosomal S6 kinase (RSK), mitogen- and stress-activated kinase (MSK), and mitogen-activated protein kinase (MAPK)-interacting kinase (MNK) families are also phosphorylated by ERK, and these kinases, in turn, phosphorylate transcription factors that regulate cell cycle progression—for example, Fos and CREB (Roux and Blenis 2004). MSKs represent the predominant kinases responsible for the nucleosomal response involving phosphorylation of histone H3 at S10, which is commonly induced by mitotic stimuli (Soloaga et al. 2003). MNKs play an important role regulating translation following mitogenic stimulation by phosphorylating the translation initiation factor eIF4E, and loss of the MNK phosphorylation site completely abrogates its ability to transform cell lines or promote tumors in animal models (Soloaga et al. 2003). Activation of RSK family members by ERK also leads to activation of the mTORC pathway through TSC2 phosphorylation and relief of mTORC inhibition. In addition, RSK regulates translation by phosphorylating eIF4B, which increases its interaction with the translation initiation factor eIF3. The promotion of translation by these mechanisms is important for cell growth and, consequently, cell proliferation.

PI3K-Akt signaling controls cell proliferation at various levels. Akt regulates cell growth during cell cycle progression by controlling mTORC1. It inhibits the GAP activity of the TSC1–TSC2 complex toward Rheb, thus allowing GTP-bound Rheb to activate mTORC1. This then phosphorylates eIF4-binding protein, releasing the eIF4E cap-binding factor and allowing it to bind mRNAs, and p70 RSK. This promotes increased protein synthesis, which is critical for enhanced cell growth during cell cycle progression (Richardson et al. 2004). Akt also phosphorylates the kinase GSK3, inhibiting its catalytic activity. Phosphorylation of cyclin D and Myc by GSK3 targets them for degradation; thus, inhibition of this kinase by Akt causes stabilization of these important cell cycle regulators (Diehl et al. 1997; Sears et al. 2000).

In addition, Akt inhibits several cell cycle inhibitors, such as the CKIs p27 (also known as KIP1) and p21 (also known as CIP1); phosphorylation leads to their sequestration in the cytoplasm by 14-3-3 proteins. In the case of p27, phosphorylation also targets it for degradation. Akt-mediated phosphorylation of p21 prevents it from forming a complex with proliferating cell nuclear antigen (PCNA) to inhibit DNA replication, reduces its binding to CDK2/CDK4, and attenuates its inhibitory activity toward CDK2 (Rossig et al. 2001). Furthermore, Akt blocks FoxO-dependent transcription of cell cycle inhibitors such as p27 and

RBL2 (retinoblastoma-like protein 2) (Burgering and Medema 2003). It also phosphorylates and activates MDM2 (Ogawara et al. 2002), a ubiquitin ligase that promotes degradation of p53, thereby releasing a key brake on the cell cycle. Later on in the cell cycle, Akt can regulate several enzymes involved in the G_2/M transition (Xu et al. 2012b).

Phosphorylation and consequent inhibition of GSK3 by Akt may, in certain contexts, lead to stabilization and nuclear translocation of the Wnt target β-catenin (Haq et al. 2003; Korkaya et al. 2009; Ma et al. 2013), a transcriptional regulator whose degradation would otherwise be promoted by GSK3 (Polakis 2001; Korkaya et al. 2009). This leads to induction of β-catenin target genes that regulate proliferation, including those encoding Myc and cyclin D. Akt can also phosphorylate β-catenin directly, causing its dissociation from cadherin cell–cell adhesion complexes (see below), thus increasing the pool of β-catenin available and its transcriptional activity (Fang et al. 2007).

Numerous other signaling pathways can of course drive cell proliferation in cancer. Cytokine and RTK signaling, for example, activate STAT3, which stimulates synthesis of Myc and cyclin D (Harrison 2012). Notch, Wnt/β-catenin, and Hedgehog, all of which have been implicated in cancer, also induce Myc and cyclin D (see below). Similarly, the transcription factor NF-κB, which can be activated by TNF and various other signals, also targets cyclin D expression. Cyclin E is induced by several of these signals. Estrogen signaling (see Sever and Glass 2013) stimulates cell proliferation via activation of the ERα subtype, which induces cyclin D and Myc. Disruption of the balance between ERα and ERβ or mutations in *ERα* that yield truncated proteins or activated proteins can dysregulate this pathway (Thomas and Gustafsson 2011; Li et al. 2013; Robinson et al. 2013; Toy et al. 2013). Note that signaling through ERs and the androgen receptor (AR) is coupled to and enhanced by Ras-ERK and PI3K-Akt signaling (Castoria et al. 2004; Renoir et al. 2013). Growth factor stimulation (e.g., EGF and insulin-like growth factor, IGF) and mutations that activate these pathways increase proliferation of ER/AR-dependent tumors. In addition, these steroid receptors form cytoplasmic complexes with Src and PI3K, which leads to activation of their downstream effectors, and ERK can phosphorylate ERα, which causes its activation in the absence of ligand and stimulation of cell proliferation.

The tumor suppressors that normally hold proliferative signaling in check are obviously also critical. Furthest downstream, pRB normally directly inhibits the transcriptional activity of the E2F proteins until it is deactivated through phosphorylation by CDKs. p53, in contrast,

normally blocks cell proliferation in response to stress signals such as DNA damage by inhibiting CDK activity via induction of CKIs. Consequently, mutations in this tumor suppressor deregulate cell proliferation under potentially dangerous, cancer-promoting conditions. The CKIs themselves directly inhibit CDKs and are also inactivated by mutation in many cancers, p16 being the most common example. Further upstream are pathway-specific tumor suppressors, such as the Ras-GAP NF1 and APC, which block Wnt/β-catenin signaling (by promoting GSK3 phosphorylation and, consequently, ubiquitin-dependent destruction of β-catenin). In each case, mutation of the tumor suppressor removes an important brake, allowing cells to proliferate despite signals that would ordinarily restrain them. The Hippo pathway plays a critical role in regulating contact inhibition of proliferation (Harvey and Hariharan 2012), and disruption of this pathway, which suppresses the transcriptional coactivator YAP, is emerging as a key tumor suppressor pathway in many cancers (Harvey et al. 2013; Lin et al. 2013; Yu and Guan 2013). The Ras-ERK and PI3K-Akt pathways intersect with Hippo pathway components to inactivate its tumor suppressive activity (O'Neill and Kolch 2005; Kim et al. 2010; Collak et al. 2012).

Go to:

5. CELL SURVIVAL

Cell death functions as a homeostatic mechanism that normally controls cell number. It is also a built-in cancer-protection mechanism that is activated during initial stages of oncogenesis because of stresses associated with unbalanced proliferative signals, excessive cell proliferation, loss of anchorage to natural niches, etc. Mutations that disable cell-death signaling can thus play an important role in cancer. Overexpression of the antiapoptotic protein Bcl2, for example, can occur as a consequence of chromosomal rearrangements in B lymphocytes, and this contributes to follicular lymphoma by preventing cells from undergoing apoptosis. p53 also regulates apoptosis, both by inducing transcription of proapoptotic regulators and binding directly to the proapoptotic protein Bax (Green and Llambi 2014). Loss of this tumor suppressor through mutation can therefore contribute to cancer by reducing cell death, as well as disabling normal cell cycle control. Other cell death regulators that are mutated in cancer include the proapo-ptotic proteins Puma and Bok (which are frequently deleted) and the antiapoptotic proteins Mcl1 and Bcl-xL (whose genes are amplified).

Control of proapoptotic regulators (e.g., Bim and Bad) and antiapoptotic regulators (e.g., Bcl2 and Mcl1) in normal cells ensures that cells undergo apoptosis in the absence of appropriate

signals supplied by growth factors or the tissue microenvironment. Hyperactivation of signaling by oncogenic mutations in the Ras-ERK and PI3K-Akt pathways, however, disrupts the balance in favor of antiapoptotic signals, thus contributing to tumor cell survival and abnormal expansion of the cells beyond normal tissue boundaries.

The PI3K-Akt and Ras-ERK pathways regulate cell death in multiple ways (Fig. 4) (review Cagnol and Chambard 2010; Zhang et al. 2011). Akt itself intervenes at several steps in apoptotic signaling from death receptors. It phosphorylates forkhead-family transcription factors such as FoxO3A, which leads to their cytoplasmic sequestration by 14-3-3 proteins, thereby blocking induction of death ligands (e.g., FasL and TRAIL) and the proapoptotic Bcl2-family member Bim. Akt and the ERK-regulated kinase RSK also phosphorylate the proapoptotic Bcl2-family protein Bad, another target for sequestration by 14-3-3 proteins. In addition, Akt phosphorylates and thereby activates the apoptosis inhibitor XIAP. Akt also activates NF-κB, which regulates multiple survival factors, including antiapoptotic proteins (Bcl2, BCLxl, and Mcl1) and the intracellular death receptor inhibitor FLIP (Shen and Tergaonkar 2009). Last, Akt-induced ubiquitylation and degradation of p53 suppresses p53-induced apoptosis (Ogawara et al. 2002).

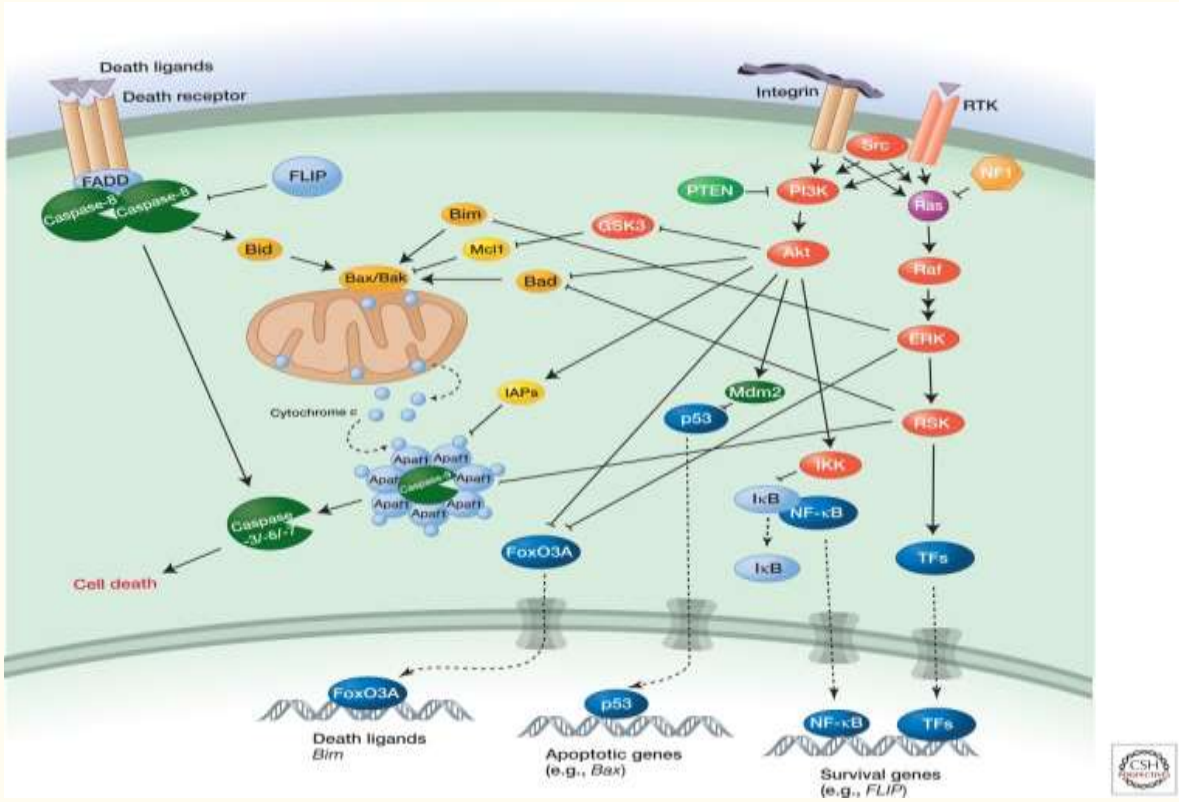


Figure 1.11:Regulation of cell death by Ras-ERK and PI3K-Akt pathways.

ERK phosphorylates Bim and the NF-κB inhibitor IκBα (Ghoda et al. 1997), which targets them for degradation. In addition, RSK phosphorylates the caspase-9 scaffolding protein APAF, which impedes the ability of cytochrome *c* to nucleate apoptosome formation and activate the downstream caspases that drive apoptosis (Kim et al. 2012).

Go to:

6. CELL METABOLISM

Cell growth needs to be coordinated with metabolic processes involved in the synthesis of macromolecules. Thus, growth factor pathways that regulate both normal and tumor cells impinge on metabolic pathways to program cells to meet the increased need for synthesis of macromolecules to produce new daughter cells (Ward and Thompson 2012b). Activation of oncogenes and loss of tumor suppressors can directly regulate components of metabolic pathways even in the absence of growth factors and, thereby, produce similar metabolic alterations (Fig. 5).

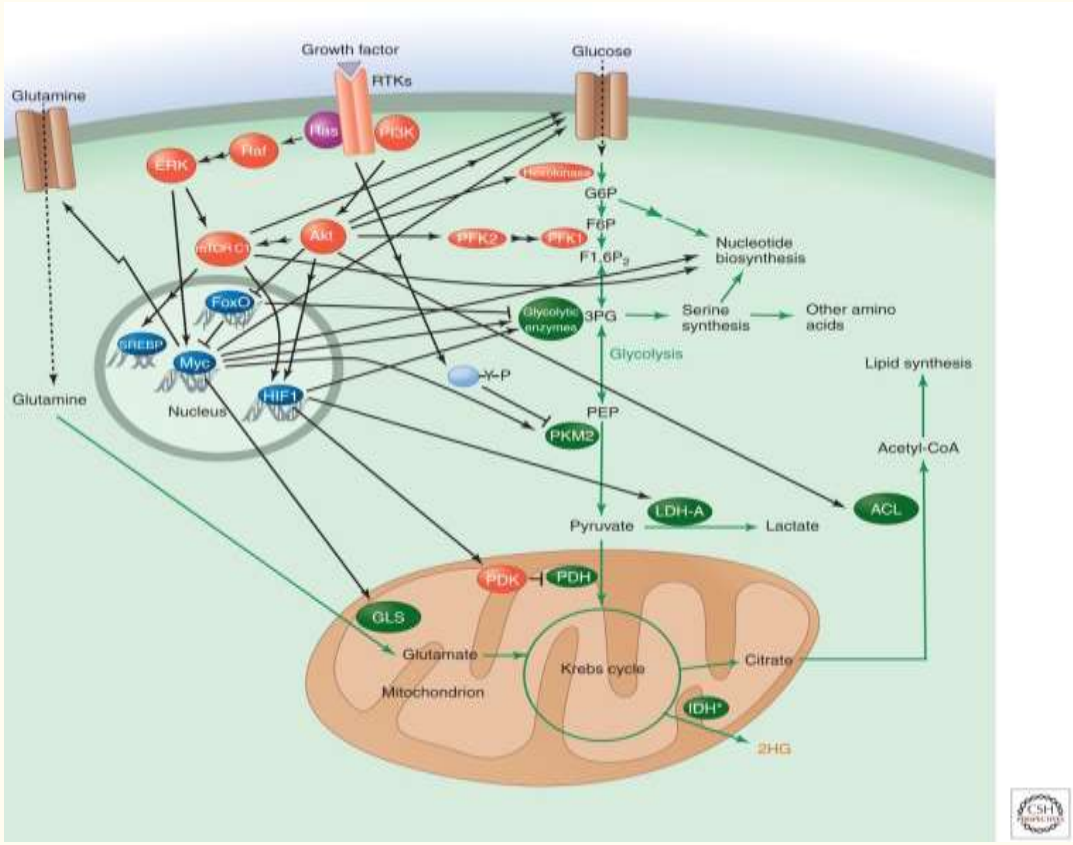


Figure 1.12:Regulation of metabolism by Ras-ERK and PI3K-Akt signaling. IDH*, mutated IDH.

The most common metabolic alteration in cancer cells is increased glucose uptake and glycolysis. At first glance, this might appear a disadvantage because glycolysis generates less ATP than oxidative phosphorylation; however, it allows cells to redirect carbon skeletons from glycolysis to anabolic reactions, such as the pentose phosphate pathway, which leads to nucleotide synthesis and regulates redox homeostasis. These also include the serine/glycine synthesis pathway, which generates several amino acids and charges tetrahydrofolate with a methyl group that is used in pyrimidine synthesis and leads to generation of *S*-adenosylmethionine, the methyl donor for multiple cellular methyltransferase reactions and methylation of essential molecules such as DNA, RNA, proteins, phospholipids, creatine, and neurotransmitters. Cancer cells show increased glutamine uptake and glutaminolysis to support oxidative phosphorylation and biosynthesis of proteins, lipids, and nucleic acids. They also up-regulate lipid synthesis by redirecting citrate from the Krebs cycle to fatty acid synthesis.

The PI3K-Akt pathway targets numerous substrates to promote these metabolic changes (Plas and Thompson 2005). Regulation of glucose transport and hexokinase by Akt promotes glycolysis, leading to generation of nucleotides and amino acids necessary for cell growth (Engelman et al. 2006). Akt2 regulates glucose transport through multiple mechanisms. Regulation of the glucose transporter GLUT4 by Akt2 is critical for circulating glucose homeostasis. The Akt substrate AS160 plays an undefined role in insulin-stimulated GLUT4 translocation and glucose transport through its Rab-GTPase-activating domain (Miinea et al. 2005), and phosphorylation of the protein synip by Akt2 triggers its dissociation from the trafficking regulator syntaxin 4 and assembly of a protein complex that mediates translocation of GLUT4 vesicles to the plasma membrane (Yamada et al. 2005). Akt2 also regulates transcription, accumulation (Barthel et al. 1999; Jensen et al. 2010), and trafficking of GLUT1, which is the principle glucose transporter expressed in most cell types (Wieman et al. 2007). Phosphorylation of TSC2 by Akt affects metabolism through mTORC1-mediated regulation of glycolysis; however, the mechanism of regulation is not known. mTORC1 may regulate glycolysis by increasing translation of glycolytic enzymes or their transcriptional regulators, such as Myc (Kim et al. 2004; Sutrias-Grau and Arnosti 2004). Other Akt targets activated by phosphorylation are hexokinase II, whose association with mitochondria is increased (Roberts et al. 2013), and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (Novellasdemunt et al. 2013). Both stimulate glycolysis.

mTORC1 signaling leads to increased synthesis of the transcription factor hypoxia-inducible factor (HIF1). HIF1 induces glycolytic enzymes and lactate dehydrogenase (LDH-A), providing another means of stimulating glycolysis. In addition, it induces pyruvate dehydrogenase kinase (PDK), which inhibits pyruvate dehydrogenase (PDH) in the mitochondrion and thereby reduces flux from glycolysis into the Krebs cycle. mTORC1 can also stimulate pyrimidine biosynthesis via S6K1 (Ben-Sahra et al. 2013; Nakashima et al. 2013).

Akt/mTORC1 promotes lipid synthesis by activating the transcription factor sterol-response-element-binding protein 1 (SREBP), a key regulator of lipid synthesis that is required for tumorigenicity (Bakan and Laplante 2012; Jeon and Osborne 2012; Guo et al. 2013). Loss of SREBP uncouples fatty acid synthase activity from stearoyl-CoA-desaturase-1-mediated desaturation. Another direct target of Akt is ATP-citrate lyase (ACL), an enzyme that converts citric acid to acetyl-CoA, which is required for fatty acid, cholesterol, and isoprenoid synthesis. mTORC1 also regulates amino acid uptake by stimulating translocation of amino acid transporters from intracellular vesicles to the plasma membrane (Berwick et al. 2002; Edinger and Thompson 2002).

Another family of Akt targets that affect cellular and organismal metabolism is FoxO transcription factors. These are negatively regulated by Akt phosphorylation, which causes their sequestration in the cytoplasm by 14-3-3 proteins. Programs regulated by FoxO transcription factors that increase the cellular capacity for oxidative metabolism are thus shut off by active Akt.

Ras-ERK signaling exerts many of its effects on metabolism via Myc. Myc regulates glucose uptake, glycolysis, and the pentose phosphate pathway (Ying et al. 2012) and induces synthesis of glutamine transporters and the enzyme glutaminase (GLS), which converts glutamine into glutamate that can be metabolized in mitochondria (Miller et al. 2012; Dang 2013). It also induces enzymes involved in nucleotide and amino acid synthesis.

The glycolytic enzyme pyruvate kinase is of particular interest in cancer cells. Although glycolysis rates are usually much higher than in noncancer cells, most cancer cells produce an alternative splice form of pyruvate kinase (PKM2) that is less active than the enzyme (PKM1) found in most terminally differentiated cells (Vander Heiden et al. 2009). PKM1 remains active under most physiological conditions, but PKM2 can be turned off by signaling via tyrosine kinases, including the upstream RTKs in the Ras-ERK and PI3K-Akt pathways (Christofk et

al. 2008; Hitosugi et al. 2009) and reactive oxygen species (ROS) (Anastasiou et al. 2011). Cancer cells can thus redirect the flux of glycolytic intermediates into anabolic pathways for ribose, serine, and glycine production or production of NADPH and glutathione needed to combat oxidative stress. PKM2 can also enter the nucleus and play a role in gene expression (Luo et al. 2011; Gao et al. 2012). However, deletion of PKM2 accelerates rather than impairs breast tumor formation, which indicates that it is the ability to turn off PKM2 activity that is most critical for tumor growth (Israelsen et al. 2013).

Clearly oncogene activation or loss of tumor suppressors such as PTEN and NF1 can drive these metabolic changes by dysregulating PI3K-Akt and Ras-ERK signaling. Other tumor suppressors also control cell metabolism, however. p53, for example, down-regulates glycolysis by inducing TIGAR, an enzyme that decreases the levels of the glycolytic activator fructose 2,6-bisphosphate. It also stimulates expression of SCO2, which is required for assembly of cytochrome *c* oxidase and promotes oxidative phosphorylation. Loss of p53 may therefore contribute to the glycolytic phenotype of cancer cells. p53 also regulates glutaminase 2, a metabolic enzyme that controls production of glutamate, which is converted to α-ketoglutarate for mitochondrial respiration and, importantly, glutathione, a critical cellular antioxidant (Hu et al. 2010; Suzuki et al. 2010). Loss of p53 leads to increased levels of ROS and oxidative damage. p53 also regulates the mevalonate pathway that controls cholesterol synthesis and generates intermediates needed for protein geranylgeranylation and farnesylation. Drugs that target this pathway to control cholesterol/cardiovascular disease have been shown to suppress tumor growth (Shibata et al. 2004; Kubatka et al. 2011).

Similarly, loss of the tumor suppressor LKB1 can lead to metabolic alterations. LKB1 activates AMP-activated protein kinase (AMPK), which acts as a cellular energy regulator and inhibits mTORC1 (Hardie 2012). Loss of LKB1 relieves this inhibition, allowing mTORC1 to promote protein synthesis and lipogenesis. Activators of AMPK, such as metformin, are currently being used in diabetes and cancer therapy.

Finally, mutations associated with cancer can lead to the elevation of metabolites uniquely elevated in cancer cells (Kaelin and McKnight 2013). For example, mutations in IDH1 and IDH2 result in the production of 2-hydroxyglutarate (2HG), a metabolite not present at significant levels in normal cells. 2HG inhibits α-ketoglutarate-dependent enzymes such as the TET family, which regulate DNA methylation, and Jumonji C domain histone demethylases. This leads to epigenetic dysregulation that can drive tumorigenesis. Other oncometabolites may

include succinate and fumarate, whose levels can increase because of mutations in succinate dehydrogenase and fumarate hydratase. Both can inhibit the activity of prolyl hydroxylases that control HIF levels, leading to induction of PDK and the other glycolytic enzymes mentioned above.

7. CELL POLARITY AND MIGRATION

As tumors progress toward malignancy, the cancer cells frequently become more migratory and develop the capacity to invade surrounding tissue. This is usually accompanied by changes in adhesion, cell polarity, cytoskeletal dynamics, and morphology. Migration is regulated by growth factors, chemokines, adhesion receptors, and other stimuli (Vicente-Manzanares and Horwitz 2011; Devreotes and Horwitz 2014), many of which are targets for dysregulated signaling in cancer. The PI3K-Akt and Ras-ERK pathways regulate migration and invasion through multiple downstream effectors, including the following (Cain and Ridley 2009):

1. Rho-family GTPases (RhoA, Rac1, Cdc42, ARF6), which control cytoskeletal regulators such as WAVE/WASP-family members, the Arp2/3 complex, formins, the actomyosin contractile machinery, the kinase LIMK, and cofilins (Raftopoulou and Hall 2004);

2. Integrins and associated matrix adhesion proteins (e.g., FAK, paxillin, and calpains) (Devreotes and Horwitz 2014);

3. Extracellular proteases, which degrade ECM proteins, facilitating tumor cell invasion by creating space for cells to move and reducing adhesive contacts that may constrain them, and also release various bioactive molecules anchored in the ECM (see below);

4. Cell–cell adhesion complexes, whose components are regulated through modulation of their stability or protein interactions that affects the strength of adhesion;

5. Transcription factors such as AP1 and Ets2 that regulate expression of many proteins that control migration/polarity, including matrix metalloproteinases (MMPs), plasminogen activator, cadherins, and actin regulators.

As with other processes regulated by oncoprotein signaling, the outcome of alterations in these pathways is highly context and isoform dependent. For example, Akt1 specifically suppresses migration in many contexts through inhibition of ERK, the transcription factor NFAT, TSC2, or phosphopalladin-induced actin bundling, whereas Akt2 promotes migration through

regulation of integrin expression and effects on the epithelial–mesenchymal transition (EMT) (see below; Chin and Toker 2011). Similarly, some isoforms of ERK target RSK to promote cell motility and invasion by altering transcription and integrin activity, whereas others impair cell motility and invasion through effects on the actin cytoskeleton (Sulzmaier and Ramos 2013).

Polarity proteins are critical regulators of tissue architecture. Three protein complexes play central roles in controlling polarity: Scribble, Par, and Crumbs complexes. Through multiple interactions, components of these pathways control signaling pathways that regulate cell polarity and tissue organization. Dysregulation of these pathways is common in tumors and, in some contexts, involves alterations in Ras-ERK and PI3K-Akt signaling. For example, Scribble inhibits ERK activation by functioning as a scaffold to link it with the protein phosphatase PP1γ (Dow et al. 2008; Nagasaka et al. 2013). Loss of Scribble enhances invasion stimulated by H-Ras (Shaikh et al. 1996) and tumor formation promoted by Ras and Myc (Wu et al. 2010). Similarly, loss of the polarity protein Par3 leads to increased invasion in several tumor models (Iden et al. 2012; McCaffrey et al. 2012; Xue et al. 2013) through multiple pathways, including PKC-dependent activation of JAK/STAT3 signaling. This induces expression of a metalloproteinase, MMP9, with subsequent destruction of the ECM and invasion (McCaffrey et al. 2012), and increased Rac activation, leading to decreased cell–cell adhesion (Xue et al. 2013).

Loss of cell polarity is often coupled to cell proliferation because the loss of cell adhesion molecules relieves contact inhibition. One example is the cytoskeletal protein merlin (also known as neurofibromin 2), a tumor suppressor that regulates the Hippo pathway and whose loss is well known to cause increased cell proliferation. Polarity signaling is also coupled to metabolism.

Some subpopulations of epithelial cells in tumors, particularly those at tumor margins, undergo at least a partial EMT. EMTs are associated with various normal physiological processes—for example, wound healing, gastrulation, and branching morphogenesis (Birchmeier and Birchmeier 1995). This developmental process is orchestrated by multiple highly coordinated pathways induced by combinations of different factors, including transforming growth factor β (TGFβ), TNF, Wnt, Notch, and some growth factors. EMT is characterized by a loss of apical-basal polarity, down-regulation of E-cadherin cell–cell adhesion molecules, adoption of a more fibroblast-like appearance, and, in some contexts, acquisition of stem- or progenitor-

cell phenotypes and anchorage independence, properties that would enhance the cell's ability to invade other tissues and initiate tumors at distant sites.

The Ras-ERK and PI3K-Akt pathways drive the EMT in certain contexts, generally under conditions in which these pathways are hyperactivated together with other pathways implicated in EMT (e.g., TGFβ, Wnt, and Notch signaling) (Larue and Bellacosa 2005). Multiple transcription factors, such as Snail, Slug, Twist, and ZEB, play critical roles driving EMT, and these are regulated by ERK and Akt. For example, Akt can phosphorylate the IκB kinases that regulate NF-κB, a transcription factor that induces Snail. Akt also phosphorylates and inactivates GSK3, which normally promotes ubiquitin-dependent degradation of Snail (Doble and Woodgett 2007); Akt activation will therefore increase Snail stability, further promoting EMT. In addition, Akt2 phosphorylates HNRNP E1, a protein that promotes translational elongation on EMT-promoting transcripts such as those encoding interleukin-like EMT inducer and the adaptor protein DAB2 (Hussey et al. 2011). AP1, which is regulated by the Ras-ERK pathway, can also induce transcription factors that promote EMT as well as other gene expression programs that control phenotypic changes associated with EMT. These include up-regulation of specific integrin heterodimers (e.g., $\alpha_5\beta_1$ and $\alpha_V\beta_6$), vimentin, and fibronectin and down-regulation of cytokeratin, polarity proteins (e.g., Crumbs, PATJ, LGL), and E-cadherin, all of which support cell motility. Interestingly, the polarity protein Scribble maintains cell–cell junctions by suppressing ERK (which stimulates ZEB1) as described above (Elsum et al. 2013; Nagasaka et al. 2013). Dysregulation of both Ras-ERK and PI3K-Akt signaling thus has the potential to play an important role in cancer progression by promoting adoption of an invasive phenotype.

Finally, it is important to note that EMT is not essential for invasion and tumor cell dissemination. Tumor cells can migrate as epithelial sheets within tissues (as occurs during wound healing) or invade by pushing through tissue borders (e.g., basement membrane).

Go to:

8. CELL FATE AND DIFFERENTIATION

Dysregulation or co-option of developmental signaling pathways is a feature of many cancers. This can disrupt the balance between cell proliferation and differentiation, alter cell fate, and/or inappropriately induce morphogenetic programs such as the EMT (see above) that promote metastasis. Although some oncogenes can directly regulate the developmental state of cells, it

is generally believed that cancer progression requires a self-renewing population of "stem-cell-like" cells. These may be induced into a stem-cell-like state by an oncogene(s), or a normal stem/progenitor cell may be the cell-of-origin that sustains the successive mutations that lead to malignancy.

The simplest examples of cancers with dysregulated development are perhaps hematopoietic malignancies in which a differentiation program is stalled before the cells reach their nonproliferative differentiated state. For example, in acute promyelocytic leukemia, a form of acute myelocytic leukemia, myeloblasts fail to differentiate into mature white blood cells because of a translocation that leads to synthesis of a fusion protein combining sequences from a protein called PML and the retinoic acid receptor (RAR). The PML-RAR fusion protein represses RAR-target genes that normally drive differentiation, thereby inactivating the RAR signaling that normally controls this. Subsequently, additional mutations cause overproliferation of the undifferentiated myeloblasts. Inappropriate Wnt signaling has a similar effect in colon cancer. Ordinarily, Wnt signaling via β-catenin (see Nusse 2012) maintains enterocytes in an undifferentiated state in colon crypts but is inactivated by APC-induced degradation of β-catenin as cells move up toward the luminal surface of the intestine. Mutation of the APC tumor suppressor in colon cancer, however, means β-catenin is not destroyed and can maintain cells in an undifferentiated state as they move away. Further mutations can then drive neoplasia.

Developmental signals can also drive cancer progression because they stimulate inappropriate cell proliferation (see above). Mutations that activate Notch, for example, contribute to acute lymphocytic leukemia because Notch signaling (Kopan 2012) can stimulate the cell cycle and also inhibits apoptosis in T cells. Importantly, Notch functions as a tumor suppressor in some other tissues. In others, the concentration of Notch dictates its growth suppressive or stimulatory effects (Mazzone et al. 2010), which illustrates the importance of the signaling context. Activation of the Hedgehog signaling pathway (see Ingham 2012) by mutations in the Patched receptor occurs in basal cell carcinomas and medulloblastomas and again drives cell proliferation. Hedgehog signaling is also hyperactivated via autocrine loops in many tumors that affect tissues derived from the embryonic gut.

Given that the Ras-ERK and PI3K-Akt signaling pathways are activated by growth factors such as EGF, IGF, and fibroblast growth factor (FGF), which play major roles in control of cell fate, they can thus be considered developmental signaling pathways that are hijacked in cancer.

Signaling by FGF4/8, for example, activates the Ras-ERK pathway to drive EMT during gastrulation and the Ras-ERK pathway is recapitulated in several cancers (Thiery 2002). The context is important, however; signaling by FGF has the potential to affect cell proliferation, apoptosis, and migration (see above), as well as angiogenesis (see below), but it can also have tumor suppressive effects, maintaining cells in a differentiated, nonproliferative state. For example, whereas FGFR2 is up-regulated in gastric cancers, its expression is reduced in bladder and prostate cancer (Turner and Grose 2010).

Go to:

9. GENOMIC INSTABILITY

Genomic instability is a common characteristic of cancer cells. Aneuploidy and large-scale DNA rearrangements are frequently observed, and many cancers display elevated mutation rates. Ordinarily, a variety of cellular enzymes repair DNA damage, and checkpoint signaling ensures that DNA replication and cytokinesis are arrested in dividing cells until potentially damaging errors are corrected. Alternatively, checkpoint signaling can induce senescence or apoptosis so that affected cells do not pass on these errors. Whether genomic instability is a cause or a consequence of cancer is still debated, but it clearly reflects a failure of checkpoint signaling and/or DNA repair mechanisms.

DNA damage signals are relayed by the kinases ATM, ATR, Chk1, and Chk2, which stimulate p53, stall the cell cycle, and activate the DNA repair machinery (Rhind and Russell 2012). Downstream of p53, the CKI p21 is induced, and this can halt DNA polymerase if DNA replication has already begun. If the damage cannot be repaired and checkpoint signaling persists, p21 and p53 will induce cells to senesce or undergo apoptosis (see above). Clearly, mutation or epigenetic silencing of these tumor suppressors or upstream kinases can inactivate checkpoint signaling, allowing DNA damage to persist and potentially fuel cancer progression. Indeed, ATM and Chk2 mutations are seen in familial leukemias and colon/breast cancers, respectively, and proteins involved in DNA repair itself are also often mutated—for example, MMR enzymes and BRCA1/2.

The mitotic checkpoint (also known as the spindle assembly checkpoint) ensures that when a cell divides each daughter receives a full complement of chromosomes. A complex containing the proteins Bub1, Bub3, and Mad1-3 monitors attachment of chromosomes to the mitotic spindle, relaying checkpoint signals that block chromosome segregation and subsequent

cytokinesis. Once paired, sister chromatids are all attached to microtubules emanating from opposite poles, the signal is switched off, and cells can move from metaphase into anaphase and, ultimately, cytokinesis can proceed (Rhind and Russell 2012). Inactivation of this checkpoint pathway has the potential to lead to aneuploidy, and mutations in Mad1/2 and Bub1 have been observed in cancer (Schvartzman et al. 2010).

Akt has been implicated in multiple aspects of DNA damage responses and genome instability (Xu et al. 2012a). It can inhibit homologous recombinational repair through direct phosphorylation of the checkpoint proteins Chk1 and TopBP1 or indirectly through recruitment of resection factors such as RPA, BRCA1, and Rad51 to sites of double-stranded breaks (DSBs) in DNA. Akt is also activated by DSBs in a DNA-dependent protein-kinase- or ATM/ATR-dependent manner and, in some contexts, can contribute to radioresistance by stimulating DNA repair by nonhomologous end joining. In addition, Akt also inhibits association of BRCA1 with DNA damage foci. As discussed above, dysregulation of the PI3K-Akt pathway suppresses apoptosis through many effectors, thus promoting survival of cells with DNA damage. Because Ras-ERK signaling also inhibits apoptosis, it too could promote survival of damaged cells. Hyperactivation of Ras-ERK signaling has been shown to lead to genomic instability, although the molecular mechanism is unclear (Saavedra et al. 1999). Akt therefore modifies both the response to and repair of genotoxic damage in complex ways that are likely to have important consequences for the therapy of tumors showing deregulation of the PI3K-Akt pathway.

The tumor suppressor PTEN can also regulate chromosome stability, independently of its 3′-phosphatase activity. PTEN regulates the expression of the DNA repair protein RAD51, and loss of PTEN causes extensive centromere breakage and chromosomal translocations (Toda et al. 1993; Liu et al. 2008; Kopan 2012).

Myc overexpression can induce genomic instability. In mammalian cells and *Drosophila*, overexpression of *Myc* increases the frequency of chromosomal rearrangements (Prochownik and Li 2007; Greer et al. 2013). Multiple mechanisms have been associated with such genomic rearrangements, including ROS-induced DSBs, suppression of checkpoints that prevent replication of damaged DNA, and telomere clustering.

Go to:

10. THE TUMOR MICROENVIRONMENT

So far, we have primarily considered how signaling within cancer cells themselves is dysregulated in cancer. However, cancer progression (at least in solid tumors) also depends on the ECM, blood vessels, immune cells, and noncancerous cells such as fibroblasts in the tumor microenvironment, all of which communicate with cancer cells by subverted signaling mechanisms (Fig. 6). Many of the changes in the tumor microenvironment during cancer progression mimic changes that occur during wound healing and/or developmental processes. As tumors evolve, the complexity of their "ecosystem" increases; reciprocal paracrine and juxtacrine interactions between populations of neoplastic cells as well as tumor cells and nonneoplastic cells within the microenvironment control cellular signaling pathways in both positive and negative fashions. Dissecting the roles of individual signaling pathways in these ecosystems is complex because it is difficult to distinguish cell-autonomous and non-cell-autonomous activities.

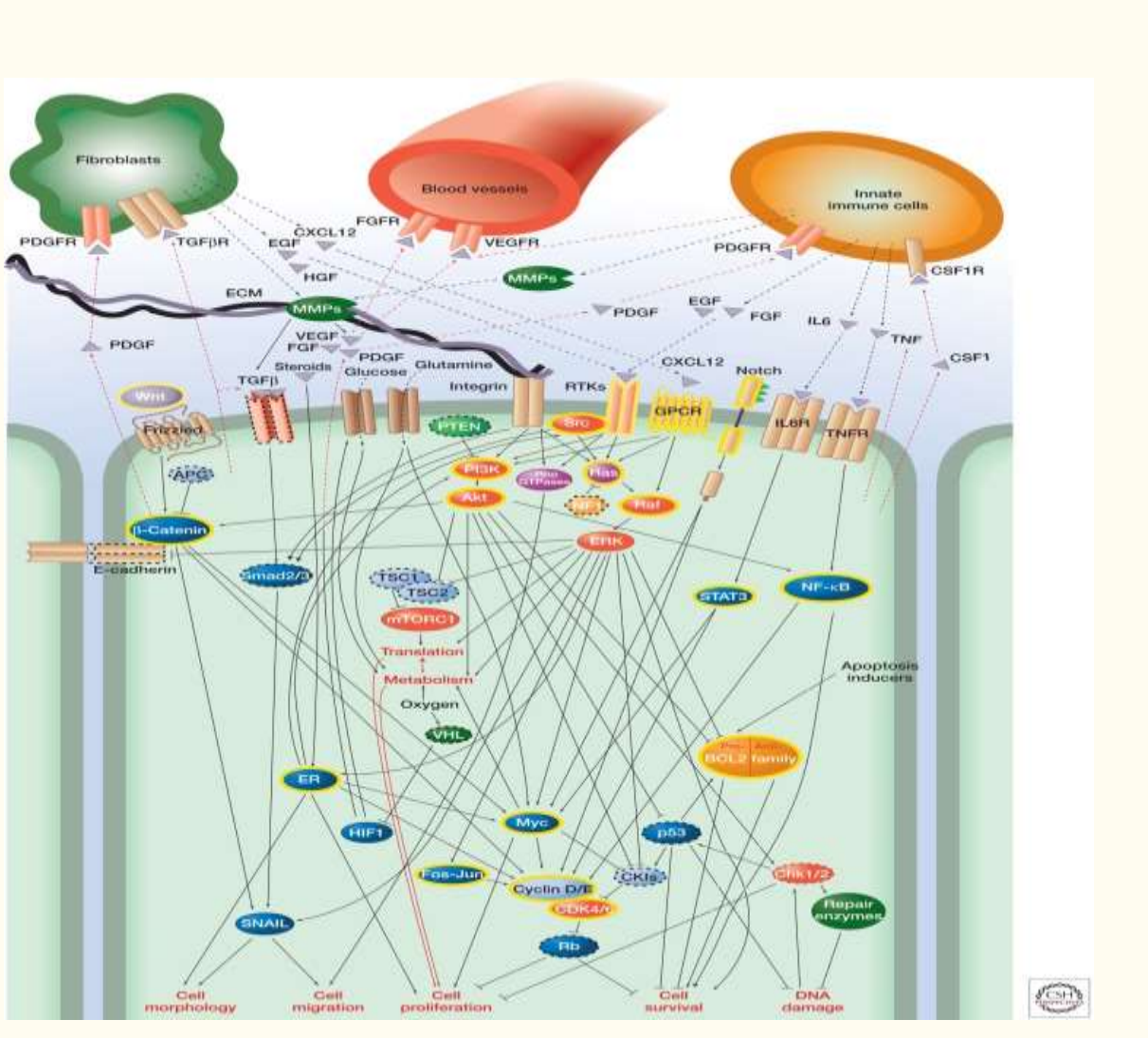


Figure 1.13: Cancer signaling networks. The figure illustrates the wide variety of intra- and intercellular signals affected in cancer, focusing on Ras-ERK and PI3K-Akt signaling. It is by no means comprehensive; many more pathways are involved and there are other stromal cells involved in paracrine signaling. Oncoproteins are indicated with yellow highlighting; tumor suppressors are indicated with dashed outlines. Arrows do not necessarily indicate direct interactions in this figure.

10.1. The ECM

The ECM is a scaffold that physically supports tissues and provides a substrate for cell adhesion and migration, as well as a source of bioactive molecules. Far from a static structure, it is constantly being remodeled, and its composition plays a critical role in control of cell behavior. Fibronectin, laminin, collagen, and various other ECM components serve as ligands that activate integrin signaling. Integrin signaling leads to activation of canonical pathways such as Ras-ERK, PI3K-Akt, and Src signaling, as well as other proteins—for example, the tyrosine kinase FAK, a scaffold that links integrins with cytoskeletal proteins, adaptors, and enzymes that transduce signals from matrix adhesion complexes. FAK also regulates p53 and members of the miR-200 family of microRNAs, which control apoptosis and epithelial phenotype (Keely 2011).

Heparin sulfate proteoglycans (HSPGs) in the ECM modulate signaling by associating with various ligands and acting as coreceptors (e.g., for FGF and FGFR). In addition, the ECM actively sequesters a variety of growth factors, including TGFβ, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF), which can be liberated and/or activated by MMPs. Collagens can also be digested and remodeled by proteinases to enhance tumor cell motility.

The ECM changes as cancer progresses (Lu et al. 2011). It stiffens as large quantities of ECM are deposited by cancer-associated fibroblasts (see below) and collagen fibers become more cross-linked by lysyl oxidases secreted by stromal cells. This increases contractility of the cells, which further fuels stiffening. The changes in stiffness of the ECM promote cell migration and integrin signaling through regulation of Rho family GTPases and other pathways, which synergize with oncogene-activated Ras-ERK and PI3K-Akt pathways to promote invasive growth and cell survival (Keely 2011).

Other changes to the ECM include increased levels of molecules such as tenascin C, a proteoglycan common around developing blood vessels that is induced during inflammation and promotes angiogenesis. MMPs are also up-regulated. These stimulate signaling in various ways and, by degrading the ECM, clear a path for cell migration. Indeed, genes encoding endogenous inhibitors of MMPs such as TIMP3 are known to be targets for hypermethylation in some cancers. HSPGs are also overproduced in cancer and may potentiate oncogenic signaling by FGF, Wnt, and Hedgehog.

10.2. Angiogenesis

Like all tissues, tumors require a blood supply. They acquire this by inducing proliferation and assembly of endothelial cells to form new blood vessels (angiogenesis), co-opting pathways that usually function in wound healing. Central to angiogenesis are signals such as VEGF, PDGF, FGFs, interleukin (IL) 8, and angiopoietin. The PI3K-Akt pathway regulates the induction of angiogenesis as well as vessel integrity (Karar and Maity 2011). Synthesis and secretion of VEGF by cancer cells is induced by HIF1. As mentioned above, HIF1 levels are increased by PI3K-Akt signaling, and hyperactivation of this pathway thus plays an important role in angiogenesis. HIF1 activity can be controlled by the von Hippel–Lindau (VHL) protein, a subunit of an E3 ligase that promotes its ubiquitin-dependent degradation under normoxic conditions when it is proline hydroxylated by proline hydroxylases (see Ward and Thompson 2012b), or through translational control. VHL functions as a tumor suppressor and inactivating VHL mutations occur in a variety of cancers. The PI3K-Akt pathway also modulates the production of other angiogenic factors, such as nitric oxide and angiopoietins. Constitutive endothelial activation of Akt1 has been shown to induce the formation of structurally abnormal blood vessels.

Following its secretion, VEGF is sequestered in the ECM and cannot exert its effects on endothelial cells until it is released by MMPs such as MMP9. These are produced by monocytes and macrophages in the tumor microenvironment (see below), which underscores the importance of immune cells in angiogenesis and existence of the wider signaling network that involves cancer cells, immune cells, and endothelial cells.

Another factor that must be overcome for angiogenesis to occur is inhibitory signals such as thrombospondin 1 (Tsp1). Tsp1 released by various cells normally keeps angiogenesis in check by inducing synthesis of FasL, which causes endothelial cells to undergo apoptosis (see Green and Llambi 2014). Tsp1 is induced by p53, but repressed by Ras, Src, and Myc. It thus

represents another control point in angiogenesis that could be activated by dysregulation of the Ras-ERK pathway. Moreover, the gene that encodes Tsp1 is hypermethylated in some cancers.

10.3. Inflammation

Inflammatory cells such as macrophages and neutrophils constitute the first defense against pathogens, but are also involved in tissue remodeling and repair. They are recruited by chemokines secreted by tumor and stromal cells to almost all tumors and secrete various molecules that promote cancer cell proliferation, survival, and migration. In many respects, the contribution of inflammatory cells to tumor progression, like that of angiogenesis, recapitulates their role in wound healing, which also involves these processes.

Signaling via the transcription factor NF-κB (see Newton and Dixit 2012) is important in both cancer cells and tumor-associated inflammatory cells because it can promote cell survival and proliferation and stimulates production of cytokines such as TNF. Oncogenic mutations affecting NF-κB or upstream regulators such as MALT1 and Bcl10 occur in some lymphoid malignancies; however, in most cancers, NF-κB activity is simply increased by cytokine signaling. For example, in colon cancer, TNF produced by macrophages increases NF-κB activity in intestinal epithelial cells, which promotes cell survival; meanwhile, other cytokines such as IL6 and IL11 increase phospho-STAT3 levels (see Harrison 2012), which promote cell proliferation. A similar phenomenon occurs in hepatocytes in hepatocellular carcinoma, the most common form of liver cancer, and prostate cancer (Karin 2009). NF-κB activation also leads to production of more TNF and synthesis of prostaglandin E2, which further fuels cell proliferation and loss of cell polarity.

In addition to cytokines, inflammatory cells secrete growth factors such as EGF and FGF. These are obviously important regulators of Ras-ERK and PI3K-Akt signaling in cancer cells and will, therefore, dysregulate control of cell proliferation, cell death, metabolism, and cell migration, as discussed above. They also lead to production of colony-stimulating factor 1 (CSF1), a key reciprocal signal that stimulates macrophages, causing them to produce more EGF. Immune cells also produce VEGF and MMPs, which promotes angiogenesis, ECM remodeling, and release of other bioactive molecules (see above). Importantly, all these factors participate in paracrine loops involving various immune cells and cancer cells that sustain chronic inflammation and promote tumor growth and progression.

Note that cells of the adaptive immune system can also be involved, producing signals such as IL17 that stimulate both cancer cells and cells of the innate immune system. Resident microbiota and pathogenic bacteria in the tumor microenvironment can also release products that promote inflammation and immune cell infiltration (Grivennikov et al. 2012).

10.4. Cancer-Associated Fibroblasts

Fibroblasts are present in most tissues, helping to shape organs and control the composition of the ECM. They are activated by tissue injury and, in cancer, produce various factors that stimulate proliferation and migration of cancer cells, along with angiogenesis and inflammation. Release of signals such as TGFβ and PDGF by macrophages and cancer cells activates fibroblasts, which, in turn, can release EGF, HGF, IGF, and chemokines such as CXCR12 (also known as stromal-cell-derived factor 1). These can then further activate Ras-ERK and PI3K-Akt signaling and other pathways in the cancer cells and drive feedback loops that amplify this. Cancer-associated fibroblasts are also responsible for the distinct ECM associated with advanced carcinomas, which also affects signaling within the tumor.

The interplay between cancer cells and these different components of the tumor microenvironment is thus incredibly complex and mimics signaling that tissues display both during development and in normal tissue homeostasis and repair. As cancers metastasize, this extends to other organs. Different cancers are known to seed secondary tumors in particular tissues. Successful colonization depends on the cell surface receptors expressed by the cancer cells and target tissue and the suitability of the microenvironment the latter provides.

Go to:

11. CONCLUDING REMARKS

Cancer cells show a number of defining characteristics. Underlying these is a dysregulation of cellular signal transduction induced by the genetic and epigenetic changes that drive cancer. This affects not only the cancer cells themselves, but the wider signaling network that encompasses other cells, the ECM, blood vessels, and the immune system. Indeed, metastatic cancer can be considered a systemic disease that affects signaling throughout the affected individual, and systemic effects are ultimately what kill patients in cancer.

Pharmacologic and antibody-based inhibitors that target signaling proteins mutated in tumors or proteins downstream from these have had significant impact as cancer treatments. For

example, inhibitors of the nonreceptor tyrosine kinase Abl and RTK ErbB2 dramatically reduce patient mortality in chronic myelogenous leukemia and breast cancer. Other inhibitors, such as those that target B-Raf, EGFR, and the kinase ALK induce remarkable reductions of tumor volume and extend survival in patients with melanoma and nonsmall-cell lung carcinomas; however, the rate of recurrence is high because of the development of drug resistance (Gainor and Shaw 2013; Giroux 2013; Holohan et al. 2013; Lito et al. 2013).

The complexity of the cancer signaling network (see Fig. 6) presents a huge challenge for efforts to develop such anticancer drugs because of the redundancy of pathways that control cell proliferation and survival, crosstalk between pathways, and feedback inhibition mechanisms that cause pathway reactivation. The fact that pathways such as Ras-ERK and Akt-PI3K signaling control so many characteristics of cancer cells, and that components of these pathways, or upstream receptors, are so commonly mutated in a variety of cancers gives reason to be optimistic that approaches based on targeting them will be successful. The efficacy of therapies that target these pathways is, however, limited by multiple factors. For example, rewiring of signaling pathways is associated with adaptive responses to inhibition of driver mutations, and this is commonly because of either loss of feedback inhibition or induction of stress pathways (Pratilas and Solit, 2010; Rodrik-Outmezguine et al. 2011; Lito et al. 2013). Moreover, factors from the tumor microenvironment may stimulate alternative pathways that maintain cell viability despite inhibition of the targeted pathways (Castells et al. 2012; Muranen et al. 2012). Alternatively, there can be selection for rare tumor cells that contain drug-resistant variants of the targeted protein or mutations in other pathways that circumvent the dependency on the targeted pathway, and epigenetic or stochastic changes in the state of tumor cells can also activate intrinsic resistance pathways (Holohan et al. 2013; Holzel et al. 2013).

Further complicating matters is the degree of intratumoral genetic heterogeneity. Recent evidence emerging from sequencing of single cells and multiple regions of tumors from individual patients has revealed this is far greater than previously imagined (Navin et al. 2011; Ruiz et al. 2011; Ding et al. 2012; Gerlinger et al. 2012; Xu et al. 2012b; Bashashati et al. 2013) In one study of kidney tumors, only ~45% of mutations were detected in all tumor regions. This heterogeneity also contributes significantly to intratumoral variation in sensitivity to drugs targeting signaling proteins mutated in cancer, and means that single biopsies may not be sufficient to customize patient treatment.

Overcoming these challenges will require a deeper understanding of the nature of resistance mechanisms and how different cellular signaling programs mediate resistant states in heterogeneous populations of tumor cells. Combination therapies that target these should increase the efficacy of targeted therapies. This is a significant challenge, but one that we feel is not insurmountable.

Cancer is a complex disease caused by genetic and/or epigenetic changes in one cell or a group of cells. These alterations disrupt 'normal' cell function and cause cancerous cells to over proliferate and avoid mechanisms that would typically control their growth, division, and migration.[1,2] Many of these 'disruptions' map to specific cell signaling pathways. This article discusses the relationship between cell signaling and cancer, highlights key signaling pathways involved in cancer, and explores how critical mediators of aberrant signaling can be turned into therapeutic targets for cancer.

THE RELATIONSHIP BETWEEN CELL SIGNALING AND CANCER

WHAT IS CELL SIGNALING?

To enable cells to respond and adapt to their environment, they must be able to receive and process information (or 'signals') that originate outside of the cell. Cell signaling – also sometimes referred to as signal transduction or transmembrane signaling - controls basic cellular activities via complex responses. Signaling pathways coordinate communication between the cell surface and nucleus, between different cells, and between cells and the extracellular matrix.[3]

"As the foremost system of communication, cell signaling enables individual cells to respond to extracellular signals with physiologically appropriate changes in behavior. Signaling enables normal cells to sense whether their state of attachment to the extracellular matrix and to other cells is appropriate and whether hormones or growth factors call them to proliferate or differentiate, move or stay put, or commit to cell death." explains Prof. Filippo Giancotti, Department of Cancer Biology, at U.T. MD Anderson Cancer Center, USA.

The Giancotti Laboratory at the MD Anderson Cancer Center investigates the molecular basis of tumor initiation and progression to metastasis with an emphasis on the role of cell adhesion and signaling. The current major focus of the lab is on identifying the mechanisms that enable the survival during dormancy and eventually the reactivation of metastatic stem cells.

Dysregulated signaling in cancer

Aberrant signaling of just one pathway can have huge implications on wider signaling networks that consequently promote cancer progression and metastasis.[1] Disrupted cell signaling in cancer is responsible for numerous specific characteristics of tumor cells that distinguish them from 'normal' cells – these features are known as 'The Hallmarks of Cancer' (Figure 1).

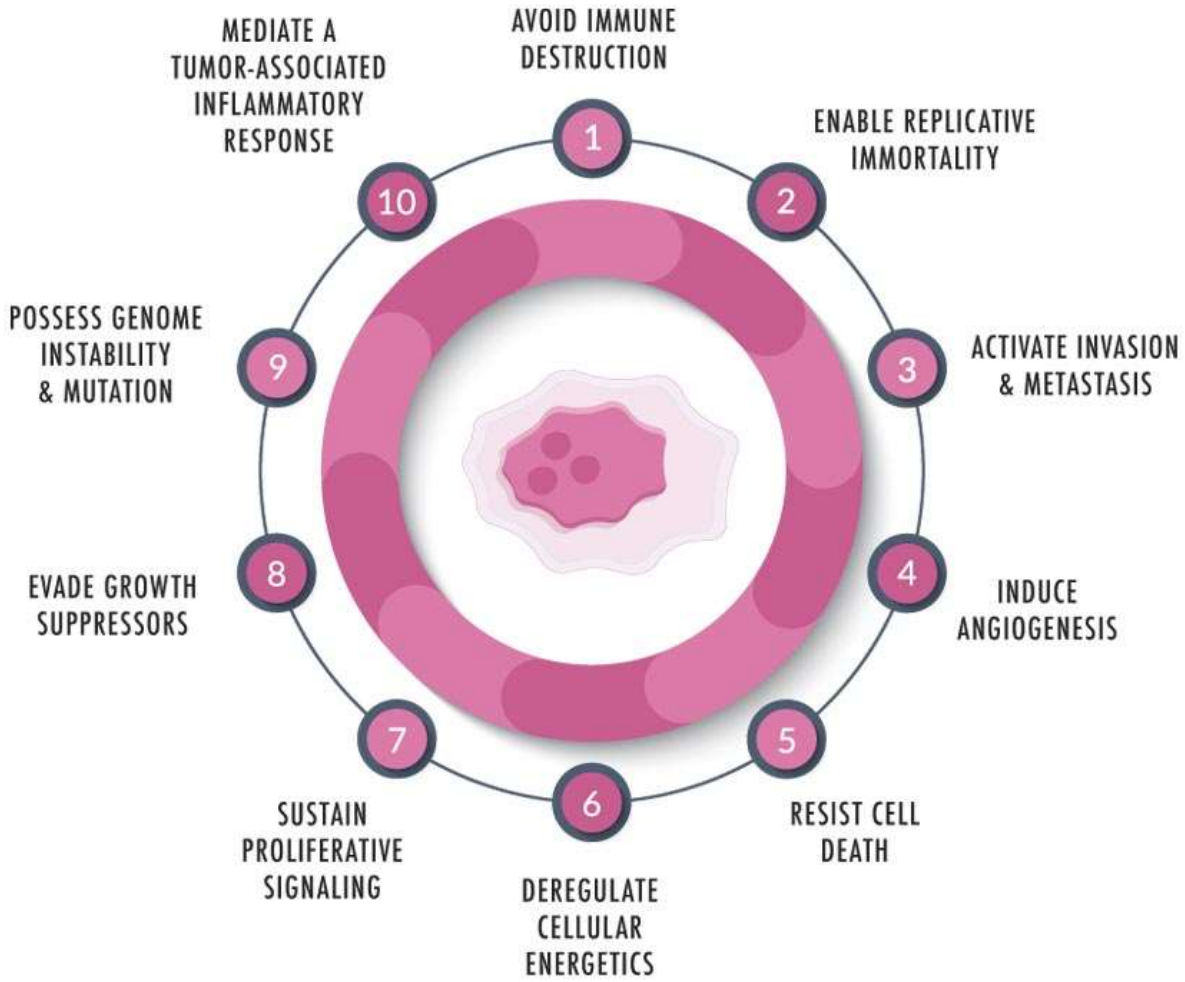


Figure 1.14:: The 10 hallmarks of cancer, as defined by Douglas Hanahan and Robert A. Weinberg, 2011.

Giancotti continues: *"Whereas many oncogenes are activated versions of signaling proteins, many tumor suppressors normally repress signaling. Thus, oncogenic mutations disrupt the signaling circuits that control cell adhesion and signaling, enabling cells that carry them to proliferate and invade in an uncontrolled fashion."*

Oncogenic mutations, aberrant signaling and tumorigenesis

Here we highlight three examples that can be used to exemplify signaling pathways that are aberrantly activated in cancer:

Ras proteins

Ras proteins act as molecular switches that control the activation and regulation of pathways, that are responsible for numerous cell behaviors.[5]

Giancotti highlights two examples of Ras-affected pathways: *"The Ras protein is a GTPase that controls activation of the Raf-MEK-extracellular signal-regulated kinase (ERK) and PI-3K-AKT signaling pathways and, through them, regulates cell survival, cell proliferation, and migration/invasion in response to matrix adhesion and growth factor stimulation."*

Mammalian cells express three distinct but closely related Ras proteins (K-Ras, H-Ras and N-Ras), which can become mutationally activated which in turn promotes oncogenesis. The mutation frequency of different Ras in human cancers varies, and of the three, K-Ras is the most frequently mutated isoform.[6]

"Ras proteins are mutated in such a way that enables constitutive signaling and therefore uncontrolled proliferation and migration/invasion in many cancer types."

The Ras-Raf-MEK-ERK signaling cascade can be activated by several different stimuli (e.g. receptor tyrosine kinase and G protein-coupled receptors). Mutations in Ras as well as other upstream receptor genes can result in abnormal Ras-Raf-MEK-ERK signal activation. This specific pathway plays a key role in the development of hepatocellular carcinoma (HCC) and breast cancers.[6]

Ras, Raf, MEK, ERK, as well as other associated molecules have gained much attention as potential therapeutic targets for cancer. Some examples of inhibitors are listed in Table 1.

Table 1.7: Examples of Ras-Raf-MEK-ERK signaling inhibitors

MEK inhibitors	**RAF inhibitor**	**RAS Inhibitor**
PD184352 PD0325901	Sorafenib (BAY 43-9006, Nexavar)	pan-Ras inhibitor 3144

Wnt/β-catenin signaling

Dysregulated Wnt signaling is linked to numerous cancers including; leukemia, melanoma, breast and gastrointestinal cancers.[7] In fact, a 2012 report by The Cancer Genome Atlas (TCGA) consortium estimated that >90% of sporadic colorectal cancers contained at least one alteration in a Wnt pathway regulator.

"Mutations that prevent degradation of β-catenin, such as certain mutations in β-catenin itself or in the destruction complex component APC, hijack regenerative signaling and contribute to the development of colorectal cancer and other malignancies." says Giancotti.

Adenomatous polyposis coli (APC) is a negative regulator of the canonical Wnt signaling (β-catenin dependent) pathway and is capable of binding to numerous proteins including β-catenin. A condition known as familial adenomatous polyposis, characterized by cancer of the colon and rectum, results from mutations in the *APC* gene.[7,8]

Vivian Li, Group Leader at the Francis Crick Institute expands on the relationship between APC, Wnt signaling and colon cancers: *"Wnt signaling is a genetic pathway that functions to promote cell growth. In normal cells this Wnt signaling pathway is carefully controlled by a gene called APC, which functions to prevent excessive cell growth and tumor formation. However, the majority of colon cancers actually have mutations in the APC gene which eventually causes hyperactivation of the pathway leading to cancer."*

Li's team's research focuses on elucidating how normal and aberrant Wnt signaling and how this affects the programming of stem cells. Using three-dimensional cell models, known as organoids, and gene-editing techniques they can alter the levels of Wnt, and other signaling molecules to determine the effect on bowel stem cells.

Numerous Wnt-signaling pathway inhibitors are being explored for a range of different cancers including colorectal, melanoma and breast.[5]

Table 1.8:: Examples of Wnt-signaling pathway inhibitors[7]

Porcupine inhibitors	**Antibodies against Wnt family proteins**	**Wnt co-activator antagonists**
LGK974 ETC-159	OMP-18R5 (vantictumab) OMP-54F28	PRI-724

Li touches on the importance of identifying the 'right' target: *"The Wnt signaling pathway is important not only for cancer cells, but also for many other healthy organs. For example – in the gut the Wnt signaling pathway is required to maintain stem cell populations for tissue repair. Identifying a tumor specific target is important for developing safe and effective drugs that target this pathway."*

The *NF2* gene

The *Neurofibromatosis Type 2 (NF2)* gene acts as a tumor suppressor and encodes a cytoskeletal protein called moesin-ezrin-radixin-like protein or 'Merlin' (sometimes also referred to as schwannomin). Merlin helps regulate several signaling pathways responsible for controlling cell shape, growth, adhesion – it stops cells from dividing in an uncontrolled way by sensing cell-to-cell contact and restricting proliferation.[9,10]

"Merlin activates the Hippo tumor suppressor pathway and represses the TOR pathway. When mutated, it contributes to the development of familial Schwann cell tumors and, in individuals

exposed to asbestos, to malignant lung mesotheliomas." says Giancotti.

Several other types of cancer are linked to mutated *NF2* and Merlin inactivation, including Glioblastoma multiforme, breast, colorectal, skin, hepatic and prostate cancer.[10,11]

Exploring the complex signaling circuits involved in cancer

According to Giancotti the most powerful methods for dissecting signaling pathways include: *"genetic analysis in Drosophila and other model organisms and biochemical analysis in xenopus oocytes and cultured mammalian cells"*. He explains that they are most powerful when used in conjunction with each other.

"More recently, chemical biology and genetic screening coupled to high-resolution imaging have added to the armamentarium of cell signaling research." He adds.

When it comes to identifying critical mediators of aberrant signaling or perhaps even identifying previously unknown signaling pathways that could be therapeutically targeted, Giancotti explains that high-throughput screening *in vitro* or in model organisms is key.

"In such assays, sh-RNA or g-RNA libraries are used to identify genes that repress activation of a reporter or a phenotype, whereas ORFeome libraries are used to identify genes that activate the same. Coupling such screens with a small molecule screen may yield novel compounds that target the pathway under examination."

One of the most challenging aspects of cancer drug discovery is at the stage of target validation – whereby you must demonstrate the functional role of the identified target in the disease phenotype.[12]

"Even the most sophisticated genetically engineered mouse models (GEMMs) or comprehensive collections of patient-derived xenografts (PDXs) do not fully recapitulate the heterogeneity of human tumors and thus their dependency on signaling pathways X, Y or Z. Moreover, tumor cells are extremely adaptable and can resist therapy by acquiring additional mutations or by changing their fate so that they no longer depend on the oncogenic pathway originally targeted."

Despite the difficulty of finding a truly efficacious drug – there are numerous success stories. Giancotti highlights some examples of therapeutics used for the treatment of cancer that target signaling: *"Imatinib (Gleevec) was the first oncogene-targeted therapy developed for cancer treatment. It is a catalytic inhibitor of the ABL tyrosine kinase, which controls proliferative signaling in myeloid cells. ABL is activated by translocation in chronic myelogenous leukemia (CML). Imatinib is extremely efficacious in CML."*

Giancotti says that the majority of patients treated with imatinib enter into a state of very durable remission and their life expectancy is comparable to that of similarly aged healthy individuals.

B-RAF inhibitors present as another example and are extremely efficacious in B-RAF mutated melanoma. "… especially if used in conjunction with immunotherapy" explains Giancotti. *"The idea here is that the cell killing consequent to B-RAF kinase inhibition generates neoantigens recognized by the patient's immune system."*

Other examples include drugs targeting the estrogen receptor (ER) in breast cancer and androgen receptor (AR) in prostate cancer, as well as monoclonal antibodies targeting the *ERBB2* tyrosine kinase, such as trastuzumab (Herceptin) which has demonstrated efficacy in particular breast cancers (those that involve amplifications of *ERBB2* which drives uncontrolled mitogenic signaling).

Cell Signaling

In order to respond to changes in their immediate environment, cells must be able to receive and process signals that originate outside their borders. Individual cells often receive many signals simultaneously, and they then integrate the information they receive into a unified action plan. But cells aren't just targets. They also send out messages to other cells both near and far.

What Kind of Signals Do Cells Receive?

Most cell signals are chemical in nature. For example, prokaryotic organisms have sensors that detect nutrients and help them navigate toward food sources. In multicellular organisms,

growth factors, hormones, neurotransmitters, and extracellular matrix components are some of the many types of chemical signals cells use. These substances can exert their effects locally, or they might travel over long distances. For instance, **neurotransmitters** are a class of short-range signaling molecules that travel across the tiny spaces between adjacent neurons or between neurons and muscle cells. Other signaling molecules must move much farther to reach their targets. One example is follicle-stimulating hormone, which travels from the mammalian brain to the ovary, where it triggers egg release.

Some cells also respond to mechanical stimuli. For example, sensory cells in the skin respond to the pressure of touch, whereas similar cells in the ear react to the movement of sound waves. In addition, specialized cells in the human vascular system detect changes in blood pressure — information that the body uses to maintain a consistent cardiac load.

How Do Cells Recognize Signals?

Cells have proteins called **receptors** that bind to signaling molecules and initiate a physiological response. Different receptors are specific for different molecules. Dopamine receptors bind dopamine, insulin receptors bind insulin, nerve growth factor receptors bind nerve growth factor, and so on. In fact, there are hundreds of receptor types found in cells, and varying cell types have different populations of receptors. Receptors can also respond directly to light or pressure, which makes cells sensitive to events in the atmosphere.

Receptors are generally transmembrane proteins, which bind to signaling molecules outside the cell and subsequently transmit the signal through a sequence of molecular switches to internal signaling pathways. Membrane receptors fall into three major classes: G-protein-coupled receptors, ion channel receptors, and enzyme-linked receptors. The names of these receptor classes refer to the mechanism by which the receptors transform external signals into internal ones — via protein action, ion channel opening, or enzyme activation, respectively. Because membrane receptors interact with both extracellular signals and molecules within the cell, they permit signaling molecules to affect cell function without actually entering the cell. This is important because most signaling molecules are either too big or too charged to cross a cell's plasma membrane (Figure 1).

Not all receptors exist on the exterior of the cell. Some exist deep inside the cell, or even in the nucleus. These receptors typically bind to molecules that can pass through the plasma membrane, such as gases like nitrous oxide and steroid hormones like estrogen.

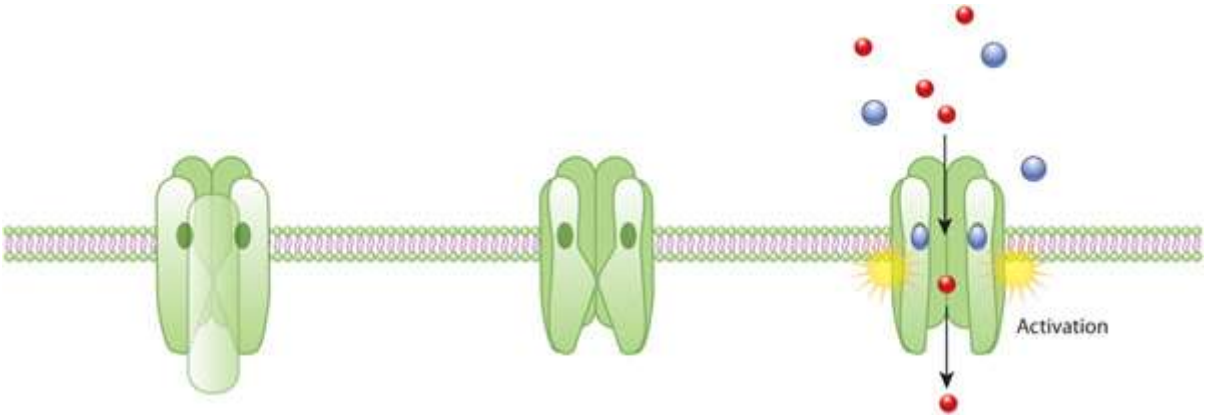


Figure 1.16: An example of ion channel activation

An acetylcholine receptor (green) forms a gated ion channel in the plasma membrane. This receptor is a membrane protein with an aqueous pore, meaning it allows soluble materials to travel across the plasma membrane when open. When no external signal is present, the pore is closed (center). When acetylcholine molecules (blue) bind to the receptor, this triggers a conformational change that opens the aqueous pore and allows ions (red) to flow into the cell.

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How Do Cells Respond to Signals?

Once a receptor protein receives a signal, it undergoes a conformational change, which in turn launches a series of biochemical reactions within the cell. These intracellular signaling pathways, also called **signal transduction cascades**, typically amplify the message, producing multiple intracellular signals for every one receptor that is bound.

Activation of receptors can trigger the synthesis of small molecules called **second messengers**, which initiate and coordinate intracellular signaling pathways. For example, **cyclic AMP** (cAMP) is a common second messenger involved in signal transduction cascades. (In fact, it was the first second messenger ever discovered.) cAMP is synthesized from ATP by the enzyme **adenylyl cyclase**, which resides in the cell membrane. The activation of adenylyl cyclase can result in the manufacture of hundreds or even thousands of cAMP molecules. These cAMP molecules activate the enzyme **protein kinase A** (PKA), which then **phosphorylates** multiple protein substrates by attaching phosphate groups to them. Each step in the cascade further amplifies the initial signal, and the phosphorylation reactions mediate both short- and long-term responses in the cell (Figure 2). How does cAMP stop signaling? It is degraded by the enzyme phosphodiesterase.

Other examples of second messengers include **diacylglycerol** (DAG) and **inositol 1,4,5-triphosphate** (IP3), which are both produced by the enzyme **phospholipase**, also a membrane

protein. IP3 causes the release of Ca^{2+} — yet another second messenger — from intracellular stores. Together, DAG and Ca^{2+} activate another enzyme called **protein kinase C** (PKC).

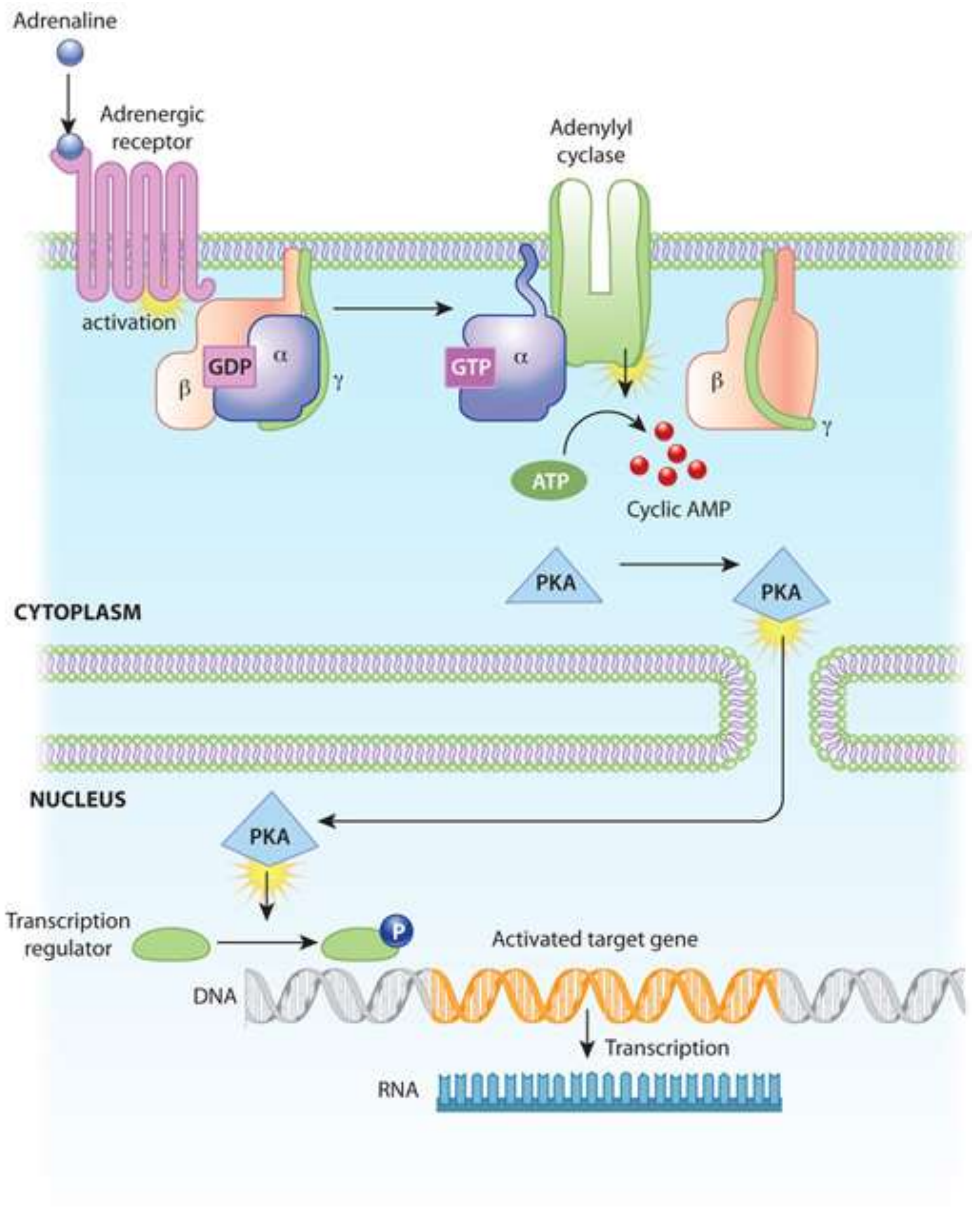

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Figure 1.17: An example of a signal transduction cascade involving cyclic AMP

The binding of adrenaline to an adrenergic receptor initiates a cascade of reactions inside the cell. The signal transduction cascade begins when adenylyl cyclase, a membrane- bound enzyme, is activated by G-protein molecules associated with the adrenergic receptor. Adenylyl cyclase creates multiple cyclic AMP molecules, which fan out and activate protein kinases (PKA, in this example). Protein kinases can enter the nucleus and affect transcription.

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How Do Signals Affect Cell Function?

Protein kinases such as PKA and PKC catalyze the transfer of phosphate groups from ATP molecules to protein molecules. Within proteins, the amino acids serine, threonine, and tyrosine are especially common sites for phosphorylation. These phosphorylation reactions control the activity of many enzymes involved in intracellular signaling pathways. Specifically, the addition of phosphate groups causes a conformational change in the enzymes, which can either activate or inhibit the enzyme activity. Then, when appropriate, protein phosphatases remove the phosphate groups from the enzymes, thereby reversing the effect on enzymatic activity.

Phosphorylation allows for intricate control of protein function. Phosphate groups can be added to multiple sites in a single protein, and a single protein may in turn be the substrate for multiple kinases and phosphatases.

At any one time, a cell is receiving and responding to numerous signals, and multiple signal transduction pathways are operating in its cytoplasm. Many points of intersection exist among these pathways. For instance, a single second messenger or protein kinase might play a role in more than one pathway. Through this network of signaling pathways, the cell is constantly integrating all the information it receives from its external environment.

Conclusion

Cells typically receive signals in chemical form via various signaling molecules. When a signaling molecule joins with an appropriate receptor on a cell surface, this binding triggers a chain of events that not only carries the signal to the cell interior, but amplifies it as well. Cells can also send signaling molecules to other cells. Some of these chemical signals — including neurotransmitters — travel only a short distance, but others must go much farther to reach their targets.

Cancer prevention: 7 tips to reduce your risk

Concerned about cancer prevention? Take charge by making changes such as eating a healthy diet and getting regular screenings.

By Mayo Clinic Staff

You've probably heard conflicting reports about cancer prevention. Sometimes a specific cancer-prevention tip recommended in one study is advised against in another.

Often, what's known about cancer prevention is still evolving. However, it's well-accepted that your chances of developing cancer are affected by the lifestyle choices you make.

So if you're interested in preventing cancer, take comfort in the fact that simple lifestyle changes can make a difference. Consider these cancer-prevention tips.

1. Don't use tobacco

Using any type of tobacco puts you on a collision course with cancer. Smoking has been linked to various types of cancer — including cancer of the lung, mouth, throat, larynx, pancreas, bladder, cervix and kidney. Chewing tobacco has been linked to cancer of the oral cavity and pancreas. Even if you don't use tobacco, exposure to secondhand smoke might increase your risk of lung cancer.

Avoiding tobacco — or deciding to stop using it — is an important part of cancer prevention. If you need help quitting tobacco, ask your doctor about stop-smoking products and other strategies for quitting.

2. Eat a healthy diet

Although making healthy selections at the grocery store and at mealtime can't guarantee cancer prevention, it might reduce your risk. Consider these guidelines:

- **Eat plenty of fruits and vegetables.** Base your diet on fruits, vegetables and other foods from plant sources — such as whole grains and beans.
- **Avoid obesity.** Eat lighter and leaner by choosing fewer high-calorie foods, including refined sugars and fat from animal sources.

- **If you choose to drink alcohol, do so only in moderation** The risk of various types of cancer — including cancer of the breast, colon, lung, kidney and liver — increases with the amount of alcohol you drink and the length of time you've been drinking regularly.
- **Limit processed meats.** A report from the International Agency for Research on Cancer, the cancer agency of the World Health Organization, concluded that eating large amounts of processed meat can slightly increase the risk of certain types of cancer.

In addition, women who eat a Mediterranean diet supplemented with extra-virgin olive oil and mixed nuts might have a reduced risk of breast cancer. The Mediterranean diet focuses mostly on plant-based foods, such as fruits and vegetables, whole grains, legumes, and nuts. People who follow the Mediterranean diet choose healthy fats, such as olive oil, over butter and fish instead of red meat.

3. Maintain a healthy weight and be physically active

Maintaining a healthy weight might lower the risk of various types of cancer, including cancer of the breast, prostate, lung, colon and kidney.

Physical activity counts, too. In addition to helping you control your weight, physical activity on its own might lower the risk of breast cancer and colon cancer.

Adults who participate in any amount of physical activity gain some health benefits. But for substantial health benefits, strive to get at least 150 minutes a week of moderate aerobic activity or 75 minutes a week of vigorous aerobic activity. You can also do a combination of moderate and vigorous activity. As a general goal, include at least 30 minutes of physical activity in your daily routine — and if you can do more, even better.

4. Protect yourself from the sun

Skin cancer is one of the most common kinds of cancer — and one of the most preventable. Try these tips:

- **Avoid midday sun.** Stay out of the sun between 10 a.m. and 4 p.m., when the sun's rays are strongest.
- **Stay in the shade.** When you're outdoors, stay in the shade as much as possible. Sunglasses and a broad-brimmed hat help, too.

- **Cover exposed areas.** Wear tightly woven, loose fitting clothing that covers as much of your skin as possible. Opt for bright or dark colors, which reflect more ultraviolet radiation than do pastels or bleached cotton.
- **Don't skimp on sunscreen.** Use a broad-spectrum sunscreen with an SPF of at least 30, even on cloudy days. Apply sunscreen generously, and reapply every two hours — or more often if you're swimming or perspiring.
- **Avoid tanning beds and sunlamps.** These are just as damaging as natural sunlight.

5. Get vaccinated

Cancer prevention includes protection from certain viral infections. Talk to your doctor about vaccination against:

- **Hepatitis B.** Hepatitis B can increase the risk of developing liver cancer. The hepatitis B vaccine is recommended for certain adults at high risk — such as adults who are sexually active but not in a mutually monogamous relationship, people with sexually transmitted infections, people who use intravenous drugs, men who have sex with men, and health care or public safety workers who might be exposed to infected blood or body fluids.
- **Human papillomavirus (HPV).** HPV is a sexually transmitted virus that can lead to cervical and other genital cancers as well as squamous cell cancers of the head and neck. The HPV vaccine is recommended for girls and boys ages 11 and 12. The U.S. Food and Drug Administration recently approved the use of vaccine Gardasil 9 for males and females ages 9 to 45.

6. Avoid risky behaviors

Another effective cancer prevention tactic is to avoid risky behaviors that can lead to infections that, in turn, might increase the risk of cancer. For example:

- **Practice safe sex.** Limit your number of sexual partners and use a condom when you have sex. The more sexual partners you have in your lifetime, the more likely you are to contract a sexually transmitted infection — such as HIV or HPV. People who have HIV or AIDS have a higher risk of cancer of the anus, liver and lung. HPV is most often associated with cervical cancer, but it might also increase the risk of cancer of the anus, penis, throat, vulva and vagina.

- **Don't share needles.** Sharing needles with people who use intravenous drugs can lead to HIV, as well as hepatitis B and hepatitis C — which can increase the risk of liver cancer. If you're concerned about drug misuse or addiction, seek professional help.

7. Get regular medical care

Regular self-exams and screenings for various types of cancers — such as cancer of the skin, colon, cervix and breast — can increase your chances of discovering cancer early, when treatment is most likely to be successful. Ask your doctor about the best cancer screening schedule for you.

TELOMERE, TELOMERASE AND CANCER

(Telomere and Telomerase in Cancer -book chapter- Telomere - A Complex End of a Chromosome, Angayarkanni Jayaraman, Kalarikkal Gopikrishnan Kiran and Palaniswamy Muthusamy, DOI: 10.5772/64721)

1. INTRODUCTION

Telomeres are specialized DNA structures consisting of tandem arrays of hexa-nucleotide (TTAGGG) DNA sequences that cap the end of chromosomes. These structures residing near the ends of chromosomes play a very vital role in maintaining the integrity of the whole genome and prevent the loss of genetic material. As a consequence of cell division, short stretches of DNA will be lost from telomeric region and eventually lead to cellular senescence and death. There are a lot of evidences to suggest that telomere length is a better biomarker for overall health status, compared to the currently used biomarkers for the same. Few of the phenomena regarding the telomere length are unanswered till now. Till date it is unclear about the mechanistic correlation between telomere size and life span of various species. To prevent senescence of cell, the preservation of telomere length is essential, which is maintained by telomerase enzyme. Telomerase is a reverse transcriptase enzyme which has recently emerged as an attractive target for cancer as it is a crucial factor required for the tumor immortalization of a subset of cells, including cancer stem cells. Studies have proved that 80–85% of the tumor cells express telomerase whereas somatic cells lack the expression of telomerase [1]. The important paradox is that telomerase-negative normal cells have lengthier telomeres than telomerase-positive cancer cells [2]. Thus difference in telomere length and cell kinetics between normal and cancerous cells shows that targeting telomerase is a more effective way to target cancer cells. Owing to the significant role of telomere and telomerase in tumor immortalization understanding their amassed influence on cancer is crucial for cancer therapy. In this context, this book chapter is focused on disseminating the integrated impact of telomere and telomerase on cancer progression.

2. Telomere construction

The basic structure of telomere is conserved among eukaryotes and consists of short tandem DNA repeats, with G-rich sequence at the three-end referred to as the G-strand and the complementary strand is called the C-strand at the five-end (Figure 1) [3]. The length of

telomeric DNA varies from 2 to 20 kilobase pairs, depending on factors such as tissue type and human age [4]. The telomere is conspicuous owing to the presence of G-overhang which extends beyond its complementary C-rich strand to form a single-stranded overhang, termed the G-tail. It has been proposed that the 3′ G-overhang can be sequestered into a lasso-like structure known as the T-loop (Figure 2) [5, 6]. The single-stranded G-overhang invades the double-stranded telomeric DNA, which displaces the bound G-strand base-pairing with the C-strand. As this displaced binding takes place at a distance from the physical end of the telomere, it generates a large duplex structure called the T-loop (Figure 2) [3, 5].

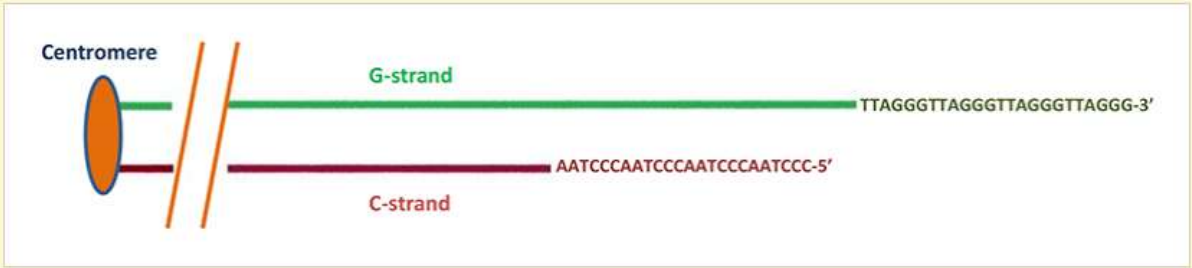

Figure 1.

Telomeric DNA.

figure 1.18: telomeric DNA

Telomeres can also fold into G-quadruplex DNA, an unusual DNA conformation that is based on a guanine quartet [7]. The repetitive and GC-rich nature of telomeric DNA endows it with the capability to form the higher-order DNA conformation, G-quadruplexes [8, 9]. To maintain such unusual structure of telomeres, a set of telomeric protein complex has evolved, termed shelterin. The shelterin complex consists of six individual proteins, telomeric repeat binding factor 1 (TRF1), TRF2, repressor/activator protein 1 (RAP1), TIN2 (TRF1 interacting protein 2), TPP1 (TINT1/PIP1/PTOP 1), and protection of telomeres 1 (POT1) [6, 10]. The proteins TRF1 and TRF2 attach to double-stranded telomeric repeats facilitating the anchoring of the complex along the length of telomeres [11–14], whereas POT1 binds to the single-stranded overhang. TPP1 and TIN2 act as bridging proteins between the above DNA-binding modules and are crucial for chromosome end protection and telomere length regulation. TRF1 and TRF2 with the help of TIN2 [15] bind with POT1 via TPP1 [16–19]. TIN2 also connects TRF1 to TRF2, and this interaction contributes to the stabilization of TRF2 on telomeres [17–19]. Besides this shelterin complex, other proteins like TEN1 and Pinx1, which are not telomere

specific, are also present at telomeres and carry out important functions in recruitment of telomerase [20].

Figure 1.19 T-loop formation

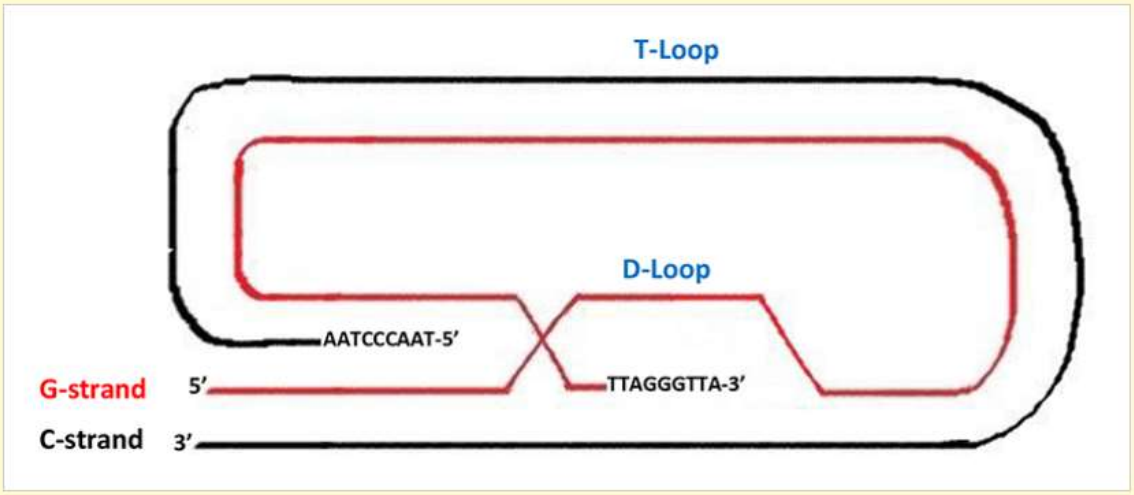

Figure 2.

T-loop formation.

Figure 1.20 : Telomere telomerase assembly

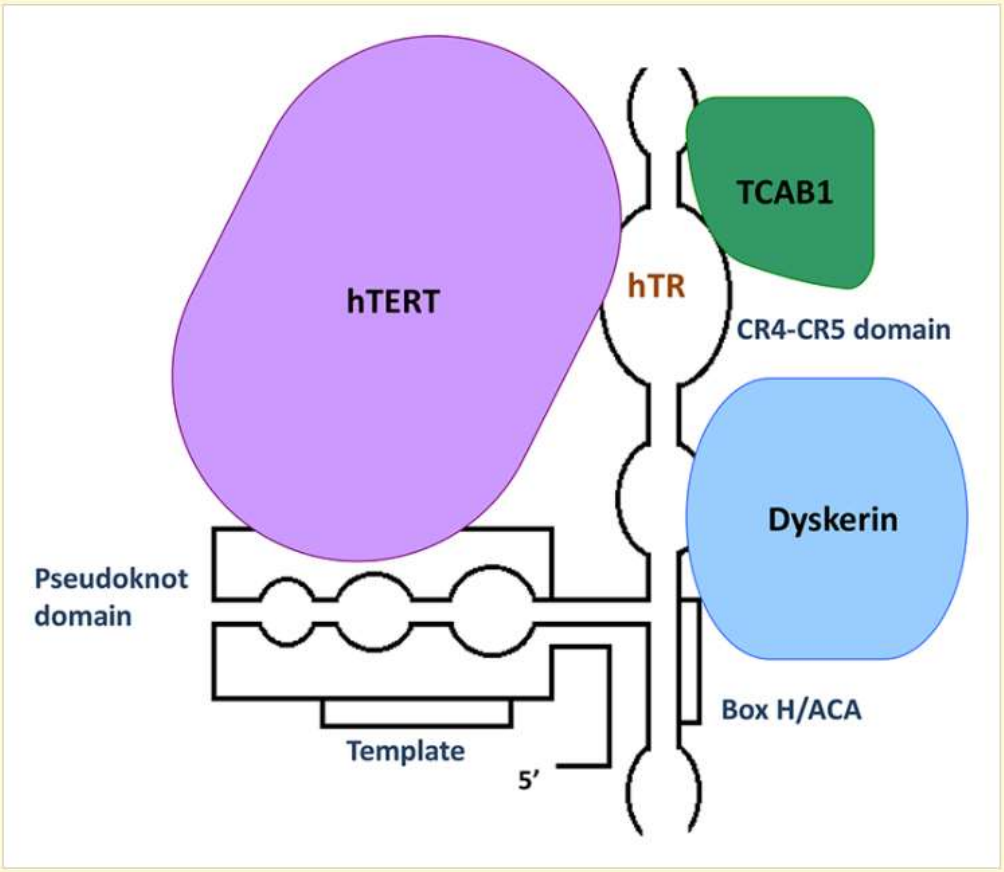

Figure 3.
Telomere-telomerase assembly.

3. Telomere: a knight cap

During the evolvement of linear genome, the natural ends of linear chromosomes resemble DNA breaks and tend to induce DNA damage response (DDR). These natural linear ends are protected by the sequestration of the ribonucleoprotein (RNP) sequence, telomeres which mask the ends from continuous exposure to the DNA damage response (DDR). Telomeres serve as protective caps, preventing the chromosomal ends from being recognized as double-strand breaks by the DNA damage repair system and the activation of the p53 or p16INK4a pathway and the start of senescence or apoptosis. If the telomere cap is removed, genome instability is induced. Telomeres with its tightly regulated complexes consisting of repetitive G-rich DNA and specialized proteins accomplish the task of not only concealing the linear chromosome ends from detection and undesired repair, but also protect from checkpoints, homologous recombination, end-to-end fusions, or other events that normally promote repair of intra-chromosomal DNA breaks acts [21]. Telomeric proteins and their interacting factors create an

environment at chromosome ends that inhibits DNA repair at that point; however, the repair machinery is also essential for proper telomere function.

The closed configuration of the T-loop of telomeric region provides a protective cap that defines the natural end of the chromosome and masks the telomere from the DDR machinery (Figure 2) [6]. In particular, T-loops could provide an architectural solution to the repression of the ataxia telangiectasia mutated (ATM) kinase pathway, which relies on a sensor (the MRN (Mre11/Rad50/Nbs1) complex) with DNA end-binding activity. In addition, T-loops could prevent the Ku70/80 heterodimer, a DNA repair factor that binds to DNA ends, from loading onto the telomere terminus, thereby blocking the initiation of the non-homologous end-joining (NHEJ) pathway (Figure 4)

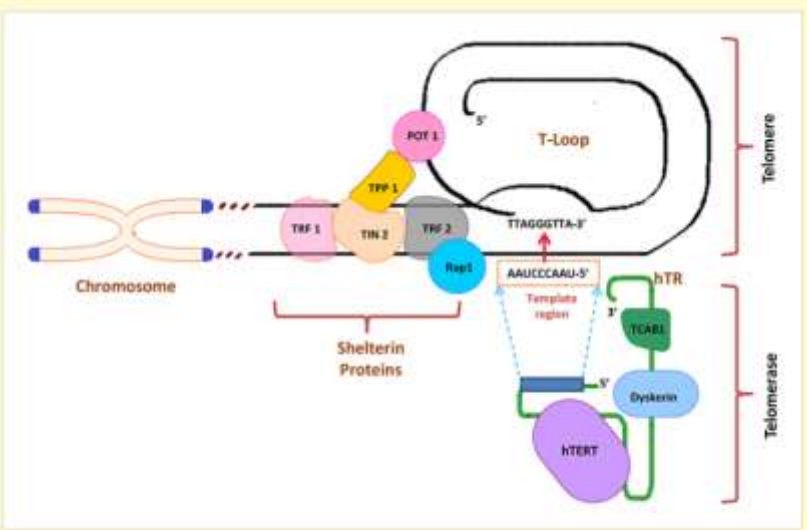

Figure 4.
DNA damage response pathway.

Figure 1.21

Among the DNA-binding proteins, TRF1 has DNA remodeling activity [5, 22] and also shown to promote efficient replication of telomeres [23, 24]. On the contrary, TRF2 engages in chromosome end protection by inducing topological changes in telomeric DNA [25], T-loop assembly [26, 27] and by suppression of ATM dependent DDR and NHEJ (Figure 4) [28, 29]. Besides that, TRF2 plays a critical role in chromatin assembly, which was demonstrated by the observation that overexpression of TRF2 resulted in aberrant nucleosome spacing and decreased abundance of the core histones H3 and H4 at chromosome ends [30]. TRF2 lacking cells are reported to be growth arrested because of up-regulation of p53 and also show other

hallmarks of ATM signaling, including the phosphorylation of ATM and Chk2 [31, 32]. Among the two DDR, the ATM kinase pathway at telomeres is repressed by TRF2 subunit, whereas POT1 is responsible for protection of telomere by suppression of ATR (ATM Rad3-related protein)-dependant DDR pathways [28, 33].

The high affinity of POT1 for single-stranded telomeric DNA makes it a G-strand binding component displaced from the T-loop and forms a closed configuration locking in the structure (Figure 2). Earlier report models suggest that POT1 and TPP1 compete with telomerase for access to the overhang [33]. Contrarily, direct interaction between TPP1 and telomerase bolsters telomerase processivity [34, 35] whereas increased loading of POT1 along the overhang block telomerase accessibility to the 3′-OH substrate. The role of RAP1 is obscure and its function has recently been elucidated. The presence of RAP1 at telomeres appears as a backup mechanism to prevent NHEJ when topology-mediated telomere protection is impaired [36]. In case of mutation in TRF2 which wraps the DNA, RAP1 has been implicated in the inhibition of NHEJ [37, 38].

Thus physically taken together, the shelterin complex and G-overhang of telomere are the protective cap that have an immensely complex role in convergence of end protection and telomere length maintenance mechanisms.

4. Telomerase activity

With each cell division, telomere length is reduced by ~50 to 200 bp [39] primarily because the lagging strand of DNA synthesis is unable to replicate the extreme 3′ end of the chromosome which is denoted as end replication problem [40, 41]. When telomeres become sufficiently short, cells enter an irreversible growth arrest called cellular senescence. In most eukaryotes, telomeres are stabilized, and the shortening telomeric DNA is replenished, by the action of the RNP reverse transcriptase telomerase. Progressive telomere loss has been experimentally demonstrated using non-immortalized cells in culture that lack detectable telomerase [42, 43].

In cells with active telomerase, such as cancer cells, the telomere length is continually being built up and shortened in a regulated way that maintains telomere length homeostasis and retains telomere functionality. Shortening of telomeres occur due to nucleolytic degradation and incomplete DNA replication. On the contrary, lengthening is primarily accomplished by the action of a specialized reverse transcriptase called telomerase [44] and occasionally by

homologous recombination (HR) [45]. Telomerase uses the 3′ G-rich strand of a chromosome as primer to elongate chromosome end by reverse-transcribing the template region of its tightly associated RNA moiety and coordinative action with the DNA replication machinery [44, 46]. For lengthening activity, telomerase requires not only hTERT catalytic subunit and RNA template (hTR) but also other factors [47, 48].

The 3′ half of the hTR resembling the box H/ACA family of small nucleolar RNAs (snoRNAs) [49, 50] is essential for proper 3′-end processing, stability and nucleolar targeting in vivo [44]. The 5′ end of hTR not only acts as template for the telomere extension at chromosome ends [5, 51] but also serves as a pseudoknot that is likely to be important for telomerase function (5, 49). A 6 bp U-rich sequence at the 5′ end of hTR also interacts directly with hnRNPs C1 and C2 (Figure 3) [52]. Even though hTR is highly expressed in all tissues regardless of telomerase activity [53], in cancer cells hTR is generally expressed fivefold higher than normal cells [54]. However, the expression (mRNA) of the telomeric catalytic component hTERT which is closely associated with telomerase activity is estimated to be less than one to five copies per cell [54]. hTERT is generally repressed in normal cells and up-regulated in immortal cells, suggesting that hTERT is the primary determinant for the enzyme activity.

Figure 1.22: teloemarase complex

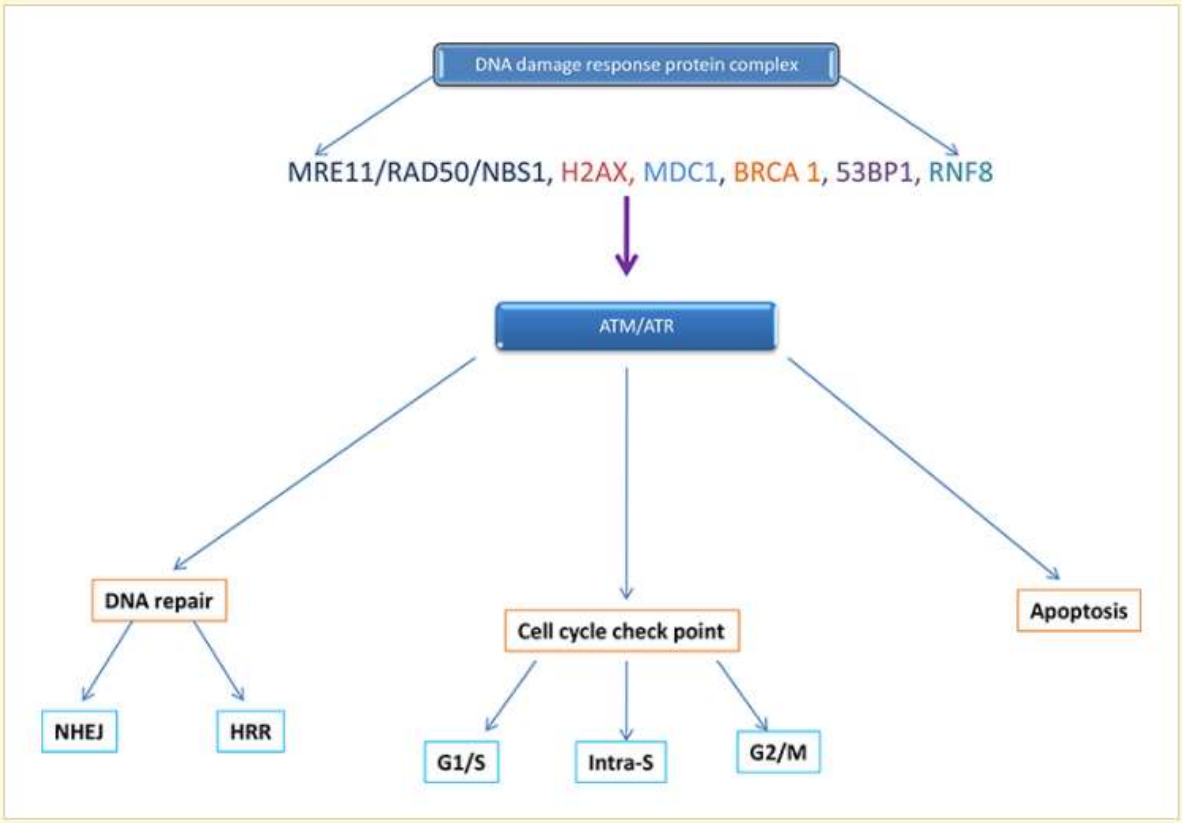

Figure 5.

Telomerase complex.

It has been suggested that in addition to telomere elongation another aspect of telomerase RNP function is to allow even short telomeres to remain functional, which in the absence of telomerase would have caused cells to stop dividing or led to telomere–telomere fusions [55]. In other words, telomerase permits cell proliferation by stabilizing short telomeres that would be unstable in the absence of functional telomerase. In recent years, evidence has accumulated that telomerase, and in particular its catalytic subunit TERT, is involved in various non-telomere-related functions such as regulation of gene expression, growth factors and cell proliferation [56–61]. It has been reported that the telomerase has a role in modulation of Wnt/β-catenin pathway [60]. TERT has been demonstrated to bind to TBE-containing promoter elements, the specific chromatin sites of Wnt/β-catenin target genes, forming a part of the β-catenin transcriptional complex, which was facilitated by interaction with BRG1. These data endorsed the precipitous role for telomerase as a transcriptional modulator of Wnt/β-catenin signaling pathway involved in progenitor cell regulation.

In addition, various groups have shown that TERT shuttles from the nucleus and translocates to mitochondria upon exogenous stress [62–67]. Singhapol and his coworkers have demonstrated that mitochondrial telomerase localization specifically decreases mitochondrial ROS generation and cellular oxidative stress after induction of exogenous stress generated by H2O2 or irradiation in cancer cells and might thereby prevent damage to nuclear DNA [68]. Thus the presence of telomerase not only maintains telomere length imparting immortality but also play multifarious role in tumorigenesis via non-telomere-dependent mechanism which demonstrated the imperative ubiquity of telomerase in cancer cells.

5. Skewed expression of telomerase

Telomerase, the RNA-dependent DNA polymerase by preventing the shortening of telomeric DNA sequences, accouters unlimited proliferation. As per the telomere hypothesis of cancer cell immortalization, telomere shortening limits the life span of telomerase-negative normal cells, whereas telomerase activation in cancer cells extends their life span [4]. In normal human cells, telomerase activity is quenched during embryonic differentiation [69]. On the contrary in some tissues, like male germ cells, activated lymphocytes, and certain types of stem cell populations, the telomerase activity is induced [15, 70]. Owing to its diverse activity, the telomerase [71] which was established to be absent in most of the normal human somatic cells is recorded to be expressed in more than 90% of cancerous cells and in vitro-immortalized cells [15, 70]. A study showed that while most of the glioma tissues possess increased telomerase activity, only few (10%) anaplastic astrocytomas are reported to be telomerase positive [72–74]. In contrast to most cancerous cells, the telomerase expression is present in only 50% of glioblastoma and retinoblastoma samples, and activity is even rarely found in meningiomas and astrocytomas [75, 76].

Induction of telomerase activity in primary human keratinocytes and mammary epithelial cells has been attributed to the effect of human papillomavirus 16 E6 protein [77]. Similarly, during the menstrual cycle involving the proliferation of endometrial cells, telomerase activity is detected in normal human endometrium [78, 79]. These reports emphasis that telomerase might be the reason for tumorigenesis in hormone-dependent cancers.

It has been suggested that up-regulated expression of telomerase is contributed by the increased copy number of hTERT which was demonstrated by the report that while hTERT protein expression was strongly positive in tumor cells, the expression of hTERT in non-neoplastic mucosal cells as well as stromal elements (except lymphocytes) was weak or negative [80]. In

most cases, hTERT expression is closely correlated not only with telomerase activity but also with cancer initiation and progression. In head and neck squamous cell carcinoma and human glioma cell lines, there was decrease in telomerase activity which has been correlated with overexpression of p53, E2F, p16, p21, and p15 individually [81, 82]. In malignant and nonmalignant human hematopoietic cell lines, primary leukemic cells, and normal T lymphocytes, IFN-α is reported to inhibit telomerase activity by suppressing hTERT transcription [83]. In addition to growth and differentiation-related regulation, telomerase activity is subject to regulation by other external and intracellular factors such as UV irradiation [84]. The telomerase having influence over several signaling pathways that determine cell proliferative or death responses when overexpressed might abrogate anti-proliferative or cell death signals. Thus cancer cells with high levels of telomerase might gain a selective growth advantage.

6. Telomerase as biomarker of cancer

Advent of latest cancer biomarkers has increased opportunities for improving cancer diagnostics by enhancing the quickness of detection and efficacy of treatment. In relation to the practice of new therapeutic interventions, proficient biomarkers are helpful in detection and prediction of remission or relapse of cancer at both gross and molecular levels. Telomerase activity is a hallmark of most cancer biopsies, but not generally detected in premalignant lesions and in normal tissue samples except germ cells and hematopoietic stem cells. Thus telomerase activity can be a promising biomarker for diagnosis of malignancies and a target for chemotherapy or gene therapy. Extent of telomerase activity in tumor tissues may be prognostic indicators of patient outcome. Thus, at the present time telomerase is being studied in anticipation of clinical usage. Many clinical trials for telomerase assay in cancer diagnosis are under trial. Fresh or fresh-frozen biopsies, fluids, and secretions are subject for these trials.

Other components of telomerase enzyme complex have also been utilized as biomarkers for telomerase activity. The expression of the RNA subunit of the telomerase complex (hTR) is also regarded as a diagnostic marker [85]. But the expression of hTR does not always correlate with telomerase protein expression in that particular cell type. hTR can be constitutively expressed in certain cell types in which even telomerase activity is not present [86]. Apart from this, mutation in genes of telomerase and associated proteins are considered as a diagnostic and prognostic marker for many genetic abnormalities collectively termed as telomeropathies. Early-onset melanoma tumor syndrome with multiple co-morbid cancers can be predicted from

telomerase gene promoter mutation analysis. In this disorder, the mutation in promoter of telomerase gene introduces an erythroblast transformation-specific transcription factor-binding site, resulting in approximately twofold up-regulation of telomerase [87].

Introduction of telomeric repeat amplification protocol (TRAP) assay has facilitated the detection of telomerase activity in tumor biopsy samples as well as cell lines [88]. Specificity of telomerase activity in malignant phenotype further enforces the reliability of this assay. The most important advantage of TRAP assay is its low detectable limit. TRAP assay has allowed the analysis of minimal tissue samples, such as fine-needle aspirates of the breast and thyroid, cervical smears, oral washings, and urine [89, 90]. Telomerase also has been used to detect circulating tumor cells also [85]. Newly emerged technique, droplet digital TRAP assay can detect telomerase activity even in a single cell [91]. However, the positive ratios of detection of telomerase vary in sedimented cells obtained from secretion, washing, brushing samples, etc. Electrochemical telomerase assay (ECTA) is another newly emerged technique to detect telomerase activity in biological samples [92]. It is comparatively simple and rapid PCR-free method. ECTA consists of a TS primer-immobilized electrode and ferrocenyl naphthalene diimide derivative as a tetraplex binder. This method has shown a high efficiency of telomerase detection in oral cancer biopsies [93]. Taken in account of all these reports, telomerase and its functionality can be utilized as a promising diagnostic and prognostic method in cancer.

7. Telomeres in prognosis

Better understanding of telomere structure and its dynamics focused the research on telomeres as biomarkers for several diseases especially in early detection and prognosis of cancers. A reduced telomere length in human hematopoietic tumors predicts a reduced survival time in patients suffering from myeloid leucaemia [94], chronic lymphocytic leucaemia [95], and myelodysplastic syndromes [96]. Although telomere length in solid tumors is suggested as a potential prognostic marker, patient survival rates vary with different cancer types. For example, a short telomere length in prostate cancer correlates with short disease-free interval and shorter overall survival time [97]. Analysis of telomere length of blood cells is also considered as predictive markers for pulmonary and esophageal neoplasia as well as of lymphoma in humans [98]. It has been suggested that the reduced TL in these patients reflects the effects of increased oxidative stress which correlates with cancer risk. Advent of latest technologies to measure relative and absolute telomere lengths has paved the way to use telomere length as diagnostic and prognostic markers. Telomere restriction fragment assay,

qFISH, flow FISH, qPCR assay, single telomere length analysis (STELA), and dot-blot telomere assay are the currently available assay methods for telomere length [99].

8. Telomerase as drug target

elomerase enzyme has recently emerged as an attractive target for cancer as it is a crucial factor required for the tumor immortalization of a subset of cells, including cancer stem cells. Studies have shown that 80–85% of the tumor cells express telomerase, whereas somatic cells lack the expression of telomerase [1]. In the present scenario, the major concern about the chemotherapeutic approaches is the specificity of action and side effects of drugs on normal cells. Difference in telomere length and cell kinetics between normal and cancerous cells shows that targeting telomerase is an effective system to target cancer cells specifically [100]. Although telomerase is not considered as an oncogene, the expression of telomerase is the major reason for the transformation of a normal cell to cancer cell [80]. Compared to most other cancer targets, telomerase antagonists are advantageous due to the wide expression of this enzyme in cancer types [1]. Telomerase also possesses extra telomeric functions which are very crucial for tumor survival and homeostasis [101]. Studies have shown that telomerase-based cancer therapies are less likely to develop resistance against the drugs compared to drugs which target growth factor receptors or signal-transducing enzymes in cancer cells [2]. This ensures that cancer drugs based on telomerase inhibition are non-cytotoxic anticancer approach and have a broad therapeutic value.

9. Conclusion

Maintenance of telomere length in cancer cells is a critical factor in imparting the ability to undergo uncontrolled multiplication and thus immortality to the cells. It is imperative to discern the factors involved in telomere length preservation. Understanding the influence of telomerase and other factors in sustaining telomere length in cancer cells paves way for perceiving the theranostic role of telomere and telomerase in cancer treatment.

How do physicians determine cancer staging?

There are a number of different staging methods used for cancers and the specific staging criteria varies among cancer types. According to the NCI, the common elements considered in most staging systems are as follows:

- Site of the primary tumor
- Tumor size and number of tumors
- Lymph node involvement (spread of cancer into lymph nodes)
- Cell type and **tumor grade** (how closely the cancer cells resemble normal tissue cells)
- The presence or absence of metastasis

However, there are two main methods that form the basis for the more specific or individual cancer type staging. The TMN staging is used for most solid tumors while the Roman numeral or stage grouping method is used by some clinicians and researchers on almost all cancer types.

The TNM system is based on the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of distant metastasis (M). A number is added to each letter to indicate the size or extent of the primary tumor and the extent of cancer spread (higher number means bigger tumor or more spread).

The following is how the NCI describes the TNM staging system:

1. **Primary tumor (T)**
    - TX - Primary tumor cannot be evaluated
    - T0 - No evidence of primary tumor
    - Tis - **Carcinoma in situ** (CIS; abnormal cells are present but have not spread to neighboring tissue; although not cancer, CIS may become cancer and is sometimes called pre-invasive cancer)
    - T1, T2, T3, T4 - Size and/or extent of the primary tumor
2. **Regional lymph nodes (N)**
    - NX - Regional lymph nodes cannot be evaluated
    - N0 - No regional lymph node involvement
    - N1, N2, N3 - Involvement of regional lymph nodes (number of lymph nodes and/or extent of spread)

3. **Distant metastasis (M)**
    - MX - Distant metastasis cannot be evaluated (some clinicians do not ever use this designation)
    - M0 - No distant metastasis
    - M1 - Distant metastasis is present

Consequently, a person's cancer could be listed as T1N2M0, meaning it is a small tumor (T1), but has spread to some regional lymph nodes (N2), and has no distant metastasis (M0).

Table 1.9:The Roman numeral or stage grouping method is described by the NCI as follows:

Stage	**Definition**
Stage 0	Carcinoma in situ.
Stage I	Higher numbers indicate more extensive disease: Larger tumor size and/or spread of the cancer beyond the organ in which it first developed to nearby lymph nodes and/or organs adjacent to the location of the primary tumor
Stage II	
Stage III	
Stage IV	The cancer has spread to another organ(s).

As mentioned above, variations of these staging methods exist. For example, some cancer registries use surveillance, epidemiology, and end results program (SEER) termed summary staging. SEER groups cancer cases into five main categories:

- **In situ**: Abnormal cells are present only in the layer of cells in which they developed.
- **Localized**: Cancer is limited to the organ in which it began, without evidence of spread.
- **Regional**: Cancer has spread beyond the primary site to nearby lymph nodes or organs and tissues.
- **Distant**: Cancer has spread from the primary site to distant organs or distant lymph nodes.
- **Unknown**: There is not enough information to determine the stage.

Staging of cancer is important; it helps the physician to decide on the most effective therapeutic protocols, provides a basis for estimating the prognosis (outcome) for the patient, and provides a system to communicate the patient's condition to other health professionals that become involved with the patients' care.

What are cancer treatment options?

- The cancer treatment is based on the type of cancer and the stage of the cancer. In some people, diagnosis and treatment may occur at the same time if the cancer is entirely surgically removed when the surgeon removes the tissue for biopsy.

Although patients may receive a unique sequenced treatment, or protocol, for their cancer, most treatments have one or more of the following components: surgery, chemotherapy, radiation therapy, or combination treatments (a combination of two or all three treatments).

Individuals obtain variations of these treatments for cancer. Patients with cancers that cannot be cured (completely removed) by surgery usually will get combination therapy, the composition determined by the cancer type and stage.

Palliative therapy (medical care or treatment used to reduce disease symptoms but unable to cure the patient) utilizes the same treatments described above. It is done with the intent to extend and improve the quality of life of the terminally ill cancer patient. There are many other palliative treatments to reduce symptoms such as pain medications and antinausea medications.

Are there home remedies or alternative treatments for cancer?

There are many claims on the Internet and in publications about substances that treat cancer (for example, broccoli, grapes, **ginseng**, soybeans, **green tea**, aloe vera, and **lycopene** and treatments like **acupuncture**, **vitamins**, and **dietary supplements**). Almost every physician suggests that a balanced **diet** and good **nutrition** will help an individual combat cancer. Although some of these treatments may help reduce symptoms, there is no good evidence they can cure any cancers. Patients are strongly recommended to discuss any home remedies or alternative treatments with their cancer doctors before beginning any of these.

What is the prognosis for cancer?

The prognosis (outcome) for cancer patients may range from excellent to poor. The prognosis is directly related to both the type and stage of the cancer. For example, many **skin cancers** can be completely cured by removing the **skin cancer** tissue; similarly, even a patient with a large tumor may be cured after surgery and other treatments like chemotherapy (note that a cure is often defined by many clinicians as a five-year period with no reoccurrence of the cancer). However, as the cancer type either is or becomes aggressive, with spread to lymph nodes or is metastatic to other organs, the prognosis decreases. For example, cancers that have higher numbers in their staging (for example, stage III or T3N2M1; see staging section above) have a worse prognosis than those with low (or 0) numbers. As the staging numbers increase, the prognosis worsens and the survival rate decreases.

This article offers a general introduction to cancers, consequently the details -- such as life expectancy for each cancer -- cannot be covered. However, cancers in general have a decreasing life expectancy as the stage of the cancer increases. Depending on the type of the cancer, as the prognosis decreases, so does life expectancy. On the positive side, cancers that are treated and do not recur (no remissions) within a five-year period in general suggest that the patient will have a normal life expectancy. Some patients will be cured, and a few others may get recurrent cancer. Unfortunately, there are no guarantees.

There are many complications that may occur with cancer; many are specific to the cancer type and stage and are too numerous to list here. However, some general complications that may occur with both cancer and its treatment protocols are listed below:

- Fatigue (both due to cancer and its treatments)
- **Anemia** (both)
- Loss of appetite (both)
- **Insomnia** (both)
- **Hair loss** (treatments mainly)
- **Nausea** (both)
- **Lymphedema** (both)
- Pain (both)
- Immune system **depression** (both)

Is it possible to prevent cancer?

Most experts are convinced that many cancers can either be prevented or the risk of developing cancers can be markedly reduced. Some of the **cancer prevention** methods are simple; others are relatively extreme, depending on an individual's view.

Cancer **prevention**, by avoiding its potential causes, is the simplest method. First on most clinicians and researchers list is to stop (or better, never start) **smoking** tobacco. Avoiding excess sunlight (by decreasing exposure or applying **sunscreen**) and many of the chemicals and toxins are excellent ways to avoid cancers. Avoiding contact with certain viruses and other pathogens also are likely to prevent some cancers. People who have to work close to cancer-causing agents (chemical workers, X-ray technicians, ionizing radiation researchers, asbestos workers) should follow all safety precautions and minimize any exposure to such compounds. Although the FDA and the CDC suggests that there is no scientific evidence that definitively says cell phones cause cancer, other agencies call for more research or indicate the risk is very low. Individuals who are concerned can limit exposure to cell phones by using an earpiece and simply make as few cell phone calls as possible.

There are two **vaccines** currently approved by the U.S. Food and Drug Administration (FDA) to prevent specific types of cancer. **Vaccines** against the **hepatitis B** virus, which is considered a cause of some liver cancers, and **vaccines** against human papillomavirus (**HPV**) types 16 and 18 are available. According to the NCI, these viruses are responsible for about 70% of cervical cancers. These virus also plays a role in cancers arising in the head and neck, as well as cancers in the anal region, and probably in others. Today, vaccination against HPV is recommended in teenagers and young adults of both sexes. The HPV virus is so common that by the age of 50,

half or more people have evidence of being exposed to it. Sipuleucel-T is a new **vaccine** approved by the FDA to help treat advanced prostate cancer. Although vaccine does not cure prostate cancer, it has been shown to help extend the lifespan of individuals with advanced prostate cancer.

People with a genetic predisposition to develop certain cancers and others with a history of cancers in their genetically linked relatives currently cannot change their genetic makeup. However, some individuals who have a high possibility of developing genetically linked cancer have taken actions to prevent cancer development. For example, some young women who have had many family members develop breast cancer have elected to have their breast tissue removed even if they have no symptoms or signs of cancer development to reduce or eliminate the possibility they will develop breast cancer. Some doctors consider this as an extreme measure to prevent cancer while others do not.

Screening tests and studies for cancer are meant to help detect a cancer at an early stage when the cancer is more likely to be potentially cured with treatment. Such screening studies are breast exams, testicular exams, colon-rectal exams (**colonoscopy**), **mammography**, certain blood tests, prostate exams, urine tests and others. People who have any suspicion that they may have cancer should discuss their concerns with their doctor as soon as possible. Screening recommendations have been the subject of numerous conflicting reports in recent years. Screening may not be cost effective for many groups of patients or lead to unnecessary further invasive tests, but individual patients' unique circumstances should always be considered by doctors in making recommendations about ordering or not ordering screening tests.

Where can people find more information about cancer?

There are many ways a person can find more information about cancer, but if they have any immediate concerns about having cancer, their first source of information should be their doctor. In addition to the references listed at the end of this article, the following is a list of information sources that are well recognized as authorities for cancer information by most clinicians:

- American Cancer Society (**http://www.cancer.org/Cancer/index**)
- National Cancer Institute (**http://www.cancer.gov/**)

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DEPARTMENT OF BIOTECHNOLOGY

UNIT – II –CANCER BIOLOGY- SBB1605

https://www.cancer.org/cancer/cancer-causes/general-info/known-and-probable-human-carcinogens.html

Known and Probable Human Carcinogens

In general, the American Cancer Society does not determine if something causes cancer (that is, if it is a carcinogen). Instead, we rely on the determinations of other respected agencies, such as the International Agency for Research on Cancer (IARC) and the US National Toxicology Program (NTP).

- The IARC and NTP act independently. Many known or suspected carcinogens appear on both organization's lists; however, **if a substance or exposure is only on one agency's list, this it does not necessarily mean there is a controversy**, as one agency may not have evaluated it.
- These lists are alphabetical, but **many of the substances and exposures here can go by different names.** This can make it hard to find a particular substance on one or both of these lists.
- **These lists include only those agents that have been evaluated by the agencies.** These agencies tend to focus on substances and exposures most likely to cause cancer, but there are many others that have not been fully studied yet.
- **These lists include agents that have been classified as known and probable human carcinogens. The lists do not include substances that have been classified as possible carcinogens, for which the evidence is not as strong.** These lists also do not include substances evaluated as "not classifiable as to its carcinogenicity in humans."
- **Most of the agents on the lists have been linked only with certain kinds of cancer, not all cancer types.** See each agency's website for more details about the substances and exposures on their lists.
- **The lists describe the level of evidence that something can cause cancer, not how likely it is that something will cause cancer in any person (or how much it might raise your risk)**. For example, IARC considers there to be strong evidence that both tobacco smoking and eating processed meat can cause cancer, so both are listed as "carcinogenic to humans." But smoking is much more likely to cause cancer than eating processed meat, even though both are in the same category.
- **Carcinogens do not cause cancer at all times, under all circumstances.** In other words, a carcinogen does not always cause cancer in every person, every time there is any kind of exposure. Some may only be carcinogenic if a person is exposed in a certain way (for example, swallowing it as opposed to touching it). Some may only cause

cancer in people who have a certain genetic makeup. Some of these agents may lead to cancer after only a very small exposure, while others might require intense exposure over many years. Again, refer to the agencies' reports for specifics.

- **Even if a substance or exposure is known or suspected to cause cancer, this does not necessarily mean that it can or should be avoided at all costs.** For example, sunlight is a major source of ultraviolet (UV) rays, which are a known cause of skin cancer, but it's not practical (or advisable) to completely avoid the sun.
- **These lists also include many commonly used medicines, particularly some hormones and drugs used to treat cancer.** For example, tamoxifen increases the risk of certain kinds of uterine cancer, but it can be very useful in treating some breast cancers, which may be more important for some women. If you have questions about a medicine that appears on one of these lists, be sure to ask your doctor.

Known human carcinogens

International Agency for Research on Cancer https://monographs.iarc.fr/cards_page/publications-monographs/.

- Acetaldehyde (from consuming alcoholic beverages)
- Acheson process, occupational exposure associated with
- Acid mists, strong inorganic
- Aflatoxins
- Alcoholic beverages
- Aluminum production
- 4-Aminobiphenyl
- Areca nut
- Aristolochic acid (and plants containing it)
- Arsenic and inorganic arsenic compounds
- Asbestos (all forms) and mineral substances (such as talc or vermiculite) that contain asbestos
- Auramine production
- Azathioprine
- Benzene
- Benzidine and dyes metabolized to benzidine
- Benzo[a]pyrene

- Beryllium and beryllium compounds
- Betel quid, with or without tobacco
- Bis(chloromethyl)ether and chloromethyl methyl ether (technical-grade)
- Busulfan
- 1,3-Butadiene
- Cadmium and cadmium compounds
- Chlorambucil
- Chlornaphazine
- Chromium (VI) compounds
- Clonorchis sinensis (infection with), also known as the Chinese liver fluke
- Coal, indoor emissions from household combustion
- Coal gasification
- Coal-tar distillation
- Coal-tar pitch
- Coke production
- Cyclophosphamide
- Cyclosporine (ciclosporin)
- 1,2-Dichloropropane
- Diethylstilbestrol (DES)
- Engine exhaust, diesel
- Epstein-Barr virus (EBV) (infection with)
- Erionite
- Estrogen-only menopausal therapy
- Estrogen-progestogen menopausal therapy (combined)
- Estrogen-progestogen oral contraceptives (combined) (Note: There is also convincing evidence in humans that these agents confer a protective effect against cancer in the endometrium and ovary)
- Ethanol in alcoholic beverages
- Ethylene oxide
- Etoposide

- Etoposide in combination with cisplatin and bleomycin
- Fission products, including strontium-90
- Fluoro-edenite fibrous amphibole
- Formaldehyde
- Haematite mining (underground)
- Helicobacter pylori (infection with)
- Hepatitis B virus (chronic infection with)
- Hepatitis C virus (chronic infection with)
- Human immunodeficiency virus type 1 (HIV-1) (infection with)
- Human papilloma virus (HPV) types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 (infection with) (Note: The HPV types that have been classified as carcinogenic to humans can differ by an order of magnitude in risk for cervical cancer)
- Human T-cell lymphotropic virus type I (HTLV-1) (infection with)
- Ionizing radiation (all types)
- Iron and steel founding (workplace exposure)
- Isopropyl alcohol manufacture using strong acids
- Kaposi sarcoma herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8) (infection with)
- Leather dust
- Lindane
- Magenta production
- Melphalan
- Methoxsalen (8-methoxypsoralen) plus ultraviolet A radiation, also known as PUVA
- Methyl-CCNU
- 4,4'-Methylenebis(chloroaniline) (MOCA)
- Mineral oils, untreated or mildly treated
- MOPP and other combined chemotherapy including alkylating agents
- 2-Naphthylamine
- Neutron radiation
- Nickel compounds

- N'-Nitrosonornicotine (NNN) and 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK)
- Opisthorchis viverrini (infection with), also known as the Southeast Asian liver fluke
- Outdoor air pollution (and the particulate matter in it)
- Painter (workplace exposure as a)
- 3,4,5,3',4'-Pentachlorobiphenyl (PCB-126)
- 2,3,4,7,8-Pentachlorodibenzofuran
- Pentachlorophenol
- Phenacetin (and mixtures containing it)
- Phosphorus-32, as phosphate
- Plutonium
- Polychlorinated biphenyls (PCBs), dioxin-like, with a Toxicity Equivalency Factor according to WHO (PCBs 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189)
- Processed meat (consumption of)
- Radioiodines, including iodine-131
- Radionuclides, alpha-particle-emitting, internally deposited (Note: Specific radionuclides for which there is sufficient evidence for carcinogenicity to humans are also listed individually as Group 1 agents)
- Radionuclides, beta-particle-emitting, internally deposited (Note: Specific radionuclides for which there is sufficient evidence for carcinogenicity to humans are also listed individually as Group 1 agents)
- Radium-224 and its decay products
- Radium-226 and its decay products
- Radium-228 and its decay products
- Radon-222 and its decay products
- Rubber manufacturing industry
- Salted fish (Chinese-style)
- Schistosoma haematobium (infection with)
- Semustine (methyl-CCNU)
- Shale oils
- Silica dust, crystalline, in the form of quartz or cristobalite

- Solar radiation
- Soot (as found in workplace exposure of chimney sweeps)
- Sulfur mustard
- Talc containing asbestiform fibres
- Tamoxifen (Note: There is also conclusive evidence that tamoxifen reduces the risk of contralateral breast cancer in breast cancer patients)
- 2,3,7,8-Tetrachlorodibenzo-para-dioxin (TCDD); "dioxin"
- Thiotepa
- Thorium-232 and its decay products
- Tobacco, smokeless
- Tobacco smoke, secondhand
- Tobacco smoking
- ortho-Toluidine
- Treosulfan
- Trichloroethylene
- Ultraviolet (UV) radiation, including UVA, UVB, and UVC rays
- Ultraviolet-emitting tanning devices
- Vinyl chloride
- Welding fumes
- Wood dust
- X- and Gamma-radiation

National Toxicology Program 14th Report on Carcinogens "Known to be human carcinogens"

https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html.

- Aflatoxins
- Alcoholic beverage consumption
- 4-Aminobiphenyl
- Analgesic mixtures containing phenacetin
- Aristolochic acids

- Arsenic and inorganic arsenic compounds
- Asbestos
- Azathioprine
- Benzene
- Benzidine
- Beryllium and beryllium compounds
- Bis(chloromethyl) ether and technical-grade chloromethyl methyl ether
- 1,3-Butadiene
- 1,4-Butanediol dimethylsulfonate (also known as busulfan)
- Cadmium and cadmium compounds
- Chlorambucil
- 1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (MeCCNU)
- Chromium hexavalent compounds
- Coal tar pitches
- Coal tars
- Coke oven emissions
- Cyclophosphamide
- Cyclosporin A
- Diethylstilbestrol (DES)
- Dyes metabolized to benzidine
- Epstein-Barr virus (EBV)
- Erionite
- Estrogens, steroidal
- Ethylene oxide
- Formaldehyde
- Hepatitis B virus
- Hepatitis C virus
- Human immunodeficiency virus type 1 (HIV-1)
- Human papilloma viruses (HPVs): some genital-mucosal types
- Human T-cell lymphotropic virus type 1 (HTLV-1)

- Kaposi sarcoma-associated herpesvirus (KSHV) (also known as human herpesvirus 8, or HHV-8)
- Melphalan
- Merkel cell polyomavirus (MCV)
- Methoxsalen with ultraviolet A therapy (PUVA)
- Mineral oils (untreated and mildly treated)
- Mustard gas
- 2-Naphthylamine
- Neutrons
- Nickel compounds
- Radon
- Silica, crystalline (respirable size)
- Solar radiation
- Soots
- Strong inorganic acid mists containing sulfuric acid
- Sunlamps or sunbeds, exposure to
- Tamoxifen
- 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD); "dioxin"
- Thiotepa
- Thorium dioxide
- Tobacco smoke, environmental
- Tobacco, smokeless
- Tobacco smoking
- o-Toluidine
- Trichloroethylene (TCE)
- Ultraviolet (UV) radiation, broad spectrum
- Vinyl chloride
- Wood dust
- X-radiation and gamma radiation

Probable carcinogens

International Agency for Research on Cancer
Group 2A: Probably carcinogenic to humans

https://monographs.iarc.fr/cards_page/publications-monographs/.

- Acrylamide
- Adriamycin (doxorubicin)
- Androgenic (anabolic) steroids
- Art glass, glass containers, and press ware (manufacture of)
- Azacitidine
- Biomass fuel (primarily wood), emissions from household combustion
- Bitumens, occupational exposure to oxidized bitumens and their emissions during roofing
- Bischloroethyl nitrosourea (BCNU), also known as carmustine
- Captafol
- Carbon electrode manufacture
- Chloral
- Chloral hydrate
- Chloramphenicol
- alpha-Chlorinated toluenes (benzal chloride, benzotrichloride, benzyl chloride) and benzoyl chloride (combined exposures)
- 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)
- 4-Chloro-ortho-toluidine
- Chlorozotocin
- Cisplatin
- Cobalt metal with tungsten carbide
- Creosotes
- Cyclopenta[cd]pyrene
- DDT (4,4'-Dichlorodiphenyltrichloroethane)
- Diazinon
- Dibenz[a,j]acridine

- Dibenz[a,h]anthracene
- Dibenzo[a,l]pyrene
- Dichloromethane (methylene chloride)
- Dieldrin, and aldrin metabolized to dieldrin
- Diethyl sulfate
- Dimethylcarbamoyl chloride
- N,N-Dimethylformamide
- 1,2-Dimethylhydrazine
- Dimethyl sulfate
- Epichlorohydrin
- Ethyl carbamate (urethane)
- Ethylene dibromide
- N-Ethyl-N-nitrosourea
- Frying, emissions from high-temperature
- Glycidol
- Glyphosate
- Hairdresser or barber (workplace exposure as)
- Human papillomavirus (HPV) type 68 (infection with)
- Hydrazine
- Indium phosphide
- IQ (2-Amino-3-methylimidazo[4,5-f]quinoline)
- Lead compounds, inorganic
- Malaria (caused by infection with Plasmodium falciparum)
- Malathion
- 2-Mercaptobenzothiazole
- Merkel cell polyomavirus (MCV)
- 5-Methoxypsoralen
- Methyl methanesulfonate
- N-Methyl-N´-nitro-N-nitrosoguanidine (MNNG)
- N-Methyl-N-nitrosourea

- Nitrate or nitrite (ingested) under conditions that result in endogenous nitrosation
- 6-Nitrochrysene
- Nitrogen mustard
- 1-Nitropyrene
- N-Nitrosodiethylamine
- N-Nitrosodimethylamine
- 2-Nitrotoluene
- Non-arsenical insecticides (workplace exposures in spraying and application of)
- Petroleum refining (workplace exposures in)
- Pioglitazone
- Polybrominated biphenyls (PBBs)
- Procarbazine hydrochloride
- 1,3-Propane sultone
- Red meat (consumption of)
- Shiftwork that involves circadian disruption
- Silicon carbide whiskers
- Styrene
- Styrene-7,8-oxide
- Teniposide
- Tetrabromobisphenol A
- 3,3′,4,4′-Tetrachloroazobenzene
- Tetrachloroethylene (perchloroethylene)
- Tetrafluoroethylene
- 1,2,3-Trichloropropane
- Tris(2,3-dibromopropyl) phosphate
- Very hot beverages (above 65 degrees Celsius)
- Vinyl bromide (Note: For practical purposes, vinyl bromide should be considered to act similarly to the human carcinogen vinyl chloride.)
- Vinyl fluoride (Note: For practical purposes, vinyl fluoride should be considered to act similarly to the human carcinogen vinyl chloride.)

National Toxicology Program 14th Report on Carcinogens "Reasonably anticipated to be human carcinogens"

https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html.

- Acetaldehyde
- 2-Acetylaminofluorene
- Acrylamide
- Acrylonitrile
- Adriamycin (doxorubicin hydrochloride)
- 2-Aminoanthraquinone
- o-Aminoazotoluene
- 1-Amino-2,4-dibromoanthraquinone
- 1-Amino-2-methylanthraquinone
- 2-Amino-3,4-dimethylimidazo[4,5-f]quinoline (MeIQ)
- 2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx)
- 2-Amino-3-methylimidazo[4,5-f]quinoline (IQ)
- 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)
- Amitrole
- o-Anisidine and its hydrochloride
- Azacitidine (5-Azacytidine, 5-AzaC)
- Basic Red 9 Monohydrochloride
- Benz[a]anthracene
- Benzo[b]fluoranthene
- Benzo[j]fluoranthene
- Benzo[k]fluoranthene
- Benzo[a]pyrene
- Benzotrichloride
- 2, 2-bis-(bromoethyl)-1,3-propanediol (technical grade)
- Bromodichloromethane
- 1-Bromopropane

- Butylated hydroxyanisole (BHA)
- Captafol
- Carbon tetrachloride
- Ceramic fibers (respirable size)
- Chloramphenicol
- Chlorendic acid
- Chlorinated paraffins (C_{12}, 60% chlorine)
- Chloroform
- 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea
- Bis(chloroethyl) nitrosourea
- 3-Chloro-2-methylpropene
- 4-Chloro-o-phenylenediamine
- Chloroprene
- p-Chloro-o-toluidine and p-chloro-o-toluidine hydrochloride
- Chlorozotocin
- Cisplatin
- Cobalt and cobalt compounds that release cobalt ions in vivo
- Cobalt-tungsten carbide: powders and hard metals
- p-Cresidine
- Cumene
- Cupferron
- Dacarbazine
- Danthron (1,8-dihydroxyanthraquinone)
- 2,4-Diaminoanisole sulfate
- 2,4-Diaminotoluene
- Diazoaminobenzene
- Dibenz[a,h]acridine
- Dibenz[a,j]acridine
- Dibenz[a,h]anthracene
- 7H-Dibenzo[c,g]carbazole

- Dibenzo[a,e]pyrene
- Dibenzo[a,h]pyrene
- Dibenzo[a,i]pyrene
- Dibenzo[a,l]pyrene
- 1,2-Dibromo-3-chloropropane
- 1,2-Dibromoethane (ethylene dibromide)
- 2,3-Dibromo-1-propanol
- 1,4-Dichlorobenzene
- 3,3'-Dichlorobenzidine and 3,3'-dichlorobenzidine dihydrochloride
- Dichlorodiphenyltrichloroethane (DDT)
- 1,2-Dichloroethane (ethylene dichloride)
- Dichloromethane (methylene chloride)
- 1,3-Dichloropropene (technical grade)
- Diepoxybutane
- Diesel exhaust particulates
- Di(2-ethylyhexyl) phthalate
- Diethyl sulfate
- Diglycidyl resorcinol ether
- 3,3'-Dimethoxybenzidine
- 4-Dimethylaminoazobenzene
- 3,3'-Dimethylbenzidine
- Dimethylcarbamoyl chloride
- 1,1-Dimethylhydrazine
- Dimethyl sulfate
- Dimethylvinyl chloride
- 1,6-Dinitropyrene
- 1,8-Dinitropyrene
- 1,4-Dioxane
- Disperse blue 1
- Dyes metabolized to 3,3'-dimethoxybenzidine

- Dyes metabolized to 3,3'-dimethylbenzidine
- Epichlorohydrin
- Ethylene thiourea
- Ethyl methanesulfonate
- Furan
- Glass wool fibers (inhalable)
- Glycidol
- Hexachlorobenzene
- Hexachloroethane
- Hexamethylphosphoramide
- Hydrazine and hydrazine sulfate
- Hydrazobenzene
- Indeno[1,2,3-cd]pyrene
- Iron dextran complex
- Isoprene
- Kepone (chlordecone)
- Lead and lead compounds
- Lindane, hexachlorocyclohexane (technical grade), and other hexachlorocyclohexane isomers
- 2-Methylaziridine (propyleneimine)
- 5-Methylchrysene
- 4,4'-Methylenebis(2-chloroaniline)
- 4-4'-Methylenebis(N,N-dimethyl)benzenamine
- 4,4'-Methylenedianiline and its dihydrochloride salt
- Methyleugenol
- Methyl methanesulfonate
- N-methyl-N'-nitro-N-nitrosoguanidine
- Metronidazole
- Michler’s ketone [4,4'-(dimethylamino) benzophenone]
- Mirex

- Naphthalene
- Nickel, metallic
- Nitrilotriacetic acid
- o-Nitroanisole
- Nitrobenzene
- 6-Nitrochrysene
- Nitrofen (2,4-dichlorophenyl-p-nitrophenyl ether)
- Nitrogen mustard hydrochloride
- Nitromethane
- 2-Nitropropane
- 1-Nitropyrene
- 4-Nitropyrene
- N-nitrosodi-n-butylamine
- N-nitrosodiethanolamine
- N-nitrosodiethylamine
- N-nitrosodimethylamine
- N-nitrosodi-n-propylamine
- N-nitroso-N-ethylurea
- 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone
- N-nitroso-N-methylurea
- N-nitrosomethylvinylamine
- N-nitrosomorpholine
- N-nitrosonornicotine
- N-nitrosopiperidine
- N-nitrosopyrrolidine
- N-nitrososarcosine
- o-Nitrotoluene
- Norethisterone
- Ochratoxin A
- 4,4'-Oxydianiline

- Oxymetholone
- Pentachlorophenol and by-products of its synthesis
- Phenacetin
- Phenazopyridine hydrochloride
- Phenolphthalein
- Phenoxybenzamine hydrochloride
- Phenytoin and phenytoin sodium
- Polybrominated biphenyls (PBBs)
- Polychlorinated biphenyls (PCBs)
- Polycyclic aromatic hydrocarbons (PAHs)
- Procarbazine and its hydrochloride
- Progesterone
- 1,3-Propane sultone
- beta-Propiolactone
- Propylene oxide
- Propylthiouracil
- Reserpine
- Riddelliine
- Safrole
- Selenium sulfide
- Streptozotocin
- Styrene
- Styrene-7,8-oxide
- Sulfallate
- Tetrachloroethylene (perchloroethylene)
- Tetrafluoroethylene
- Tetranitromethane
- Thioacetamide
- 4,4'-Thiodianaline
- Thiourea

- Toluene diisocyanates
- Toxaphene
- 2,4,6-Trichlorophenol
- 1,2,3-Trichloropropane
- Tris(2,3-dibromopropyl) phosphate
- Ultraviolet A (UVA) radiation
- Ultraviolet B (UVB) radiation
- Ultraviolet C (UVC) radiation
- Urethane
- Vinyl bromide
- 4-Vinyl-1-cyclohexene diepoxide
- Vinyl fluoride

Cancer Staging

Stage refers to the extent of your cancer, such as how large the tumor is, and if it has spread. Knowing the stage of your cancer helps your doctor:

Understand how serious your cancer is and your chances of survival

Plan the best treatment for you

Identify clinical trials that may be treatment options for you

A cancer is always referred to by the stage it was given at diagnosis, even if it gets worse or spreads. New information about how a cancer has changed over time gets added on to the original stage. So, the stage doesn't change, even though the cancer might.

How Stage Is Determined

To learn the stage of your disease, your doctor may order x-rays, lab tests, and other tests or procedures. See the section on Diagnosis to learn more about these tests.

Systems that Describe Stage

There are many staging systems. Some, such as the TNM staging system, are used for many types of cancer. Others are specific to a particular type of cancer. Most staging systems include information about:

Where the tumor is located in the body

The cell type (such as, adenocarcinoma or squamous cell carcinoma)

The size of the tumor

Whether the cancer has spread to nearby lymph nodes

Whether the cancer has spread to a different part of the body

Tumor grade, which refers to how abnormal the cancer cells look and how likely the tumor is to grow and spread

The TNM Staging System

The TNM system is the most widely used cancer staging system. Most hospitals and medical centers use the TNM system as their main method for cancer reporting. You are likely to see your cancer described by this staging system in your pathology report, unless you have a cancer for which a different staging system is used. Examples of cancers with different staging systems include brain and spinal cord tumors and blood cancers.

In the TNM system:

The T refers to the size and extent of the main tumor. The main tumor is usually called the primary tumor.

The N refers to the the number of nearby lymph nodes that have cancer.

The M refers to whether the cancer has metastasized. This means that the cancer has spread from the primary tumor to other parts of the body.

When your cancer is described by the TNM system, there will be numbers after each letter that give more details about the cancer—for example, T1N0MX or T3N1M0. The following explains what the letters and numbers mean:

Primary tumor (T)

TX: Main tumor cannot be measured.

T0: Main tumor cannot be found.

T1, T2, T3, T4: Refers to the size and/or extent of the main tumor. The higher the number after the T, the larger the tumor or the more it has grown into nearby tissues. T's may be further divided to provide more detail, such as T3a and T3b.

Regional lymph nodes (N)

NX: Cancer in nearby lymph nodes cannot be measured.

N0: There is no cancer in nearby lymph nodes.

N1, N2, N3: Refers to the number and location of lymph nodes that contain cancer. The higher the number after the N, the more lymph nodes that contain cancer.

Distant metastasis (M)

MX: Metastasis cannot be measured.

M0: Cancer has not spread to other parts of the body.

M1: Cancer has spread to other parts of the body.

Other Ways to Describe Stage

The TNM system helps describe cancer in great detail. But, for many cancers, the TNM combinations are grouped into five less-detailed stages. When talking about your cancer, your doctor or nurse may describe it as one of these stages:

Stage	What it means
Stage 0	Abnormal cells are present but have not spread to nearby tissue. Also called carcinoma in situ, or CIS. CIS is not cancer, but it may become cancer.
Stage I, Stage II, and Stage III	Cancer is present. The higher the number, the larger the cancer tumor and the more it has spread into nearby tissues.
Stage IV	The cancer has spread to distant parts of the body.

Another staging system that is used for all types of cancer groups the cancer into one of five main categories. This staging system is more often used by cancer registries than by doctors. But, you may still hear your doctor or nurse describe your cancer in one of the following ways:

In situ—Abnormal cells are present but have not spread to nearby tissue.

Localized—Cancer is limited to the place where it started, with no sign that it has spread.

Regional—Cancer has spread to nearby lymph nodes, tissues, or organs.

Distant—Cancer has spread to distant parts of the body.

Unknown—There is not enough information to figure out the stage.

To learn more about staging for your type of cancer, see the PDQ® cancer treatment summaries for adult and childhood cancers.

https://www.cancer.gov/about-cancer/diagnosis-staging/staging

PATHOLOGY REPORTS

WHAT IS A PATHOLOGY REPORT?

A pathology report is a document that contains the diagnosis determined by examining cells and tissues under a microscope. The report may also contain information about the size, shape, and appearance of a specimen as it looks to the naked eye. This information is known as the gross description.

A pathologist is a doctor who does this examination and writes the pathology report. Pathology reports play an important role in cancer diagnosis and staging (describing the extent of cancer within the body, especially whether it has spread), which helps determine treatment options.

HOW IS TISSUE OBTAINED FOR EXAMINATION BY THE PATHOLOGIST?

In most cases, a doctor needs to do a biopsy or surgery to remove cells or tissues for examination under a microscope.

Some common ways a biopsy can be done are as follows:

A needle is used to withdraw tissue or fluid.

An endoscope (a thin, lighted tube) is used to look at areas inside the body and remove cells or tissues.

Surgery is used to remove part of the tumor or the entire tumor. If the entire tumor is removed, typically some normal tissue around the tumor is also removed.

Tissue removed during a biopsy is sent to a pathology laboratory, where it is sliced into thin sections for viewing under a microscope. This is known as histologic (tissue) examination and is usually the best way to tell if cancer is present. The pathologist may also examine cytologic (cell) material. Cytologic material is present in urine, cerebrospinal fluid (the fluid around the brain and spinal cord), sputum (mucus from the lungs), peritoneal (abdominal cavity) fluid, pleural (chest cavity) fluid, cervical/vaginal smears, and in fluid removed during a biopsy.

HOW IS TISSUE PROCESSED AFTER A BIOPSY OR SURGERY? WHAT IS A FROZEN SECTION?

The tissue removed during a biopsy or surgery must be cut into thin sections, placed on slides, and stained with dyes before it can be examined under a microscope. Two methods are used to make the tissue firm enough to cut into thin sections: frozen sections and paraffin-embedded (permanent) sections. All tissue samples are prepared as permanent sections, but sometimes frozen sections are also prepared.

Permanent sections are prepared by placing the tissue in fixative (usually formalin) to preserve the tissue, processing it through additional solutions, and then placing it in paraffin wax. After the wax has hardened, the tissue is cut into very thin slices, which are placed on slides and stained. The process normally takes several days. A permanent section provides the best quality

for examination by the pathologist and produces more accurate results than a frozen section (1).

Frozen sections are prepared by freezing and slicing the tissue sample. They can be done in about 15 to 20 minutes while the patient is in the operating room (1). Frozen sections are done when an immediate answer is needed; for example, to determine whether the tissue is cancerous so as to guide the surgeon during the course of an operation.

HOW LONG AFTER THE TISSUE SAMPLE IS TAKEN WILL THE PATHOLOGY REPORT BE READY?

The pathologist sends a pathology report to the doctor within 10 days after the biopsy or surgery is performed. Pathology reports are written in technical medical language. Patients may want to ask their doctors to give them a copy of the pathology report and to explain the report to them. Patients also may wish to keep a copy of their pathology report in their own records (1).

WHAT INFORMATION DOES A PATHOLOGY REPORT USUALLY INCLUDE?

The pathology report may include the following information (1):

Patient information: Name, birth date, biopsy date

Gross description: Color, weight, and size of tissue as seen by the naked eye

Microscopic description: How the sample looks under the microscope and how it compares with normal cells

Diagnosis: Type of tumor/cancer and grade (how abnormal the cells look under the microscope and how quickly the tumor is likely to grow and spread)

Tumor size: Measured in centimeters

Tumor margins: There are three possible findings when the biopsy sample is the entire tumor:

Positive margins mean that cancer cells are found at the edge of the material removed

Negative, not involved, clear, or free margins mean that no cancer cells are found at the outer edge

Close margins are neither negative nor positive

Other information: Usually notes about samples that have been sent for other tests or a second opinion

Pathologist's signature and name and address of the laboratory

WHAT MIGHT THE PATHOLOGY REPORT SAY ABOUT THE PHYSICAL AND CHEMICAL CHARACTERISTICS OF THE TISSUE?

After identifying the tissue as cancerous, the pathologist may perform additional tests to get more information about the tumor that cannot be determined by looking at the tissue with routine stains, such as hematoxylin and eosin (also known as H&E), under a microscope (2). The pathology report will include the results of these tests. For example, the pathology report may include information obtained from immunochemical stains (IHC). IHC uses antibodies to identify specific antigens on the surface of cancer cells. IHC can often be used to:

Determine where the cancer started

Distinguish among different cancer types, such as carcinoma, melanoma, and lymphoma

Help diagnose and classify leukemias and lymphomas (3)

The pathology report may also include the results of flow cytometry. Flow cytometry is a method of measuring properties of cells in a sample, including the number of cells, percentage of live cells, cell size and shape, and presence of tumor markers on the cell surface. Tumor markers are substances produced by tumor cells or by other cells in the body in response to cancer or certain noncancerous conditions.) Flow cytometry can be used in the diagnosis, classification, and management of cancers such as acute leukemia, chronic lymphoproliferative disorders, and non-Hodgkin lymphoma (2).

Finally, the pathology report may include the results of molecular diagnostic and cytogenetic studies. Such studies investigate the presence or absence of malignant cells, and genetic or molecular abnormalities in specimens.

WHAT INFORMATION ABOUT THE GENETICS OF THE CELLS MIGHT BE INCLUDED IN THE PATHOLOGY REPORT?

Cytogenetics uses tissue culture and specialized techniques to provide genetic information about cells, particularly genetic alterations. Some genetic alterations are markers or indicators of a specific cancer. For example, the Philadelphia chromosome is associated with chronic myelogenous leukemia (CML). Some alterations can provide information about prognosis, which helps the doctor make treatment recommendations (3). Some tests that might be performed on a tissue sample include:

Fluorescence in situ hybridization (FISH): Determines the positions of particular genes. It can be used to identify chromosomal abnormalities and to map genes.

Polymerase chain reaction (PCR): A method of making many copies of particular DNA sequences of relevance to the diagnosis.

Real-time PCR or quantitative PCR: A method of measuring how many copies of a particular DNA sequence are present.

Reverse-transcriptase polymerase chain reaction (RT-PCR): A method of making many copies of a specific RNA sequence.

Southern blot hybridization: Detects specific DNA fragments.

Western blot hybridization: Identifies and analyzes proteins or peptides.

CAN INDIVIDUALS GET A SECOND OPINION ABOUT THEIR PATHOLOGY RESULTS?

Although most cancers can be easily diagnosed, sometimes patients or their doctors may want to get a second opinion about the pathology results (1). Patients interested in getting a second opinion should talk with their doctor. They will need to obtain the slides and/or paraffin block from the pathologist who examined the sample or from the hospital where the biopsy or surgery was done.

Many institutions provide second opinions on pathology specimens. NCI-designated cancer centers or academic institutions are reasonable places to consider. Patients should contact the facility in advance to determine if this service is available, the cost, and shipping instructions.

What research is being done to improve the diagnosis of cancer?

NCI, a component of the National Institutes of Health, is sponsoring clinical trials that are designed to improve the accuracy and specificity of cancer diagnoses. Before any new method can be recommended for general use, doctors conduct clinical trials to find out whether it is safe and effective.

People interested in taking part in a clinical trial should talk with their doctor. Information about clinical trials is available from NCI's Cancer Information Service (CIS) at 1–800–4–CANCER and on NCI's clinical trials page.

(https://www.cancer.gov/about-cancer/diagnosis-staging/diagnosis)

HOW CANCER IS DIAGNOSED

X-rays use low doses of radiation to create pictures of the inside of your body.

If you have a symptom or a screening test result that suggests cancer, your doctor must find out whether it is due to cancer or some other cause. The doctor may start by asking about your personal and family medical history and do a physical exam. The doctor also may order lab tests, imaging tests (scans), or other tests or procedures. You may also need a biopsy, which is often the only way to tell for sure if you have cancer.

This page covers tests that are often used to help diagnose cancer. Depending on the symptoms you have, you may have other tests, too. To learn more about how specific cancers are diagnosed, see the PDQ® cancer treatment summaries for adult and childhood cancers. These summaries include detailed information about and pictures of diagnostic tests and procedures for each specific type of cancer.

LAB TESTS

High or low levels of certain substances in your body can be a sign of cancer. So, lab tests of your blood, urine, or other body fluids that measure these substances can help doctors make a diagnosis. However, abnormal lab results are not a sure sign of cancer. Learn more about laboratory tests and how they are used to diagnose cancer.

Some lab tests involve testing blood or tissue samples for tumor markers. Tumor markers are substances that are produced by cancer cells or by other cells of the body in response to cancer. Most tumor markers are made by normal cells and cancer cells but are produced at much higher levels by cancer cells. Learn more about tumor markers and how they are used to diagnose cancer.

IMAGING TESTS

Imaging tests create pictures of areas inside your body that help the doctor see whether a tumor is present. These pictures can be made in several ways:

CT SCAN

A CT scan uses an x-ray machine linked to a computer to take a series of pictures of your organs from different angles. These pictures are used to create detailed 3-D images of the inside of your body.

Sometimes, you may receive a dye or other contrast material before you have the scan. You might swallow the dye, or it may be given by a needle into a vein. Contrast material helps make the pictures easier to read by highlighting certain areas in the body.

During the CT scan, you will lie still on a table that slides into a donut-shaped scanner. The CT machine moves around you, taking pictures. Learn more about CT scans and how they are used to diagnose cancer.

MRI

An MRI uses a powerful magnet and radio waves to take pictures of your body in slices. These slices are used to create detailed images of the inside of your body, which can show the difference between healthy and unhealthy tissue.

When you have an MRI, you lie still on a table that is pushed into a long, round chamber. The MRI machine makes loud thumping noises and rhythmic beats.

Sometimes, you might have a special dye injected into your vein before or during your MRI exam. This dye, called a contrast agent, can make tumors show up brighter in the pictures.

NUCLEAR SCAN

A nuclear scan uses radioactive material to take pictures of the inside of the body. This type of scan may also be called radionuclide scan.

Before this scan, you receive an injection of a small amount of radioactive material, which is sometimes called a tracer. It flows through your bloodstream and collects in certain bones or organs.

During the scan, you lie still on a table while a machine called a scanner detects and measures the radioactivity in your body, creating pictures of bones or organs on a computer screen or on film.

After the scan, the radioactive material in your body will lose its radioactivity over time. It may also leave your body through your urine or stool.

BONE SCAN

Bone scans are a type of nuclear scan that check for abnormal areas or damage in the bones. They may be used to diagnose bone cancer or cancer that has spread to the bones (also called metastatic bone tumors).

Before this test, a very small amount of radioactive material is injected into your vein. As it travels through the blood, the material collects in abnormal areas in the bone. Areas where the material collects show up on pictures taken by a special scanner. These areas are called “hot spots.”

PET SCAN

A PET scan is a type of nuclear scan that makes detailed 3-D pictures of areas inside your body where glucose is taken up. Because cancer cells often take up more glucose than healthy cells, the pictures can be used to find cancer in the body.

Before the scan, you receive an injection of a tracer called radioactive glucose. During the scan, you will lie still on a table that moves back and forth through a scanner.

ULTRASOUND

An ultrasound exam uses high-energy sound waves that people cannot hear. The sound waves echo off tissues inside your body. A computer uses these echoes to create pictures of areas inside your body. This picture is called a sonogram.

During an ultrasound exam, you will lie on a table while a tech slowly moves a device called a transducer on the skin over the part of the body that is being examined. The transducer is covered with a warm gel that makes it easier to glide over the skin.

X-rays

X-rays use low doses of radiation to create pictures inside your body. An x-ray tech will put you in position and direct the x-ray beam to the correct part of your body. While the images are taken, you will need to stay very still and may need to hold your breath for a second or two.

Biopsy

In most cases, doctors need to do a biopsy to diagnose cancer. A biopsy is a procedure in which the doctor removes a sample of tissue. A pathologist looks at the tissue under a microscope and runs other tests to see if the tissue is cancer. The pathologist describes the findings in a pathology report, which contains details about your diagnosis. Pathology reports play an important role in diagnosing cancer and helping decide treatment options. Learn more about pathology reports and the type of information they contain.

The biopsy sample may be obtained in several ways:

With a needle: The doctor uses a needle to withdraw tissue or fluid. This method is used for bone marrow aspirations, spinal taps, and some breast, prostate, and liver biopsies.

With endoscopy: The doctor uses a thin, lighted tube called an endoscope to examine areas inside the body. Endoscopes go into natural body openings, such as the mouth or anus. If the doctor sees abnormal tissue during the exam, he will remove the abnormal tissue along with some of the surrounding normal tissue through the endoscope.

Examples of endoscopy exams include:

Colonoscopy, which is an exam of the colon and rectum. In this type of exam, an endoscope goes through the anus, allowing the doctor to examine the rectum and colon. If the doctor sees polyps, she will remove them and send them to a lab for testing.

Bronchoscopy, which is an exam of the trachea, bronchi, and lungs. In this type of exam, an endoscope goes through the mouth or nose and down the throat.

With surgery: A surgeon removes an area of abnormal cells during an operation. Surgery may be excisional or incisional.

In an **excisional biopsy**, the surgeon removes the entire area of abnormal cells. Often some of the normal tissue around these cells is also removed.

In an **incisional biopsy**, the surgeon removes just part of the abnormal area.

Some biopsies may require a sedative or anesthesia.

Sedatives are medicine that help you relax and stay very still or sleep during a biopsy.

Anesthesia keeps you from feeling pain. It refers to drugs or other substances that cause you to lose feeling or awareness. There are three types of anesthesia:

Local anesthesia, which causes loss of feeling in one small area of the body

Regional anesthesia, which causes loss of feeling in a part of the body, such as an arm or leg

General anesthesia, which causes loss of feeling and a complete loss of awareness that seems like a very deep sleep

After Cancer Is Diagnosed

If the biopsy and other tests show that you have cancer, you may have more tests to help your doctor plan treatment. For instance, your doctor will need to figure out the stage of your cancer. For some cancers, knowing the grade of the tumor or risk group that you fall into are important for deciding on the best treatment. Your tumor may also be tested further for other tumor or genetic markers.

To learn more about other tests that may be used to plan treatment for your cancer, see the PDQ® cancer treatment summaries for adult and childhood cancers for your type of cancer.

https://www.cancer.org/treatment/understanding-your-diagnosis/tests/ct-scan-for-cancer.html

CT Scan for Cancer

Other names for this test: Computed tomography scan, CT scan, CAT scan, and spiral or helical CT

A CT scan can help doctors find cancer and show things like a tumor's shape and size. CT scans are most often an outpatient procedure. The scan is painless and takes about 10 to 30 minutes.

What does it show?

CT scans show a slice, or cross-section, of the body. The image shows your bones, organs, and soft tissues more clearly than standard x-rays.

CT scans can show a tumor's shape, size, and location. They can even show the blood vessels that feed the tumor – all without having to cut into the patient.

Doctors often use CT scans to help them guide a needle to remove a small piece of tissue. This is called a *CT-guided biopsy*. CT scans can also be used to guide needles into tumors for some types of cancer treatments, such as radiofrequency ablation (RFA), which uses heat to destroy a tumor.

By comparing CT scans done over time, doctors can see how a tumor is responding to treatment or find out if the cancer has come back after treatment.

How does it work?

In a way, CT scans are like standard x-ray tests. But an x-ray test aims a broad beam of radiation from only one angle. A CT scan uses a pencil-thin beam to create a series of pictures taken from different angles. The information from each angle is fed into a computer, which then creates a black and white picture that shows a slice of a certain area of the body – much like looking at a single slice from a loaf of bread.

Special contrast materials can be used to get a clearer picture. These can be swallowed as a liquid, put into a vein, or put into the intestines through the rectum as an enema.

By layering CT image slices on top of each other, the machine can create a 3-dimensional (3-D) view. The 3-D image can be rotated on a computer screen to look at different angles.

Doctors are now taking CT technology one step further in a technique called *virtual endoscopy*. They can look at the inside surfaces of organs such as the lungs (virtual bronchoscopy) or colon (virtual colonoscopy or CT colonography) without actually having to put scopes into the body. The 3-D CT images are arranged to create a black and white view on the computer screen. This looks a lot like it would if they were doing an actual endoscopy.

How do I get ready for the test?

CT scans are most often done on an outpatient basis, so you don't have to be in a hospital to get one.

Ask your doctor if you will get contrast dye as part of the CT scan. Before getting the dye, be sure to let your health care team know if you've ever had a reaction to contrast dye, seafood, or iodine in the past. This is important because reactions to these things may put you at risk for reacting to the contrast dye used in CT scans. If there's a risk that you might have an allergic reaction, you may be given a test dose of the contrast dye first. People who have had a severe reaction in the past may need to take drugs (usually a steroid, like prednisone) to help prevent another reaction. Sometimes these drugs need to be started the day before the scan.

In some cases, your doctor may tell you not to eat or drink overnight or for several hours before the test. Or you might need to use a laxative or an enema to clean out your bowel and remove material that could get in the way of seeing inside the belly and intestines.

What is it like having the test?

You may be asked to undress, put on a robe, and remove underwire bras, jewelry, piercings, or any other metal objects that may get in the way of the image. You may be asked remove dentures, hearing aids, hair clips, and so on, as they can affect the CT pictures.

A radiology technologist does the CT scan. Let the technologist know if you have a pacemaker, infusion port, or other implanted medical device. This will not keep you from getting a CT scan, but extra care can be taken if that area will be scanned.

The scanner is a large, doughnut-shaped machine. You lie on a thin, flat table that slides back and forth inside the hole in the middle of the scanner. As the table moves into the opening, an x-ray tube rotates within the scanner, sending out many tiny x-ray beams at precise angles. These beams quickly pass through your body and are detected on the other side of the scanner. You may hear buzzing and clicking as the scanner switches on and off.

You will be alone in the exam room during the CT scan, but the technologist will be able to see, hear, and talk to you at all times.

A CT is painless but you may find it uncomfortable to hold still in certain positions for minutes at a time. You may also be asked to hold your breath for a short time, since chest movement can affect the image.

During a CT head scan, your head may be held still in a special device. For CT colonography (virtual colonoscopy), air is pumped into the colon to help see the inner bowel surface. This can be uncomfortable.

Depending on the part of the body being studied, you may need to drink contrast liquid or get a contrast enema right before the test.

If you’re going to get contrast dye in a vein, an intravenous (IV) catheter might be put into a vein in your arm or hand. You’ll probably have a scan done, then get the contrast dye and have another scan done. When the contrast is given, you may get a feeling of warmth that spreads through your body. Some people say that this can feel like they “wet their pants.” This is only a feeling, and it goes away quickly. You might also get a bitter or metallic taste in your mouth.

How long does it take?

A CT scan can take anywhere from 10 to 30 minutes, depending on what part of the body is being scanned. It also depends on how much of your body the doctors want to look at and whether contrast dye is used. It often takes more time to get you into position and give the contrast dye than to take the pictures. After the test, you may be asked to wait while the pictures

are checked to make sure they are clear and show all of the body part. If not, more pictures may be needed.

What are the possible complications and side effects?

Some people react to the contrast dye. Possible reactions include:

- Rash
- Nausea
- Wheezing
- Shortness of breath
- Itching or facial swelling that can last up to an hour

These symptoms usually are mild and most often go away on their own. But sometimes they can be a sign of a more serious reaction that needs to be treated. Be sure to let your radiology technologist and your health care team know if you notice any changes after getting the contrast dye.

In rare cases, people can have a severe allergic reaction that causes low blood pressure or trouble breathing. This must be treated right away.

The IV contrast dye can also cause kidney problems. This is rare, and it's more common in someone whose kidneys already don't work well. If you need a scan with contrast dye, your doctor may first do a blood test to check your kidney function. You may also get extra fluids in an IV or medicines to help your kidneys get rid of the dye safely.

What else should I know about this test?

- Although a CT scan is sometimes described as a "slice" or a "cross-section," no cutting is involved.
- The amount of radiation you get during a CT scan is a good deal more than that with a standard x-ray.
- People who are very overweight may have trouble fitting into the CT scanner.
- Be sure to tell your doctor if you have any allergies or are sensitive to iodine, seafood, or contrast dyes.
- Tell your doctor if you could be pregnant or are breastfeeding.

- CT scans can cost up to 10 times as much as a standard x-ray. You may want to be sure your health insurance will cover this test before you have it.

https://www.cancer.org/treatment/understanding-your-diagnosis/tests/mri-for-cancer.html

MRI for Cancer

Other names for this test: magnetic resonance imaging, MRI, magnetic resonance, MR, and nuclear magnetic resonance (NMR) imaging

MRI helps doctors find cancer in the body and look for signs that it has spread. MRI also can help doctors plan cancer treatment, like surgery or radiation. MRI is painless and you don't have to do anything special to get ready for this test. But, it's very important to tell your doctor and the technologist (the person who does the test) if you have any metal in your body.

What does it show?

MRI creates cross-section pictures of your insides. But MRI uses strong magnets to make the images – not radiation. An MRI scan takes cross-sectional slices (views) from many angles, as if someone were looking at a slice of your body from the front, from the side, or from above your head. MRI creates pictures of soft tissue parts of the body that are sometimes hard to see using other imaging tests.

MRI is very good at finding and pinpointing some cancers. An MRI with contrast dye is the best way to see brain and spinal cord tumors. Using MRI, doctors can sometimes tell if a tumor is or isn't cancer.

MRI can also be used to look for signs that cancer may have metastasized (spread) from where it started to another part of the body.

MRI images can also help doctors plan treatment such as surgery or radiation therapy.

(A specific kind of MRI can be used to look inside the breast. Learn more about breast MRI.)

How does it work?

An MRI scanner is a long cylinder or tube that holds a large, very strong magnet. You lie on a table that slides into the tube, and the machine surrounds you with a powerful magnetic field. The machine uses a powerful magnetic force and a burst of radiofrequency waves to pick up

signals from the nuclei (centers) of hydrogen atoms in your body. A computer converts these signals them into a black and white picture.

Contrast materials can be put into the body through a vein to clearer images. Once absorbed by the body, the contrast speeds up the rate at which tissue responds to the magnetic and radio waves. The stronger signals give clearer pictures.

How do I get ready for the test?

MRI scans are most often done on an outpatient basis, so you don't have to be in a hospital to get one.

You don't usually need to follow a special diet or do anything to get ready for an MRI, but follow any instructions you are given.

If being in a small, enclosed space is a problem for you (you have claustrophobia), you might need to take medicine to help you relax while in the scanner. Sometimes talking with the technologist or a patient counselor, or seeing the MRI machine before the test can help. In some cases, you can arrange to have an *open MRI* which allows more space around your body (see the next section).

Sometimes a contrast material is used for MRI imaging. You may have to swallow the contrast, or you may have an intravenous (IV) catheter put in a vein in your arm so the contrast can be given into your bloodstream. The contrast material used for an MRI exam is called gadolinium. (This is not the same as the contrast dye used in CT scans.) Let your doctor and the technologist know if you have any kind of allergies or have had problems with any contrast used in imaging tests in the past.

If you have any of these implants, you should not even enter the MRI scanning area unless told to do so by a radiologist or technologist who knows you have:

- An implanted defibrillator or pacemaker
- Clips used on a brain aneurysm
- A cochlear (ear) implant
- Metal coils put inside blood vessels

Also be sure the technologist knows if you have other permanent metal objects, such as surgical clips, staples, screws, plates, or stents; artificial joints; metal fragments (shrapnel); tattoos or permanent makeup; artificial heart valves; implanted infusion ports; implanted nerve stimulators; and so on.

You may need to have an x-ray to check for metal objects if there's any doubt.

What is it like having the test?

You may be asked to undress and put on a gown or other clothes without zippers or metal. Be sure to remove any metal objects you can, like hair clips, jewelry, dental work, and body piercings. Before the scan, the technologist will ask you if you have any metal in your body.

You will lie down on a narrow, flat table. The technologist may use straps or pillows to make you comfortable and help keep you from moving. The table slides into a long, narrow cylinder. The part of your body that's being scanned will be in the center of the cylinder. The scanned part of your body may feel a little warm during the test, this is normal and nothing to worry about.

You'll be in the exam room alone, but you can talk to the technologist, who can see and hear you at all times.

The test is painless, but you have to lie inside the cylinder with its surface a few inches from your face. It's important to stay very still while the images are being made, which can take a few minutes at a time. You may be asked to hold your breath during certain parts of the test. Tell the technologist if you need to move or take a break.

The machine makes loud, thumping, clicking, and whirring noises, much like the sound of a washing machine, as the magnet switches on and off. You may be given earplugs or headphones with music to block noise out during the scan.

Special, open MRI machines that are less restrictive may be easier for some people. These machines replace the narrow cylinder with a larger ring. This design lessens the banging sound and the feeling of lying in an enclosed space. But the machine doesn't create as strong a magnetic field, and the pictures may not be as clear or detailed as they are with standard MRI. Sometimes, this can lead to getting rescanned on a standard MRI machine.

How long does it take?

MRI scans usually take between 45 and 60 minutes, but can sometimes take up to 2 hours. After the test, you may be asked to wait while the pictures are checked to make sure that they are clear and show all of the body part. If not, more pictures may be needed.

What are the possible complications?

People can be hurt in MRI machines if they take metal items into the room or if other people leave metal items in the room.

Some people become very uneasy and even panic when lying inside the MRI scanner.

Some people react to the contrast material. Such reactions can include:

- Nausea
- Pain at the needle site
- A headache that develops a few hours after the test is over
- Low blood pressure leading to a feeling of lightheadedness or faintness (this is rare)

Be sure to let your health care team know if you have any of these symptoms or notice any other changes after you get the contrast material.

Gadolinium, the contrast material used for MRI, can cause a special complication when it's given to patients on dialysis or who have severe kidney problems, so it's rarely given to these people. Your doctor will discuss this with you if you have severe kidney problems and need an MRI with contrast.

Small amounts of gadolinium can stay in the brain, bones, skin and other parts of your body for a long time (several months to years) after the test. It's not known if this might have any health effects, but so far, studies haven't found any harmful effects in patients with normal kidneys.

What else should I know about this test?

- MRI can cost a lot. You may want to be sure your health insurance will cover this test before you have it.

- People who are overweight may have trouble fitting into the MRI machine.
- The use of MRI during pregnancy has not been well studied. MRI is usually not done in the first 12 weeks of pregnancy unless there's a strong medical reason to use it.
- Do not bring credit cards or other items with magnetic scanning strips with you into the exam room – the magnet could wipe out the information stored on them.
- MRI does not expose you to radiation.

How do I get ready for the test?

The steps needed to prepare for a nuclear medicine scan depend on the type of test and the tissue that will be studied. Some scans require that you don't eat or drink for 2 to 12 hours before the test. For others, you may be asked to take a laxative or use an enema. Be sure your doctor or nurse knows everything you take, even over-the-counter drugs, vitamins, and herbs. You may need to avoid some medicines (prescription and over-the-counter) before the test. Your health care team will give you instructions.

Reactions to the radioactive material are very rare. Still, be sure to tell your doctor about any allergies and if you've had problems with nuclear medicine scans in the past.

You may get the radioactive material anywhere from a few minutes to many hours before the test. For example, in a bone scan, the tracer is put into a vein in your arm about 2 hours before the test begins. For gallium scans, the tracer is given a few days before the test.

What is it like having the test?

In most cases you will be given a tracer that sends out small doses of radiation. If it's put into your blood, a needle will be used to put it into a vein in your hand or arm.

Because of the special materials and equipment needed, these scans are usually done in the radiology or nuclear medicine department of a hospital. You might be able to wear your own clothing or you might be given a gown to wear during the test. You'll need to remove all jewelry or metal items that could interfere with the scans.

The scanner has a hole in the middle and looks like a large doughnut. You lie on a padded table which moves back and forth through the hole in the scanner. You will need to be very still while the scans are done. The technician may ask you to change positions to allow different views to be taken. The table may become uncomfortable after a while.

For a thyroid scan, you may sit in a chair that faces the scanner. The scanner is set up so that it's right in front of your neck and your chin rests on top of it. (The thyroid gland is in the front of the neck.)

To get a MUGA scan, you lie on a flat table and a large camera is positioned above your chest.

How long does it take?

A nuclear scan usually takes about 30 to 60 minutes, plus the waiting time after the radioactive material is given.

For **bone scans**, the material takes 2 to 3 hours to be absorbed. During this time, you'll stay in the radiology clinic and will be asked to drink a lot of water to help flush out any tracer that doesn't collect in the bones. The scan itself takes another hour or so.

PET scans take 20 to 30 minutes, but you must wait about an hour while the tracer collects in the organ being studied.

For a **thyroid scan**, you take the radioactive tracer as a liquid or pill about 24 hours before the scan. The scan takes less than 30 minutes.

MUGA scans can take up to 3 hours, depending on how many pictures are needed.

Gallium scans take several days between the injection and the actual scan. Sometimes people are scanned more than once after the injection. The scan takes 30 to 60 minutes.

Results of nuclear scans are usually available within a few days.

What are the possible complications?

For the most part, nuclear scans are safe tests. The doses of radiation are very small, and the radionuclides have a low risk of being toxic or causing an allergic reaction.

Some people may have pain or swelling at the site where the material is injected into a vein.

Rarely, some people will develop a fever or allergic reaction when given a monoclonal antibody.

What else should I know about these tests?

- The radiation exposure from a nuclear scan comes from the radionuclides used – the scanner itself does not put out radiation. The radioactive material in your body will naturally decay and lose its radioactivity over time. It may also leave your body through your urine or stool within a few hours or a few days. Talk to your health care team about whether you need to take precautions about having sex, or being close to children or pregnant women after these tests.
- You will be asked to drink a lot of water to flush out the radioactive material.
- To reduce the risk of being exposed to radioactive material in your urine after a scan, you should put the lid down and flush the toilet right after you use it.
- Nuclear scans are rarely recommended for pregnant women, so let your doctor know if you are or might be pregnant.
- If you are breastfeeding, be sure to tell the doctor ahead of time. You may need to pump breast milk and discard it until the radionuclide is gone from your system.

http://www.mayfieldclinic.com/

Overview

A single photon emission computed tomography (SPECT) scan is an imaging test that shows how blood flows to tissues and organs. It may be used to help diagnose seizures, stroke, stress fractures, infections, and tumors in the spine.

How does a SPECT scan work?

SPECT is a nuclear imaging scan that integrates computed tomography (CT) and a radioactive tracer. The tracer is what allows doctors to see how blood flows to tissues and organs.

Before the SPECT scan, a tracer is injected into your bloodstream. The tracer is radiolabeled, meaning it emits gamma rays that can be detected by the CT scanner. The computer collects the information emitted by the gamma rays and displays it on the CT cross-sections. These cross-sections can be added back together to form a 3D image of your brain.

The radioisotopes typically used in SPECT to label tracers are iodine-123, technetium-99m, xenon-133, thallium-201, and fluorine-18. These radioactive forms of natural elements will pass through your body and be detected by the scanner. Various drugs and other chemicals can be labeled with these isotopes.

The type of tracer used depends on what your doctor wants to measure. For example, if your doctor is looking at a tumor, he or she might use radiolabled glucose (FDG) and watch how it is metabolized by the tumor.

The test differs from a PET scan in that the tracer stays in your blood stream rather than being absorbed by surrounding tissues, thereby limiting the images to areas where blood flows. SPECT scans are cheaper and more readily available than higher resolution PET scans.

What does a SPECT scan show?

A SPECT scan is primarily used to view how blood flows through arteries and veins in the brain. Tests have shown that it might be more sensitive to brain injury than either MRI or CT scanning because it can detect reduced blood flow to injured sites.

SPECT scanning is also useful for presurgical evaluation of medically uncontrolled seizures (Fig. 1). The test can be performed between seizures (interictal) or during a seizure (ictal) to determine blood flow to areas where the seizures originate.

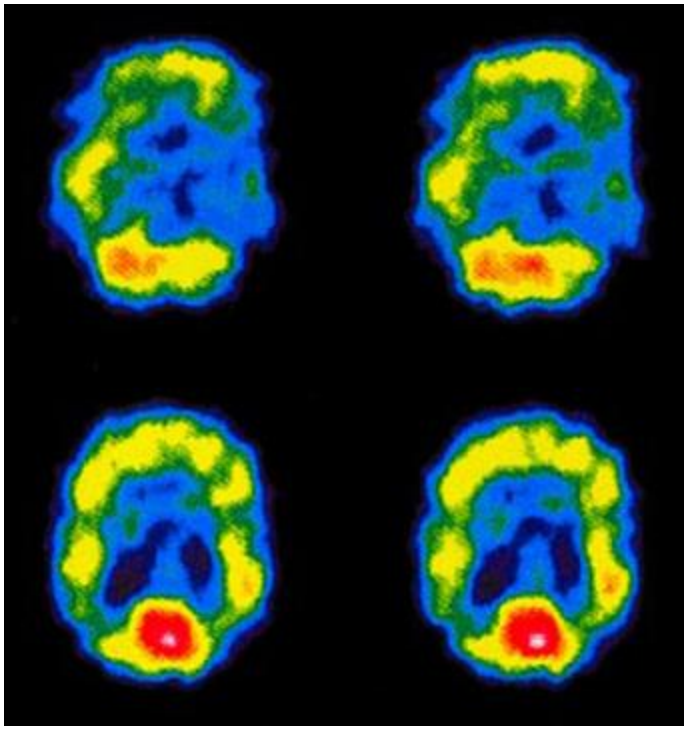

Figure 1. A SPECT scan of a patient with uncontrolled complex partial seizures. The temporal lobe on the left side of the brain shows less blood flow than the right, confirming for the surgeon the nonfunctioning area of the brain causing seizures.

This type of scanning is also useful in diagnosing stress fractures in the spine (spondylolysis), blood deprived (ischemic) areas of brain following a stroke, and tumors.

Who performs the test?

A specially trained nuclear medicine technologist will perform the test in the Nuclear Medicine department of the hospital, or at an outpatient imaging center.

How should I prepare for the test?

Wear comfortable clothing and be prepared to stay for 1 to 2 hours.

What happens during the test?

First, you will receive an injection of a small amount of radioactive tracer. You'll be asked to rest for about 10-20 minutes until the tracer reaches your brain. Next, you'll lie comfortably on a scanner table while a special camera rotates around your head. Be sure to remain as still as possible so that the machine can take accurate pictures.

Once the scan is complete, you can leave. Be sure to drink plenty of fluids to flush the tracer from your body.

What are the risks?

The tracer is radioactive, which means your body is exposed to radiation. This exposure is limited, however, because the radioactive chemicals have short half-lives. They breakdown quickly and are removed from the body through the kidneys.

The long-term risk of radiation exposure is usually worth the benefits of diagnosing serious medical conditions. Your exposure risk could vary, however, depending on how many CT or other scans you have had. If you have concerns about your cumulative radiation exposure, talk to your doctor.

Women who are pregnant or nursing should not undergo a SPECT scan.

Some people may have an allergic reaction to the tracer or the contrast agent.

How do I get the test results?

The nuclear medicine doctor will promptly review your images and communicate directly with your referring doctor, who in turn will discuss the results with you.

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Overview of Metastases

The majority of deaths (about 90%) associated with cancer are due to the metastasis of the original tumor cells to sites distant from the initial or primary tumor. Metastasis is the process by which cancer cells migrate throughout the body.

In order for cells to move through the body, they must first climb over/around neighboring cells. They do this by rearranging their cytoskeleton and attaching to the other cells and the extracellular matrix via proteins on the outside of their plasma membranes. By extending part of the cell forward and letting go at the back end, the cells can migrate forward. The cells can crawl until they hit a blockage which cannot be bypassed. Often this block is a thick layer of proteins and glycoproteins surrounding the tissues, called the basal lamina or basement membrane. In order to cross this layer, cancer cells secrete a mixture of digestive enzymes that degrade the proteins in the basal lamina and allow them to crawl through.

The proteins secreted by cancer cells contain a group of enzymes called matrix metalloproteases (MMP). These enzymes act as 'molecular scissors' to cut through the proteins that inhibit the movement of the migrating cancer cells. Once the cells have traversed the basal lamina, they can spread through the body in several ways. They can enter the bloodstream by squeezing between the cells that make up the blood vessels.

Once in the blood stream, the cells float through the circulatory system until they find a suitable location to settle and re-enter the tissues. The cells can then begin to grow in this new location, forming a new tumor.

The process of metastasis formation is **very inefficient** process but leads to the majority of deaths associated with cancer. This is because the number of cells that leave a tumor can be in the millions per day. Even if only a small fraction of the cells that leave a tumor are able to survive to form a new tumor, the large number of attempts means that a distant growth is likely to occur at some point

Migrating cancer cells can die from a variety of causes, including:

- Cells normally live tightly connected to their neighbors and the meshwork of proteins surrounding them. Detachment from the surface of other cells can lead to cell death (called anoikis 'an-oh-e-kus').
- Cancer cells are often quite large in comparison to the cells that normally live in the lymphatic system or blood system. When they travel through the vessels they can get damaged or stuck, leading to cell death.
- Cancer cells can be recognized and destroyed by cells of the immune system

Additionally, it is important to note that even if a cancer cell does not die, it does not mean that it will form a tumor. The cells may exist at locations far from the original tumor without multiplying enough to cause any problems.

Watch Emory Winship Cancer Institute Researcher Adam Marcus describe his research on cancer metastasis. Contains actual video of cancer cells moving.

Formation of Metastases

Colony Formation

A metastatic tumor cell must successfully "set up shop" in a new organ to form a secondary tumor, this process is termed colony formation. The metastatic cell must create favorable surroundings within a hostile foreign environment that will allow for their growth and survival. This appears to be the make or break step in metastasis. In an experimental model of metastatic melanoma, more than 80% of injected cancer cells survived in the circulation and exited to the liver. Of these, only 1 cell out of 40 formed micrometastases within 3 days, and of those only 1 cell in 100 formed macrometastases within 10 days. Creating a friendly environment appears to be a difficult process that limits a metastatic cell's ability to form a secondary tumor.[3]

Obstacles to Colony Formation

What makes colony formation such an inefficient step? The surrounding tissue (stroma) of the new organ will be very different from that of the original site and in most cases will be unfriendly to tumor cell survival. If the metastatic cell cannot change the new stroma into a more friendly environment, it will not successfully colonize the new site (for example, promote angiogenesis), and a secondary tumor will be unable to form.[4]In these cases the tumor cells are said to be dormant: they do not die, but they are incapable of growing. Aquisition of additional mutations often allow these dormant micrometastases to overcome the difficulties they face in new tissues and to successfully colonize it, forming a true metastatic tumor. [5]

Routes of Metastasis

There are three primary ways tumors can spread to distant organs:

1. Through the circulatory (blood) system (hematogenous)

2. Through the lymphatic system
3. Through the body wall into the abdominal and chest cavities (transcoelomic).

The circulatory system is the primary route of spread to distant organs, while lymphatic vessels provide a route to local lymph nodes, after which metastases often travel through the blood 4While the circulatory system appears to be the most common route, the extent of lymphatic versus hematogenous spread appears to depend on the origin and location of the primary tumor.6For example, bone and soft tissue tumors (sarcomas) spread primarily through the blood, while melanoma, breast, lung and gastrointestinal tumors spread through the lymphatic system.7Transcoelomic spread is fairly uncommon, and appears to be restricted to mesotheliomas and ovarian carcinomas.8

In order for tumor cells to gain access to lymphatic or blood vessels, tumors need to promote the growth of these vessels into and around the tumor. Growth of blood vessels is called angiogenesis, and growth of lymphatic vessels is lymphangiogenesis.

Learn more about angiogenesis

The Lymphatic System

The lymphatic system plays an important role in controlling the movement of fluid throughout the body. Specifically the lymphatic system controls the flow of lymph, a colorless fluid containing oxygen, proteins, sugar (glucose) and lymphocytes (cyte=cell). There are some similarities and differences between the (more well known) circulatory system and the lymphatic system.

Small lymphatic vessels merge into larger ones and these large vessels eventually empty into lymph nodes. Lymph nodes are kidney bean shaped tissues that are found in grape-like clusters in several locations around the body. Lymph nodes are sites of immune system activation and immune cell proliferation (growth). The fluid in this extensive network flows throughout the body, much like the blood supply. It is the movement of cancer cells into the lymphatic system, specifically the lymph nodes, that is used in the detection of metastatic disease. The staging of cancer is discussed in more detail in the Diagnosis and Detection section.

The Anatomic Model

In the anatomic model of metastsis, secondary tumors occur in the organs which they encounter first during their dissemination from the primary tumor. This scenario appears to occur in regional metastases, where tumor cells gain access to nearby tissue or lymph nodes through the blood or lymphatic circulation. 9For example, liver metastasis is a major occurrence in patients with colorectal cancer. In this case, the capillary bed of the liver is the first encountered by the tumor cells after leaving the colon, and the liver seems to provide a suitable environment for the growth of these secondary

tumors. [3]However, metastasis to distant organs occurs through a different mechanism (see next section).

The Seed and Soil Hypothesis

Early cancer researchers noticed a propensity for certain cancers to metastasize to the same organ. In 1889 Stephen Paget observed that patients with breast cancer often developed secondary tumors in the liver. He considered it unlikely that this occurrence was due primarily to accessibility of the liver by the blood supply, as other organs receiving equivalent blood supply rarely developed metastases. He instead developed the "Seed and Soil" hypothesis, in which certain tumor cells (the seeds) can only successfully colonize selective organs (the soil) that have suitable growth environments [10]

The current view of the Seed and Soil Hypothesis consists of three important concepts.

1. Primary tumors and their metastases consist of genetically diverse tumor and host cells (for more on the role of the host cells in cancer, see the section on *Tumor Microenvironment*).
2. Metastasis selects for cells that can succeed in all phases of the metastatic process. In essence, a successful metastatic cell must be a decathalete: good in all the events, and not just one or two.
3. Metastases generally develop in a site specific way. Because the microenvironments (the soil) of each organ is different, individual cancer cells may be able to colonize one specific organ.[9]

At the heart of the Seed and Soil hypothesis is the idea that successful metastasis depends on the interaction of the metastasizing tumor cells with the cells of the target organ (the stroma, or tumor microenvironment). Not only must tumor cells must be able to *produce* factors that alter the stromal cells in such a way as to better serve the survival and growth of the tumor, but the environment in which the cancer cell finds itself must be capable of *responding* to those signals. If the cancer cell finds itself in an inhospitable soil (i.e. it cannot subvert the stroma to serve its needs), successful metastsis will be impossible. [4]

Recent studies examining the profile of genes expressed in tumors that metastasis to specific organs have identified specific genetic signatures of these tumors. For example, genes that mediate the metastasis of breast cancer to bone are different than those that mediate metastasis to the lung. In essence, different sets of genes allow tumor cells to specifically interact with the stromal cells of the target organ. These findings may lead to therapeutic strategies to target the metastatic properties of tumors.[11]

How Metastases Form New Tumors

Barriers to Metastasis

In certain cases tumor cells invade a foreign tissue, but fail to colonize it; in effect, they remain dormant. What causes the inability of these cells to successfully establish secondary tumors? They may be incapable of promoting sufficient angiogenesis, or they may be unable to reproduce, either of which might be due to a lack of the proper interactions between the tumor cell and its new environment. Additional mutations appear to be required for these cells to overcome the difficulties encountered in new tissues[5]

Dissecting the interactions of the tumor and its environment is very challenging. The vast number of growth factors, cytokines, and other factors present, as well as the many signaling pathways involved in cross-talk between these two entities makes mechanisms difficult to unravel, and almost any outcome is seemingly possible. However, the importance of the tumor microenvironment is now very obvious, and as more is learned about it, greater numbers of therapeutic strategies targeting the environment alone or in conjunction with the tumor itself will become available.

Learn more about tumor-host interactions.

Drugs That Target Metastasis

Metastatic Suppressors

Recent work has uncovered a group of molecules that act to induce or suppress metastasis *without* affecting the growth of the primary tumor. Many molecules, termed *Metastatic Suppressors*, have been identified. These molecules are critical for different stages of metastasis, and may function to inhibit cell death upon loss of cell adhesion, or enhance the ability of cells to migrate through the stroma. Researchers are hopeful that these molecules may prove valuable as anti-cancer/anti-metastasis targets.[12]

It is important to realize that the majority of current anti-cancer drug studies are conducted using primary or cultured tumor cells, and the efficacy of each drug is measured by its ability to reduce the size of primary tumors or kill cells being grown in laboratories. However, because metastatic suppressors *do not* affect growth of the primary tumor, it is likely like many potentially useful anti-metastatic drugs have been overlooked. New methods of analyzing the ability of drugs to inhibit metastasis, rather than primary tumor growth, are being developed, and should lead to a useful new class of therapeutic compounds.[3]

Anti-angiogenesis Therapy

Because metastasis relies on the growth of new blood vessels in both the primary and secondary tumors, drugs that inhibit angiogenesis may inhibit metastasis. Currently, the combination of anti-angiogenesis drugs with chemotherapy/radiation is the most effect treatment. Unfortunately, many tumors become resistant to the anti-angiogenesis treatment, so this is generally not a longterm solution. 5

Current research into inhibiting metastasis is focusing on understanding which step of metastasis is the most amenable to therapy. The identification of metastatic suppressor genes has opened up many exciting new potential targets for preventing and inhibiting this deadly event.

Challenges to the Development of Anti-metastasis Drugs

Finding potential drugs that block metastasis is difficult, but getting those drugs evaluated in humans can be even more difficult. Most clinical trials are designed to find out if drugs can kill cancer cells or prevent tumors from growing. A drug that prevents metastasis may not show either of these two activities. Some researchers feel that it is important to come up with new kinds of clinical trials that would specifically look at the ability of drugs to prevent the spread of cancer.13

Section Summary: Metastasis

Metastasis

- Metastasis is the process by which cancer cells spread to distant locations in the body.
- The majority of death associated with cancer is due to the metastasis of the original tumor cells.
- Metastasizing cancer cells must secrete a mixture of digestive enzymes in order to degrade barriers.
- Cancer cells may use the circulatory system to move to a suitable location to settle.
- Metastasis is a very inefficient process. Most cancer cells die once they leave the original tumor.

Lymphatic Metastasis

- Cancer can use the lymphatic system as well as the circulatory system to metastasize.
- The movement of cancer cells via the lymphatic system into lymph nodes is used in the detection of metastatic disease and tumor staging.

Some cancers may spread through direct contact with other organs, as in the gut cavity. Metastatic tumors often interfere with the functions of affected organs.

HALLMARKS OF CANCER

What are ‘ hallmarks of cancer ‘ ?

- Biologic capabilities acquired by cancer cells during the multistep process of development of human tumors
- ***Essential Alterations In Cell Physiology That Collectively Lead To Malignant Growth Of A Normal Cells.***
- Described by Douglas Hanahan & Robert Weinberg in 2000

Originally *<u>six</u>* hallmarks of cancer proposed :

- Self-sufficiency in growth signals
- Insensitivity to growth-inhibitory (antigrowth) signals.
- Evading apoptosis.
- Limitless replicative potential.
- Sustained angiogenesis.
- Tissue invasion and metastasis.

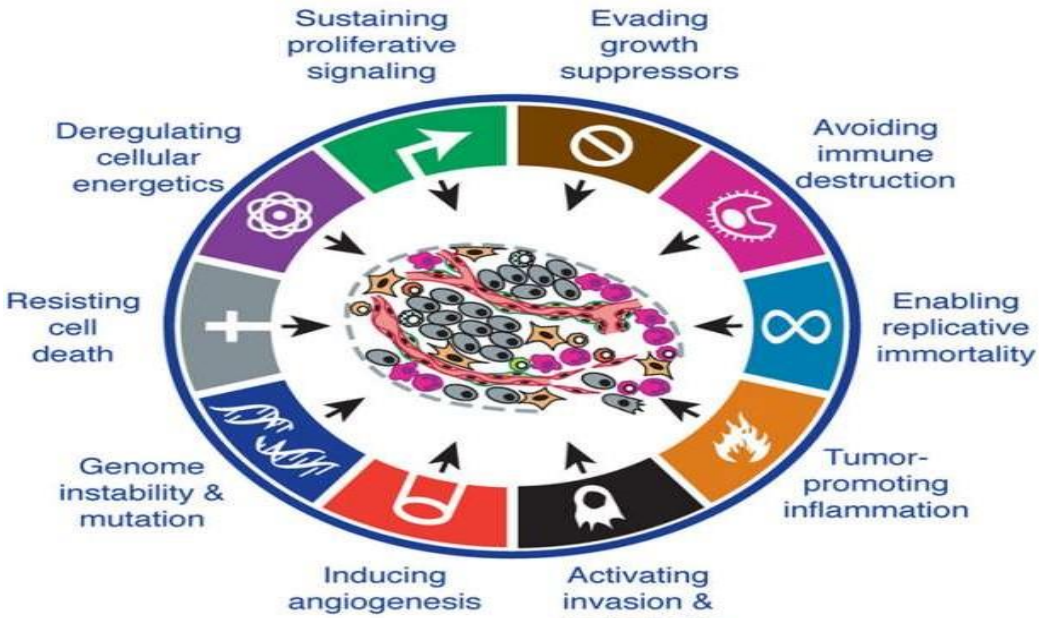
With development in genetics and epigenetics Hanahan and Weinberg again redefined “Hallmarks of cancer” in 2011.

<u>Two additional hallmarks of cancer are</u>:

- Evading immune destruction.

Deregulating cellular metabolism or energetics

EIGHT HALLMARKS OF CANCER



1. Sustained Proliferative Signalling

- Cancer cells : 'master of their own destinies'
- Normal cells require growth signals to enter from a quiescent state into an active proliferative state.
- These signals are transmitted into the cell through transmembrane receptors that binds to a particular class of signaling molecules.
- Tumor cells generate their own growth signals and thereby reducing their dependence on external stimulation from their normal tissue microenvironment.

Alteration of extracellular growth signals	• Many cancer cells acquire the ability to synthesize abundance of GFs to which they are responsive, creating a positive feedback signaling loop
Alternation of transcellular receptor of those signals	• Receptor overexpression may enable the cancer cell to become hyperresponsive to ambient levels of GF that normally would not trigger proliferation
Alternation of intracellular circuits that translate those signals into action.	• Alterations in components of the downstream cytoplasmic circuitry that receives and processes the signals emitted by GF receptors can release a flux of signals into cells, without ongoing stimulation by their normal upstream regulators

- **Somatic Mutations activate additional downstream pathways that promote sustained growth**
- RAS-RAF-MAPK PATHWAY
- 90% Pancreatic adenocarcinomas carry mutant K-RAS alleles

- 40% melanomas contain activating mutations affecting B-RAF

Disruptions of Negative-Feedback Mechanisms that Attenuate Proliferative Signaling –

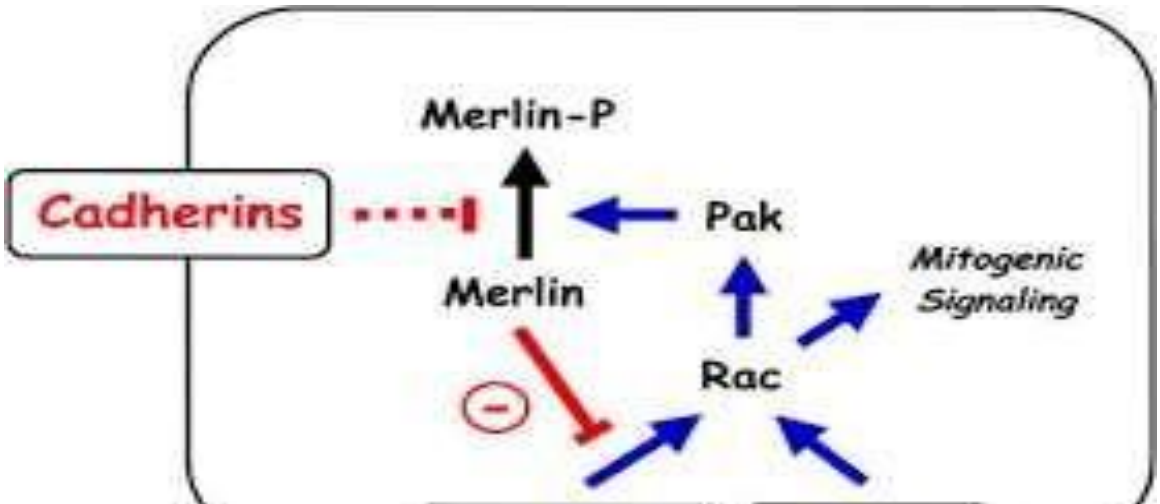
- Defect in negative feed back mechanism leads to uncontrolled proliferative signaling .
- The prototype of this type of regulation involves the RAS oncoprotein.
- The oncogenic mutations of RAS genes impair the intrinsic GTPase activity of RAS that normally serves to turn its activity off, ensuring that active signal transmission is transient.

Excessive Proliferative Signaling Can Trigger Cell Senescence

- Excessively elevated signaling by oncoproteins, such as RAS, MYC, and RAF in a normal cell provoke protective response such as **induction of cell death.**
- Alternatively, cancer cells expressing high levels of these oncoproteins may be forced to enter into the nonproliferative but viable state called **senescence.**
- Whenever these tumor cells get the favorable microenvironment they enter into proliferative phase.

2. Evading Growth Suppressors

- Growth suppressors are acting as the break mechanism to overrule the initiation or "turning off" of cell division.
- The two prototype tumor suppressor genes encode the retinoblastoma **(RB)-**associated and **P53** proteins.
- The RB protein integrates signals from diverse extracellular and intracellular sources and, in response, decides whether or not a cell should proceed through its growth and division cycle.
- **Mechanisms of Contact Inhibition and Its Evasion –**
- Healthy cell stops dividing when comes in contact with other cells but cancer cell does not.



- Merlin, the cytoplasmic NF2 gene product, activate contact inhibition by coupling cell-surface adhesion molecules like E- cadherin to transmembrane receptor tyrosine kinases.
- Merlin strengthens the adhesiveness of cadherin-mediated cell-to-cell attachments and thus inhibits the mitogenic signals.
- Thus, the mutation of NF-2 gene results in loss of this property and thus grow in uncontrolled manner.
- Role of TGF-B
- In normal cells, its exposure blocks their progression through the G1 phase of cell cycle; in many late stage tumors, however, its signalling is redirected away from suppression to activation of a cellular program termed "epithelial to mesenchymal transition"

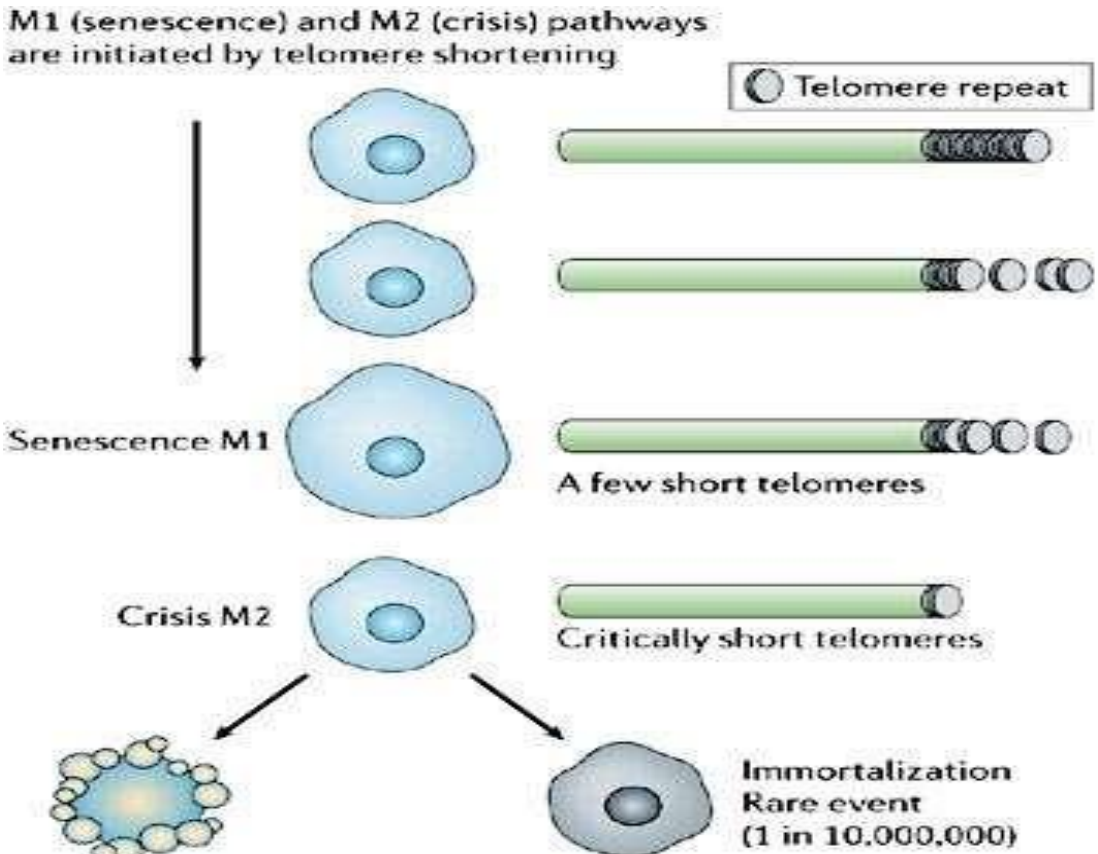
3. Resisting Cell Death

- Normally when cells become old or damaged they are programmed to die in a process called apoptosis.
- But cancer cells escapes normal cell death and continue to accumulate in the body.
- Tumor cells develops a variety of strategies to escape apoptosis.
- **Cancer cells acquires anti apoptotic regulators:-**
- Most common is the loss of P53 tumor suppressor function, which eliminates this critical damage sensor from the apoptosis-inducing circuit.
- Alternatively, tumors may escape apoptosis by increasing the expression of antiapoptotic regulators (Bcl-2, Bcl-XL Mcl- 1).
- By downregulating proapoptotic Bcl-2–related factors (Bax, Bim,Apaf-1).

- **Autophagy Mediates Both Tumor Cell Survival and Death –**
- Nutrient starvation, radiotherapy, and certain cytotoxic drugs can induce elevated levels of autophagy that apparently protect cancer cells via resistance to apoptosis.
- Moreover, severely stressed cancer cells have been shown to shrink via autophagy to a state of reversible dormancy.
- This particular survival response may enable the cancer cells to survive during anticancer therapy or during shortage of nutrition.
- **Necrosis has proinflammatory & tumor promoting potential**
- Necrotic cells can release bioactive regulatory factors which can directly stimulate viable neighbouring cells to proliferate

4. Enabling Replicative Immortality

- In normal cell division, a small portion of the end of each chromosome called telomere, is lost every time DNA is copied.
- Loss of telomere reaches a critical point and cell will no longer divide and replicate and undergo p53 dependent cell cycle arrest or apoptosis. In this way healthy cells self limit their replication.
- But in cancer cells activation of an enzyme called telomerase can maintain telomeres and allow cells to replicate limitlessly.



5.Inducing Angiogenesis

The formation of new blood vessels out of pre-existing capillaries.

ANGIOGENIC SWITCH OF TUMORS

INVOLVES : Sprouting

Splitting

Remodeling of the existing vessels

WHY IT IS IMPORTANT?

- Supply of oxygen and nutrients
- Removal of waste products

TUMOR ANGIOGENESIS

Three major steps

(A) Initiation of the angiogenic response.

(B) Endothelial cell(EC) migration, proliferation and tube formation.

(C) Finally the maturation of the neovasculature.

(A) Initiation of the angiogenic response

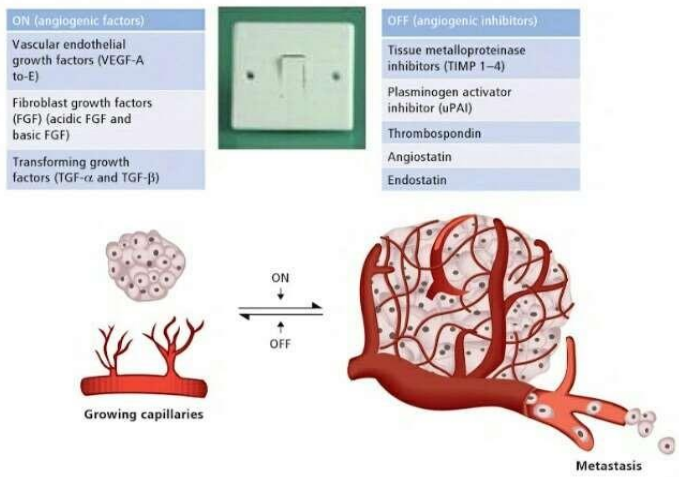
The first step in the formation of a capillary sprout from a pre-existing mature blood vessel. This occurs as a consequence of proangiogenic growth factors secreted by the tumor cell population.

Proteolytic enzymes such as MMPs,Cathepsins etc.

- localized degradation of the surrounding basement membrane
- (B) Endothelial cell(EC) migration, proliferation and tube formation
- Next step is stimulus directed migration of ECs towards tumor mass emanating from tumor itself
- Followed by division of ECs and lengthening the stalk of ECs sprout
- Lumen formation occurs with completion of capillary sprouts and loops

(C) Maturation of the neovasculature.

- Single layer of periendothelial smooth muscle cells that wraps around the endothelial cells are known as pericytes.
- Critical for the development of new mature vascular network.
- Provide mechanical support, stability, regulate the diameter of vessel and vascular permeability.
-



- **Epigenetic induction** **Genetic induction**

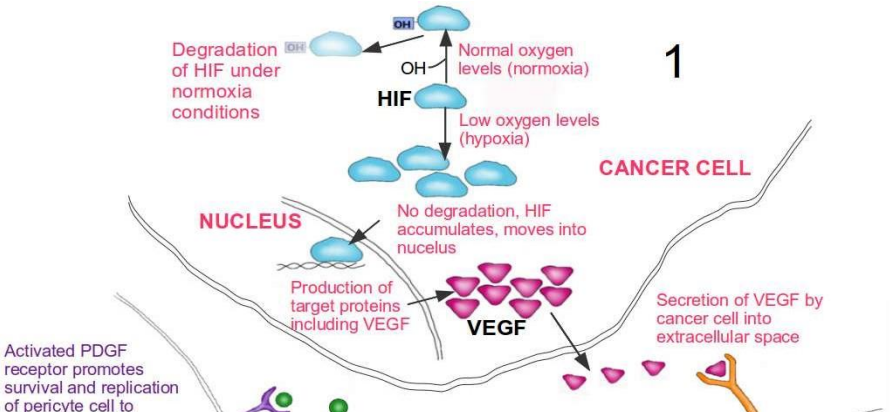
Hypoxia, low Ph, cytokines(IL-6),bFGF, Sex hormones

mutant p53,VHL activated oncogene

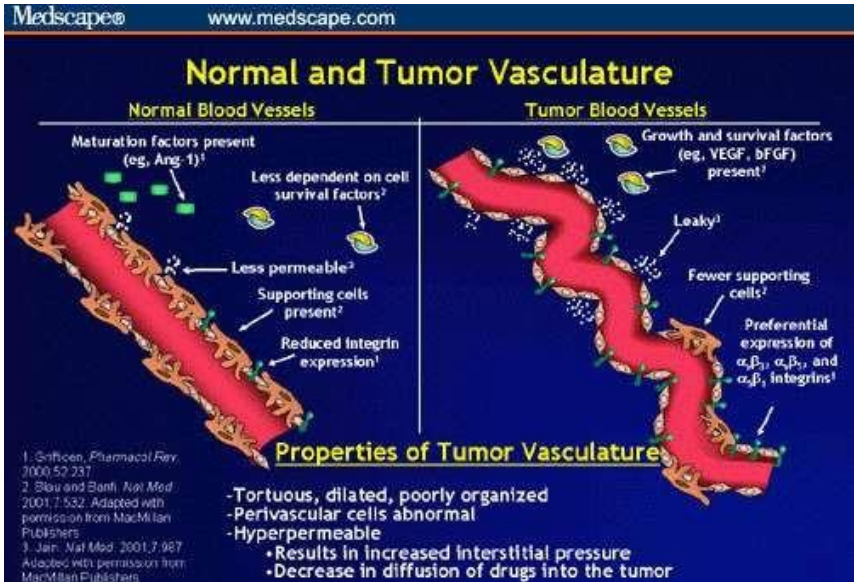
VEGF A and VEGF165

VEGFR-1 VEGF-2 VEGF-3 → Lymphogenesis

Vascular permeability, Migration, Mobilization, Proliferation, Survival

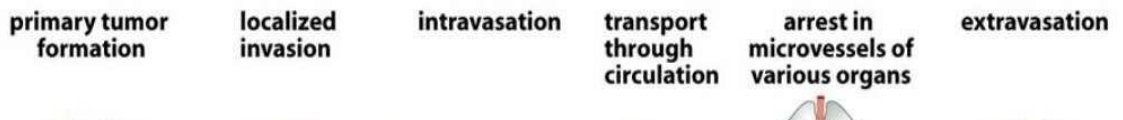


- **Pericytes Are Important Components of the Tumor Neovasculature-**
  - They provide important mechanical and physiologic support to the endothelial cells
  - Pericyte also secrete PDGF which helps in recruitment of pericytes and smooth muscle cells.
  - **A Variety of Bone Marrow-Derived Cells Contribute to tumor Angiogenesis-**
  - These include cells of the innate immune system including macrophages, neutrophils, mast cells, and myeloid progenitor.
  - This tumor associated inflammatory cells can help to trigger the angiogenic switch by providing tumor microenvironment and secreate various growth factors.

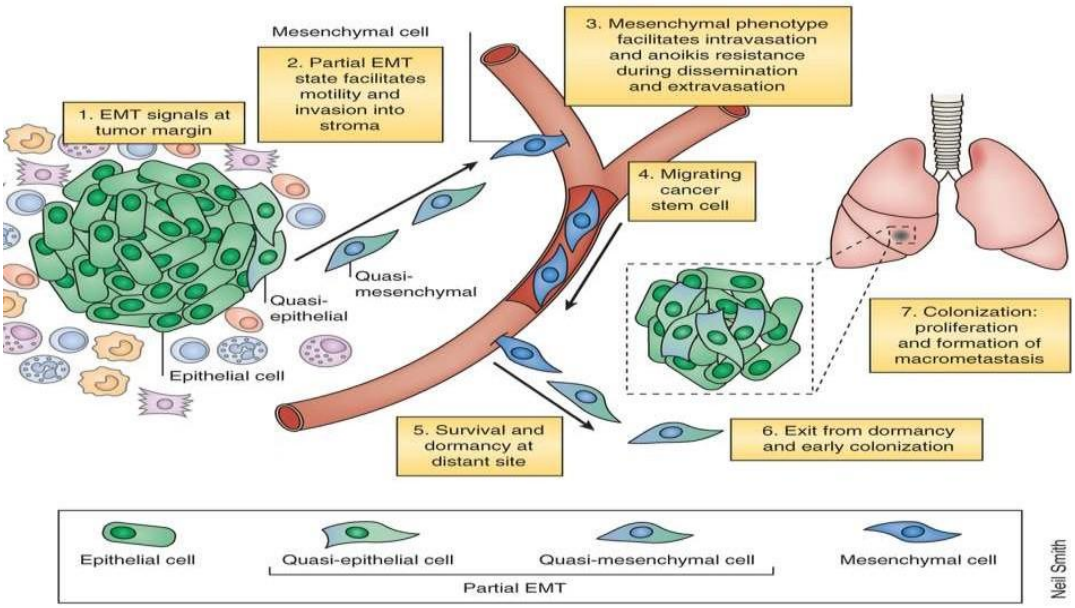


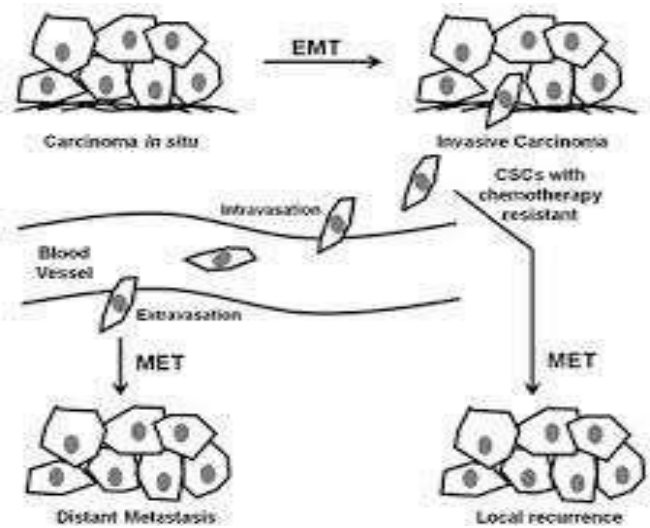
- Steps in activating invasion and metastasis
- Carcinoma development and acquire invasive potential
    - Tumor supressor genes mutation
    - Proto oncogene mutations
- Expansion of growth and invasion of basement membrane
    - Enhanced protease activity(e.g. MMPs)
    - Enhanced cell motility / interaction with surrounding tissue.
    - Decreased cell to cell adhesion and contact(e.g.E-cadherin loss)
    - Intravasation and transport through BM
    - Intravasation through BM into blood vessel.
    - Interaction with vascular cells
    - Survival in circulation / immune eversion
    - Arrest and extravasation at secoundary site
    - Tumor cells interact with vascular cells.
    - Invasion into secondary tissue and formation of micro or macrometastasis
    - Intraction and adaptation to tissue microenvironment.
    - Establishment of new vasculature.
    - Secondary tumor establishment or dormancy.

Invasion-Metastasis Cascade Adapted from Fidler, Nat. Rev. Cancer 3: 453-458, 2003



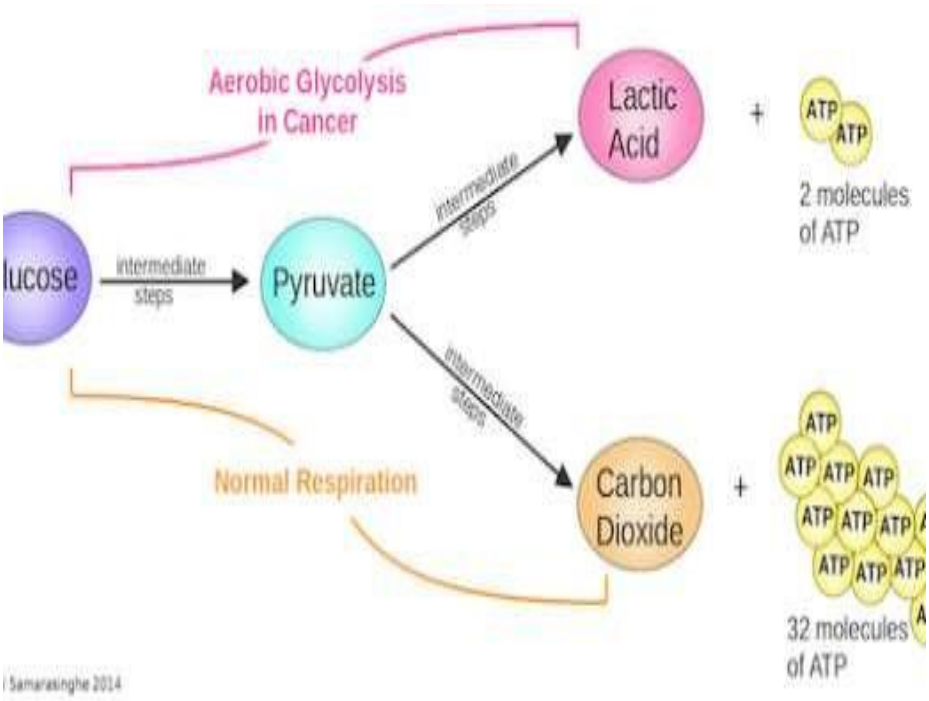
Epithelial to mesenchymal transition program





- Reprogramming Energy Metabolism

- Cancer metabolism is different than normal tissue metabolism. First time it was noted in 1920 by biochemist Otto Warburg that when cancer cells are provided with glucose , they generate large amount of lactate regardless of whether oxygen is present or not.
- This metabolic difference is referred as THE WARBURG EFFECT……
- the normal cells utilize aerobic respiration to completely catabolize glucose and generate cellular energy.
- Cancer cells rely primarily on glycolysis for their metabolism to make lactate and it is called **aerobic glycolysis..**
-



- Aerobic gylcolysis also generates ATP but less than aerobic respiration.
- Cancer cells metabolize glucose for purpose other than generating ATPs.
- Lactate produced from aerobic gylcolysis causes acidification of tumor cell which has been shown to promote invasion and metastasis.

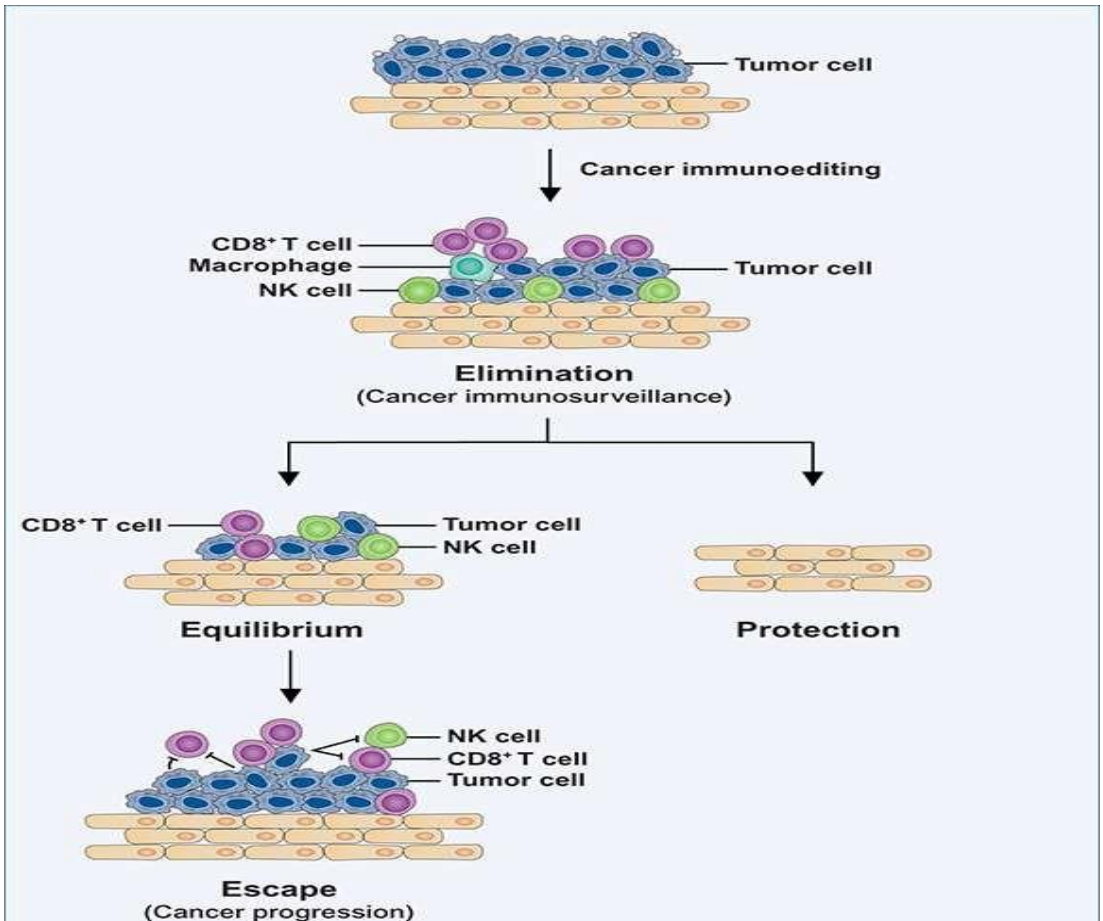
- Lactate can also act as a nutrient for some cells in the tumor.

Mutation in metabolic enzymes causing cancer

- FH[fumarate hydratase]– metabolizes fumarate in TCA…mutation leads to RCC ,leiomyomas.
- IDH [isocitrate dehydrogenase]– in glioma, glioblastoma, AML, myelodysplastic syndrome,ALL, prostate, colorectal cancer.

Targeting metabolism to treat cancer

- Folate– it can enhance cell proliferation. So antifolate is used as chemotherapy.
- Metformin– recently two studies have shown that cancer related mortality is decreased with metformin use—may be toxic to the cancer cell—may decrease the effect of IGF-1 on cell growth.
- Evading Immune Destruction



Mechanisms by which tumor cells escape immune recognization and destruction:

- Low immunogenicity of tumor cells –
    - Failure to produce tumor antigen
    - Mutation in MHC gene needed for antigen processing.
    - Inability to recognize tumor cells by immune system.
- Tumor induced immune supression-
    - Factors secreted by tumor cells eg. TGF-b inhibit T cells directly.
- Tumor induced privileged site-
    - Factors secreted by tumor cells create a physical barrier to the immune system.
- Tumor treated as self antigen-
    - Tumor antigens are taken up and presented by APCs in absence of co-stimulation taken as self antigens and escape from immune destruction.

Genome Instability and Mutation

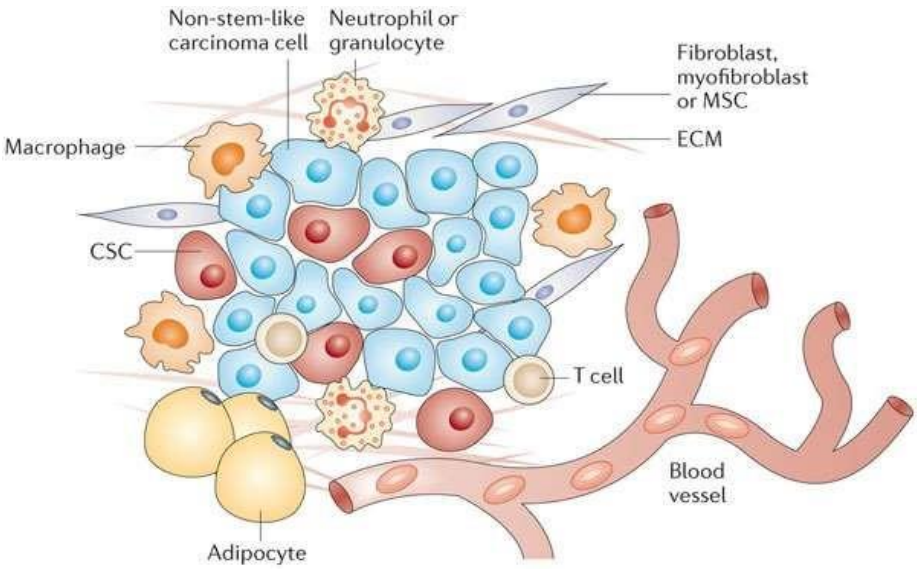
- DNA damage or mutation in a normal cell results in cell cycle arrest followed by DNA repair or apoptosis.
- Interference in this process may occur either by lack of recognizing and repair of damaged DNA or abnormal gatekeeping of cell cycle.
- Genomic instability and mutation acts as enabling hallmark of cancer i.e facilitator of hallmark capabilities.

- These mutations can include change in nucleic acid sequence, chromosomal rearrangements or aneuploidy.
- DNA damage from external cause or impaired DNA repair mechanism due to epigenetic mechanism such as DNA methylation and histone modifications.
- Cancer cells generally have severe chromosomal abnormalities
- Based on the level of disruption types of gene instablity are-
- Nucleotide instablity-
    - Include nucleotide substitution, deletion or insertion
    - E.g. xeroderma pigmentosum, MYH associated polyposis
- Microsatellite instablity-
    - Include defect in mismatch repair leads to contraction or expansion of microsatellite
    - E.g. Lynch syndrome
- Chromosomal instablity-
    - Most prominent form
    - 90% of human cancer exhibiting chromosomal abnormalities.it include chromosomal anuploidy, amplifications, deletions, translocations and inversions.
    - E.g. Breast, prostate, non small cell lung cancer, leukaemia, neuroblastoma etc.
- Defects in these caretaker genes results in-
    - DNA damage and inactivation of repair machinery
    - Inability to inactivate mutagenic molecules resulting in DNA

  damage.
- CGH (comparative genomic hybridization)- one method of molecular genetic analysis to compare patient DNA to reference DNA to check the gains and losses of gene copies in the patients cell genome by using florescent dye .

  Tumor-Promoting Inflammation
- Virtually every tumor contains immune cells present at varying densities.

- Such immune responses are largely thought to reflect an attempt by the immune system to eradicate tumors
- However, tumor-associated inflammatory response is shown to have paradoxical effect of enhancing tumorigenesis and progression.
- Inflammation can contribute to multiple hallmark capabilities by supplying bioactive molecules for favourable tumor microenvironment including:
    - Growth factors that sustain proliferative signaling
    - Survival factors that limit cell death
    - Proangiogenic factors
    - Extracellular matrix-modifying enzymes that facilitate angiogenesis, invasion and metastasis.
    - THE TUMOR MICROENVIRONMENT



Nature Reviews | Drug Discovery

Cancer-Associated Fibroblasts

- Cancer-associated fibroblasts (CAFs) constitutes at least two distinct cell types:

- Cells with similarities to the fibroblasts that provides structural support to most of normal epithelial tissues
- Myofibroblasts, whose biologic roles and properties differ markedly from those of the widely distributed tissue-derived fibroblasts.
- They have been demonstrated to enhance tumor phenotypes, notably cancer cell proliferation, angiogenesis, invasion, and metastasis.

Endothelial Cells

- Forming the tumor-associated vasculature.
- Activated (*angiogenic) tumor* vasculature has been revealed as a functional suppressor of cytotoxic T cells thus, tumor endothelial cells can contribute to the hallmark capability for evading immune destruction.

Pericytes

- Specialized mesenchymal cell type with fingerlike projections that wrap around the endothelial tubing of blood vessels.
- Provide supportive framework to endothelial cells.

Immune Inflammatory Cells

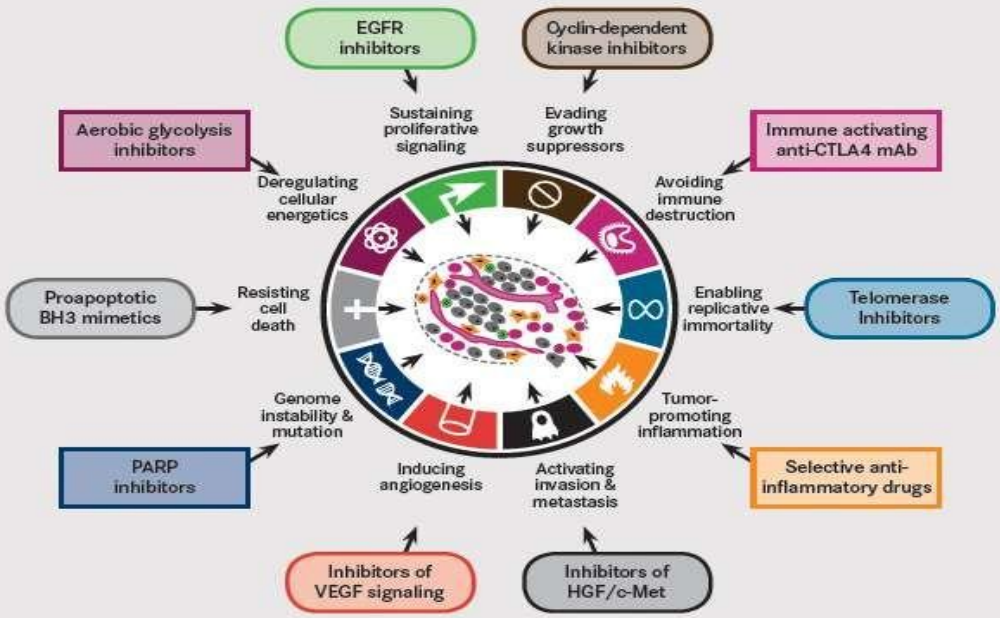
- Macrophage subtypes, mast cells, neutrophils as well as T and B lymphocytes
- EGF, VEGF-A/C, FGF2, chemokines, cytokines , MMP-9, cysteine cathepsin proteases etc.
- facilitate tissue invasion, and to support the metastatic dissemination and seeding of cancer cells.

Stem and Progenitor Cells of the Tumor Stroma

- Also known as cancer initiating cell.
- Cell type capable of initiating and sustaining growth of the tumor.
- These fraction of tumor cells were capable of tumor development and have great proliferative within a tumor.

Co evolution of the Tumor Microenvironment During Carcinogenesis

- Tumor microenvironment is not static and undergo co evolution with time.
- Continuous changes in composition of stroma-associated cell types.
- Second, as cancer cells enter into different locations, they encounter distinct stromal microenvironments.
- Thus, the microenvironment in the interior of a primary tumor will likely be distinct both from locally invasive breakout lesions and from the one encountered by disseminated cells in distant organs.
- THERAPEUTIC TARGETING OF THE HALLMARKS OF CANCER



This figure illustrates some of the many approaches employed in developing therapeutics targeted to the known and emerging hallmarks of cancer.

EGFR indicates epidermal growth factor receptor; CTLA4, cytotoxic T lymphocyte-associated antigen 4; mAb, monoclonal antibody; HGF, hepatocyte growth factor; VEGF, vascular endothelial growth factor; PARP, poly-(ADP ribose) polymerase.

Source: Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011; 144:646-674. Reprinted with permission.

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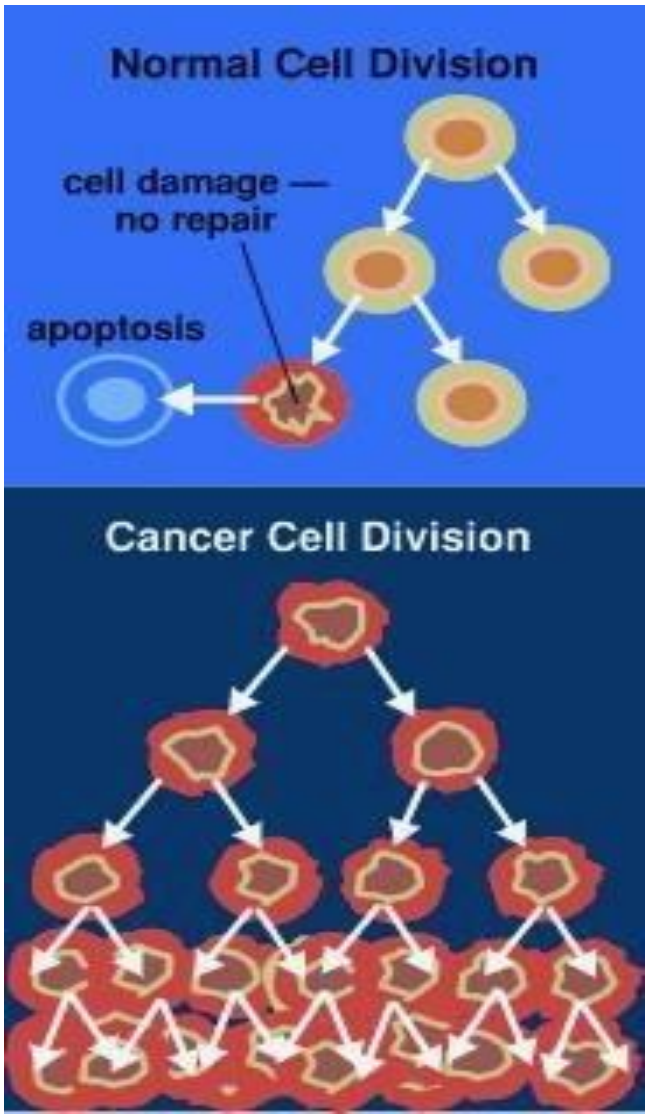
UNIT – IV –CANCER BIOLOGY- SBB1605

MOLECULAR BASIS OF CANCER

Cellular Basis of Cancer

- **Cancer is characterized by abnormal and uncontrolled growth**
- **Cancer arises from a loss of normal growth control**
- **In normal tissues, the rates of new cell growth and old cell death are kept in balance**
- **In cancer, this balance is disrupted**
- **This disruption can result from**
    1) **uncontrolled cell growth or**
- **2) loss of a cell's ability to undergo apoptosis**

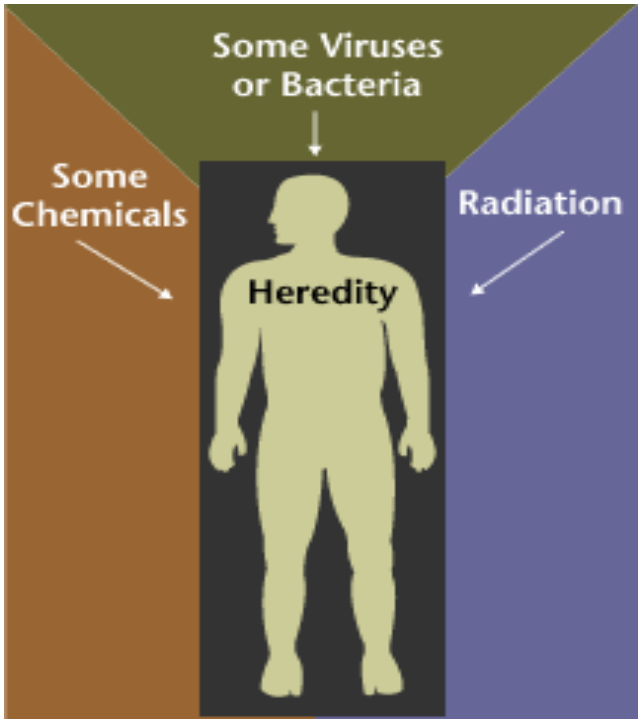


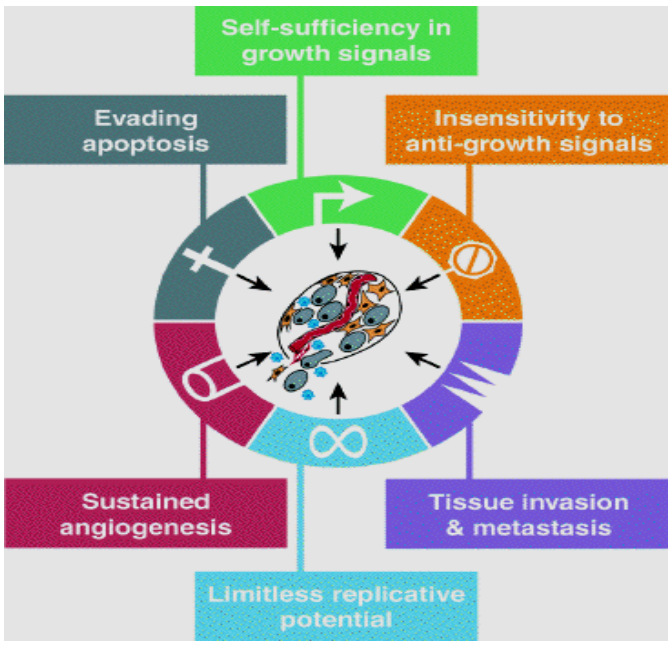
Cancer Cell Do Not Grow Faster Than Normal Cells

Rather, Their Growth is Just Uncontrolled

What causes Cancer?

- **Cancer is caused by alterations or mutations in the genetic code**
- **Can be induced in somatic cells by:**
  - **Carcinogenic chemicals**
  - **Radiation**
  - **Some viruses**
- **Heredity - 5%**





- ***What is the molecular basis of cancer?***
- **Cancer is <u>a genetic disease</u>.**
    - **Mutations in genes result in altered proteins**

⁻ **During cell division**

⁻ **External agents**

⁻ **Random event**

- **Most cancers result from mutations in somatic cells**
- **Some cancers are caused by mutations in germline cells**

THEORIES OF CANCER GENESIS

Standard Dogma

- **Proto-oncogenes (Ras – melanoma)**
- **Tumor suppressor genes (p53 – various cancers)**

Modified Dogma

- **Mutation in a DNA repair gene leads to the accumulation of unrepaired mutations (xeroderma pigmentosum)**

Early-Instability Theory

- **Master genes required for adequate cell reproduction are disabled, resulting in aneuploidy (Philadelphia chromosome)**

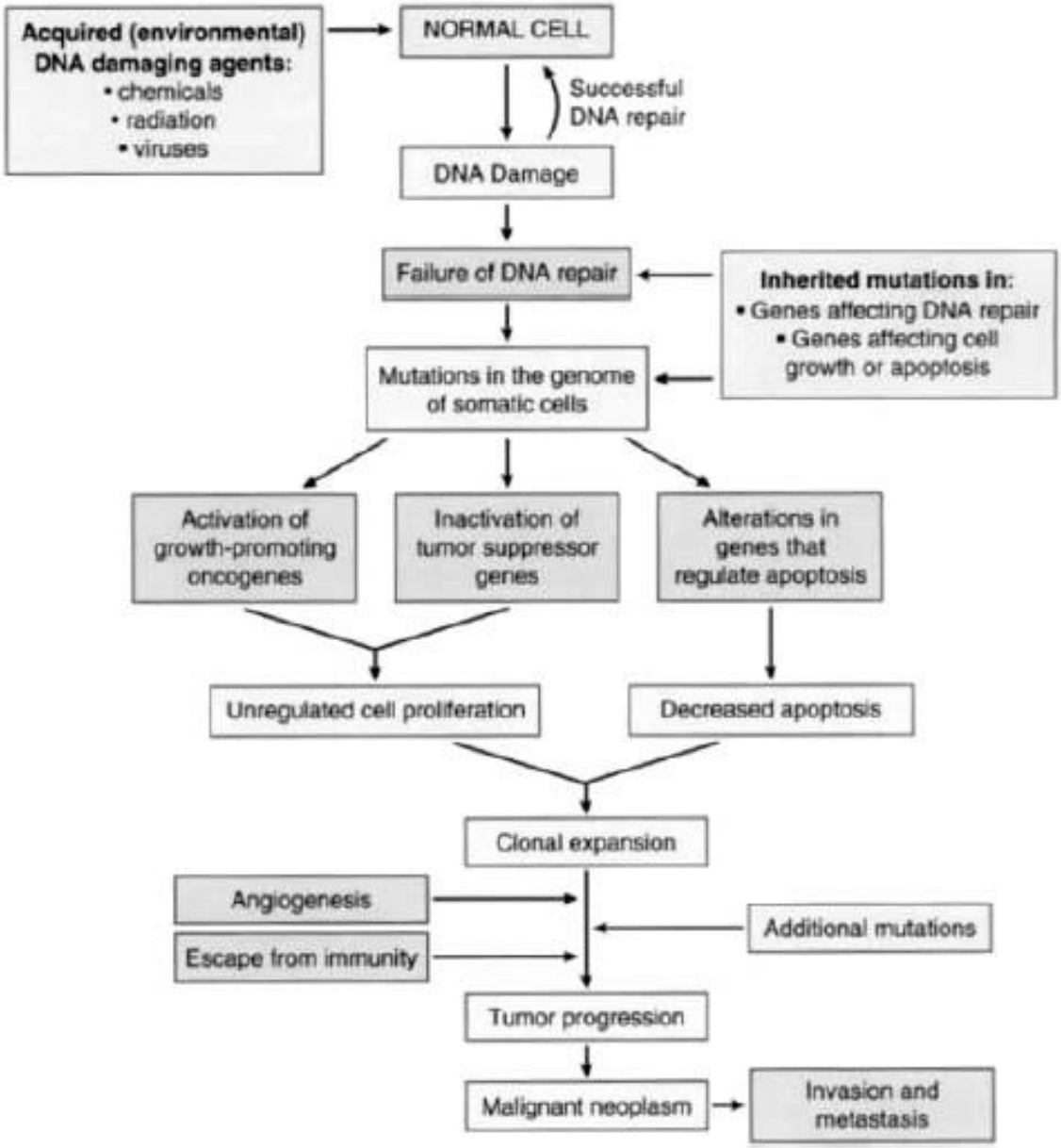
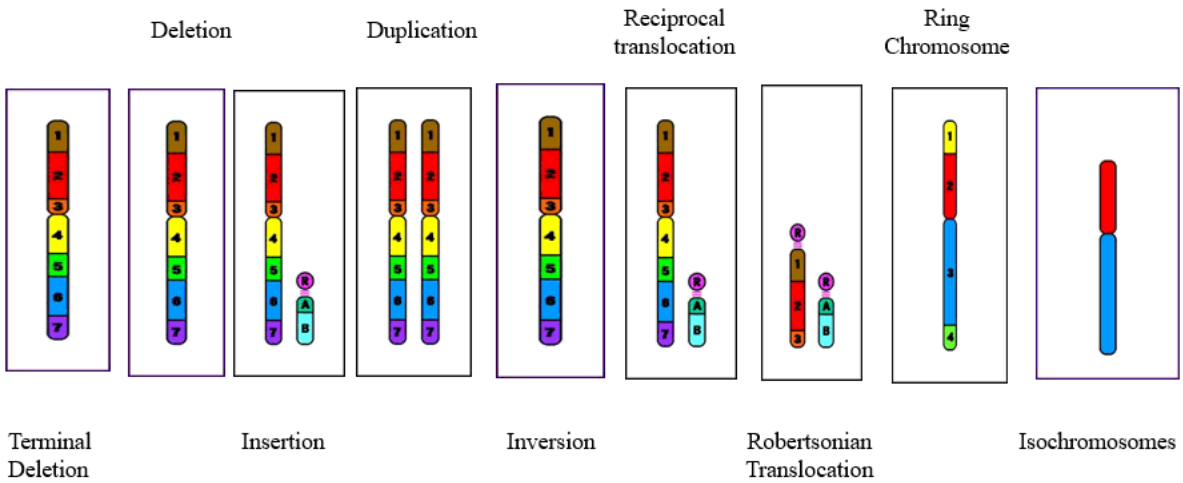


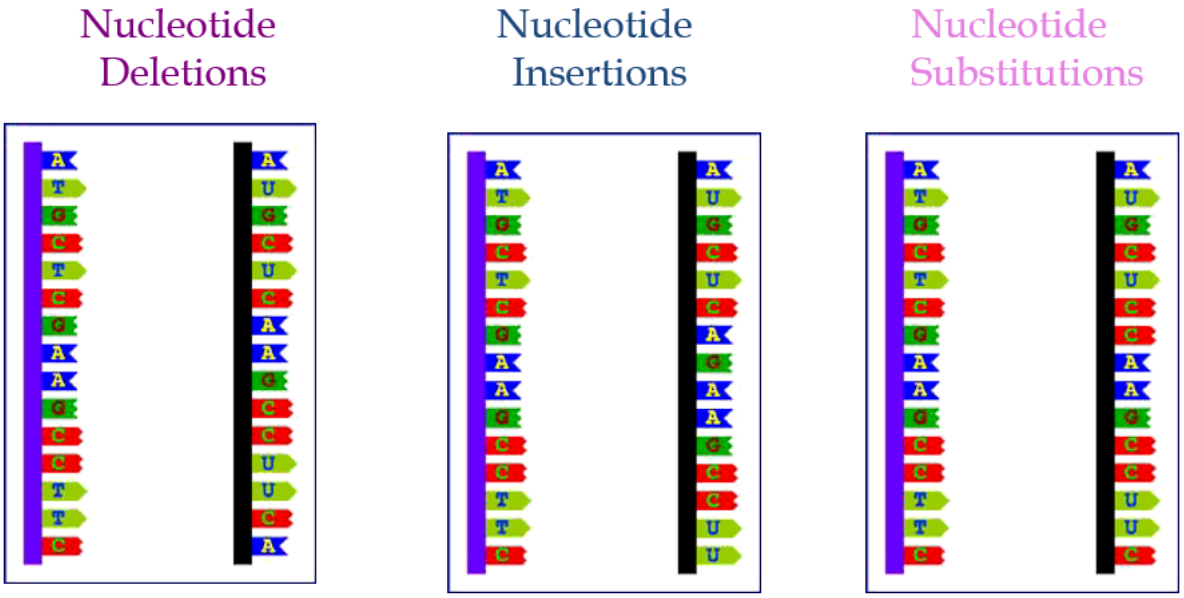
Figure 7-27 Flow chart depicting a simplified scheme of the molecular basis of cancer.

Chromosomal changes in the genome of cancer cells: tip* of *the iceberg



http://www.tokyo-med.ac.jp/genet/cai-e.htm[10]

Nucleotide changes in the genome of cancer cells:* unseen *site* of *the iceberg



http://www.tokyo-med.ac.jp/genet/[1]c[1]ai-e.h

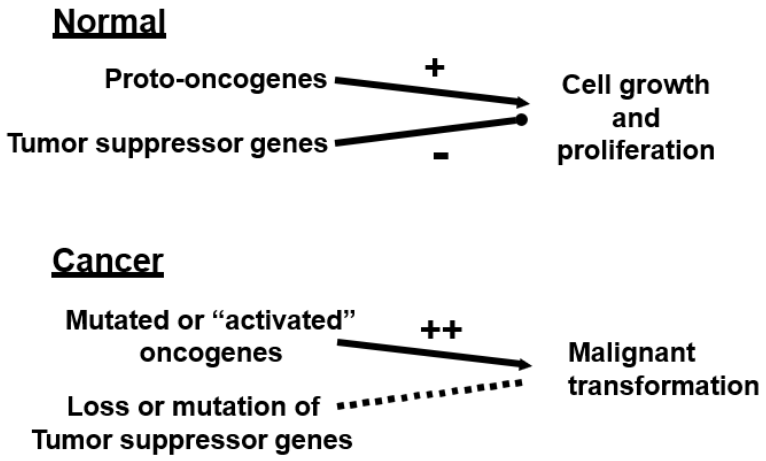
CANCER AND GENTICS

- **Approximately 90-95% of all cancers are sporadic.**
- **5-10% are inherited.**

GENES PLAYING ROLE IN CANCER DEVELOPMENT**Oncogenes**

- **Tumor suppressor genes**
- **DNA repair genes**

What are the genes responsible for tumorigenic cell growth?



ONCOGENES

- **Oncogenes are mutated forms of cellular proto-oncogenes.**
- **Proto-oncogenes code for cellular proteins which regulate normal cell growth and differentiation.**

Five types of proteins encoded by proto- oncogenes participate in control of cell growth:

Class I: Growth Factors

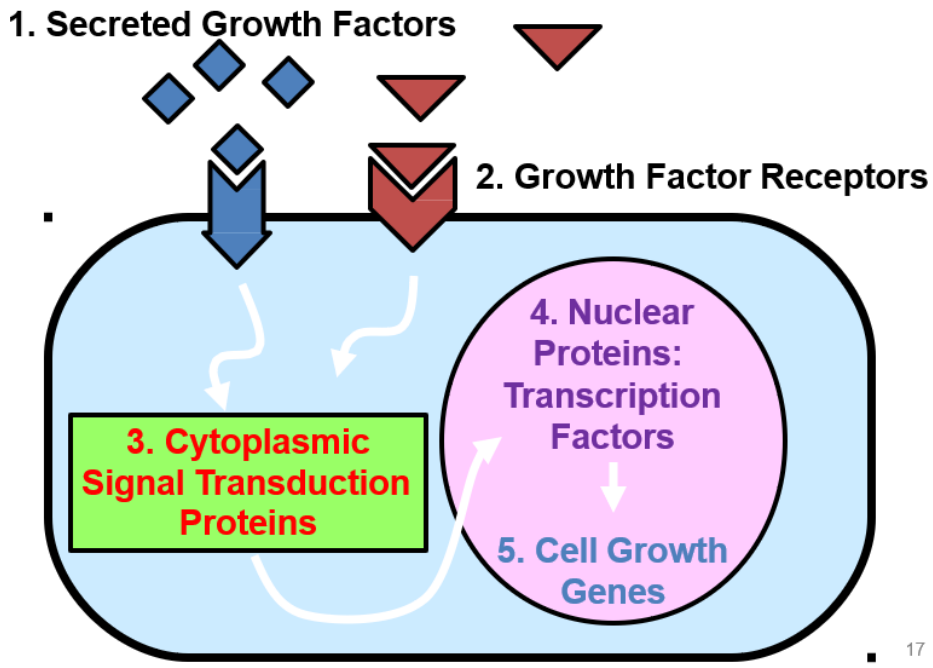
Class II: Receptors for Growth Factors and Hormones

Class III: Intracellular Signal Transducers

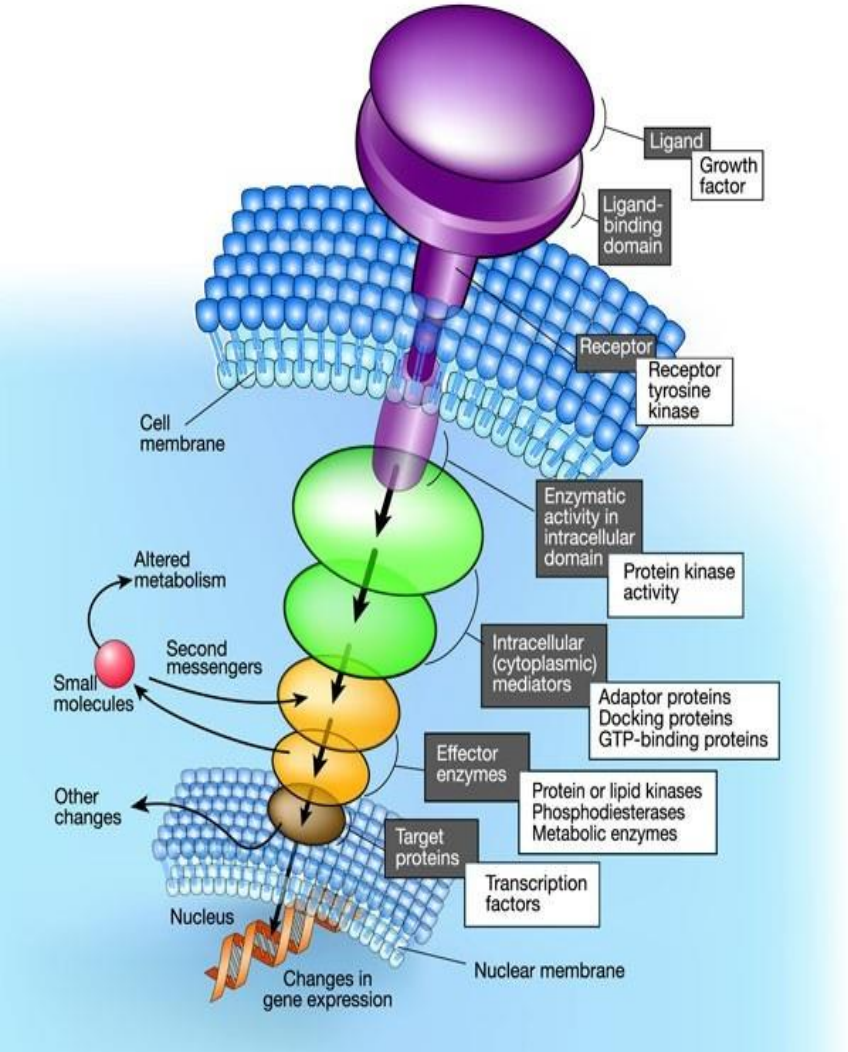
Class IV: Nuclear Transcription Factors

Class V: Cell-Cycle Control Proteins

Functions of Cellular Proto-Oncogenes

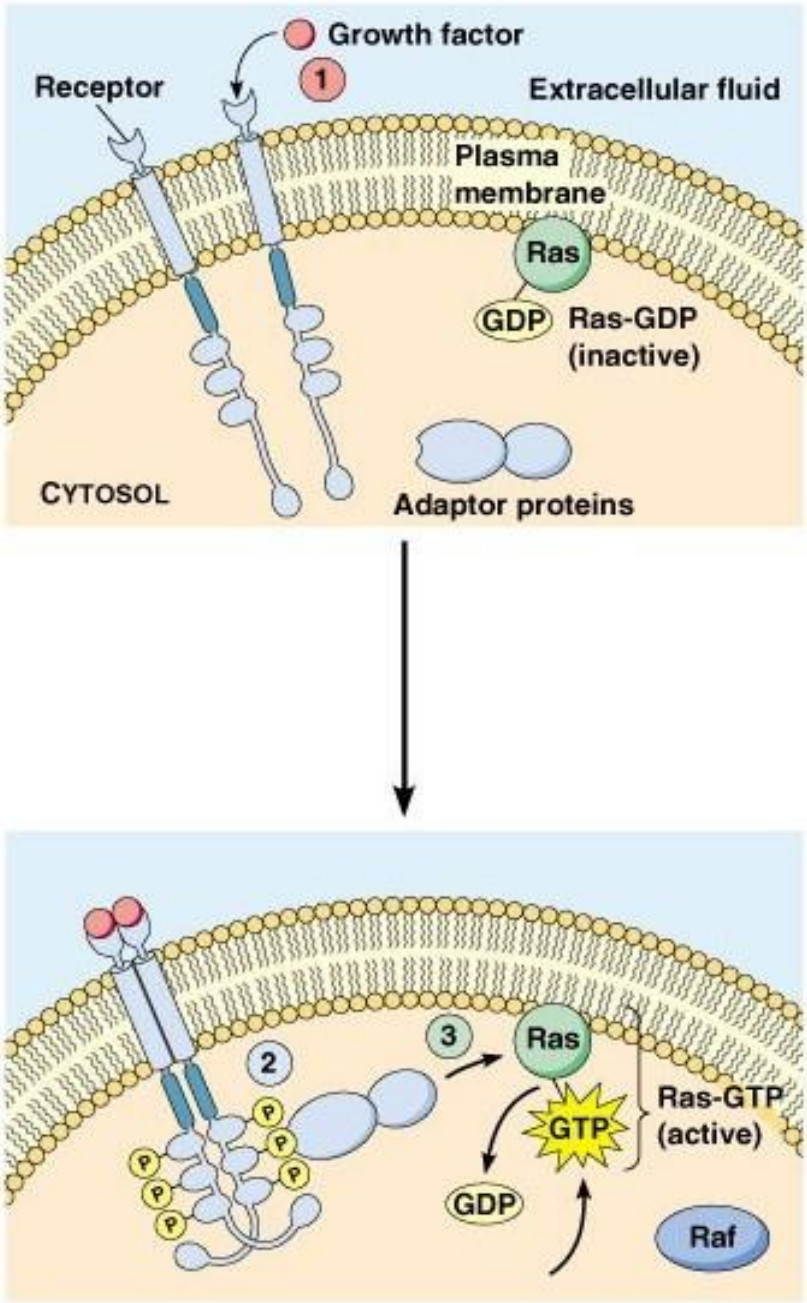


A generic signalling pathway



ONCOGENES

- **proto-oncogene = *ras***
- **Oncogene = mutated *ras***
- **Always activated**
- **Always stimulating**
- **proliferation**



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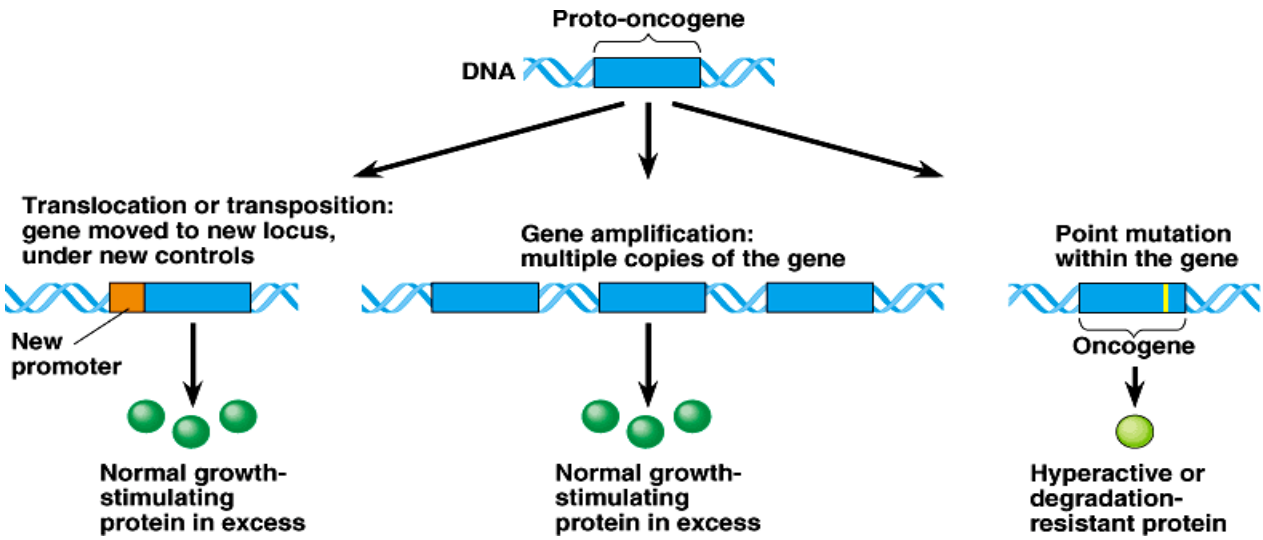
Amino acid substitutions in Ras family proteins (inactivates GTPase)

amino acid position

Ras gene	**12**	**59**	**61**	**Tumor**
c-ras (H, K, N)	**Gly**	**Ala**	**Gln**	**normal cells**
H-ras **K-ras** **N-ras**	**Gly Val** **Cys Arg** **Val Gly** **Gly**	**Ala** **Ala** **Ala** **Ala** **Ala** **Ala** **Ala**	**Leu Gln** **Gln Gln** **Gln Lys** **Arg**	**lung carcinoma bladder** **carcinoma lung** **carcinoma lung** **carcinoma colon** **carcinoma** **neuroblastoma lung** **carcinoma**
				Murine sarcoma virus
H-ras	**Arg**	**Thr**	**Gln**	**Harvey strain**
K-ras	**Ser**	**Thr**	**Gln**	**Kirsten strain**

Activation mechanisms of proto-oncogenes

proto-oncogene --> oncogene



CHROMOSOMAL REARRANGEMENTS OR TRANSLOCATIONS

Neoplasm	Translocation	Proto-oncogene
Burkitt lymphoma	t(8;14) 80% of cases	c-myc[1]
	t(8;22) 15% of cases t(2;8) 5% of cases	
Chronic myelogenous leukemia	t(9;22) 90-95% of cases	bcr-abl[2]
Acute lymphocytic Leukemia	t(9;22) 10-15% of cases	bcr-abl[2]

[1]c-myc is translocated to the IgG locus, which results in its activated expression

[2]bcr-abl fusion protein is produced, which results in a constitutively active abl kinase.

GENE AMPLIFICATION

Oncogene	Amplification	Source of tumor
c-myc	~20-fold	leukemia and lung carcinoma
N-myc	5-1,000-fold	neuroblastoma retinoblastoma
L-myc	10-20-fold	small-cell lung cancer
c-abl	~5-fold	chronic myoloid leukemia
c-myb	5-10-fold	acute myeloid leukemia colon carcinoma
c-erbB	~30-fold	epidermoid carcinoma
K-ras	4-20-fold 30-60-fold	colon carcinoma adrenocortical carcinoma

Oncogenes are usually dominant (gain of function)

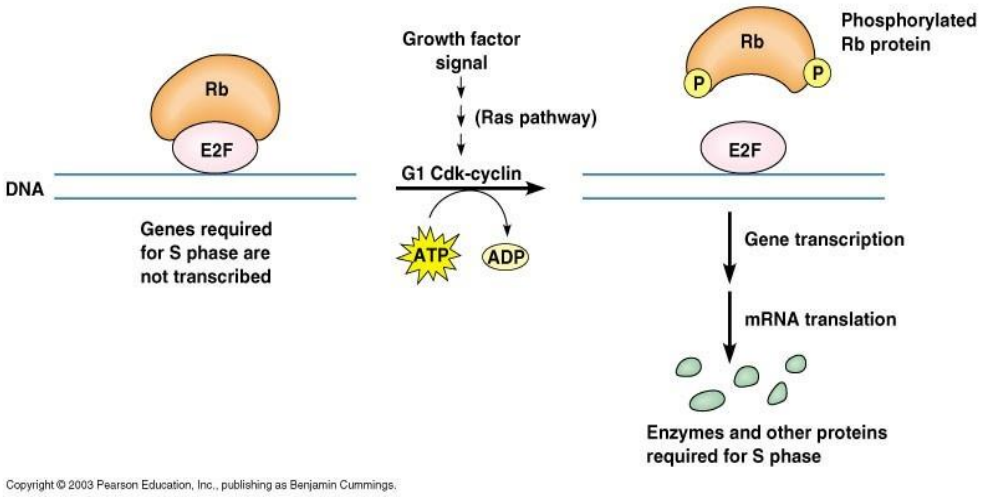
- **cellular proto-oncogenes that have been mutated (and "activated")**
- **cellular proto-oncogenes that have been captured by retroviruses and have been mutated in the process (and "activated")**
- **virus-specific genes that behave like cellular proto- oncogenes that have been mutated to oncogenes (i.e., "activated")**
- ***The result*:**
- **Overproduction of growth factors Flooding of the cell with replication signals**
- **Uncontrolled stimulation in the intermediary pathways**

- **Cell growth by elevated levels of transcription factors**

  TUMOR SUPPRESSOR GENES

- **LOSS OF FUNCTION**
- **Normal function - inhibit cell proliferation Absence/inactivation of inhibitor --> cancer Both gene copies must be defective**

Rb gene



- Rb protein controls cell cycle moving past **G1 checkpoint**
- Rb protein binds regulatory transcription factor **E2F**
- **E2F required for synthesis of replication enzymes**
- E2F - Rb bound = no transcription/replication
- Growth factor --> Ras pathway --> G1Cdk-cyclin synthesized
- Active G1 Cdk-cyclin kinase phosphorylates Rb
- Phosphorylated Rb cannot bind E2F --> S phase
  - Disruption/deletion of *Rb* gene
  - Inactivation of Rb protein

  --> uncontrolled cell proliferation --> cancer

Phosphyorylated p53 activates transcription of *p21* gene

p21 Cdk inhibitor (binds Cdk- cyclin complex --> inhibits kinase activity)

Cell cycle arrested to allow DNA to be repaired

If damage cannot be repaired

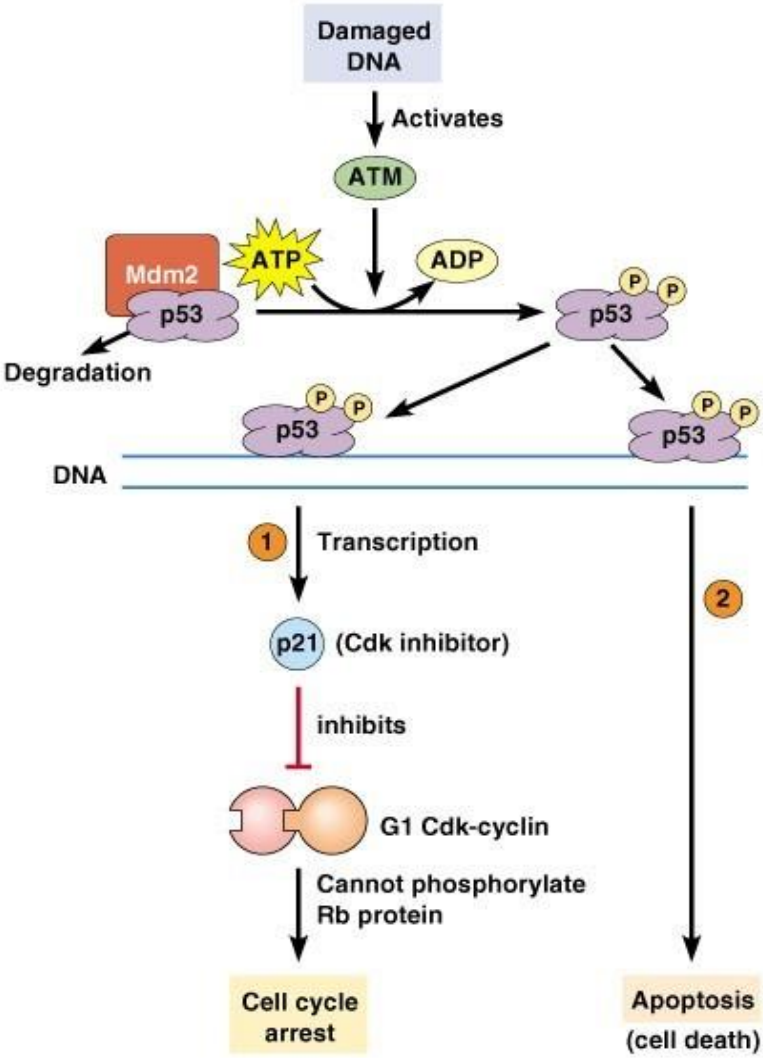
--> cell death (apoptosis)

Disruption/deletion of *p53* gen Inactivation of p53 protein

--> uncorrected DNA damage

--> uncontrolled cell proliferation

--> cancer



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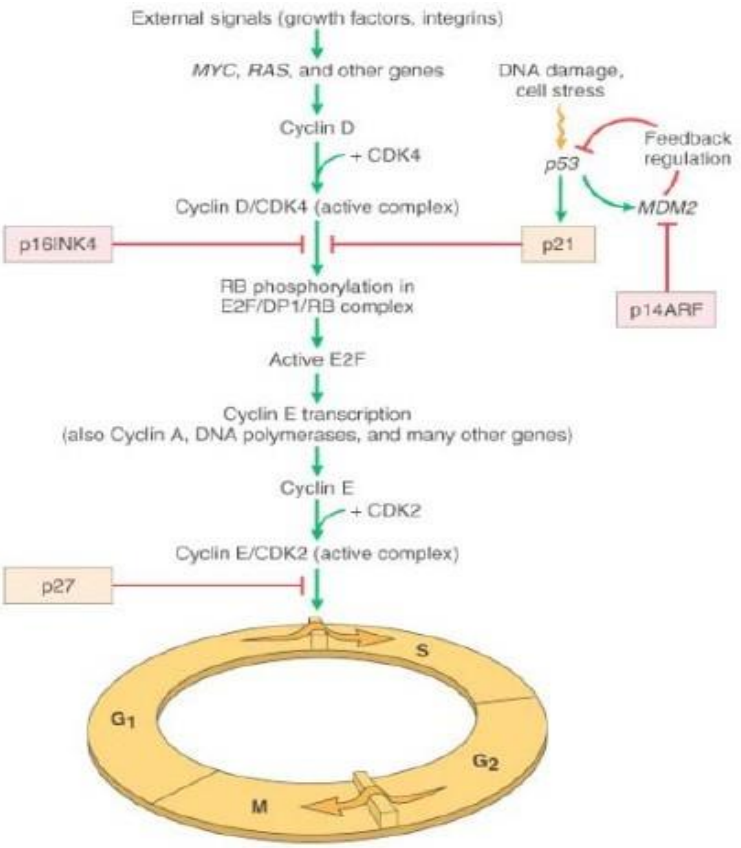
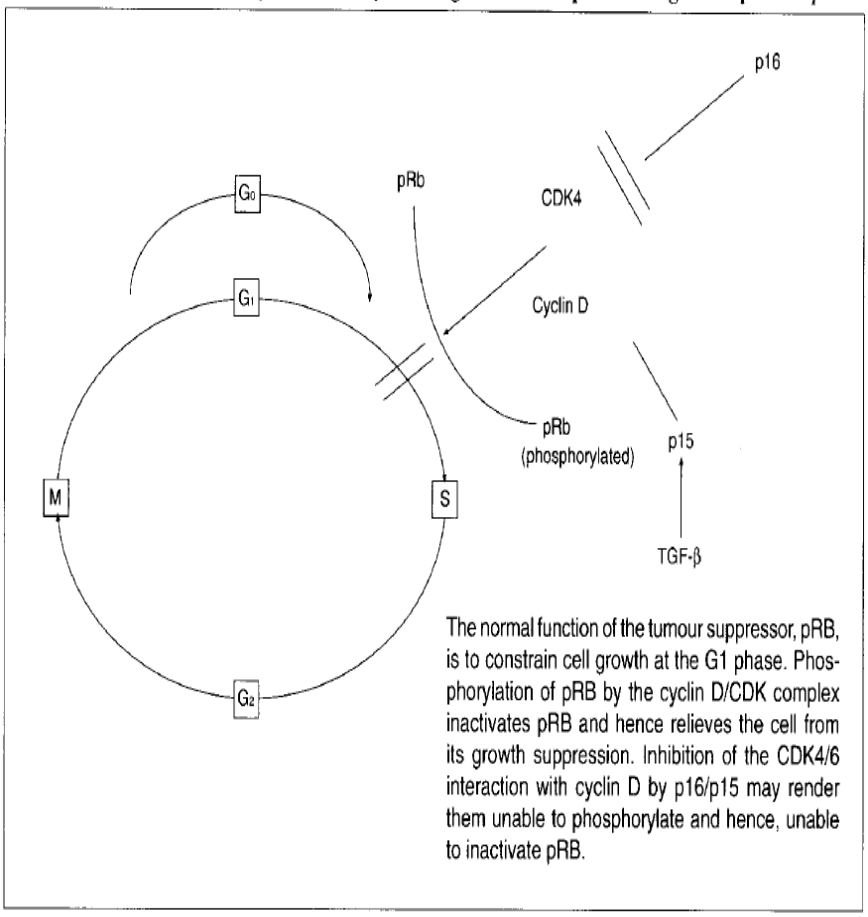


Figure 7-29 Schematic illustration of the role of cyclins, CDKs, and cyclin-dependent kinase inhibitors in regulating the G_1/S cell-cycle transition. External signals activate multiple signal

Fig 2. The cell cycle is normally controlled by the *RB* gene and the up-stream regulators *p16* and *p15*



TUMOR SUPPRESSOR GENES

		Disorders in which gene is affected	
Gene (locus)	Function	Familial	Sporadic
DCC (18q)	cell surface interactions	unknown	colorectal cancer
WT1 (11p)	transcription	Wilm's tumor	lung cancer
Rb1 (13q)	transcription	retinoblastoma	small-cell lung carcinoma
p53 (17p)	transcription	Li-Fraumeni syndrome	breast, colon, & lung cancer
BRCA1(17q)	transcriptional	breast cancer	breast/ovarian tumors
BRCA2 (13q)	regulator/DNA repair		

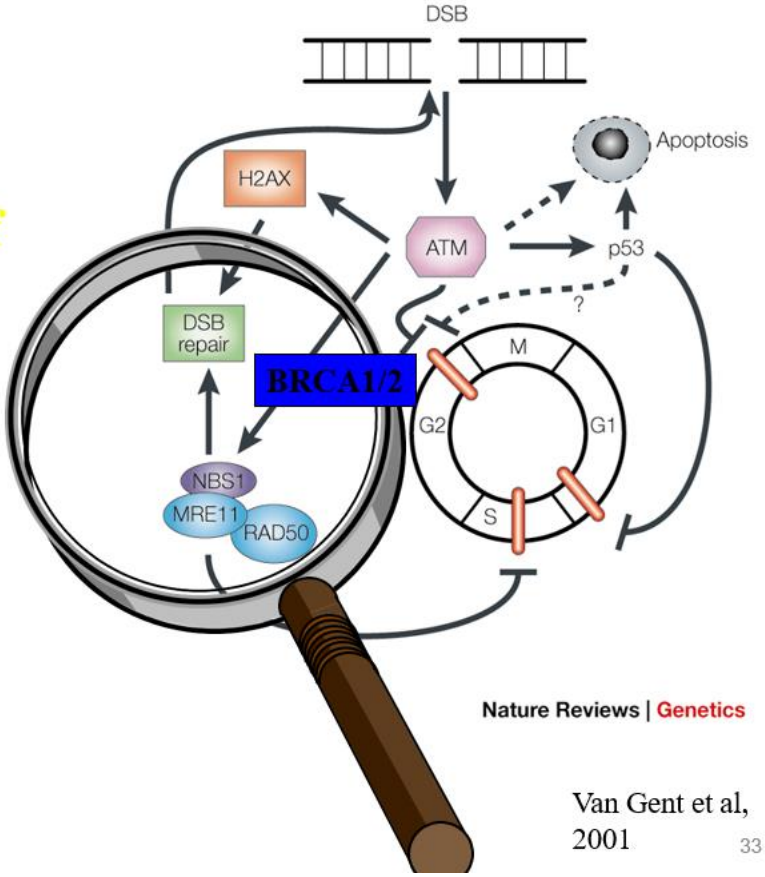
DNA REPAIR GENES

These are genes that ensure each strand of genetic information is accurately copied during cell division of the cell cycle.

Mutations in DNA repair genes lead to an increase in the frequency of mutations in other genes, such as proto- oncogenes and tumor suppressor genes.

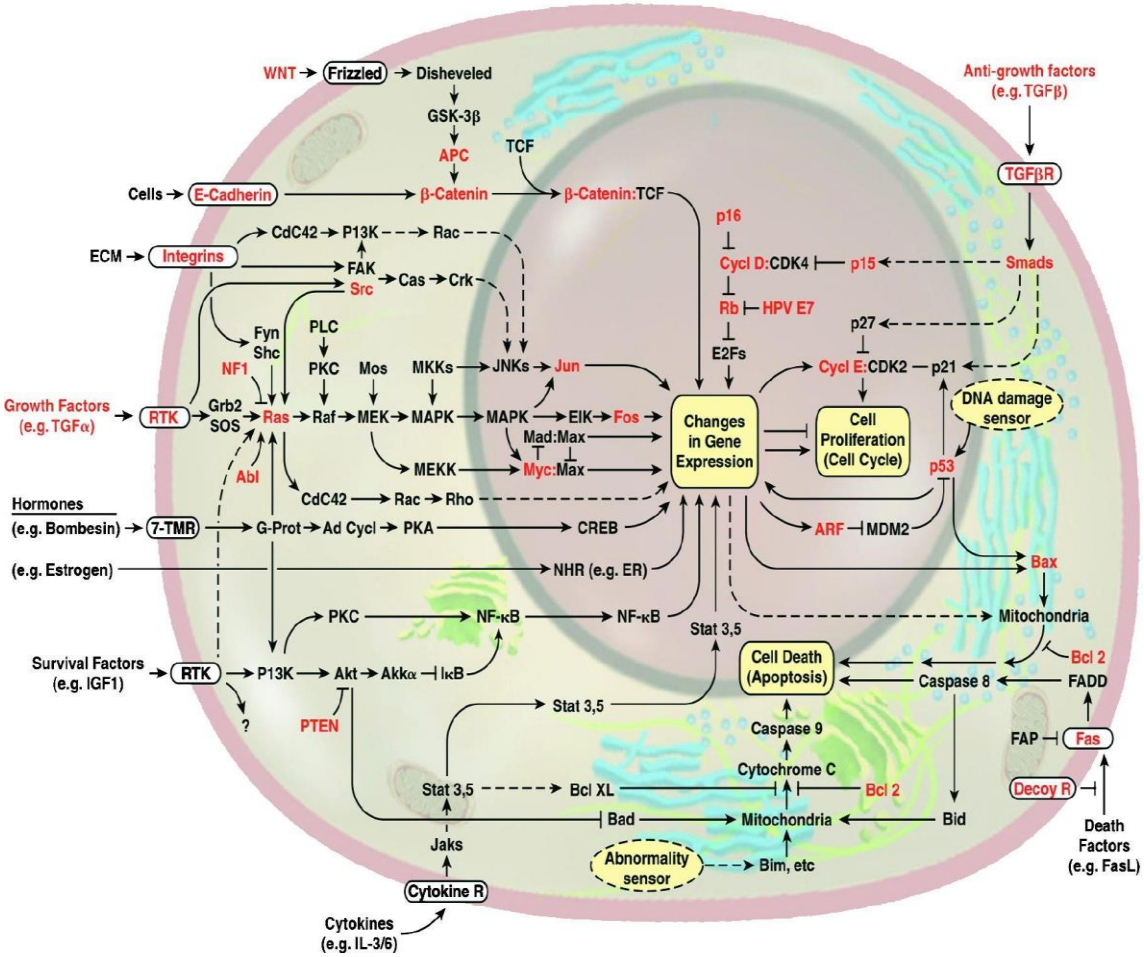
i.e. Breast cancer susceptibility genes (BRCA1 and BRCA2) Hereditary non-polyposis colon cancer susceptibility genes (MSH2, MLH1, PMS1, PMS2) have DNA repair functions. Their mutation will cause tumorigenesis.

Molecular mechanisms of DNA double strand break repair



Van Gent et al, 2001

Summary of 30 years of research (1971-2001)



Translocation and Bcr-Abl fusion in CML

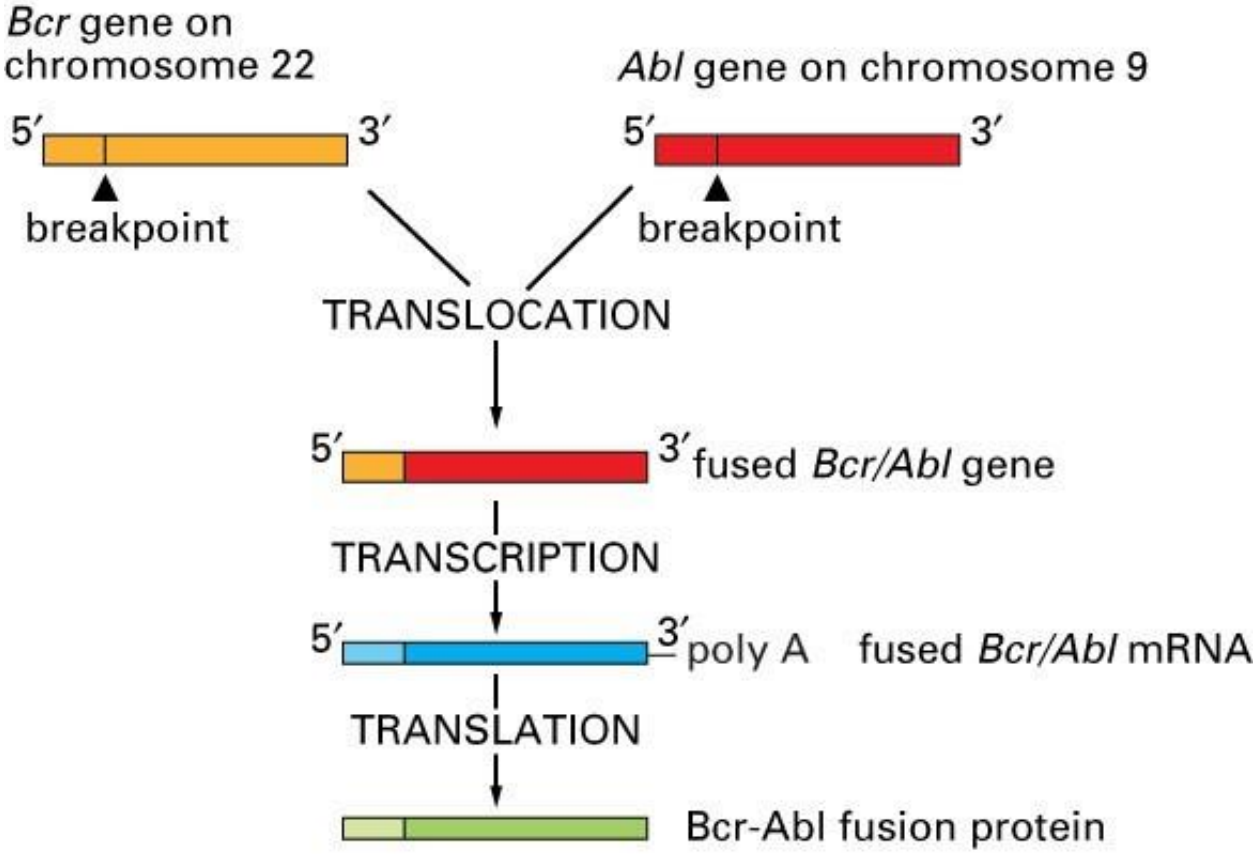


Figure 23–44. Molecular Biology of the Cell, 4th Edition.

Smart bullet STI-571 lockes itself to the target molecule

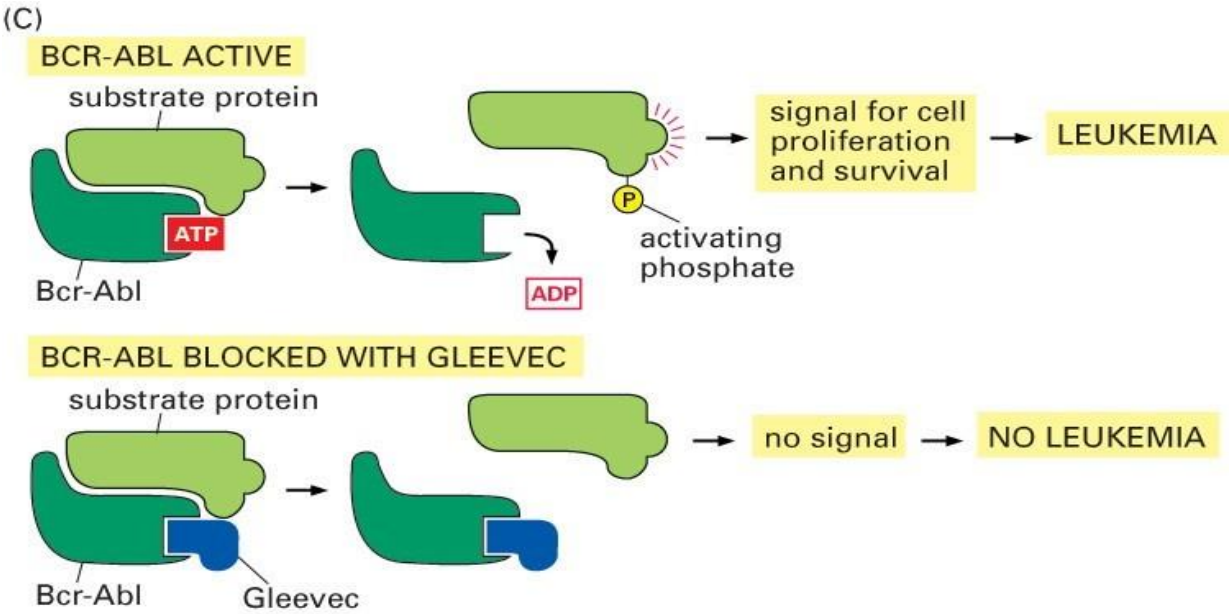


Figure 23–45 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

STI-571 against Bcr-Abl

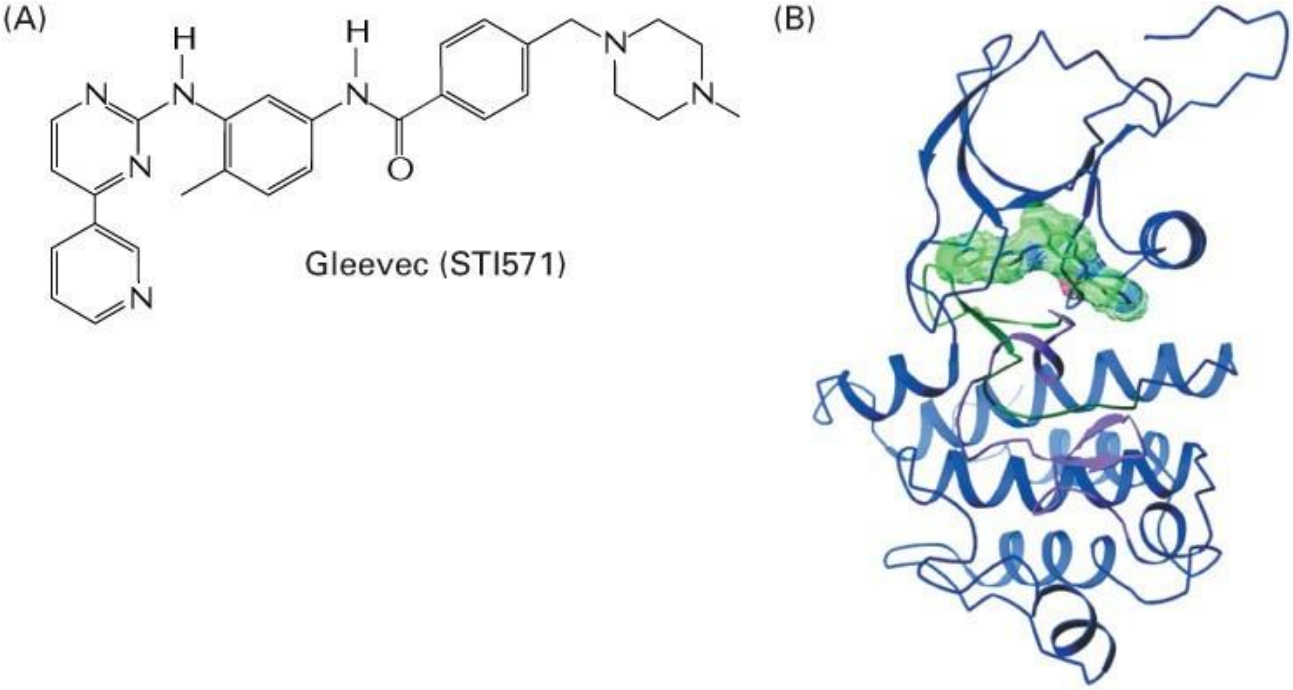
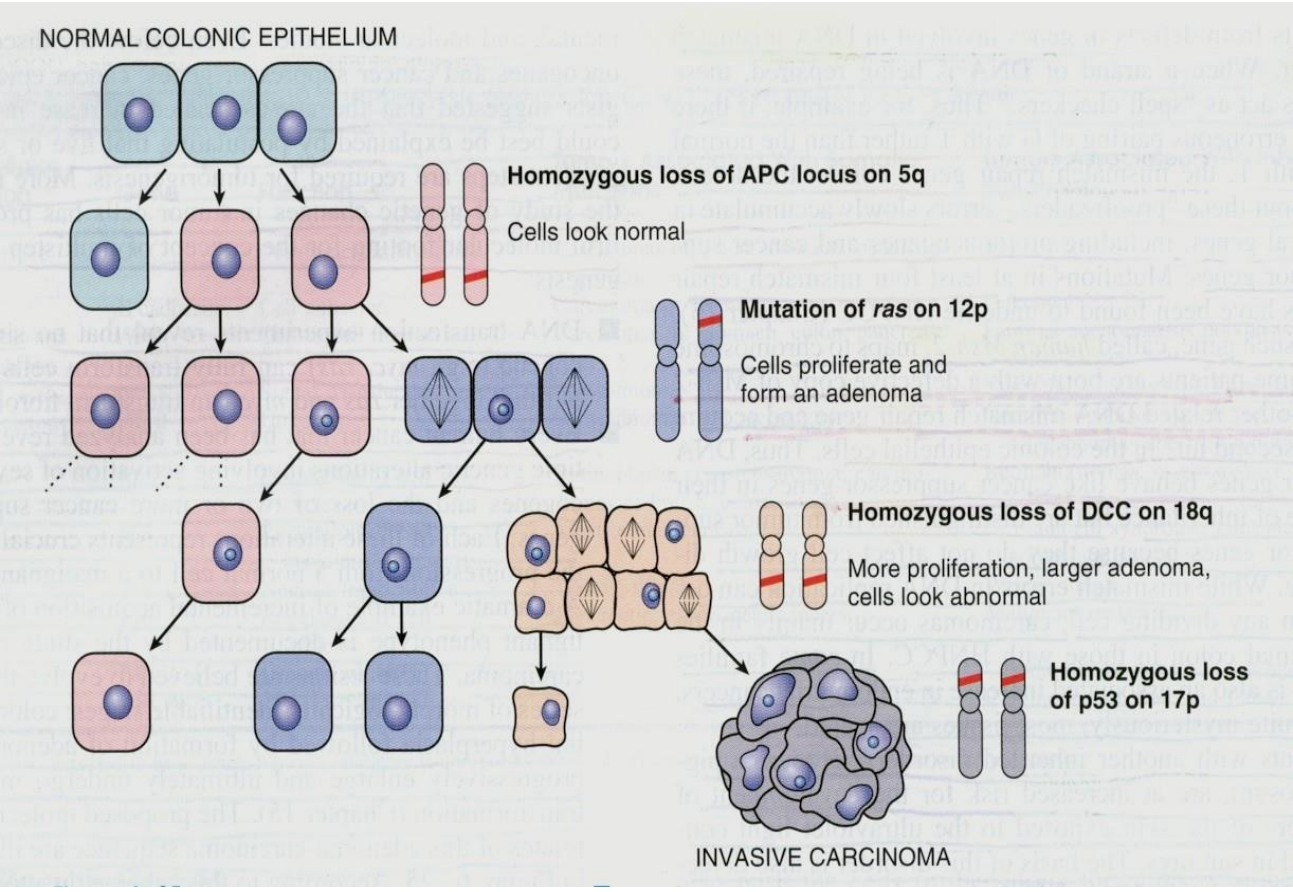


Figure 23–45 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Molecular Basis of Multistep Carcinogenesis



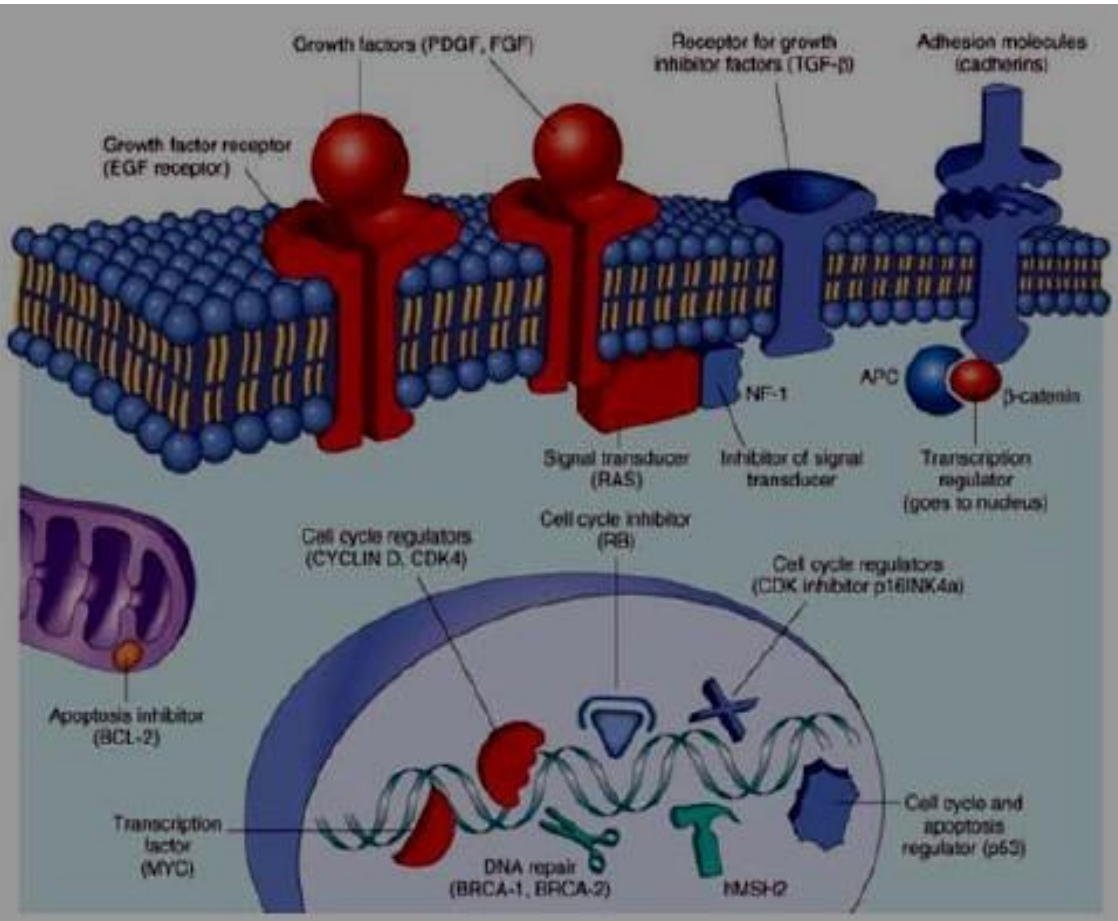
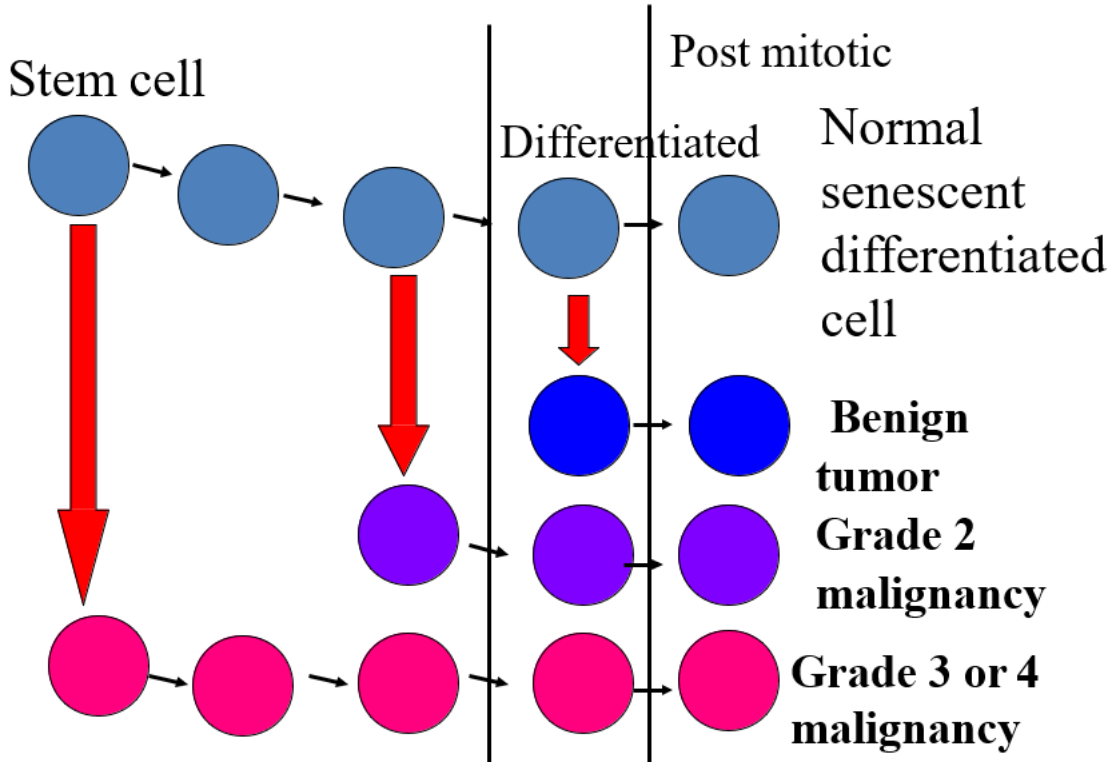


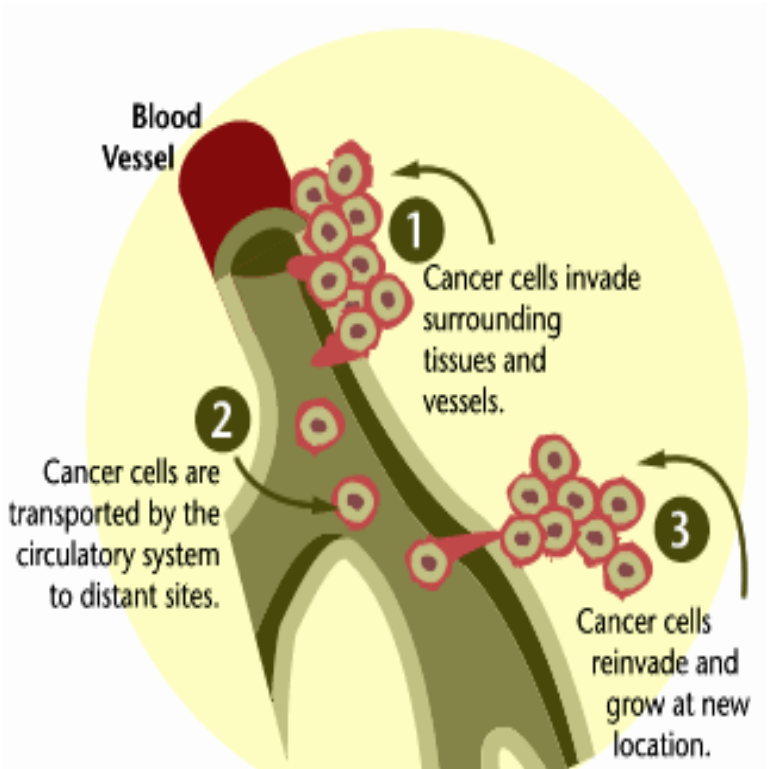
Figure 7-31 Subcellular localization and functions of major classes of cancer-associated genes. The protooncogenes are colored red, cancer suppressor genes blue, DNA repair genes green, and genes that regulate apoptosis purple.

Stem cells as the target of carcinogens



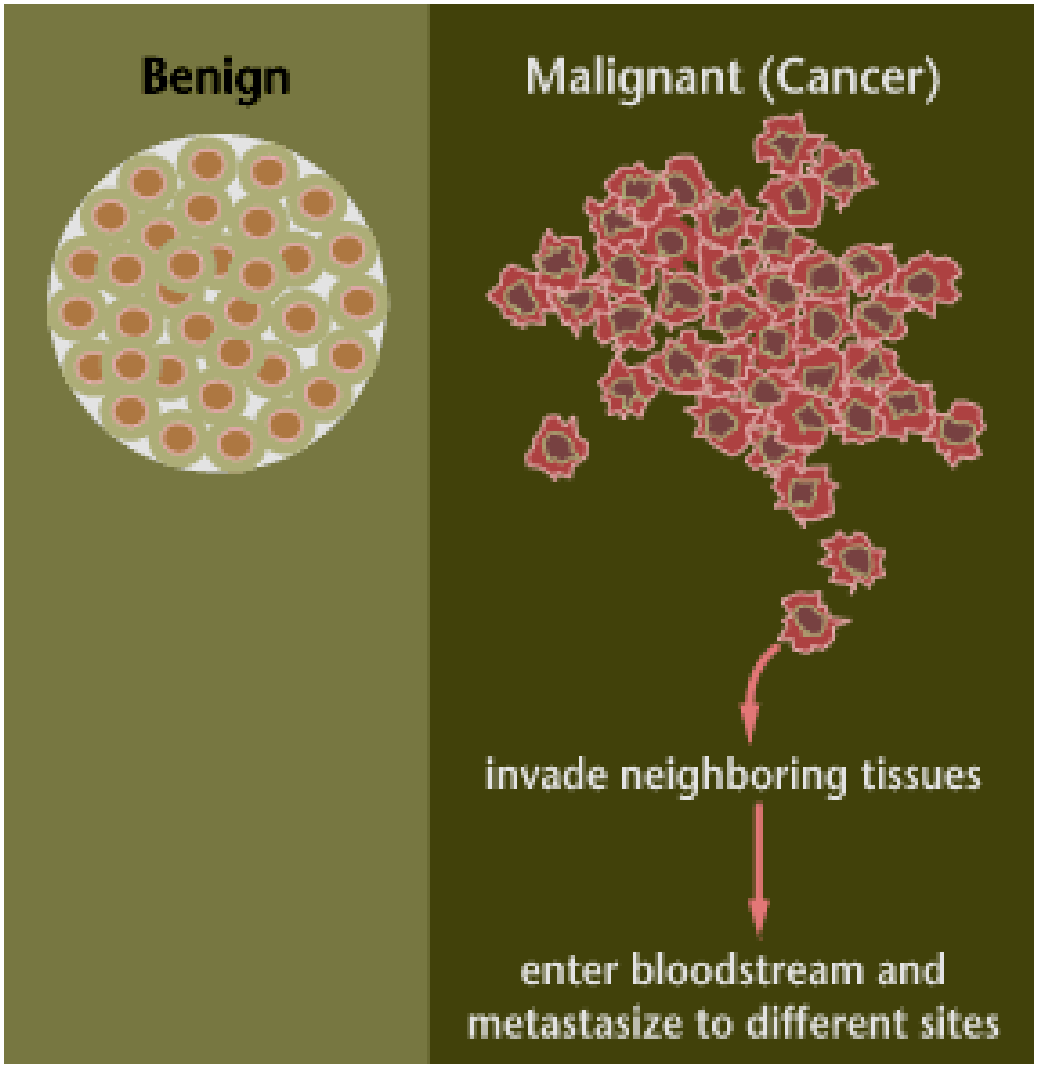
Invasion and Metastasis

- ***Abnormal cells proliferate and spread (metastasize) to other parts of the body***
- ***Invasion - direct migration and penetration into neighboring tissues***
- ***Metastasis - cancer cells penetrate into lymphatic system and blood vessels***

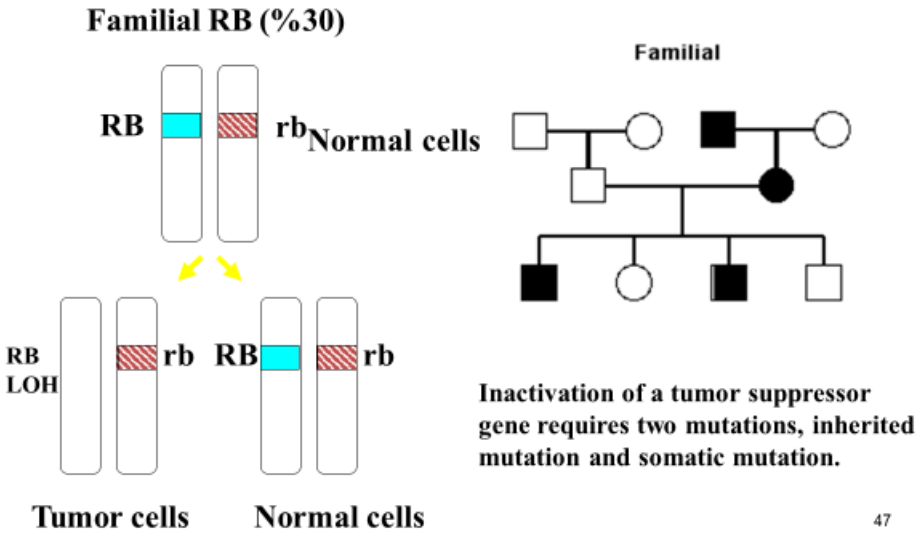


Malignant versus Benign Tumors

- ***Benign tumors generally do not spread by invasion or metastasis***
- ***Malignant tumors are capable of spreading by invasion and metastasis***
-

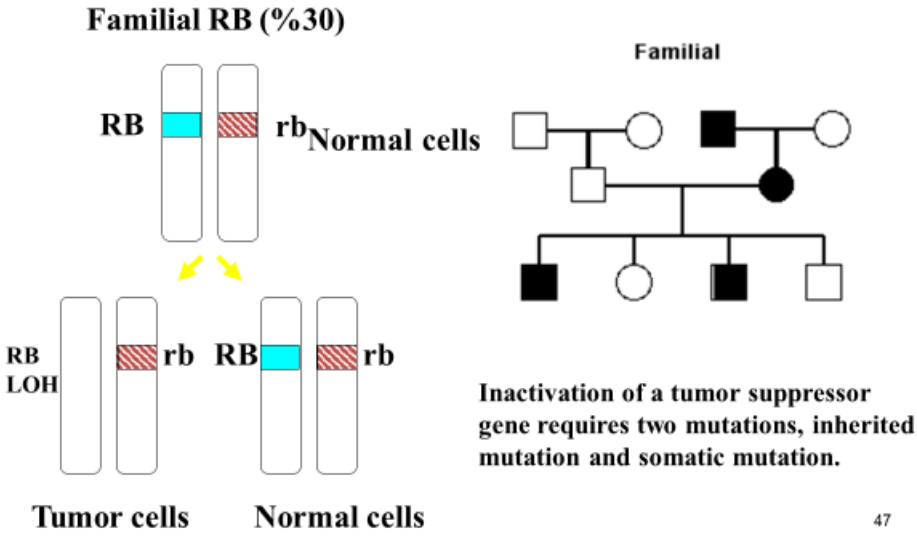


KNUDSON TWO HIT HYPOTHESIS IN FAMILIAL CASES



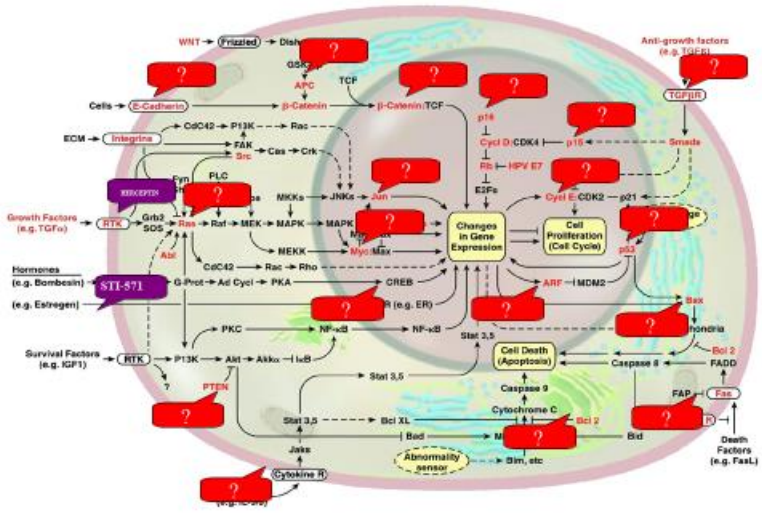
Inactivation of a tumor suppressor gene requires two mutations, inherited mutation and somatic mutation.

KNUDSON TWO HIT HYPOTHESIS IN FAMILIAL CASES



Inactivation of a tumor suppressor gene requires two mutations, inherited mutation and somatic mutation.

Thousands of Targets



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(https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types (AMERICAN CANCER SOCIETY)

https://www.mayoclinic.org/tests-procedure)

CANCER TREATMENT

Overview

Cancer treatment is the use of surgery, radiation, medications and other therapies to cure a cancer, shrink a cancer or stop the progression of a cancer.

Many cancer treatments exist. Depending on patient particular situation, you may receive one treatment or you may receive a combination of treatments.

Why it's done

The goal of cancer treatment is to achieve a cure for patient cancer, allowing you to live a normal life span. This may or may not be possible, depending on patient specific situation. If a cure isn't possible, patient treatments may be used to shrink patient cancer or slow the growth of patient cancer to allow you to live symptom free for as long as possible.

Cancer treatments may be used as:

- **Primary treatment.** The goal of a primary treatment is to completely remove the cancer from patient body or kill all the cancer cells.

  Any cancer treatment can be used as a primary treatment, but the most common primary cancer treatment for the most common types of cancer is surgery. If patient cancer is particularly sensitive to radiation therapy or chemotherapy, you may receive one of those therapies as patient primary treatment.

- **Adjuvant treatment.** The goal of adjuvant therapy is to kill any cancer cells that may remain after primary treatment in order to reduce the chance that the cancer will recur.

  Any cancer treatment can be used as an adjuvant therapy. Common adjuvant therapies include chemotherapy, radiation therapy and hormone therapy.

  Neoadjuvant therapy is similar, but treatments are used before the primary treatment in order to make the primary treatment easier or more effective.

- **Palliative treatment.** Palliative treatments may help relieve side effects of treatment or signs and symptoms caused by cancer itself. Surgery, radiation, chemotherapy and hormone therapy can all be used to relieve symptoms. Other medications may relieve symptoms such as pain and shortness of breath.

  Palliative treatment can be used at the same time as other treatments intended to cure patient cancer.

What you can expect

Many cancer treatments are available. Patient treatment options will depend on several factors, such as the type and stage of patient cancer, patient general health, and patient preferences. Together you and patient doctor can weigh the benefits and risks of each cancer treatment to determine which is best for you.

Cancer treatment options include:

- **Surgery.** The goal of surgery is to remove the cancer or as much of the cancer as possible.

- **Chemotherapy.** Chemotherapy uses drugs to kill cancer cells.

- **Radiation therapy.** Radiation therapy uses high-powered energy beams, such as X-rays or protons, to kill cancer cells. Radiation treatment can come from a machine outside patient body (external beam radiation), or it can be placed inside patient body (brachytherapy).

- **Bone marrow transplant.** Patient bone marrow is the material inside patient bones that makes blood cells from blood stem cells. A bone marrow transplant, also knowns as a stem cell transplant, can use patient own bone marrow stem cells or those from a donor.

  A bone marrow transplant allows patient doctor to use higher doses of chemotherapy to treat patient cancer. It may also be used to replace diseased bone marrow.

- **Immunotherapy.** Immunotherapy, also known as biological therapy, uses patient body's immune system to fight cancer. Cancer can survive unchecked in patient body because patient immune system doesn't recognize it as an intruder. Immunotherapy can help patient immune system "see" the cancer and attack it.

- **Hormone therapy.** Some types of cancer are fueled by patient body's hormones. Examples include breast cancer and prostate cancer. Removing those hormones from the body or blocking their effects may cause the cancer cells to stop growing.

- **Targeted drug therapy.** Targeted drug treatment focuses on specific abnormalities within cancer cells that allow them to survive.

- **Cryoablation.** This treatment kills cancer cells with cold. During cryoablation, a thin, wandlike needle (cryoprobe) is inserted through patient skin and directly into the cancerous tumor. A gas is pumped into the cryoprobe in order to freeze the tissue. Then the tissue is allowed to thaw. The freezing and thawing process is repeated several times during the same treatment session in order to kill the cancer cells.

- **Radiofrequency ablation.** This treatment uses electrical energy to heat cancer cells, causing them to die. During radiofrequency ablation, a doctor guides a thin needle through the skin or through an incision and into the cancer tissue. High-frequency energy passes through the needle and causes the surrounding tissue to heat up, killing the nearby cells.

- **Clinical trials.** Clinical trials are studies to investigate new ways of treating cancer. Thousands of cancer clinical trials are underway.

Other treatments may be available to you, depending on patient type of cancer.

How Surgery Is Used for Cancer

Surgery is used to prevent, diagnose, stage, and treat cancer. Surgery can also relieve (palliate) discomfort or problems related to cancer. Sometimes, one surgery can take care of more than one of these goals. In other cases, different operations may be needed over time. You will find specific cancer operations discussed in treatment information for each cancer type.

Surgery to diagnose cancer

Surgery is one way to help diagnose cancer. In most cases, the only way to know if a person has cancer and what kind of cancer it is, is by taking out a small piece of tissue (called a *sample*) and testing it. The diagnosis is made by looking at cells from the sample with a microscope or by doing other lab tests on it.

This procedure is called a *biopsy*. Biopsies taken during surgery are often referred to as *surgical biopsies*.

How a sample is taken depends on where the tumor is and what type of cancer is suspected. For example, the method used for prostate biopsies is different from those used for lung biopsies.

Learn more about different types of biopsies in Testing Biopsy and Cytology Specimens for Cancer.

Surgery to stage cancer

Staging surgery is done to find out how much cancer there is and how far it has spread. During this surgery, the area around the cancer including lymph nodes and nearby organs is examined. This is important because it provides information to guide future treatment decisions and predict how people will respond to treatment. To learn more about this, see Cancer Staging.

Curative surgery

Curative or primary surgery is usually done when cancer is found in only one part of the body, and it’s likely that all of the cancer can be removed. It is called "curative" because the purpose of the surgery is to remove all of the cancer completely. In this case, surgery can be the main treatment. It may be used along with other treatments like chemotherapy or radiation therapy given before or after the operation, but surgery can also be used alone.

Surgery to debulk cancer

Debulking surgery is used to remove some, but not all, of the cancer. It's called "debulking" because the tumor being treated is a large, bulky object and might be located very close to important organs or tissues. So, "de-bulking" the tumor can help make it smaller. This surgery is sometimes done when taking out the entire tumor would cause too much damage to nearby organs or tissues. For example, it may be used for advanced cancer of the ovary and some lymphomas. In these cases, the doctor may take out as much of the tumor as possible and then treat what’s left with radiation, chemotherapy, or other treatments.

Palliative surgery

This type of surgery is used to treat problems caused by advanced cancer. Palliative surgery can be used with other treatments to correct a problem that’s causing discomfort or disability. For example, some cancers in the belly (abdomen) may grow large enough to block (obstruct) the intestine. If this happens, surgery can be used to remove the blockage. Palliative surgery may also be used to treat pain when the pain is hard to control with medicine. Palliative surgery helps ease problems caused by cancer and helps people feel better, but because the cancer is usually in an advanced stage, it’s not done to treat or cure the cancer itself.

Supportive surgery

Supportive surgery is done to help make it easier for people to get other types of treatment. For example, a vascular access device such as a Port-A-Cath® or Infusaport® is a thin, flexible tube that can be surgically placed into a large vein and connected to a small drum-like device that’s placed just under the skin. A needle is put into the drum of the port to give treatments and draw blood, instead of putting needles in the hands and arms each time IV fluids, blood transfusions, or treatments are given.

Restorative (reconstructive) surgery

Reconstructive surgery is used to improve the way a person looks after major cancer surgery. It's also used to restore the function of an organ or body part after surgery. Examples include breast reconstruction after mastectomy or the use of tissue flaps, bone grafts, or prosthetic (metal or plastic) materials after surgery for head and neck cancers.

Preventive (prophylactic) surgery

Preventive or prophylactic surgery is done to remove body tissue that's likely to become cancer – even though there are no signs of cancer at the time of the surgery.

Sometimes an entire organ is removed when a person has a condition that puts them at very high risk for having cancer there. The surgery is done to reduce cancer risk and help prevent the chance of cancer, but it doesn't guarantee cancer prevention.

For example, some women with a strong family history of breast cancer have an inherited change in a breast cancer gene (called *BRCA1* or *BRCA2*). Because the risk of breast cancer is very high, removing the breasts (prophylactic mastectomy) may be considered. This means the breasts are removed before cancer is found.

Getting Ready for and Recovering from Cancer Surgery

Having surgery can be an overwhelming experience - not just the surgery itself, but the process of getting ready to have surgery, as well as recovering afterwards. But it's not always as difficult as you might fear. Your experience will depend on many things, including the type of cancer you have, the type of operation being done, and your overall health. Knowing what to expect and being prepared can help. It's important to:

- Learn as much as you can beforehand
- Ask questions so you know what to expect
- Understand that each person's situation is different

How long is too long to wait?

How soon you might need to have surgery after a cancer diagnosis can vary. It depends on the type of cancer and other factors. Sometimes cancer surgery needs to happen as soon as possible. Other times, waiting a while is not a problem. And sometimes you might need chemotherapy or radiation before having surgery. It's not unusual for patients to wait a few weeks after learning they have cancer to have surgery. Talk to your doctor and others on your health care team about how long to wait before having surgery. Don't be afraid to ask questions! You might want to ask if you have time to think about other options or get a second opinion.

Getting ready for surgery

Before surgery is called the *pre-operative phase*. There are many kinds of surgical procedures. But almost all types of operations have certain steps in common during the pre-operative phase.

Informed consent

Your health care team will give you details of the surgery before you give permission for them to do it. This is called informed consent. Sometimes details about informed consent vary from state to state, but your health care team will most likely do the following:

- Talk to you about your options, including how long it will be before surgery is scheduled
- Teach you about the operation, including the benefits, risks, and side effects
- Teach you what to expect before, during, and after surgery
- Have you sign consent forms
- Order some testing that will help them know you're healthy enough for surgery
- Give you hints, tips, and pointers to get you organized and ready for surgery and the recovery period

Other things that could affect surgery

Tobacco: If you smoke, your surgeon may ask you to stop before surgery. Using tobacco tightens (constricts) blood vessels and reduces the supply of oxygen to your body tissues. Smoking can delay healing and recovery. It can also increase the risk of complications after surgery.

Diet and alcohol: Being overweight or obese may affect surgery and recovery. Your surgeon may ask you to improve your diet, lose weight, or actively exercise before surgery. You may be advised to stop drinking alcohol, too.

Medications: Often the surgeon will ask you to stop taking certain medications, such as anti-inflammatory pain medications and blood thinners. This is because those medications can increase your risk of bleeding during the surgery.

Other drugs: Be sure to tell your doctor and surgeon about all medications, including vitamins, supplements, and marijuana or street drugs you may use. Some of these may lead to problems before and after surgery.

Anesthesia history: You will probably be asked if you or your family members have had problems in the past with anesthesia. This is because there are things that can be done to prevent problems, such as nausea, vomiting, and being overly sleepy after getting anesthesia.

Pre-operative testing

You'll probably need some tests so your health care team can understand your overall health and to find out if you can tolerate surgery. The tests you might need will depend on your situation, but here are some of the common tests that might be done:.

- Blood tests to check your blood count, blood sugar, kidney and liver function, and your risk for bleeding
- Urine test to make sure your kidneys are working and to check for infection
- Chest x-ray to check your lungs
- Electrocardiogram (ECG or EKG) to check your heart
- Other x-rays, tests, or scans

Prep for surgery

Usually a "prep" is needed before surgery that involves getting anesthesia. You will most likely be told to stop eating food and drinking liquids at a certain time before surgery. Sometimes you will be told to stop eating solid foods at a certain time, and then liquids will be stopped later. Some surgeries require you to take a laxative or enema beforehand to be sure your bowels are empty. You may need to have an area of your body shaved before surgery to keep hair away from the surgical site and your skin will be cleaned well before the operation to reduce the risk of infection.

Getting Anesthesia

Anesthesia makes you unable to feel pain for a period of time. Depending on the type and extent of the operation, you may get drugs to make you sleep, too. In some cases, you may have a choice as to which type of anesthesia you prefer.

- *Local anesthesia* is often used for minor surgeries, such as biopsies near the body surface. A needle is used to put a drug into the area. This numbs the nerves that cause pain. You stay awake and usually feel only pressure during the procedure. You can usually go home shortly afterwards.

- *Topical anesthesia* is rubbed or sprayed onto a body surface instead of being put in with a needle. For example, a spray is sometimes used to numb the throat before a scope is passed down to the stomach or lungs. Like local anesthesia, you can usually go home shortly afterwards.
- *Regional anesthesia* (such as a nerve block or spinal anesthesia) numbs a larger part of the body, but you stay awake. For example, a needle can be used to put medicine into an area around the spinal cord, which affects certain nerves coming out of it. But a nerve block may also mean injecting medicine around nerves in the arms or legs. The location the injection is given depends on what part of the body needs to be numb. Medicine may be given as a single injection or as an ongoing IV infusion. You stay awake, but you may be given something to help you relax. You will go to the recovery room until some of the anesthesia wears off.
- *Twilight anesthesia* is a mild dose of a drug through an IV that sedates you. It does not make you become unconscious, but you are sedated and asleep. You won't remember the surgery and the time right after. You will go to the recovery room until some of the anesthesia wears off.
- *General anesthesia* puts you into a deep sleep so you are unconscious for the surgery. It’s often started by having you breathe in a drug through a face mask or by putting a drug into a vein in your arm. Once you are asleep, an endotracheal or ET tube is put in your throat to make it easy for you to breathe. Your heart rate, breathing rate, and blood pressure will be closely watched during the surgery. A doctor or nurse who specializes in giving anesthesia (either an anesthesiologist or nurse anesthetist) takes care of you while you are asleep. They also take out the ET tube when the operation is over. You won't remember the surgery and the time right after is often very hazy. You will go to the recovery room until some of the anesthesia wears off.

Recovering from surgery

How fast you recover from surgery depends on the kind of surgery you had and your overall health. Be sure to ask your health care team what you might expect in the period right after your surgery.

Tubes and catheters

Your throat may be sore for a while if you had an endotracheal (ET) tube. You might also have tube (called a *Foley catheter*) draining urine from your bladder into a bag. This is usually taken out as soon as possible after surgery to prevent infection..

Surgical drains

You may have a tube or tubes (called *drains*) coming out of the surgical opening in your skin. Drains allow the excess fluid that collects at the surgery site to leave the body. Your doctor will take them out as soon as possible when they stop collecting fluid, depending on the type of surgery you had.

Eating and drinking

You may not feel like eating or drinking after surgery, but this is an important part of the recovery process. Your health care team may start you out with ice chips or clear liquids. If you have a catheter collecting your urine, they will check that you are passing urine normally after they take it out. They may want to measure the amount of urine you make by having you go in a special container.

The stomach and intestines (digestive tract) is one of the last parts of the body to recover from the drugs used during surgery. You'll need to have signs of stomach and bowel activity before you'll be allowed to eat. Along with checking your surgical wound and other parts of your body, your doctor or nurse will listen for bowel sounds in your belly and will ask if you have passed gas. These are signs that your digestive tract is starting to work normally again. You will probably be on a clear liquid diet until this happens. Once it does, you may get to try solid foods.

Activity

Your health care team will probably try to have you move around as soon as possible after surgery. Sometimes they will even have you walk or go to physical therapy the same day or next day. While moving around or getting used to the devices may be hard at first, these things help speed your recovery by getting your digestive tract moving, helps your circulation, and helps prevent blood clots. Again, be sure to let your team know if you're having pain that is affecting your activity, so they can give you medicine to control it.

Some patients will have devices wrapped around their legs that squeeze gently and release every so often to also help your circulation and prevent blood clots.

Your team may also encourage you to do deep breathing exercises. You might have a device called a spirometer that you will need to use. This helps fully inflate your lungs and reduces the risk of lung infection (pneumonia).

Going home after surgery

Discharge planning to go home or to another setting will start very soon after surgery. The plans get more final once you're eating, drinking, and walking. Of course, this will depend on other factors too, such as the results of the surgery and tests done afterward.

Pain control is important, both while you are in the hospital, and at home if you need it. If you're in pain, be sure to let your health care team know.

Recovery is different for everyone. Wounds heal at different rates, and some operations are more involved than others. You may need help at home for a while after surgery. If family members or friends are unable to do all that's needed, your health care team may be able to arrange to have a nurse or nurse's aide visit you at home for a short while.

Fully understanding the likely result of the operation before it's done is an important part of helping you adjust to the changes that have been made to your body. It is completely normal to need to take time to get used to any permanent changes in your body. Sometimes these changes can be really hard to get used to, and it's ok to feel sad or angry about them. Your health care team is ready to help you with those feelings, and won't be surprised if you tell them that you feel this way. It's important to let your care team know if you are feeling. Be as specific as you need to with your questions, and make sure your health care team gives answers you can understand.

When to call your doctor after cancer surgery

At this time, you're probably more in tune with your body than you've ever been in your life. You notice every physical change. Don't take any physical symptoms you may have lightly.

Be sure you know how to contact your health care team members after hours and on weekends and holidays.

Some surgery side effects may come and go quickly, but others may be a sign of serious problems. Tell your doctor or nurse right away if you suffer from any of the following symptoms after surgery:

- A fever (instructions for this can vary so check to be sure what fever is high enough to call about)
- Intense (shaking) chills
- Bleeding from your surgical site or drain site, or unexplained bruising and bleeding anywhere else
- Pain or soreness at the surgical site that's getting worse or not relieved with the pain medicine
- Unusual pain anywhere, including in your legs, chest, belly, and intense headaches
- Shortness of breath or trouble breathing
- Having trouble urinating; pain when you urinate; or bloody, bad smelling, or cloudy urine
- Any other signs mentioned by your doctor or nurse

Don't hesitate to let your doctor know about any new problems or concerns you have. It's always best to find out the cause of a problem so it can be dealt with right away.

Risks of Cancer Surgery

Before you decide to have surgery or any other procedure, it's important that you understand the risks. Any type of medical procedure has risks. Different procedures have different kinds of risks and side effects. Be sure to discuss the details of your case with your health care team, who can give you a better idea about what your risks might be. It is important that the expected benefits of the surgery outweigh the possible risks.

Preventing side effects of cancer surgery

Your surgical team will take many steps to reduce your risk of side effects and complications. This includes things like shaving and cleaning the area before cutting the skin to avoid infection, use of special leg pumps and low-dose blood thinners to avoid blood clots, and breathing treatments (respiratory therapy) to help prevent pneumonia. Ask your doctor about the possible complications of your surgery and what can and will be done to help prevent them.

Possible side effects of cancer surgery

Possible complications during surgery may be caused by the surgery itself, drugs used, and your overall health. Generally speaking, the more complex the surgery is, the greater the risk of side effects.

Minor operations and taking tissue samples (biopsies) usually have less risk than a bigger surgery. Pain at the surgery site is the most common problem. Infections at the site and reactions to the drugs used to numb the area (local anesthesia) are also possible.

Some side effects are possible during and after surgery. Generally, these side effects are not expected to be life threatening. They can include:

- Bleeding
- Blood clots
- Damage to nearby tissues
- Drug reactions
- Damage to other organs
- Pain
- Infections
- Slow recovery of other body functions

Bleeding

Bleeding is part of any surgery and is usually controlled. Bleeding can happen either inside the body (internally) or outside the body (externally). Bleeding can occur if a blood vessel was not sealed off during surgery or if a wound opens up.

Doctors try to limit the risk of bleeding by being very careful when working near blood vessels. They also look out for other factors that can make it easier to bleed such as checking lab tests to make sure a person's blood can clot normally. Serious bleeding may require another operation to find the source of the bleeding and stop it. This kind of bleeding may also require a blood transfusion to replace the blood that's been lost.

Blood clots

Blood clots can form in the deep veins of the legs after surgery, especially if a person stays in bed for a long time. Such a clot can become a serious problem if it breaks loose and travels to another part of the body, such as a lung. This is a big reason why you'll be encouraged to get out of bed to sit, stand, and walk as soon as possible.

Damage to nearby tissues

Internal organs and blood vessels can be damaged during surgery. Again, doctors are careful to do as little damage as possible.

Drug reactions

Some people have reactions to the drugs used (anesthesia) or other medicines needed during surgery. Although rare, these can be serious because they can cause dangerously low blood pressure. Your heart rate, breathing rate, blood pressure, and other signs will be watched closely throughout the surgery to prevent, look for, or correct this.

Damage to other organs

Surgery can lead to problems with other organs, such as the lungs, heart, or kidneys. These problems are very rare but can be life-threatening. They are more likely to happen to people who already have problems with these organs. This is why doctors get a complete medical history and do tests to look for possible risks before surgery is done.

Pain

Almost everyone has some pain after surgery. Pain is normal, but it should not be allowed to slow down your recovery. There are many ways to deal with and help control surgical pain. Medicines for pain can range from acetaminophen (Tylenol) to anti-inflammatory medicines or stronger drugs, like morphine.

See Cancer Pain for more information on pain medicines..

Infections

Because getting an infection is serious, you may be asked to help prevent infection by washing with a special soap for a few days before surgery. This soap is especially good at killing bacteria, and can help to prepare your skin for surgery. This is one way you can help prevent an infection from happening. Even though you do things like this before surgery, and the surgical team takes great care to prevent infection, an infection at the site of the incision (cut) is a possible problem. Antibiotics, either as a pill or given through a vein in your arm (IV), are able to treat most infections.

A lung infection (pneumonia) can occur, especially in patients with reduced lung function, such as people who have a chronic lung illness or people who smoke. Doing deep breathing exercises as soon as possible after surgery helps lessen this risk.

Other infections can develop within the body, especially if the stomach or intestines were opened during the operation, or if a catheter to drain urine was used and left in place for a while. Doctors and nurses check for infection and monitor any changes in your temperature, skin or wounds to try to prevent this. But if it happens, antibiotics will be needed.

Slow recovery of other body functions

Some body functions, such as bowel activity, can be slow to recover and can sometimes become serious, too. Your energy level can drop, too. Getting out of bed and walking around as soon as possible after surgery can help lower this risk.

Possible long-term side effects of cancer surgery

Ask if there could be any long-term effects from the surgery. Long-term side effects depend on the type of surgery done. You might want to ask about effects on your ability to have a baby or father a child (fertility) if surgery is being done on or around your reproductive organs. People who have colorectal cancer surgery may need an opening in the belly to which the end of the colon is attached (a colostomy). Men having their prostate removed (radical prostatectomy) are at risk for losing control of their urine (incontinence) or becoming unable to get or keep an erection (impotence). Your doctor should talk to you about the possible long-term effects of surgery before the operation.

Can surgery cause cancer to spread?

You may have heard that surgery for cancer can cause the cancer to spread. It's very rare for surgery to cause cancer to spread. Advances in equipment used during surgery and more detailed imaging tests have helped make this risk very low. Still, there are some important situations when this can happen. Doctors who have a lot of experience in treating cancer with surgery are very careful to avoid these situations.

In the past, larger needles were used to take a piece of the tumor (biopsy) to look at under a microscope in the lab. Back then, the chance of spread or “seeding” from the biopsy was higher. Now, it’s more likely that a small needle is used to remove a piece of the tissue (called a *needle biopsy*). With the smaller needle, the chances of a biopsy causing a cancer to spread or “seed” are very low. Still, some liver (hepatic), kidney (renal), and other tumors have a very small risk of this happening during a biopsy procedure.

Most types of cancers can be safely sampled by what is called an *incisional biopsy*, where the surgeon cuts through the skin to remove a small part of the tumor. But there are a few exceptions, such as certain tumors in the eyes or in the testicles. Doctors may treat these types of cancer first, without taking a biopsy, or may recommend removing (resecting) the entire tumor if it’s likely to be cancer. Sometimes, a needle biopsy can be used safely, and then if the tumor is found to be cancer, the whole tumor is removed.

Needle biopsies can't be used for some tumors. In these cases, the tumor may need to be partially or totally removed. There are a few kinds of tumors that do have a low risk of cancer spread from the resection procedure. Examples include parathyroid and gallbladder tumors, and some sarcomas. However, this only rarely happens due to the advances in equipment and imaging tests.

A common myth about cancer is that it will spread if it's exposed to air during surgery. Some people may believe this because they often feel worse after surgery than they did before. But it's normal to feel this way when recovering from any surgery. Another reason people may believe this is because during surgery the doctor may find more cancer than was expected from scans and x-rays. This can happen, but it's not because of the surgery – the cancer was already there – it just didn't show up on the tests that were done. Cancer does not spread because it has been exposed to air. If you delay or refuse surgery because of this myth, you may be harming yourself by not getting effective treatment.

Less Invasive Cancer Surgery Techniques

When people think of surgery, they usually think of a surgeon making large incisions (cuts) through the skin, muscle, and other layers. Or, they picture a doctor using a surgical knife (scalpel) and other surgical instruments to cut into and remove, repair, or replace parts of the body affected by disease. This standard or traditional kind of surgery is called *conventional surgery*. You can learn more about it in How Surgery Is Used for Cancer.

Newer surgical techniques are less invasive, meaning they use different types of surgical instruments, usually need smaller incisions, and lead to less pain and shorter recovery times. Some of these techniques are described here.

Laser surgery

A laser is a highly focused and powerful beam of light energy which can be used for very precise surgical work. It can be used instead of a blade or scalpel to cut through tissue. It can also be used to burn and destroy (vaporize) tumors or precancerous growths and treat cancers of the cervix, penis, vagina, vulva, lung, and skin.

Even though burning with a laser sounds very damaging, laser surgery involves less cutting and damage because it's less invasive than conventional surgery. For instance, with fiber optics and special scopes, the laser can be directed inside a natural body opening without having to make a large cut. The laser is then precisely aimed to destroy the tumor.

Lasers are also used in a type of surgery called *photoablation* or *photocoagulation* to destroy tissues or seal tissues or blood vessels. This type of surgery is often used to relieve symptoms, such as when large tumors block the windpipe (trachea) or swallowing tube (esophagus), causing problems breathing or eating.

You can learn more details about lasers in Lasers in Cancer Treatment.

Cryosurgery

Cryosurgery uses a liquid nitrogen spray or a very cold probe to freeze and kill abnormal cells. This technique is sometimes used to treat pre-cancerous conditions, like those affecting the skin, cervix, and penis. Cryosurgery can also be used to treat some cancers, like those in the liver and prostate. A scan (like an ultrasound or CT scan) might be used to guide the probe to where the cancer cells are. This limits damage to nearby healthy tissue.

Electrosurgery

A high-frequency electrical current can be used to destroy cells. This may be done for some cancers of the skin and mouth.

Radiofrequency ablation

Radiofrequency ablation, or RFA, is a type of hyperthermia - a treatment that uses heat to destroy cancer cells. In RFA, high-energy radio waves are sent through a needle to heat and destroy cancer cells. RFA may be used to treat cancer tumors in the liver, lungs, kidney, and other organs.

Mohs surgery

Mohs micrographic surgery is also called microscopically controlled surgery. It's used to remove certain skin cancers by shaving off one very thin layer at a time. After each layer is removed, the doctor looks at the tissue with a microscope to check for cancer cells. This procedure is repeated until all the cells in a layer look normal.

Mohs surgery is used when the extent of the cancer is not known or when as much healthy tissue as possible needs to be saved, such as when treating skin cancers on the face.

Laparoscopic surgery

A laparoscope is a long, thin, flexible tube that can be put through a small cut to look inside the body. It's sometimes used for biopsy procedures (taking pieces of tissue to check for cancer). Research has found that by making small holes and using special long, thin instruments, the laparoscope can also be used to remove some tumors. This can help reduce blood loss during surgery and pain afterward. It can also shorten hospital stays and allow people to heal faster. Laparoscopic surgery is used commonly today for many operations.

Doctors can safely and effectively use laparoscopic surgeries for some cancers of the colon, rectum, liver, prostate, uterus, and kidney. Uses on other types of cancer are being studied.

Thoracoscopic surgery

A thoracoscope is a thin tube with a tiny video camera on the end that can be put through a small cut into the chest after the lung is collapsed. This allows the doctor to see inside the chest. Tissue samples of any areas of concern on the lining of the chest wall can be taken out, fluid can be drained, and small tumors on the surface of the lung can be removed.

This type of surgery leads to less cutting and has even been used to remove parts of the lung that contain cancer. Studies have shown that for early-stage lung cancer, results using this approach are much the same as removing part of the lung through a cut in the side of the chest.

Robotic surgery

Robotic surgery is a type of laparoscopic (or thoracoscopic) surgery where the doctor uses precise robotic arms to control some of the surgical instruments. The advantages of this type of surgery are largely the same as laparoscopic and thoracoscopic surgery: it can help reduce blood loss during surgery and pain afterward. It can also shorten hospital stays and let people to heal faster.

Robotic surgery is sometimes used to treat cancers of the colon, prostate, and uterus.

Stereotactic radiation therapy

As doctors have learned how to better control the energy waves used in radiation therapy, newer radiation techniques have been developed that blur the lines between traditional types of treatment. Stereotactic radiation therapy is a radiation technique that is so precise it's sometimes called *stereotactic radiosurgery*, even though no cut is actually made. In fact, the machines used to deliver this treatment have names like Gamma Knife and CyberKnife, even though no knife is involved. By using radiation sources from different angles, stereotactic radiation therapy delivers a large precise radiation dose to a small tumor area. The brain is the most common site that can be treated using this technique, but it’s also used on some head, neck, lung, spine, and other tumors. Researchers are looking for ways to use it to treat other types of cancer, too. You can learn more about this kind of treatment in Radiation Therapy.

- **TREATMENTS AND SIDE EFFECTS**

- **TREATMENT TYPES**

- **CANCER SURGERY**

Ostomies

An ostomy (or stoma) is a surgical opening made in the skin when a problem is not allowing a part of the body to function well. Learn the different types of ostomies, why they might be needed, and how they might affect a person's life.

Types of Ostomies

These guides will help you better understand what an ostomy is, why it's needed, and how to manage it.

- Colostomy Guide
- Ileostomy Guide
- Urostomy Guide
- Tracheostomy Guide

Radiation therapy

Radiation therapy is a type of cancer treatment that uses beams of intense energy to kill cancer cells. Radiation therapy most often uses X-rays, but protons or other types of energy also can be used.

The term "radiation therapy" most often refers to external beam radiation therapy. During this type of radiation, the high-energy beams come from a machine outside of patient body that aims the beams at a precise point on patient body. During a different type of radiation treatment called brachytherapy (brak-e-THER-uh-pee), radiation is placed inside patient body.

Radiation therapy damages cells by destroying the genetic material that controls how cells grow and divide. While both healthy and cancerous cells are damaged by radiation therapy, the goal of radiation therapy is to destroy as few normal, healthy cells as possible. Normal cells can often repair much of the damage caused by radiation

Why it's done

More than half of all people with cancer receive radiation therapy as part of their cancer treatment. Doctors use radiation therapy to treat just about every type of cancer. Radiation therapy is also useful in treating some noncancerous (benign) tumors.

How radiation therapy is used in people with cancer

Patient doctor may suggest radiation therapy as an option at different times during patient cancer treatment and for different reasons, including:

- As the only (primary) treatment for cancer
- Before surgery, to shrink a cancerous tumor (neoadjuvant therapy)
- After surgery, to stop the growth of any remaining cancer cells (adjuvant therapy)
- In combination with other treatments, such as chemotherapy, to destroy cancer cells
- In advanced cancer to alleviate symptoms caused by the cancer

Risks

Radiation therapy side effects depend on which part of patient body is being exposed to radiation and how much radiation is used. You may experience no side effects, or you may experience several. Most side effects are temporary, can be controlled and generally disappear over time once treatment has ended.

Part of body being treated	**Common side effects**
Source: National Cancer Institute, 2016	
Any part	Hair loss at treatment site (sometimes permanent), skin irritation at treatment site, fatigue
Head and neck	Dry mouth, thickened saliva, difficulty swallowing, sore throat, changes in the way food tastes, nausea, mouth sores, tooth decay
Chest	Difficulty swallowing, cough, shortness of breath
Abdomen	Nausea, vomiting, diarrhea
Pelvis	Diarrhea, bladder irritation, frequent urination, sexual dysfunction

Some side effects may develop later. For example, in rare circumstances a new cancer (second primary cancer) that's different from the first one treated with radiation may develop years

later. Ask patient doctor about potential side effects, both short and long term, that may occur after patient treatment.

How you prepare

Before you undergo external beam radiation therapy, patient health care team guides you through a planning process to ensure that radiation reaches the precise spot in patient body where it's needed. Planning typically includes:

- **Radiation simulation.** During simulation, patient radiation therapy team works with you to find a comfortable position for you during treatment. It's imperative that you lie still during treatment, so finding a comfortable position is vital. To do this, you'll lie on the same type of table that's used during radiation therapy. Cushions and restraints are used to position you in the right way and to help you hold still. Patient radiation therapy team will mark the area of patient body that will receive the radiation. Depending on patient situation, you may receive temporary marking with a marker or you may receive small permanent tattoos.
- **Planning scans.** Patient radiation therapy team will have you undergo computerized tomography (CT) scans to determine the area of patient body to be treated.

After the planning process, patient radiation therapy team decides what type of radiation and what dose you'll receive based on patient type and stage of cancer, patient general health, and the goals for patient treatment.

The precise dose and focus of radiation beams used in patient treatment is carefully planned to maximize the radiation to patient cancer cells and minimize the harm to surrounding healthy tissue.

What you can expect

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External beam radiation therapyOpen pop-up dialog box

External beam radiation therapy is usually conducted using a linear accelerator — a machine that directs high-energy beams of radiation into patient body.

As you lie on a table, the linear accelerator moves around you to deliver radiation from several angles. The linear accelerator can be adjusted for patient particular situation so that it delivers the precise dose of radiation patient doctor has ordered.

You typically receive external beam radiation on an outpatient basis five days a week over a certain period of time. In most instances, treatments are usually spread out over several weeks to allow patient healthy cells to recover in between radiation therapy sessions.

Expect each treatment session to last approximately 10 to 30 minutes. In some cases, a single treatment may be used to help relieve pain or other symptoms associated with more-advanced cancers.

During a treatment session, you'll lie down in the position determined during patient radiation simulation session. You might be positioned with molds to hold you in place.

The linear accelerator machine may rotate around patient body to reach the target from different directions. The machine makes a buzzing sound.

You'll lie still and breathe normally during the treatment, which takes only a few minutes. For some patients with lung or breast cancer, you might be asked to hold patient breath while the machine delivers the treatment.

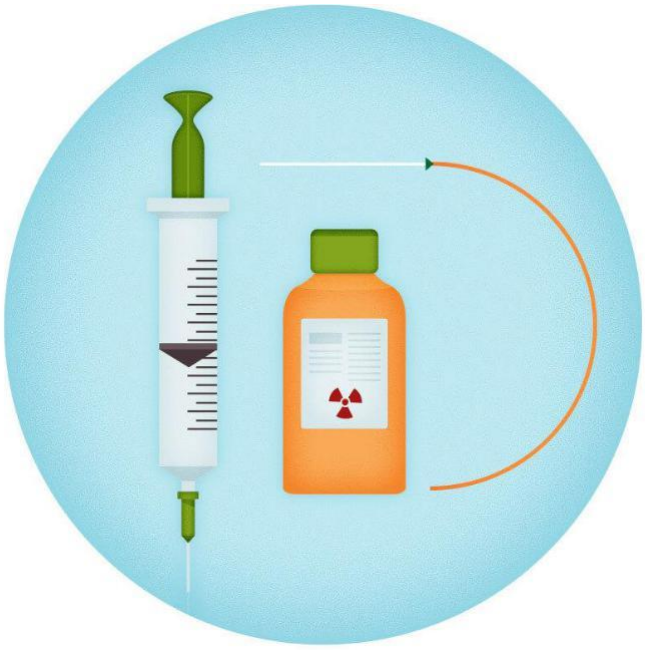
Patient radiation therapy team stays nearby in a room with video and audio connections so that you can talk to each other. You should speak up if you feel uncomfortable, but you shouldn't feel any pain during patient radiation therapy session.

Results

If you're receiving radiation to a tumor, patient doctor may have you undergo periodic scans after patient treatment to see how patient cancer has responded to radiation therapy.

In some cases, patient cancer may respond to treatment right away. In other cases, it may take weeks or months for patient cancer to respond. Some people aren't helped by radiation therapy.

Internal Breast Cancer Radiation



Internal radiation is a form of *partial breast radiation*. During the treatment, the physician or surgeon inserts a radioactive liquid using needles, wires, or a catheter in order to target the area where the cancer originally began to grow and tissue closest to the tumor site to kill any possible remaining cancer cells.

Brachytherapy (Internal Radiation) Delivered Via Implantable Device

The doctor places a device inside the breast at the time of the surgery or shortly thereafter which carries targeted radiation to the tissue where the cancer originally grew (also known as the tumor bed). This type of radiation may take only one treatment delivered in the operating room or may take 5-7 days given on an outpatient basis in the radiation therapy department.

In nearly all cases, the appropriate method is determined by the radiation oncologist based on the location and size of the tumor.

Chemotherapy

Overview

Chemotherapy is a drug treatment that uses powerful chemicals to kill fast-growing cells in patient body.

Chemotherapy is most often used to treat cancer, since cancer cells grow and multiply much more quickly than most cells in the body.

Many different chemotherapy drugs are available. Chemotherapy drugs can be used alone or in combination to treat a wide variety of cancers.

Though chemotherapy is an effective way to treat many types of cancer, chemotherapy treatment also carries a risk of side effects. Some chemotherapy side effects are mild and treatable, while others can cause serious complications.

Why it's done

Chemotherapy is used to kill cancer cells in people with cancer.

There are a variety of settings in which chemotherapy may be used in people with cancer:

- **To cure the cancer without other treatments.** Chemotherapy can be used as the primary or sole treatment for cancer.
- **After other treatments, to kill hidden cancer cells.** Chemotherapy can be used after other treatments, such as surgery, to kill any cancer cells that might remain in the body. Doctors call this adjuvant therapy.
- **To prepare you for other treatments.** Chemotherapy can be used to shrink a tumor so that other treatments, such as radiation and surgery, are possible. Doctors call this neoadjuvant therapy.

- **To ease signs and symptoms.** Chemotherapy may help relieve signs and symptoms of cancer by killing some of the cancer cells. Doctors call this palliative chemotherapy.

Chemotherapy for conditions other than cancer

Some chemotherapy drugs have proved useful in treating other conditions, such as:

- **Bone marrow diseases.** Diseases that affect the bone marrow and blood cells may be treated with a bone marrow transplant, also known as a stem cell transplant. Chemotherapy is often used to prepare for a bone marrow transplant.
- **Immune system disorders.** Lower doses of chemotherapy drugs can help control an overactive immune system in certain diseases, such as lupus and rheumatoid arthritis.

Risks

Side effects of chemotherapy drugs can be significant. Each drug has different side effects, and not every drug causes every side effect. Ask patient doctor about the side effects of the particular drugs you'll receive.

Side effects that occur during chemotherapy treatment

Common side effects of chemotherapy drugs include:

- Nausea
- Vomiting
- Diarrhea
- Hair loss
- Loss of appetite
- Fatigue
- Fever

- Mouth sores
- Pain
- Constipation
- Easy bruising
- Bleeding

Many of these side effects can be prevented or treated. Most side effects subside after treatment ends.

Long-lasting and late-developing side effects

Chemotherapy drugs can also cause side effects that don't become evident until months or years after treatment. Late side effects vary depending on the chemotherapy drug but can include:

- Damage to lung tissue
- Heart problems
- Infertility
- Kidney problems
- Nerve damage (peripheral neuropathy)
- Risk of a second cancer

Ask patient doctor if you have a risk of any late side effects. Ask what signs and symptoms you should be aware of that may signal a problem.

How you prepare

How you prepare for chemotherapy depends on which drugs you'll receive and how they'll be administered. Patient doctor will give you specific instructions to prepare for patient chemotherapy treatments. You may need to:

- **Have a device surgically inserted before intravenous chemotherapy.** If you'll be receiving patient chemotherapy intravenously — into a vein — patient doctor

may recommend a device, such as a catheter, port or pump. The catheter or other device is surgically implanted into a large vein, usually in patient chest. Chemotherapy drugs can be given through the device.

- **Undergo tests and procedures to make sure patient body is ready to receive chemotherapy.** Blood tests to check kidney and liver functions and heart tests to check for heart health can determine whether patient body is ready to begin chemotherapy. If there's a problem, patient doctor may delay patient treatment or select a different chemotherapy drug and dosage that's safer for you.

- **See patient dentist.** Patient doctor may recommend that a dentist check patient teeth for signs of infection. Treating existing infections may reduce the risk of complications during chemotherapy treatment, since some chemotherapy may reduce patient body's ability to fight infections.

- **Plan ahead for side effects.** Ask patient doctor what side effects to expect during and after chemotherapy and make appropriate arrangements. For instance, if patient chemotherapy treatment will cause infertility, you may wish to consider patient options for preserving patient sperm or eggs for future use. If patient chemotherapy will cause hair loss, consider planning for a head covering.

- **Make arrangements for help at home and at work.** Most chemotherapy treatments are given in an outpatient clinic, which means most people are able to continue working and doing their usual activities during chemotherapy. Patient doctor can tell you in general how much the chemotherapy will affect patient usual activities, but it's difficult to predict exactly how you'll feel.

  Ask patient doctor if you'll need time off work or help around patient home after treatment. Ask patient doctor for the details of patient chemotherapy treatments so that you can make arrangements for work, children, pets or other commitments.

- **Prepare for patient first treatment.** Ask patient doctor or chemotherapy nurses how to prepare for chemotherapy. It may be helpful to arrive for patient first chemotherapy treatment well rested. You might wish to eat a light meal beforehand in case patient chemotherapy medications cause nausea.

  Have a friend or family member drive you to patient first treatment. Most people can drive themselves to and from chemotherapy sessions. But the first time you

may find that the medications make you sleepy or cause other side effects that make driving difficult.

What you can expect

Determining which chemotherapy drugs you'll receive

Patient doctor chooses which chemotherapy drugs you'll receive based on several factors, including:

- Type of cancer
- Stage of cancer
- Overall health
- Previous cancer treatments
- Patient goals and preferences

Discuss patient treatment options with patient doctor. Together you can decide what's right for you.

How chemotherapy drugs are given

Chemotherapy drugs can be given in different ways, including:

- **Chemotherapy infusions.** Chemotherapy is most often given as an infusion into a vein (intravenously). The drugs can be given by inserting a tube with a needle into a vein in patient arm or into a device in a vein in patient chest.
- **Chemotherapy pills.** Some chemotherapy drugs can be taken in pill or capsule form.
- **Chemotherapy shots.** Chemotherapy drugs can be injected with a needle, just as you would receive a shot.
- **Chemotherapy creams.** Creams or gels containing chemotherapy drugs can be applied to the skin to treat certain types of skin cancer.

- **Chemotherapy drugs used to treat one area of the body.** Chemotherapy drugs can be given directly to one area of the body. For instance, chemotherapy drugs can be given directly in the abdomen (intraperitoneal chemotherapy), chest cavity (intrapleural chemotherapy) or central nervous system (intrathecal chemotherapy). Chemotherapy can also be given through the urethra into the bladder (intravesical chemotherapy).
- **Chemotherapy given directly to the cancer.** Chemotherapy can be given directly to the cancer or, after surgery, where the cancer once was. As an example, thin disk-shaped wafers containing chemotherapy drugs can be placed near a tumor during surgery. The wafers break down over time, releasing chemotherapy drugs. Chemotherapy drugs may also be injected into a vein or artery that directly feeds a tumor.

How often you receive chemotherapy treatments

Patient doctor determines how often you'll receive chemotherapy treatments based on what drugs you'll receive, the characteristics of patient cancer and how well patient body recovers after each treatment. Chemotherapy treatment schedules vary. Chemotherapy treatment can be continuous, or it may alternate between periods of treatment and periods of rest to let you recover.

Where you receive chemotherapy treatments

Where you'll receive patient chemotherapy treatments depends on patient situation. Chemotherapy treatments can be given:

- In an outpatient chemotherapy unit
- In a doctor's office
- In the hospital
- At home, such as when taking chemotherapy pills

Results

You'll meet with patient cancer doctor (oncologist) regularly during chemotherapy treatment. Patient oncologist will ask about any side effects you're experiencing, since many can be controlled.

Depending on patient situation, you may also undergo scans and other tests to monitor patient cancer during chemotherapy treatment. These tests can give patient doctor an idea of how patient cancer is responding to treatment, and patient treatment may be adjusted accordingly.

Types of Chemotherapy

Alkylating Agents

Alkylating agents are most active in the resting phase of the cell. These types of drugs are cell-cycle non-specific. There are several types of alkylating agents used in chemotherapy treatments:

- Mustard gas derivatives: Mechlorethamine, Cyclophosphamide, Chlorambucil, Melphalan, and Ifosfamide.
- Ethylenimines: Thiotepa and Hexamethylmelamine.
- Alkylsulfonates: Busulfan.
- Hydrazines and Triazines: Altretamine, Procarbazine, Dacarbazine and Temozolomide.
- Nitrosureas: Carmustine, Lomustine and Streptozocin. Nitrosureas are unique because, unlike most types of chemo treatments, they can cross the blood-brain barrier. They can be useful in treating brain tumors.
- Metal salts: Carboplatin, Cisplatin, and Oxaliplatin.

Plant Alkaloids

Plant alkaloids are chemotherapy treatments derived made from certain types of plants. The vinca alkaloids are made from the periwinkle plant (catharanthus rosea). The taxanes are made from the bark of the Pacific Yew tree (taxus). The vinca alkaloids and taxanes are also known as antimicrotubule agents. The podophyllotoxins are derived from the May apple plant. Camptothecan analogs are derived from the Asian "Happy Tree" (Camptotheca acuminata). Podophyllotoxins and camptothecan analogs are also known as topoisomerase inhibitors, which are used in certain types of chemotherapy. The plant alkaloids are cell-cycle specific. This means they attack the cells during various phases of division.

- Vinca alkaloids: Vincristine, Vinblastine and Vinorelbine.
- Taxanes: Paclitaxel and Docetaxel.
- Podophyllotoxins: Etoposide and Tenisopide.
- Camptothecan analogs: Irinotecan and Topotecan.

Antitumor Antibiotics

Antitumor antibiotics are chemo treatments made from natural products produced by species of the soil fungus Streptomyces. These drugs act during multiple phases of the cell cycle and are considered cell-cycle specific. There are several types of antitumor antibiotics:

- Anthracyclines: Doxorubicin, Daunorubicin, Epirubicin, Mitoxantrone, and Idarubicin.
- Chromomycins: Dactinomycin and Plicamycin.
- Miscellaneous: Mitomycin and Bleomycin.

Antimetabolites

Antimetabolites are types of chemotherapy treatments that are very similar to normal substances within the cell. When the cells incorporate these substances into the cellular metabolism, they are unable to divide. Antimetabolites are cell-cycle specific. They attack cells at very specific phases in the cycle. Antimetabolites are classified according to the substances with which they interfere.

- Folic acid antagonist: Methotrexate.
- Pyrimidine antagonist: 5-Fluorouracil, Foxuridine, Cytarabine, Capecitabine, and Gemcitabine.
- Purine antagonist: 6-Mercaptopurine and 6-Thioguanine.
- Adenosine deaminase inhibitor: Cladribine, Fludarabine, Nelarabine and Pentostatin.

Topoisomerase Inhibitors

Toposiomerase inhibitors are types of chemotherapy drugs that interfere with the action of topoisomerase enzymes (topoisomerase I and II). During the process of chemo treatments, topoisomerase enzymes control the manipulation of the structure of DNA necessary for replication.

- Topoisomerase I inhibitors: Ironotecan, topotecan
- Topoisomerase II inhibitors: Amsacrine, etoposide, etoposide phosphate, teniposide

Miscellaneous Antineoplastics

Several useful types of chemotherapy drugs are unique:

- Ribonucleotide reductase inhibitor: Hydroxyurea.
- Adrenocortical steroid inhibitor: Mitotane
- Enzymes: Asparaginase and Pegaspargase.
- Antimicrotubule agent: Estramustine
- Retinoids: Bexarotene, Isotretinoin, Tretinoin (ATRA)

Beyond the aforementioned types of chemotherapy, many other types of chemo treatments exist, such as targeted therapy, immunotherapy, and hormone therapy.

Targeted Therapy

What is targeted therapy?

Targeted therapy is a type of cancer treatment that uses drugs designed to "target" cancer cells without affecting normal cells.

Cancer cells typically have changes in their genes that make them different from normal cells. Genes are part of a cell's DNA that tell the cell to do certain things. When a cell has certain gene changes, it doesn't behave like a normal cell. For example, gene changes in cancer cells might allow the cell to grow and divide very quickly. These types of changes are what make it a cancer cell.

But there are many different types of cancer, and not all cancer cells are the same. For example, colon cancer and breast cancer cells have different gene changes that help them grow and/or spread. Even among different people with the same general type of cancer (such as colon cancer), the cancer cells can have different gene changes, making one person's specific type of colon cancer different from another person's.

Researchers have also learned that the environment in which different cancers start, grow, and thrive are not always the same. For example, some cancers have certain types of proteins or enzymes send certain messages to tell the cancer cell to grow and copy itself.

Knowing these details has led to the development of drugs that can “target” these proteins or enzymes and block the messages being sent. Targeted drugs can block or turn off signals that make cancer cells grow, or can signal the cancer cells to destroy themselves.

Targeted therapy is an important type of cancer treatment, and researchers will develop more targeted drugs as they learn more about specific changes in cancer cells. But so far, only a few type of cancers are routinely treated using only these drugs. Most people getting targeted therapy also need surgery, chemotherapy, radiation therapy, or hormone therapy.

How is targeted therapy different from chemotherapy?

Targeted therapy drugs, like other drugs used to treat cancer, are technically considered chemotherapy. But targeted therapy drugs don’t work the same way as traditional or standard chemotherapy (chemo) drugs. Targeted drugs zero in on some of the changes that make cancer cells different from normal cells. This makes them work differently from chemotherapy in two key ways:

- Because of their targeted action, these drugs have an effect on the cancer cells and mostly leave normal, healthy cells alone. Traditional chemotherapy is *cytotoxic* to most cells, meaning it can damage normal, healthy cells in addition to damaging and killing cancer cells.
- Targeted drugs often work by blocking cancer cells from copying themselves. This means they can help stop a cancer cell from dividing and making new cancer cells. Traditional chemotherapy, however, kills cancer cells that have already been made.

How targeted therapy works

Targeted therapies are made to find and attack specific areas or substances in cancer cells, or can detect and block certain kinds of messages sent inside a cancer cell that tell it to grow. Some of the substances in cancer cells that become the "targets" of targeted therapies are:

- Too much of a certain protein on a cancer cell
- A protein on a cancer cell that is not on normal cells
- A protein that is mutated (changed) in some way on a cancer cell
- Gene (DNA) changes that aren't in a normal cell.

The action of targeted drugs can work to:

- **Block or turn off chemical signals** that tell the cancer cell to grow and divide
- **Change proteins** within the cancer cells so the cells die
- **Stop making new blood vessels** to feed the cancer cells
- **Trigger your immune system** to kill the cancer cells
- **Carry toxins to the cancer cells** to kill them, but not normal cells

The action of the drugs can affect where these drugs work and what side effects they cause.

Targeted therapy as precision medicine

Targeted therapy is sometimes called *precision medicine* or *personalized medicine*. This is because they are made to exactly target specific changes or substances in cancer cells, and these targets can be different even when people have the same type of cancer. Certain types of tumors are tested for different targets after a biopsy or surgery, and this can help find the most effective treatment. Finding a specific target makes matching patients with treatment more precise or personalized.

Some targeted drugs are more “targeted” than others. Targeted therapies are classified as either small or large molecule drugs.

- **Small molecule drugs** are tiny enough to enter a cancer cell once they find it. They work by targeting a specific substance inside the cell and blocking it.
- **Large molecule drugs** usually can't fit into a cell. They work by attacking then weakening or destroying proteins or enzymes on the surface of the cell. They are often described as a "lock and key" because the molecule is like a key that opens the enzyme or protein on the surface of the cell like a lock. The key fits into the lock, allowing the drug to work.

Types of targeted therapy

Many kinds of cancer can be treated with targeted therapies, and there are many different types of targeted therapies. Here are some types with a few examples of how they are used.

- **Angiogenesis inhibitors:** These block the formation of new blood vessels that feed and nourish the cancer cells. Example: bevacizumab (many different cancers).
- **Monoclonal antibodies:** These might deliver molecules by themselves or molecules with drugs into or onto the cancer cell to kill it. Examples: alemtuzumab (certain chronic leukemias), trastuzumab (certain breast cancers), cetuximab (certain colorectal, lung, head and neck cancers). NOTE: Some monoclonal antibodies are referred to as

targeted therapy because they have a specific target on a cancer cell that they aim to find, attach to, and attack. But other monoclonal antibodies act like immunotherapy because they make the immune system respond better to allow the body to find and attack cancer cells more effectively.

- **Proteasome inhibitors:** These disrupt normal cell functions so the cancer cells die. Example: bortezomib (multiple myeloma)
- **Signal transduction inhibitors:** These disrupt cell signals so that they change the actions of the cancer cell. Example: imatinib (certain chronic leukemias).

IMMUNOTHERAPY

Immunotherapy is treatment that uses certain parts of a person's immune system to fight diseases such as cancer. This can be done in a couple of ways:

- Stimulating, or boosting, the natural defenses of your immune system so it works harder or smarter to find and attack cancer cells
- Making substances in a lab that are just like immune system components and using them to help restore or improve how your immune system works to find and attack cancer cells

In the last few decades immunotherapy has become an important part of treating some types of cancer. New immunotherapy treatments are being tested and approved, and new ways of working with the immune system are being discovered at a very fast pace.

Immunotherapy works better for some types of cancer than for others. It's used by itself for some of these cancers, but for others it seems to work better when used with other types of treatment.

What the immune system does

Your immune system is a collection of organs, special cells, and substances that help protect you from infections and some other diseases. Immune cells and the substances they make travel through your body to protect it from germs that cause infections. They also help protect you from cancer in some ways.

The immune system keeps track of all of the substances normally found in the body. Any new substance that the immune system doesn't recognize raises an alarm, causing the immune system to attack it. For example, germs contain substances such as certain proteins that are not normally found in the human body. The immune system sees these as "foreign" and attacks them. The immune response can destroy anything containing the foreign substance, such as germs or cancer cells.

The immune system has a tougher time targeting cancer cells, though. This is because cancer starts when normal, healthy cells become changed or altered and start to grow out of control. Because cancer cells actually start in normal cells, the immune system doesn't always recognize them as foreign.

Clearly there are limits on the immune system's ability to fight cancer on its own, because many people with healthy immune systems still develop cancer:

- Sometimes the immune system doesn't see the cancer cells as foreign because the cells aren't different enough from normal cells.
- Sometimes the immune system recognizes the cancer cells, but the response might not be strong enough to destroy the cancer.
- Cancer cells themselves can also give off substances that keep the immune system from finding and attacking them.

To overcome this, researchers have found ways to help the immune system recognize cancer cells and strengthen its response so that it will destroy them. In this way, your own body is actually getting rid of the cancer, with some help from science.

Types of cancer immunotherapy

There are several main types of immunotherapy used to treat cancer, and many are being studied. **For more information about immunotherapy as a treatment for a specific cancer, please see Cancer A-Z and choose a cancer type.**

- **Checkpoint inhibitors:** These drugs basically take the 'brakes' off the immune system, which helps it recognize and attack cancer cells.
- **Chimeric antigen receptor (CAR) T-cell therapy:** This therapy takes some T-cells from a patient's blood, mixes them with a special virus that makes the T-cells learn how to attach to tumor cells, and then gives the cells back to the patient so they can find, attach to, and kill the cancer.

- **Cytokines**: This treatment uses *cytokines* (small proteins that carry messages between cells) to stimulate the immune cells to attack cancer.
- **Immunomodulators**: This group of drugs generally boosts parts of the immune system to treat certain types of cancer.
- **Cancer vaccines:** Vaccines are substances put into the body to start an immune response against certain diseases. We usually think of them as being given to healthy people to help prevent infections. But some vaccines can help prevent or treat cancer.
- **Monoclonal antibodies (mAbs or MoAbs):** These are man-made versions of immune system proteins. mAbs can be very useful in treating cancer because they can be designed to attack a very specific part of a cancer cell.
- **Oncolytic viruses**: This treatment uses viruses that have been modified in a lab to infect and kill certain tumor cells..

Monoclonal Antibodies and Their Side Effects

One way the body's immune system attacks foreign substances is by making large numbers of antibodies. An antibody is a protein that sticks to a specific protein called an *antigen*. Antibodies circulate throughout the body until they find and attach to the antigen. Once attached, they can force other parts of the immune system to destroy the cells containing the antigen.

Researchers can design antibodies that specifically target a certain antigen, such as one found on cancer cells. They can then make many copies of that antibody in the lab. These are known as *monoclonal antibodies* (mAbs or Moabs).

Monoclonal antibodies are used to treat many diseases, including some types of cancer. To make a monoclonal antibody, researchers first have to identify the right antigen to attack. Finding the right antigens for cancer cells is not always easy, and so far mAbs have proven to be more useful against some cancers than others.

NOTE: Some monoclonal antibodies used to treat cancer are referred to as *targeted therapy* because they have a specific target on a cancer cell that they aim to find, attach to, and

attack. But other monoclonal antibodies act like immunotherapy because they make the immune system respond better to allow the body to find and attack cancer cells more effectively.

What mAbs are made of

Monoclonal antibodies are man-made proteins that act like human antibodies in the immune system. There are 4 different ways they can be made and are named based on what they are made of.

- **Murine:** These are made from mouse proteins and the names of the treatments end in -omab.
- **Chimeric:** These proteins are a combination of part mouse and part human and the names of the treatments end in -ximab.
- **Humanized:** These are made from small parts of mouse proteins attached to human proteins and the names of the treatments end in -zumab
- **Human:** These are fully human proteins and the names of the treatments end in -umab.

Types of mAbs used to treat cancer

Naked monoclonal antibodies

Naked mAbs are antibodies that have no drug or radioactive material attached to them. They work by themselves. These are the most common type of mAbs used to treat cancer. Most naked mAbs attach to antigens on cancer cells, but some work by binding to antigens on other, non-cancerous cells, or even free-floating proteins. Naked mAbs can work in different ways.

- Some boost a person's immune response against cancer cells by attaching to them and acting as a marker for the body's immune system to destroy them. An example is alemtuzumab (Campath®), which is used to treat some patients with chronic lymphocytic leukemia (CLL). Alemtuzumab binds to the CD52 antigen, which is found on cells called *lymphocytes* (which include the leukemia cells). Once attached, the antibody attracts immune cells to destroy these cells.

- Some naked mAbs boost the immune response by targeting immune system checkpoints. (See Immune Checkpoint Inhibitors and Their Side Effects.)
- Other naked mAbs work mainly by attaching to and blocking antigens on cancer cells (or other nearby cells) that help cancer cells grow or spread. For example, trastuzumab (Herceptin) is an antibody against the HER2 protein. Breast and stomach cancer cells sometimes have large amounts of this protein on their surface. When HER2 is activated, it helps these cells grow. Trastuzumab binds to these proteins and stops them from becoming active.

Conjugated monoclonal antibodies

Conjugated mAbs are combined with a chemotherapy drug or a radioactive particle. These mAbs are used as a homing device to take one of these substances directly to the cancer cells. The mAb circulates throughout the body until it can find and hook onto the target antigen. It then delivers the toxic substance where it is needed most. This lessens the damage to normal cells in other parts of the body. Conjugated mAbs are also sometimes referred to as *tagged*, *labeled*, or *loaded* antibodies.

- **Radiolabeled antibodies:** Radiolabeled antibodies have small radioactive particles attached to them. Ibritumomab tiuxetan (Zevalin) is an example of a radiolabeled mAb. This is an antibody against the CD20 antigen, which is found on lymphocytes called *B cells*. The antibody delivers radioactivity directly to cancer cells. It is made of both an mAb drug (rituximab) and a radioactive substance (Yttrium-90). Treatment with this type of antibody is sometimes known as *radioimmunotherapy* (RIT). The drug and radiation are delivered directly to the target cells because the mAb looks for the target, then the radiation affects the target and nearby cells to a certain extent.
- **Chemolabeled antibodies:** These mAbs have powerful chemotherapy (or other) drugs attached to them. Examples include:
    - Brentuximab vedotin (Adcetris), an antibody that targets the CD30 antigen (found on lymphocytes), attached to a chemo drug called *MMAE*.
    - Ado-trastuzumab emtansine (Kadcyla, also called TDM-1), an antibody that targets the HER2 protein, attached to a chemo drug called DM1.

Bispecific monoclonal antibodies

These drugs are made up of parts of 2 different mAbs, meaning they can attach to 2 different proteins at the same time. An example is blinatumomab (Blincyto), which is used to treat some types of leukemia. One part of blinatumomab attaches to the CD19 protein, which is found on some leukemia and lymphoma cells. Another part attaches to CD3, a protein found on immune cells called *T cells*. By binding to both of these proteins, this drug brings the cancer cells and immune cells together, which is thought to cause the immune system to attack the cancer cells.

Possible side effects of monoclonal antibodies

Monoclonal antibodies are given intravenously (injected into a vein). The antibodies themselves are proteins, so giving them can sometimes cause something like an allergic reaction. This is more common while the drug is first being given. Possible side effects can include:

- Fever
- Chills
- Weakness
- Headache
- Nausea
- Vomiting
- Diarrhea
- Low blood pressure
- Rashes

Compared with chemotherapy drugs, naked mAbs tend to have fewer serious side effects. But they can still cause problems in some people. Some mAbs can have side effects that are related to the antigens they target. For example:

- Bevacizumab (Avastin) is an mAb that targets a protein called *VEGF* that affects tumor blood vessel growth. It can cause side effects such as high blood pressure, bleeding, poor wound healing, blood clots, and kidney damage.
- Cetuximab (Erbitux) is an antibody that targets a cell protein called *EGFR*, which is found on normal skin cells (as well as some types of cancer cells). This drug can cause serious rashes in some people.

CAR T-cell Therapy and Its Side Effects

Your immune system works by keeping track of all the substances normally found in your body. Any new substance the immune system doesn't recognize raises an alarm, causing the immune system to attack it. **Chimeric antigen receptor (CAR) T-cell therapy** is a promising new way to get immune cells called *T cells* (a type of white blood cell) to fight cancer by changing them in the lab so they can find and destroy cancer cells. CAR T-cell therapies are sometimes talked about as a type of *gene* or *cell therapy*, or *immune effect cell therapy*.

How CAR T-cell therapy works

Immune receptors and foreign antigens

The immune system recognizes foreign substances in the body by finding proteins called *antigens* on the surface of those cells. Immune cells called *T cells* have their own proteins called *receptors* that attach to foreign antigens and help trigger other parts of the immune system to destroy the foreign substance.

The relationship between antigens and immune receptors is like a lock and key. Just as every lock can only be opened with the right key, each foreign antigen has a unique immune receptor that is able to bind to it. Cancer cells also have antigens, but if your immune cells do not have the right receptors, they cannot attach to the antigens and help destroy the cancer cells.

Chimeric antigen receptors (CARs)

The T cells used in CAR T-cell therapies get changed in the lab by adding a man-made receptor (called a *chimeric antigen receptor* or *CAR*). This helps them better identify specific cancer

cell antigens. Since different cancers have different antigens, each CAR is made for a specific cancer's antigen. For example, certain kinds of leukemia or lymphoma will have an antigen on the outside of the cancer cells called CD19. The CAR T-cell therapies to treat those cancers are made to connect to the CD-19 antigen and will not work for a cancer that does not have the CD19 antigen. The patient's own T cells are used to make the CAR T cells.

Getting CAR T-cell therapy

The process for CAR T-cell therapy can take a few weeks.

Collecting the T cells

First, white blood cells (which include T cells) are removed from the patient’s blood using a procedure called *leukapheresis*. During this procedure, patients usually lie in bed or sit in a reclining chair. Two IV lines are needed because blood is removed through one line, and then put back into the bloodstream through the other line, after the white blood cells have been removed. Sometimes a special type of IV line is used called a *central venous catheter*, that has both IV lines built in. The patient will need to stay still for 2 to 3 hours during the procedure. Sometimes calcium levels can drop during leukapheresis, which can cause numbness and tingling or muscle spasms. This can be easily treated with calcium, which may be given by mouth or through an IV .

Making the CAR T cells

After the white cells are removed, the T-cells are separated, sent to the lab, and genetically altered by adding the specific chimeric antigen receptor (CAR). This makes them CAR T cells. It can take a few weeks to make the large number of CAR T cells needed for this therapy.

Receiving the CAR T-cell infusion

Once enough CAR T cells have been made, they will be given back to the patient to launch a precise attack against the cancer cells. A few days before a CAR T-cell infusion, the patient might be given chemotherapy to help lower the number of other immune cells. This gives the CAR T cells a better chance to get activated to fight the cancer. This chemotherapy is usually

not very strong because CAR T cells work best when there are some cancer cells to attack. Once the CAR T cells start binding with cancer cells, they start to increase in number and can destroy even more cancer cells.

Approved CAR T-cell therapies

CAR T-cell therapy is FDA approved for some kinds of lymphomas, and for certain patients with relapsed or hard to treat leukemia. Many clinical trials are underway with the hope of treating even more patients. One problem with some types of cancer is that they don't have the same antigens for the CAR T cell to work with because the proteins are inside the cells, not on the cell surface. This may mean that the CAR T cell needs a special "armor" to be able to get into the cell to work. More research is needed to study this.

Examples of CAR T-cell therapies currently approved include:

- Tisagenlecleucel (Kymriah)
- Axicabtagene ciloleucel (Yescarta)
- Brexucabtagene autoleucel (Tecartus)

CAR T-cell therapy side effects

Some people have had serious side effects from this treatment, especially as the CAR T cells multiply in the body to fight the cancer. As CAR T cells multiply, they cause massive amounts of chemicals called *cytokines* to be released into the blood. Serious side effects of this release can include very high fevers and dangerously low blood pressure in the days after treatment is given. This is called **cytokine release syndrome**, or **CRS**. Even though it can be a scary side effect, it's important to remember that it means the CAR T cells are working. And as doctors have gained more experience with CAR T-cell therapy, they have learned how to recognize this side effect early, as well as how to treat it.

Other serious side effects include neurotoxicity or changes in the brain that cause swelling, confusion, seizures, or severe headaches.

One other problem is that the CAR T cells can kill off some of the good B cells that help fight germs, so the patient may be at higher risk for infection.

Immune Checkpoint Inhibitors and Their Side Effects

An important function of the immune system is its ability to tell between normal cells in the body and those it sees as “foreign.” This lets the immune system attack the foreign cells while leaving the normal cells alone. To do this, it uses “checkpoints.” Immune checkpoints are molecules on certain immune cells that need to be activated (or inactivated) to start an immune response.

Cancer cells sometimes find ways to use these checkpoints to avoid being attacked by the immune system. But drugs that target these checkpoints hold a lot of promise as cancer treatments. These drugs are called *checkpoint inhibitors*.

It's important to know that checkpoint inhibitors used to treat cancer don't work directly on the tumor at all. They only take the brakes off an immune response that has begun but hasn't yet been working at its full force.

Checkpoint inhibitor drugs that target PD-1 or PD-L1

PD-1 is a checkpoint protein on immune cells called *T cells*. It normally acts as a type of “off switch” that helps keep the T cells from attacking other cells in the body. It does this when it attaches to PD-L1, a protein on some normal (and cancer) cells. When PD-1 binds to PD-L1, it basically tells the T cell to leave the other cell alone. Some cancer cells have large amounts of PD-L1, which helps them hide from an immune attack.

Monoclonal antibodies that target either PD-1 or PD-L1 can block this binding and boost the immune response against cancer cells. These drugs have shown a great deal of promise in treating certain cancers.

PD-1 inhibitors: These drugs are given by IV (intravenously). Examples of drugs that target PD-1 include:

- Pembrolizumab (Keytruda)
- Nivolumab (Opdivo)
- Cemiplimab (Libtayo)

These drugs have been shown to be helpful in treating several types of cancer, and new cancer types are being added as more studies show these drugs to be effective.

PD-L1 inhibitors: Examples of drugs that target PD-L1 include:

- Atezolizumab (Tecentriq)
- Avelumab (Bavencio)
- Durvalumab (Imfinzi)

These drugs have also been shown to be helpful in treating different types of cancer, and are being studied for use against others.

Checkpoint inhibitor drugs that target CTLA-4

CTLA-4 is another protein on some T cells that acts as a type of “off switch” to keep the immune system in check.

Ipilimumab (Yervoy) is a monoclonal antibody that attaches to CTLA-4 and stops it from working. This can boost the body’s immune response against cancer cells.

This drug is used to treat melanoma of the skin and continues to be tested for other cancers.

Side effects of checkpoint inhibitors

The most common side effects of checkpoint inhibitors are:

- Diarrhea
- Pneumonitis (inflammation in the lungs)

- Rashes and itchiness
- Problems with some hormone levels
- Kidney infections

If the side effects are severe, your doctor might delay giving the checkpoint inhibitor for a period of time to allow the body to recover. Less severe side effects can often be helped with medications.

Cancer Vaccines and Their Side Effects

Most of us know about vaccines given to healthy people to help prevent infections, such as measles and chicken pox. These vaccines use weakened or killed germs like viruses or bacteria to start an immune response in the body. Getting the immune system ready to defend against these germs helps keep people from getting infections.

Most vaccines used to treat cancer work the same way, but they make the person's immune system attack cancer cells. The goal is to help treat cancer or to help keep it from coming back after other treatments. But there are also some vaccines that may actually help prevent certain cancers.

Vaccines to help prevent cancer

Some cancers are caused by viruses. Vaccines that help protect against infections with these viruses might also help prevent some of these cancers.

- Some strains of the human papillomavirus (HPV) have been linked to cervical, anal, throat, vaginal, vulvar, and penile cancers. In fact, most cervical cancers are caused by infection with HPV. Vaccinating children and certain young adults against HPV helps protect against cervical cancer and the other 5 cancers HPV can cause. Read more in Protect Against HPV.
- People who have chronic (long-term) infections with the hepatitis B virus (HBV) are at higher risk for liver cancer. Getting the vaccine to help prevent HBV infection may lower some people's risk of getting liver cancer.

These are traditional preventive vaccines that target the viruses that can cause certain cancers. They may help protect against some cancers, but they don't target cancer cells directly because cancer cells have not yet been formed or found.

These types of vaccines are only useful for cancers known to be caused by infections. But most cancers, including colorectal, lung, prostate, and breast cancers, are not thought to be caused by infections.

Vaccines to treat cancer

Cancer treatment vaccines are different from the vaccines that work against viruses. These vaccines try to get the immune system to mount an attack against cancer cells in the body. Instead of preventing disease, they are meant to get the immune system to attack a disease that already exists.

Some cancer treatment vaccines are made up of cancer cells, parts of cells, or pure antigens (certain proteins on the cancer cells). Sometimes a patient's own immune cells are removed and exposed to these substances in the lab to create the vaccine. Once the vaccine is ready, it's injected into the body to increase the immune response against cancer cells.

Vaccines are often combined with other substances or cells called *adjuvants* that help boost the immune response even further.

Cancer vaccines cause the immune system to attack cells with one or more specific antigens. Because the immune system has special cells for memory, it's hoped that the vaccine might continue to work long after it's given.

- **Sipuleucel-T (Provenge):**This drug is used to treat advanced prostate cancer that is no longer being helped by hormone therapy. Side effects are usually mild and can include fever, chills, fatigue, back and joint pain, nausea, and headache. A few men may have more severe symptoms, including problems breathing and high blood pressure.

- **Talimogene laherparepvec (T-VEC):** This vaccine is approved to treat advanced melanoma skin cancer. It is made from a herpes virus that has been altered in the lab to produce a substance that the body normally produces, called a *cytokine*. This cytokine boosts the immune system and can cause flu-like symptoms for a short time.

Cytokines and Their Side Effects

Cytokines are small proteins that are crucial in controlling the growth and activity of other immune system cells and blood cells. When released, they signal the immune system to do its job. Cytokines affect the growth of all blood cells and other cells that help the body's immune and inflammation responses. They also help to boost anti-cancer activity by sending signals that can help make abnormal cells die and normal cells live longer.

One specific type of cytokine is called a *chemokine*. A chemokine can make immune cells move toward a target. There are different kinds of chemokines, including *interleukins, interferons, tumor necrosis factors,* and *growth factors*.

Some cytokines can be made in a lab and are used to treat cancer. Some are used to help prevent or manage chemotherapy side effects. They are injected, either under the skin, into a muscle, or into a vein. The most common ones are interleukins and interferons.

Interleukins

Interleukins are a group of cytokines that act as chemical signals between white blood cells. Interleukin-2 (IL-2) helps immune system cells grow and divide more quickly. A man-made version of IL-2 is approved to treat advanced kidney cancer and metastatic melanoma. IL-2 can be used as a single drug treatment for these cancers, or it can be combined with chemotherapy or with other cytokines such as interferon-alfa.

Side effects of IL-2 can include flu-like symptoms such as chills, fever, fatigue, and confusion. Some have nausea, vomiting, or diarrhea. Many people develop low blood pressure, which can be treated with other medicines. Rare but potentially serious side effects include an abnormal

heartbeat, chest pain, and other heart problems. Because of these possible side effects, if IL-2 is given in high doses, it must be done in a hospital.

Other interleukins, such as IL-7, IL-12, and IL-21, continue to be studied for use against cancer too, both as adjuvants and as stand-alone agents.

Interferons

Interferons are chemicals that help the body resist virus infections and cancers. The types of interferon (IFN) are named after the first 3 letters of the Greek alphabet:

- IFN-alfa
- IFN-beta
- IFN-gamma

Only IFN-alfa is used to treat cancer. It boosts the ability of certain immune cells to attack cancer cells. It may also slow the growth of cancer cells directly, as well as the blood vessels that tumors need to grow.

IFN-alfa can be used to treat these cancers:

- Hairy cell leukemia
- Chronic myelogenous leukemia (CML)
- Follicular non-Hodgkin lymphoma
- Cutaneous (skin) T-cell lymphoma
- Kidney cancer
- Melanoma
- Kaposi sarcoma

Side effects of interferons can include:

- Flu-like symptoms (chills, fever, headache, fatigue, loss of appetite, nausea, vomiting)
- Low white blood cell counts (which increase the risk of infection)
- Skin rashes
- Thinning hair

These side effects can be severe and can make treatment with interferon hard for many people to tolerate. Most side effects don't last long after the treatment stops, but fatigue can last longer. Other rare long-term effects include damage to nerves, including those in the brain and spinal cord.

Immunomodulators and Their Side Effects

Immunomodulators are a group of drugs that mainly target the pathways that treat multiple myeloma and a few other cancers. They have many ways to work, including working on the immune system directly by turning down some proteins and turning up others.

Thalidomide, lenalidomide, and pomalidomide

Thalidomide (Thalomid), lenalidomide (Revlimid), and pomalidomide (Pomalyst) are known as *immunomodulating drugs* (or IMiDs).

These drugs can cause side effects such as drowsiness, fatigue, constipation, low blood cell counts, and neuropathy (painful nerve damage). There is also an increased risk of serious blood clots (that start in the leg and can travel to the lungs). These tend to be more likely with thalidomide than with the other drugs.

These drugs can also cause severe birth defects if taken during pregnancy.

Bacillus Calmette-Guérin

Bacillus Calmette-Guérin (BCG) is a germ that doesn't cause serious disease in humans, but it does infect human tissues and helps activate the immune system. This makes BCG useful as a

form of cancer immunotherapy. BCG was one of the earliest immunotherapies used against cancer and is still being used today.

BCG is used to treat early stage bladder cancer. It is a liquid put into the bladder through a catheter. BCG attracts the body's immune system cells to the bladder, where they can attack the bladder cancer cells. Treatment with BCG can cause symptoms that are like having the flu, such as fever, chills, and fatigue. It can also cause a burning feeling in the bladder. BCG can also be used to treat some melanoma skin cancers by injecting it directly into the tumors. It's also used as a vaccine against tuberculosis.

Imiquimod

Imiquimod is a drug that is applied to the skin as a cream. It stimulates a local immune response against skin cancer cells. It is used to treat some very early stage skin cancers (or pre-cancers), especially if they are in sensitive areas such as on the face.

The cream is applied anywhere from once a day to twice a week for several months. Some people have serious skin reactions to this drug.

Immunotherapy Safety

Much is known about the need to protect others from exposure to traditional or standard chemotherapy because it is hazardous. This is why there are safety rules and recommendations for people who handle chemo drugs. However, because immunotherapy drugs are newer, there is not as much information about long-term effects of exposure. To be safe, many experts recommend treating immunotherapy drugs as hazardous and taking the same precautions. This is especially true when immunotherapy drugs are given to treat cancer in combination with other drugs that are known to be hazardous, so your cancer care team will take precautions to protect themselves and others from exposure to them.

Precautions the cancer care team might take

You may notice special clothing and protective equipment being worn by the nurses and other members of your cancer care team. Pharmacists and nurses who prepare drugs to treat cancer use a special type of pharmacy that must meet certain regulations. If you are being cared for in a treatment center, the nurses and others who give treatment and help take care of patients afterwards wear protective clothing, such as 2 pairs of special gloves and a gown, and sometimes goggles or a face shield. If you're getting immunotherapy through an IV, there might be a disposable pad under the infusion tubing to protect the surface of the bed or chair.

Special precautions when taking oral or topical immunotherapy

Oral immunotherapy that you take by mouth and swallow, or topical immunotherapy that you rub on your skin, is usually taken at home. Some are considered hazardous. There might be special precautions for storing and handling an immunotherapy drug. You might be told to be careful not to let others come into contact with it or your body fluids while taking it and for a time after taking it. Sometimes you need to wear gloves when touching the pills or capsules. Some drugs have to be kept in the bottle or box they came in. And some drugs and the packages they come in need to be disposed of in a certain way. Some might have to be taken back to the drug store to be thrown away safely. If you are taking an oral drug, talk to your cancer care team about whether special precautions are needed at home.

Keeping family and friends safe

Unless your health care team tells you differently, you can usually be around family and friends during the weeks and months you're getting immunotherapy. If you're getting treatment at a center, family and friends can often come with you. However, some treatment centers only allow patients in the infusion area and visitors may need to stay in the waiting room.

You are the only person who should be exposed to the drug you are getting, but any spilled IV drug, and any powder or dust from a pill or capsule, or any liquid from oral or topical immunotherapy might be hazardous to others if they are around it.

It's important to talk to your cancer care team and be aware of any special precautions that might be needed while you are taking an immunotherapy drug.

Stem Cell or Bone Marrow Transplant

A stem cell transplant, also called a bone marrow transplant, can be used to treat certain types of cancer. This procedure might be called peripheral stem cell transplant or cord blood transplant, depending on where the stem cells come from. Here we'll explain stem cells and stem cell transplant, cover some of the issues that come with transplants, and describe what it's like to donate stem cells.

How Stem Cell and Bone Marrow Transplants Are Used to Treat Cancer

What are stem cells?

All of the blood cells in your body - white blood cells, red blood cells, and platelets - start out as young (immature) cells called **hematopoietic stem cells**. Hematopoietic means blood-forming. These are very young cells that are not fully developed. Even though they start out the same, these stem cells can mature into any type of blood cell, depending on what the body needs when each stem cell is developing.

Stem cells mostly live in the bone marrow (the spongy center of certain bones). This is where they divide to make new blood cells. Once blood cells mature, they leave the bone marrow and enter the bloodstream. A small number of the immature stem cells also get into the bloodstream. These are called **peripheral blood stem cells**.

Why stem cells are so important

Stem cells make red blood cells, white blood cells, and platelets. We need all of these types of blood cells to keep us alive. For these blood cells to do their jobs, you need to have enough of each of them in your blood.

Red blood cells (RBCs)

Red blood cells carry oxygen away from the lungs to all of the cells in the body. They bring carbon dioxide from the cells back to the lungs to be exhaled. A blood test called

a **hematocrit** shows how much of your blood is made up of RBCs. The normal range is about 35% to 50% for adults. People whose hematocrit is below this level have anemia. This can make them look pale and feel weak, tired, and short of breath.

White blood cells (WBCs)

White blood cells help fight infections caused by bacteria, viruses, and fungi. There are different types of WBCs.

Neutrophils are the most important type in fighting infections. They are the first cells to respond to an injury or when germs enter the body. When they are low, you have a higher risk of infection. The absolute neutrophil count (ANC) is a measure of the number of neutrophils in your blood. When your ANC drops below a certain level, you have **neutropenia**. The lower the ANC, the greater the risk for infection.

Lymphocytes are another type of white blood cell. There are different kinds of lymphocytes, such as T lymphocytes (T cells), B lymphocytes (B cells), and natural killer (NK) cells. Some lymphocytes make antibodies to help fight infections. The body depends on lymphocytes to recognize its own cells and reject cells that don't belong in the body, such as invading germs or cells that are transplanted from someone else.

Platelets (thrombocytes)

Platelets are pieces of cells that seal damaged blood vessels and help blood to clot, both of which are important in stopping bleeding. A normal platelet count is usually between 150,000/cubic mm and 450,000/cubic mm, depending on the lab that does the test. A person whose platelet count drops below normal is said to have **thrombocytopenia**, and may bruise more easily, bleed longer, and have nosebleeds or bleeding gums. Spontaneous bleeding (bleeding with no known injury) can happen if a person's platelet count drops lower than 20,000/mm^3. This can be dangerous if bleeding occurs in the brain, or if blood begins to leak into the intestines or stomach.

You can get more information on blood counts and what the numbers mean in Understanding Your Lab Test Results.

Where stem cells for transplants come from

Depending on the type of transplant that's being done, there are 3 possible sources of stem cells to use for transplants:

- Bone marrow (from you or someone else)
- The bloodstream (peripheral blood – from you or someone else)
- Umbilical cord blood from newborns

Bone marrow

Bone marrow is the spongy liquid tissue in the center of some bones. It has a rich supply of stem cells, and its main job is to make blood cells that circulate in your body. The bones of the pelvis (hip) have the most marrow and contain large numbers of stem cells. For this reason, cells from the pelvic bone are used most often for a bone marrow transplant. Enough marrow must be removed to collect a large number of healthy stem cells.

The bone marrow is harvested (removed) while the donor is under general anesthesia (drugs are used to put the patient into a deep sleep so they don't feel pain). A large needle is put through the skin on the lower back and into the back of the hip bone. The thick liquid marrow is pulled out through the needle. This is repeated until enough marrow has been taken out. (For more on this, see What's It Like to Donate Stem Cells?)

The harvested marrow is filtered, stored in a special solution in bags, and then frozen. When the marrow is to be used, it's thawed and then put into the patient's blood through a vein, just like a blood transfusion. The stem cells travel to the bone marrow, where they engraft or "take" and start to make blood cells. Signs of the new blood cells usually can be measured in the patient's blood tests in a few weeks.

Peripheral blood

Normally, not many stem cells are found in the blood. But giving stem cell donors shots of hormone-like substances called **growth factors** a few days before the harvest makes their stem cells grow faster and move from the bone marrow into the blood.

For a peripheral blood stem cell transplant, the stem cells are taken from blood. A special thin flexible tube (called a catheter) is put into a large vein in the donor and attached to tubing that carries the blood to a special machine. The machine separates the stem cells from the rest of the blood, which is returned to the donor during the same procedure. This takes several hours, and may need to be repeated for a few days to get enough stem cells. The stem cells are filtered, stored in bags, and frozen until the patient is ready for them. (For more on this, see What's It Like to Donate Stem Cells?)

When they're given to the patient, the stem cells are put into a vein, much like a blood transfusion. The stem cells travel to the bone marrow, engraft, and then start making new, normal blood cells. The new cells are usually found in the patient's blood in about 4 weeks.

Umbilical cord blood

The blood of newborn babies normally has large numbers of stem cells. After birth, the blood that's left behind in the placenta and umbilical cord (known as **cord blood**) can be taken and stored for later use in a stem cell transplant. Cord blood can be frozen until needed. A cord blood transplant uses blood that normally is thrown out after a baby is born. After the baby is born, specially trained members of the health care team make sure the cord blood is carefully collected. The baby is not harmed in any way. More information on donating cord blood can be found in What's It Like to Donate Stem Cells?

Even though the blood of newborns has large numbers of stem cells, cord blood is only a small part of that number. So, a possible drawback of cord blood is the smaller number of stem cells in it. But this is partly balanced by the fact that each cord blood stem cell can form more blood cells than a stem cell from adult bone marrow. Still, cord blood transplants can take longer to take hold and start working. Cord blood is given into the patient's blood just like a blood transfusion.

Cancers that affect the bone marrow

Some cancers start in the bone marrow and others can spread to it. Cancer attacks the bone marrow, causing it to make too many of some cells that crowd out others, or causing it to make cells that aren’t healthy and don't work like they should. For these cancers to stop growing, they need bone marrow cells to work properly and start making new, healthy cells.

Most of the cancers that affect bone marrow function are leukemias, multiple myeloma, and lymphomas. All of these cancers start in blood cells. Other cancers can spread to the bone marrow, which can affect how blood cells function, too.

For certain types of leukemia, lymphoma, and multiple myeloma, a stem cell transplant can be an important part of treatment. The goal of the transplant is to wipe out the cancer cells and the damaged or non-healthy cells that aren't working right, and give the patient new, healthy stem cells to “start over."

How a stem cell transplant works to treat cancer

Stem cell transplants are used to replace bone marrow cells that have been destroyed by cancer or destroyed by the chemo and/or radiation used to treat the cancer.

There are different kinds of stem cell transplants. They all use very high doses of chemo (sometimes along with radiation) to kill cancer cells. But the high doses can also kill all the stem cells a person has and can cause the bone marrow to completely stop making blood cells for a period of time. In other words, all of a person's original stem cells are destroyed on purpose. But since our bodies need blood cells to function, this is where stem cell transplants come in. The transplanted stem cells help to "rescue" the bone marrow by replacing the body’s stem cells that have been destroyed by treatment. So, transplanting the healthy cells lets doctors use much higher doses of chemo to try to kill all of the cancer cells, and the transplanted stem cells can grow into healthy, mature blood cells that work normally and reproduce cells that are free of cancer.

There's another way a stem cell transplant can work, if it's a transplant that uses stem cells from another person (not the cancer patient). In these cases, the transplant can help treat certain types of cancer in a way other than just replacing stem cells. Donated cells can often find and kill cancer cells better than the immune cells of the person who had the cancer ever could. This is called the “graft-versus-cancer” or “graft-versus-leukemia” effect. The "graft" is the donated cells. The effect means that certain kinds of transplants actually help kill off the cancer cells, along with rescuing bone marrow and allowing normal blood cells to develop from the stem cells.

Types of Stem Cell and Bone Marrow Transplants

Stem cell transplants are used to give back stem cells when the bone marrow has been destroyed by disease, chemotherapy (chemo), or radiation. Depending on where the stem cells come from, the transplant procedure may be called:

- Bone marrow transplant (BMT)
- Peripheral blood stem cell transplant
- Cord blood transplant

They can all be called hematopoietic stem cell transplants.

In a typical stem cell transplant for cancer, very high doses of chemo are used, sometimes along with radiation therapy, to try to kill all the cancer cells. This treatment also kills the stem cells in the bone marrow. This is called **myeloablation** or **myeloablative therapy**. Soon after treatment, stem cells are given (transplanted) to replace those that were destroyed. The replacement stem cells are given into a vein, much like a blood transfusion. The goal is that over time, the transplanted cells settle in the bone marrow, begin to grow and make healthy blood cells. This process is called **engraftment**.

There are 2 main types of transplants. They are named based on who donates the stem cells.

- **Autologous:** Auto means **self**. The stem cells in autologous transplants come from the same person who will get the transplant, so the patient is their own donor.

- **Allogeneic:** Allo means **other**. The stem cells in allogeneic transplants are from a person other than the patient, either a matched related or unrelated donor.

Autologous stem cell transplants

In this type of transplant, the first step is to remove or **harvest** your own stem cells. Your stem cells are removed from either your bone marrow or your blood, and then frozen. (You can learn more about this process at What's It Like to Donate Stem Cells?) After you get high doses of chemo and/or radiation as your myeloablative therapy, the stem cells are thawed and given back to you.

Benefits of autologous stem cell transplant: One advantage of autologous stem cell transplant is that you're getting your own cells back. When you get your own stem cells back, you don't have to worry about them (called the engrafted cells or the "graft") being rejected by your body.

Risks of autologous stem cell transplant: The grafts can still fail, which means the transplanted stem cells don't go into the bone marrow and make blood cells like they should. Also, autologous transplants can't produce the "graft-versus-cancer" effect. A possible disadvantage of an autologous transplant is that cancer cells might be collected along with the stem cells and then later put back into your body. Another disadvantage is that your immune system is the same as it was before your transplant. This means the cancer cells were able to escape attack from your immune system before, and may be able to do so again.

This kind of transplant is mainly used to treat certain leukemias, lymphomas, and multiple myeloma. It's sometimes used for other cancers, like testicular cancer and neuroblastoma, and certain cancers in children. Doctors can use autologous transplants for other diseases, too, like systemic sclerosis, multiple sclerosis (MS), and systemic lupus erythematosis (lupus).

Getting rid of cancer cells in stem cells saved for autologous transplants

To help prevent any remaining cancer cells from being transplanted along with stem cells, some centers treat the stem cells before they're given back to the patient. This may be called **purging**. While this might work for some patients, there haven't been enough studies yet to know if this

is really a benefit. A possible downside of purging is that some normal stem cells can be lost during this process. This may cause your body to take longer to start making normal blood cells, and you might have very low and unsafe levels of white blood cells or platelets for a longer time. This could increase the risk of infections or bleeding problems.

Another treatment to help kill cancer cells that might be in the returned stem cells involves giving anti-cancer drugs after the transplant. The stem cells are not treated. After transplant, the patient gets anti-cancer drugs to get rid of any cancer cells that may be in the body. This is called ***in vivo* purging**. For instance, lenalidomide (Revlimid®) may be used in this way for multiple myeloma. The need to remove cancer cells from transplanted stem cells or transplant patients and the best way to do it continues to be researched.

Tandem (double autologous) transplants

Doing 2 autologous transplants in a row is known as a **tandem transplant** or a **double autologous transplant**. In this type of transplant, the patient gets 2 courses of high-dose chemo as myeloablative therapy, each followed by a transplant of their own stem cells. All of the stem cells needed are collected before the first high-dose chemo treatment, and half of them are used for each transplant. Usually, the 2 courses of chemo are given within 6 months. The second one is given after the patient recovers from the first one.

Tandem transplants have become the standard of care for certain cancers. High-risk types of the childhood cancer neuroblastoma and adult multiple myeloma are cancers where tandem transplants seem to show good results. But doctors don’t always agree that these are really better than a single transplant for certain cancers. Because this treatment involves 2 transplants, the risk of serious outcomes is higher than for a single transplant.

Sometimes an autologous transplant followed by an allogeneic transplant might also be called a tandem transplant. (See Mini-transplants below.)

Allogeneic stem cell transplants

Allogeneic stem cell transplants use donor stem cells. In the most common type of allogeneic transplant, the stem cells come from a donor whose tissue type closely matches yours. (This is discussed in Matching patients and donors.) The best donor is a close family member, usually a brother or sister. If you don't have a good match in your family, a donor might be found in the general public through a national registry. This is sometimes called a **MUD** (matched unrelated donor) **transplant**. Transplants with a MUD are usually riskier than those with a relative who is a good match.

An allogeneic transplant works about the same way as an autologous transplant. Stem cells are collected from the donor and stored or frozen. After you get high doses of chemo and/or radiation as your myeloablative therapy, the donor's stem cells are thawed and given to you.

Blood taken from the placenta and umbilical cord of newborns is a type of allogeneic transplant. This small volume of **cord blood** has a high number of stem cells that tend to multiply quickly. Cord blood transplants are done for both adults and children. By 2017, an estimated 700,000 units (batches) of cord blood had been donated for public use. And, even more have been collected for private use. In some studies, the risk of a cancer not going away or coming back after a cord blood transplant was less than after an unrelated donor transplant.

Benefits of allogeneic stem cell transplant: The donor stem cells make their own immune cells, which could help kill any cancer cells that remain after high-dose treatment. This is called the **graft-versus-cancer** or **graft-versus-tumor** effect. Other advantages are that the donor can often be asked to donate more stem cells or even white blood cells if needed, and stem cells from healthy donors are free of cancer cells.

Risks of allogeneic stem cell transplants: The transplant, or graft, might not take – that is, the transplanted donor stem cells could die or be destroyed by the patient's body before settling in the bone marrow. Another risk is that the immune cells from the donor may not just attack the cancer cells – they could attack healthy cells in the patient's body. This is called **graft-versus-host disease**. There is also a very small risk of certain infections from the donor cells, even though donors are tested before they donate. A higher risk comes from infections you had previously, and which your immune system has had under control. These infections may surface after allogeneic transplant because your immune system is held in check (suppressed)

by medicines called **immunosuppressive** drugs. Such infections can cause serious problems and even death.

Allogeneic transplant is most often used to of leukemia, treat certain types lymphomas, multiple myeloma, myelodysplastic syndrome, and other bone marrow disorders such as aplastic anemia.

Mini-transplants (non-myeloablative transplants)

For some people, age or certain health conditions make it more risky to do myeloablative therapy that wipes out all of their bone marrow before a transplant. For those people, doctors can use a type of allogeneic transplant that's sometimes called a mini-transplant. Your doctor might refer to it as a **non-myeloablative transplant** or mention **reduced-intensity conditioning (RIC)**. Patients getting a mini transplant typically get lower doses of chemo and/or radiation than if they were getting a standard myeloablative transplant. The goal in the mini-transplant is to kill some of the cancer cells (which will also kill some of the bone marrow), and suppress the immune system just enough to allow donor stem cells to settle in the bone marrow.

Unlike the standard allogeneic transplant, cells from both the donor and the patient exist together in the patient's body for some time after a mini-transplant. But slowly, over the course of months, the donor cells take over the bone marrow and replace the patient's own bone marrow cells. These new cells can then develop an immune response to the cancer and help kill off the patient's cancer cells – the graft-versus-cancer effect.

One advantage of a mini-transplant is that it uses lower doses of chemo and/or radiation. And because the stem cells aren't all killed, blood cell counts don't drop as low while waiting for the new stem cells to start making normal blood cells. This makes it especially useful for older patients and those with other health problems. Rarely, it may be used in patients who have already had a transplant.

Mini-transplants treat some diseases better than others. They may not work well for patients with a lot of cancer in their body or people with fast-growing cancers. Also, although there

might be fewer side effects from chemo and radiation than those from a standard allogeneic transplant, the risk of graft-versus-host disease is the same. Some studies have shown that for some cancers and some other blood conditions, both adults and children can have the same kinds of results with a mini-transplant as compared to a standard transplant.

Syngeneic stem cell transplants (for those with an identical sibling)

This is a special kind of allogeneic transplant that can only be used when the patient has an identical sibling (twin or triplet) – someone who has the exact same tissue type. An advantage of syngeneic stem cell transplant is that graft-versus-host disease will not be a problem. Also, there are no cancer cells in the transplanted stem cells, as there might be in an autologous transplant.

A disadvantage is that because the new immune system is so much like the recipient's immune system, there's no graft-versus-cancer effect. Every effort must be made to destroy all the cancer cells before the transplant is done to help keep the cancer from coming back.

Half-matched transplants

Improvements have been made in the use of family members as donors. This kind of transplant is called a half-match (**haploidentical**) transplant for people who don't have fully matching or identical family member. This can be another option to consider, along with cord blood transplant and matched unrelated donor (MUD) transplant.

The importance of matching patients and donors

If possible, it is very important that the donor and recipient are a close tissue match to avoid graft rejection. Graft rejection happens when the recipient's immune system recognizes the donor cells as foreign and tries to destroy them as it would a bacteria or virus. Graft rejection can lead to graft failure, but it's rare when the donor and recipient are well matched.

A more common problem is that when the donor stem cells make their own immune cells, the new cells may see the patient's cells as foreign and attack their new "home." This is

called **graft-versus-host disease**. (See Stem Cell Transplant Side Effects for more on this). The new, grafted stem cells attack the body of the person who got the transplant. This is another reason it's so important to find the closest match possible.

What makes a stem cell donor a match? What does being an HLA match mean?

Many factors play a role in how the immune system knows the difference between self and non-self, but the most important for transplants is the **human leukocyte antigen (HLA)** system. Human leukocyte antigens are proteins found on the surface of most cells. They make up a person's tissue type, which is different from a person's blood type.

Each person has a number of pairs of HLA antigens. We inherit them from both of our parents and, in turn, pass them on to our children. Doctors try to match these antigens when finding a donor for a person getting a stem cell transplant.

How well the donor's and recipient's HLA tissue types match plays a large part in whether the transplant will work. A match is best when all 6 of the known major HLA antigens are the same – a 6 out of 6 match. People with these matches have a lower chance of graft-versus-host disease, graft rejection, having a weak immune system, and getting serious infections. For bone marrow and peripheral blood stem cell transplants, sometimes a donor with a single mismatched antigen is used – a 5 out of 6 match. For cord blood transplants a perfect HLA match doesn't seem to be as important, and even a sample with a couple of mismatched antigens may be OK.

Doctors keep learning more about better ways to match donors. Today, fewer tests may be needed for siblings, since their cells vary less than an unrelated donor. But to reduce the risks of mismatched types between unrelated donors, more than the basic 6 HLA antigens may be tested. For example, sometimes doctors to try and get a 10 out of 10 match. Certain transplant centers now require high-resolution matching, which looks more deeply into tissue types and allow more specific HLA matching.

Finding a match

There are thousands of different combinations of possible HLA tissue types. This can make it hard to find an exact match. HLA antigens are inherited from both parents. If possible, the search for a donor usually starts with the patient's brothers and sisters (siblings), who have the same parents as the patient. The chance that any one sibling would be a perfect match (that is, that you both received the same set of HLA antigens from each of your parents) is 1 out of 4.

If a sibling is not a good match, the search could then move on to relatives who are less likely to be a good match – parents, half siblings, and extended family, such as aunts, uncles, or cousins. (Spouses are no more likely to be good matches than other people who are not related.) If no relatives are found to be a close match, the transplant team will widen the search to the general public.

As unlikely as it seems, it's possible to find a good match with a stranger. To help with this process, the team will use transplant registries, like those listed here. Registries serve as matchmakers between patients and volunteer donors. They can search for and access millions of possible donors and hundreds of thousands of cord blood units.

Be the Match (formerly the **National Marrow Donor Program)**
Toll-free number: 1-800-MARROW-2 (1-800-627-7692)
Website: www.bethematch.org

Blood & Marrow Transplant Information Network
Toll-free number: 1-888-597-7674
Website: www.bmtinfonet.org

Depending on a person's tissue typing, several other international registries also are available. Sometimes the best matches are found in people with a similar racial or ethnic background. When compared to other ethnic groups, white people have a better chance of finding a perfect match for stem cell transplant among unrelated donors. This is because ethnic groups have differing HLA types, and in the past there was less diversity in donor registries, or fewer non-White donors. However, the chances of finding an unrelated donor match improve each year, as more volunteers become aware of registries and sign up for them.

Finding an unrelated donor can take months, though cord blood may be a little faster. A single match can require going through millions of records. Also, now that transplant centers are more often using high-resolution tests, matching is becoming more complex. Perfect 10 out of 10 matches at that level are much harder to find. But transplant teams are also getting better at figuring out what kinds of mismatches can be tolerated in which particular situations – that is, which mismatched antigens are less likely to affect transplant success and survival.

Keep in mind that there are stages to this process – there may be several matches that look promising but don't work out as hoped. The team and registry will keep looking for the best possible match for you. If your team finds an adult donor through a transplant registry, the registry will contact the donor to set up the final testing and donation. If your team finds matching cord blood, the registry will have the cord blood sent to your transplant center.

Stem Cell or Bone Marrow Transplant Side Effects

Problems soon after transplant

Many of the problems that can happen shortly after the transplant come from having the bone marrow wiped out by medicines or radiation just before the transplant. Others may be side effects of the conditioning treatments themselves.

Your transplant team can help you cope with side effects. Some can be prevented, and most can be treated to help you feel better.This is not a complete list and you should tell your doctor or transplant team about any problems you have or changes you notice. Some of these problems can be life-threatening, so it's important to be able to reach your doctor or transplant team at night, on weekends, and during holidays. Ask for their after hours contact numbers to make sure you will be able to do this.

Mouth and throat pain

Mucositis (inflammation or sores in the mouth) is a short-term side effect that can happen with chemo and radiation. It usually gets better within a few weeks after treatment, but it can make it very painful to eat and drink.

Good nutrition is important for people with cancer. If mouth pain or sores make it hard to eat or swallow, your transplant team can help you develop a plan to manage your symptoms.

Nausea and vomiting

Because chemotherapy drugs can cause severe nausea and vomiting, doctors often give anti-nausea medicines at the same time as chemo to try to prevent it. As much as possible, the goal is to prevent nausea and vomiting, because it's easier to prevent it than it is to stop it once it starts. Preventive treatment should start before chemo is given and should continue for as long as the chemo is likely to cause vomiting, which can be up to 7 to 10 days after the last dose.

No one drug can prevent or control chemo-related nausea and vomiting 100% of the time. In many cases, two or more medicines are used. You'll need to tell your transplant team how well the medicines are controlling your nausea and vomiting. If they aren't working, they will need to be changed.

Infection

For at least the first 6 weeks after transplant, until the new stem cells start making white blood cells (engraftment), you can easily get serious infections. Bacterial infections are most common during this time, but viral infections that were controlled by your immune system can become active again. Fungal infections can also be an issue. And even infections that cause only mild symptoms in people with normal immune systems can be quite dangerous for you. This is because right after the transplant you don't have many white blood cells that are working well, and they are the primary immune cells that fight off infections.

You may be given antibiotics to try to prevent infections until your blood counts reach a certain level. For instance, pneumocystis pneumonia (often called PCP) is a common infection that's easy to catch. Even though the germ doesn't harm people with normal immune systems, for others it can cause fever, cough, and serious breathing problems. Antibiotics are often used to keep transplant patients from getting this.

Your doctor may check you before the transplant for signs of certain infections that may become active after transplant, and give you special medicines to keep those germs under control. For example, the virus called **CMV** (cytomegalovirus) is a common infection that many adults have or had in the past. Adults with healthy immune systems may not have any symptoms because their immune system can keep the virus under control. But, CMV can be a cause of serious pneumonia in people who have had transplants, because the transplant lowers the amount of white blood cells they have. Pneumonia from CMV mainly happens to people who were already infected with CMV, or whose donor had the virus. If neither you nor your donor had CMV, the transplant team might follow special precautions to prevent this infection while you are in the hospital.

After engraftment, the risk of infection is lower, but it still can happen. It can take 6 months to a year after transplant for the immune system to work as well as it should. It can take even longer for patients with graft-versus-host disease (GVHD, see below). It's important to talk to your cancer care team about your risk for infection during this time.

Because of the increased risk, you will be watched closely for signs of infection, such as fever, cough, shortness of breath, or diarrhea. Your doctor may check your blood often, and extra precautions will be needed to keep you from being exposed to germs. While in the hospital, everyone who enters your room must wash their hands well. They may also wear gowns, shoe coverings, gloves, and masks.

Since flowers and plants can carry bacteria and fungi, they’re not allowed in your room. For the same reason, you may be told not to eat certain fresh fruits and vegetables. All your food must be well cooked and handled very carefully by you and family members. You might need to avoid certain foods for a while.

You may also be told to avoid contact with soil, feces (stool, both human and animal), aquariums, reptiles, and exotic pets. Your team may tell you to avoid being near disturbed soil, bird droppings, or mold. You will need to wash your hands after touching pets. Your family may need to move the cat’s litter box away from places you eat or spend your time. Also, you should not clean pet cages or litter boxes during this time. Instead, give this task to a family member or friend.

Your transplant team will tell you and your family in detail about the precautions you need to follow. There are many viruses, bacteria, and fungi that can cause infection after your transplant. You may be at risk for some more than others.

Despite all these precautions, patients often develop fevers, one of the first signs of infection. In fact, sometimes fever is the only sign of infection, so it's very important to contact your cancer care team if you have one or if you have any other signs of infection. You'll probably be asked to take your temperature by mouth every day or twice a day for a while. And your cancer care team will let you know when you should call in your temperature to them. If you get a fever, tests will be done to look for possible causes of the infection (chest x-rays, urine tests, and blood cultures) and antibiotics will be started.

Bleeding and transfusions

After transplant, you’re at risk for bleeding because the conditioning treatment destroys your body’s ability to make platelets. Platelets are the blood cells that help blood to clot. While you wait for your transplanted stem cells to start working, your transplant team may have you follow special precautions to avoid injury and bleeding.

Platelet counts are low for at least several weeks after transplant. In the meantime, you might notice easy bruising and bleeding, such as nosebleeds and bleeding gums. If your platelet count drops below a certain level, a platelet transfusion may be needed. You’ll need to follow precautions until your platelet counts stay at safe levels.

It also takes time for your bone marrow to start making red blood cells, and you might need red blood cell transfusions from time to time as you recover.

For more information on the transfusion process, see Blood Transfusion and Donation.

Interstitial pneumonitis and other lung problems

Pneumonitis is a type of inflammation (swelling) in lung tissue that's most common in the first 100 days after transplant. But some lung problems can happen much later – even 2 or more years after transplant.

Pneumonia caused by infection happens more often, but pneumonitis may be caused by radiation, graft-versus-host disease, or chemo rather than germs. It's caused by damage to the areas between the cells of the lungs (called interstitial spaces).

Pneumonitis can be severe, especially if total body irradiation was given with chemo as part of the pre-transplant (conditioning) treatment. Chest x-rays will be taken in the hospital to watch for pneumonitis as well as pneumonia. Some doctors will do breathing tests every few months if you have graft-versus-host disease (see next section).

You should report any shortness of breath or changes in your breathing to your doctor or transplant team right away. There are many other types of lung and breathing problems that also need to be handled quickly.

Graft-versus-host disease

Graft-versus-host disease (GVHD) can happen in allogeneic transplants when the immune cells from the donor see your body as foreign. (Remember: The recipient's immune system has mostly been destroyed by conditioning treatment and cannot fight back, so the new stem cells make up most of the immune system after transplant.) The donor immune cells may attack certain organs, most often the skin, gastrointestinal (GI) tract, and liver. This can change the way the organs work and increase the chances of infection.

GVHD reactions are very common and can range from barely noticeable to life-threatening. Doctors think of GVHD as acute or chronic. Acute GVHD starts soon after transplant and lasts a short time. Chronic GVHD starts later and lasts a long time. A person could have one, both, or neither type of GVHD.

Acute GVHD

Acute GVHD can happen 10 to 90 days after a transplant, though the average time is around 25 days.

About one-third to one-half of allogeneic transplant recipients will develop acute GVHD. It's less common in younger patients and in those with closer HLA matches between donor and the patient.

The first signs are usually a rash, burning, and redness of the skin on the palms and soles. This can spread over the entire body. Other symptoms can include:

- Nausea
- Vomiting
- Stomach cramps
- Diarrhea (watery and sometimes bloody)
- Loss of appetite
- Yellowing of the skin and eyes (jaundice)
- Abdominal (belly) pain
- Weight loss

Doctors try to prevent acute GVHD by giving drugs that suppress the immune system, such as steroids (glucocorticoids), methotrexate, cyclosporine, tacrolimus, or certain monoclonal antibodies. These drugs are given before acute GVHD starts and can help prevent serious GVHD. Still, mild GVHD will almost always happen in allogeneic transplant patients. Other drugs are being tested in different combinations for GVHD prevention.

The risk of acute GVHD can also be lowered by removing immune cells called T-cells from the donor stem cells before the transplant. But this can also increase the risk of viral infection, leukemia relapse, and graft failure (which is discussed later). Researchers are looking at new ways to remove only certain cells, called **alloactivated T-cells**, from donor grafts. This would reduce the severity of GVHD and still let the donor T-cells destroy any cancer cells left.

If acute GVHD does occur, it is most often mild, mainly affecting the skin. But sometimes it can be more serious, or even life-threatening.

Mild cases can often be treated with a steroid drug applied to the skin (topically) as an ointment, cream, or lotion, or with other skin treatments. More serious cases of GVHD might need to be treated with a steroid drug taken as a pill or injected into a vein. If steroids aren't effective, other drugs that affect the immune system can be used.

Chronic GVHD

Chronic GVHD can start anywhere from about 90 to 600 days after the stem cell transplant. A rash on the palms of the hands or the soles of the feet is often the earliest sign. The rash can spread and is usually itchy and dry. In severe cases, the skin may blister and peel, like a bad sunburn. A fever may also develop. Other symptoms of chronic GVHD can include:

- Decreased appetite
- Diarrhea
- Abdominal (belly) cramps
- Weight loss
- Yellowing of the skin and eyes (jaundice)
- Enlarged liver
- Bloated abdomen (belly)
- Pain in the upper right part of the abdomen (belly)
- Increased levels of liver enzymes in the blood (seen on blood tests)
- Skin that feels tight
- Dry, burning eyes
- Dryness or painful sores in the mouth
- Burning sensations when eating acidic foods

- Bacterial infections
- Blockages in the smaller airways of the lungs

Chronic GVHD is treated with medicines that suppress the immune system, much like those used for acute GVHD. These drugs can increase your risk of infection for as long as you are treated for GVHD. Most patients with chronic GVHD can stop the immunosuppressive drugs after their symptoms improve.

Hepatic veno-occlusive disease (VOD)

Hepatic veno-occlusive disease (VOD) is a serious problem in which tiny veins and other blood vessels inside the liver become blocked. It’s not common, and it only happens in people with allogeneic transplants, and mainly in those who got the drugs busulfan or melphalan as part of conditioning, or treatment that was given before the transplant.

VOD usually happens within about 3 weeks after transplant. It’s more common in older people who had liver problems before the transplant, and in those with acute GVHD. It starts with yellowing skin and eyes, dark urine, tenderness below the right ribs (this is where the liver is), and quick weight gain (mostly from fluid that bloats the belly). It is life-threatening, so early diagnosis of VOD is very important. Researchers continue to find ways to try to measure a person's chances of getting VOD so that treatment can start as soon as possible.

Graft failure

Grafts fail when the body does not accept the new stem cells (the graft). The stem cells that were given do not go into the bone marrow and multiply like they should. Graft failure is more common when the patient and donor are not well matched and when patients get stem cells that have had the T-cells removed. It can also happen in patients who get a low number of stem cells, such as a single umbilical cord unit. Still, it’s not very common.

Graft failure can lead to serious bleeding and/or infection. Graft failure is suspected in patients whose counts do not start going up within 3 to 4 weeks of a bone marrow or peripheral blood transplant, or within 7 weeks of a cord blood transplant.

Although it can be very upsetting to have this happen, these people can get treated with a second dose of stem cells, if they are available. Grafts rarely fail, but if they do it can result in death.

Transplant problems that may show up later

The type of problems that can happen after a transplant depend on many factors, such as the type of transplant done, the pre-transplant chemo or radiation treatment used, the patient's overall health, the patient's age when the transplant was done, the length and degree of immune system suppression, and whether chronic graft-versus-host-disease (GVHD) is present and how bad it is. The problems can be caused by the conditioning treatment (the pre-transplant chemotherapy and radiation therapy), especially total body irradiation, or by other drugs used during transplant (such as the drugs that may be needed to suppress the immune system after transplant). Possible long-term risks of transplant include:

- Organ damage
- Relapse (the cancer comes back)
- Secondary (new) cancers
- Abnormal growth of lymph tissues
- Infertility (the inability to produce children)
- Hormone changes, such as changes in the thyroid or pituitary gland
- Cataracts (clouding of the lens of the eye, which causes vision loss)

The medicines used in transplants can harm the body's organs, such as the heart, lungs, kidneys, liver, bones/joints, and nervous system. You may need careful follow-up with close monitoring and treatment of the long-term organ problems that the transplant can cause. Some of these, like infertility, should be discussed before the transplant, so you can prepare for them.

It's important to find and quickly treat any long-term problems. Tell your doctor right away if you notice any changes or problems. Physical exams by your doctor, blood work, imaging tests, lung/breathing studies, and other tests will help look for and keep tabs on organ problems.

As transplant methods have improved, more people are living longer and doctors are learning more about the long-term results of stem cell transplant. Researchers continue to look for better ways to care for these survivors to give them the best possible quality of life.

Cancer that comes back

The goal of a stem cell transplant in cancer is to prolong life and, in many cases, even cure the cancer. But in some cases, the cancer comes back (sometimes called relapse or recurrence depending on when it might occur after a transplant). Relapse or recurrence can happen a few months to a few years after transplant. It happens much more rarely 5 or more years after transplant.

If cancer comes back, treatment options are often quite limited. A lot depends on your overall health at that point, and whether the type of cancer you have responds well to drug treatment. Treatment for those who are otherwise healthy and strong may include chemotherapy or targeted therapy. Some patients who have had allogeneic transplants may be helped by getting white blood cells from the same donor (this is called **donor lymphocyte infusion**) to boost the graft-versus-cancer effect. Sometimes a second transplant is possible. But most of these treatments pose serious risks even to healthier patients, so those who are frail, older, or have chronic health problems are often unable to have them.

Other options may include palliative (comfort) care, or a clinical trial of an investigational treatment. It’s important to know what the expected outcome of any further treatment might be, so talk with your doctor about the purpose of the treatment. Be sure you understand the benefits and risks before you decide.

Second cancers (new cancers caused by treatment)

Along with the possibility of the original cancer coming back (relapse) after it was treated with a stem cell transplant, there is also a chance of having a second cancer after transplant. Studies have shown that people who have had allogeneic transplants have a higher risk of second cancer than people who got a different type of stem cell transplant.

A cancer called post-transplant lymphoproliferative disease (PTLD), if it occurs, usually develops within the first year after the transplant. Other conditions and cancers that can happen are solid tumor cancers in different organs, leukemia, and myelodysplastic syndromes. These other conditions, if they occur, tend to develop a few years or longer after the transplant.

Risk factors for developing a second cancer are being studied and may include:

- Radiation (such as total body irradiation) and high-dose chemo as part of the conditioning treatment
- Previous chemo or radiation treatment that was not part of the transplant process; the younger a person is when radiation is given, the more that person is at risk for certain types of cancer.
- Immune system problems (such as graft-versus-host disease, HLA-mismatched allogeneic transplant, and immunosuppressant therapy)
- Infection with viruses such as Epstein-Barr (EBV), cytomegalovirus (CMV), hepatitis B (HBV), or hepatitis C (HCV)
- The type of cancer you received the transplant for: for people who had their transplant when younger than 30 years old, those who had certain leukemias had a higher risk of having another cancer than people who did not have these leukemias.

Successfully treating a first cancer gives a second cancer time (and the chance) to develop. No matter what type of cancer is treated, and even without the high doses used for transplant, treatments like radiation and chemo can lead to a second cancer in the future.

Post-transplant lymphoproliferative disorder

Post-transplant lymphoproliferative disorder (PTLD) is an out-of-control growth of lymph cells, actually a type of lymphoma, that can develop after an allogeneic stem cell transplant. It’s linked to T-cells (a type of white blood cell that is part of the immune system) and the presence of Epstein-Barr virus (EBV). T-cells normally help rid the body of cells that contain viruses. When the T-cells aren’t working well, EBV-infected B-lymphocytes (a type of white blood cell) can grow and multiply. Most people are infected with EBV at some time during their lives, but the infection is controlled by a healthy immune system. The pre-transplant

treatment given weakens the immune system, allowing the EBV infection to get out of control, which can lead to a PTLD.

Still, PTLD after allogeneic stem cell transplant is fairly rare. It most often develops within 1 to 6 months after allogeneic stem cell transplant, when the immune system is still very weak.

PTLD is life-threatening. It may show up as lymph node swelling, fever, and chills. There's no one standard treatment, but it's often treated by cutting back on immunosuppressant drugs to let the patient's immune system fight back. Other treatments include white blood cell (lymphocyte) transfusions to boost the immune response, using drugs like rituximab to kill the B cells, and giving anti-viral drugs to treat the EBV.

Even though PTLD doesn't often happen after transplant, it's more likely to occur with less well-matched donors and when strong suppression of the immune system is needed. Studies are being done to identify risk factors for PTLD and look for ways to prevent it in transplant patients who are at risk.

Stem cell transplants and fertility

Most people who have stem cell transplants become infertile (unable to have children). This is not caused by the cells that are transplanted, but rather by the high doses of chemo and/or radiation therapy used. These treatments affect both normal and abnormal cells, and often damage reproductive organs.

If having children is important to you, or if you think it might be important in the future, talk to your doctor about ways to protect your fertility before treatment. Your doctor may be able to tell you if a particular treatment will be likely to cause infertility.

After chemo or radiation, some women may find their menstrual periods become irregular or stop completely. This doesn't always mean they cannot get pregnant, so birth control should be used before and after a transplant. The drugs used in transplants can harm a growing fetus.

The drugs used during transplant can also damage sperm, so men should use birth control to avoid starting a pregnancy during and for some time after the transplant process. Transplants may cause temporary or permanent infertility for men as well. Fertility returns in some men, but the timing is unpredictable. Men might consider storing their sperm before having a transplant.

Hormone Therapy

How hormone therapy is used to treat cancer

Hormones are proteins or substances made by the body that help to control how certain types of cells work. For example, some parts of the body rely on sex hormones, such as estrogen, testosterone, and progesterone, to function properly. There are other types of hormones in our bodies, too, such as thyroid hormones, cortisol, adrenaline, and insulin. Different types of hormones are made by different organs or glands.

Some cancers depend on hormones to grow. Because of this, treatments that block or alter hormones can sometimes help slow or stop the growth of these cancers. Treating cancer with hormones is called *hormone therapy, hormonal therapy,* or *endocrine therapy*. Hormone therapy is mostly used to treat certain kinds of breast cancer and prostate cancer that depend on sex hormones to grow. A few other cancers can be treated with hormone therapy, too.

Hormone therapy is considered a *systemic* treatment because the hormones they target circulate in the body. The drugs used in hormone therapy travel throughout the body to target and find the hormones. This makes it different from treatments that affect only a certain part of body, like most types of surgery and radiation therapy. Treatments like these are called *local* treatments because

they affect one part of the body. (However, surgery to remove hormone-making organs can also be used as a form of hormone therapy, as discussed below.)

The information below describes hormone therapy used to treat cancer. If you are a transgender person with cancer, and hormone therapy is a treatment option, please talk to your cancer care team for more information about how the treatment affects your situation.

How hormone therapy works

Hormone therapy travels throughout the body to find and target hormones. Different types of hormone therapy work in different ways. They can:

- Stop the body from making the hormone
- Block the hormone from attaching to cancer cells
- Alter the hormone so it doesn't work like it

should Hormone therapy can be used to:

- Treat a certain kind of cancer by stopping or slowing its growth
- Lessen symptoms related to a certain type of cancer

Types of hormone therapy

There are several different types of hormone therapy. Here are some examples and the cancers they might be used to treat.

Breast cancer

- Aromatase inhibitors (AIs), such as anastrozole, exemestane, and letrozole
- Selective estrogen receptor modulators (SERMs), such as tamoxifen and raloxifene
- Estrogen receptor antagonists, such as fulvestrant and toremifene
- Luteinizing hormone-releasing hormone (LHRH) agonists, such as goserelin, leuprolide, and triptorelin
- Surgery to remove the ovaries (known as an oophorectomy)

See Hormone Therapy for Breast Cancer to learn more.

Prostate cancer

- Anti-androgens, such as apalutamide, enzalutamide, darolutamide, bicalutamide, flutamide, and nilutamide (also called androgen deprivation therapy or ADT)
- CYP17 inhibitors, such as abiraterone and ketoconazole
- Luteinizing hormone-releasing hormone (LHRH) agonists and antagonists, such as goserelin, leuprolide, triptorelin, and degarelix
- Surgery to remove the testicles (known as an orchiectomy or surgical castration)

See Hormone Therapy for Prostate Cancer to learn more.

Endometrial (lining of the uterus or womb) cancer

- Progestins, such as medroxyprogesterone acetate or megestrol acetate
- Selective estrogen receptor modulators (SERMs), such as tamoxifen and raloxifene
- Luteinizing hormone-releasing hormone (LHRH) agonists, such as goserelin, and leuprolide
- Aromatase inhibitors (AIs), such as letrozole, anastrozole, and

exemestane See Hormone Therapy for Endometrial Cancer to learn more.

Adrenal cancer

- Adrenolytics, such as mitotane
- Estrogen receptor antagonists, such as fulvestrant and toremifene
- Selective estrogen receptor modulators (SERMs), such as tamoxifen and raloxifene

See Chemotherapy for Adrenal Cancer and Other Drugs Used to Treat Adrenal Cancer to learn more.

Getting hormone therapy

Oral drugs

Many types of hormone therapy are drugs that are taken by mouth. In these cases, you swallow the pill, capsule, or liquid just like other medicines. These are usually taken at home. How often they are taken depends on the drug being given and the type of cancer being treated. Because of this, it’s very important to make sure you know exactly how it should be taken and to follow instructions exactly. There may be special precautions to take, depending on the drug you're prescribed. You can read more about special precautions for oral cancer drugs and what you should ask your cancer care team in the section on Oral Chemo in Getting Oral or Topical Chemotherapy.

Injectable drugs

Some types of hormone therapy are injections given in the arm, leg, or hip. These are called intramuscular (or IM) injections. There are also types that are given just under the skin of the abdomen (belly). These are called subcutaneous (SC or sub-Q) injections. How often they are given depends on the drug and type of cancer being treated. The injections might be given in your treatment center or doctor's office. Sometimes patients are taught to give their own injections or a caregiver can be taught to give them.

Surgery to remove hormone-making organs

Some types of surgery can also be forms of hormone therapy. For example, an orchiectomy (surgery to remove the testicles, the body’s main source of testosterone) can be an option for some men with prostate cancer who need

hormone therapy as part of their treatment. Likewise, an oophorectomy (surgery to remove the ovaries, the body's main source of estrogen and progesterone) can be an option for some women with breast cancer.

Side effects from this type of hormone therapy tend to be like those from drugs that lower hormone levels in the body (see below). An advantage of this type of hormone therapy is that it is done all at once, and it doesn't require long-term treatment with medicines. A possible downside is that it is permanent, so once it's done, it can't be reversed.

Hormone therapy side effects

Each patient's side effects can be different, and will depend on the type of hormone therapy they're getting and other factors. It's very important to know about possible side effects when making treatment decisions. It's also important to balance the benefits and risks of any treatment. Talk to your cancer care team, and ask any questions you have about hormone therapy.

Men who get hormone therapy for prostate cancer might have these possible side effects:

- Hot flashes
- Decreased sexual desire
- Erectile dysfunction (trouble getting an erection)
- Bone loss and a higher risk for fractures
- Fatigue

- Weight gain (especially around the belly) with decreased muscle mass
- Memory problems
- Increased risk of other health problems

Women getting hormone therapy for breast or endometrial cancer might have these possible side effects:

- Hot flashes
- Vaginal discharge, dryness, or irritation
- Decreased sexual desire
- Fatigue
- Nausea
- Pain in muscles and joints
- Bone loss and a higher risk for fractures
- Higher risk of other types of cancer, stroke, blood clots, cataracts, and heart disease

Men with breast cancer who are getting hormone therapy can also experience many of these same side effects, along with having erectile dysfunction.

Read more about these side effects in Hormone Therapy for Breast Cancer, Hormone Therapy for Prostate Cancer, or Hormone Therapy for Endometrial Cancer. See Managing Cancer-related Side Effects to learn about what to watch for and how to manage side effects.

Hormone therapy drug safety

Much is known about the need to protect others from exposure to standard chemotherapy because it is hazardous. This is why there are safety rules and recommendations for people who handle chemo drugs. Some hormone therapy drugs also have precautions. **Talk to your cancer care team about any special precautions that might be needed to protect yourself and others while you are taking hormone therapy.**

Overview

Gene therapy involves altering the genes inside your body's cells in an effort to treat or stop disease.

Genes contain your DNA — the code that controls much of your body's form and function, from making you grow taller to regulating your body systems. Genes that don't work properly can cause disease.

Gene therapy replaces a faulty gene or adds a new gene in an attempt to cure disease or improve your body's ability to fight disease. Gene therapy holds promise for treating a wide range of diseases, such as cancer, cystic fibrosis, heart disease, diabetes, hemophilia and AIDS.

Researchers are still studying how and when to use gene therapy. Currently, in the United States, gene therapy is available only as part of a clinical trial.

Why it's done

Gene therapy is used to correct defective genes in order to cure a disease or help your body better fight disease.

Researchers are investigating several ways to do this, including:

- **Replacing mutated genes.** Some cells become diseased because certain genes work incorrectly or no longer work at all. Replacing the defective genes may help treat certain diseases. For instance, a gene called p53 normally prevents tumor growth. Several types of cancer have been linked to problems with the p53 gene. If doctors could replace the defective p53 gene, that might trigger the cancer cells to die.
- **Fixing mutated genes.** Mutated genes that cause disease could be turned off so that they no longer promote disease, or healthy genes that help prevent disease could be turned on so that they could inhibit the disease.
- **Making diseased cells more evident to the immune system.** In some cases, your immune system doesn't attack diseased cells because it doesn't recognize them as intruders. Doctors could use gene therapy to train your immune system to recognize the cells that are a threat.

Risks

Gene therapy has some potential risks. A gene can't easily be inserted directly into your cells. Rather, it usually has to be delivered using a carrier, called a vector.

The most common gene therapy vectors are viruses because they can recognize certain cells and carry genetic material into the cells' genes. Researchers remove the original disease-causing genes from the viruses, replacing them with the genes needed to stop disease.

This technique presents the following risks:

- **Unwanted immune system reaction.** Your body's immune system may see the newly introduced viruses as intruders and attack them. This may cause inflammation and, in severe cases, organ failure.
- **Targeting the wrong cells.** Because viruses can affect more than one type of cells, it's possible that the altered viruses may infect additional cells — not just the targeted cells containing mutated genes. If this happens, healthy cells may be damaged, causing other illness or diseases, such as cancer.
- **Infection caused by the virus.** It's possible that once introduced into the body, the viruses may recover their original ability to cause disease.
- **Possibility of causing a tumor.** If the new genes get inserted in the wrong spot in your DNA, there is a chance that the insertion might lead to tumor formation.

The gene therapy clinical trials underway in the U.S. are closely monitored by the Food and Drug Administration and the National Institutes of Health to ensure that patient safety issues are a top priority during research.

What you can expect

Currently, the only way for you to receive gene therapy is to participate in a clinical trial. Clinical trials are research studies that help doctors determine whether a gene therapy approach is safe for people. They also help doctors understand the effects of gene therapy on the body.

Your specific procedure will depend on the disease you have and the type of gene therapy being used.

For example, in one type of gene therapy:

- You may have blood drawn or you may need bone marrow removed from your hipbone with a large needle.
- Then, in a lab, cells from the blood or bone marrow are exposed to a virus or another type of vector that contains the desired genetic material.
- Once the vector has entered the cells in the lab, those cells are injected back into your body into a vein or into tissue, where your cells take up the vector along with the altered genes.

Viruses aren't the only vectors that can be used to carry altered genes into your body's cells. Other vectors being studied in clinical trials include:

- **Stem cells.** Stem cells are the cells from which all other cells in your body are created. For gene therapy, stem cells can be trained in a lab to become cells that can help fight disease.
- **Liposomes.** These fatty particles have the ability to carry the new, therapeutic genes to the target cells and pass the genes into your cells' DNA.

Results

The possibilities of gene therapy hold much promise. Clinical trials of gene therapy in people have shown some success in treating certain diseases, such as:

- Severe combined immune deficiency
- Hemophilia
- Blindness caused by retinitis pigmentosa
- Leukemia

But several significant barriers stand in the way of gene therapy becoming a reliable form of treatment, including:

- Finding a reliable way to get genetic material into cells

- Targeting the correct cells
- Reducing the risk of side effects

Gene therapy continues to be a very important and active area of research aimed at developing new, effective treatments for a variety of diseases.