SATHYABAMA
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SCHOOL OF BIO AND CHEMICAL ENGINEERING

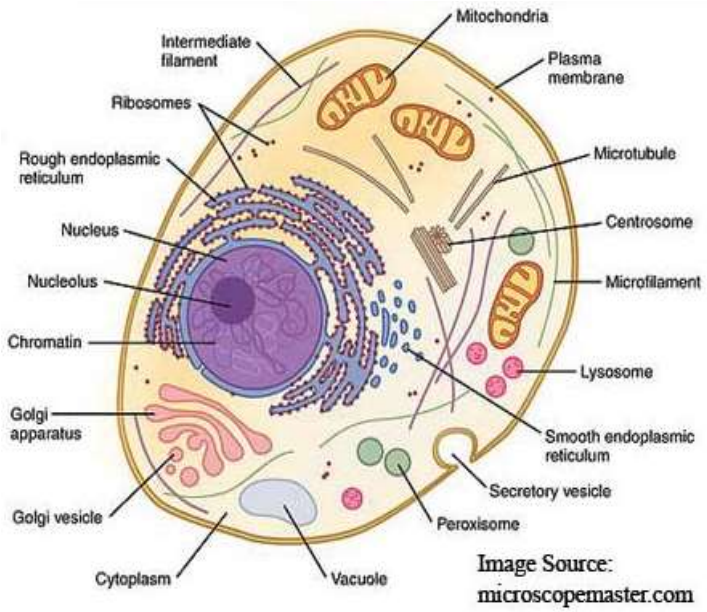
DEPARTMENT OF BIOINFORMATICS

UNIT – I - CELL BIOLOGY & BIOCHEMISTRY-SBIA1102

UNIT 1

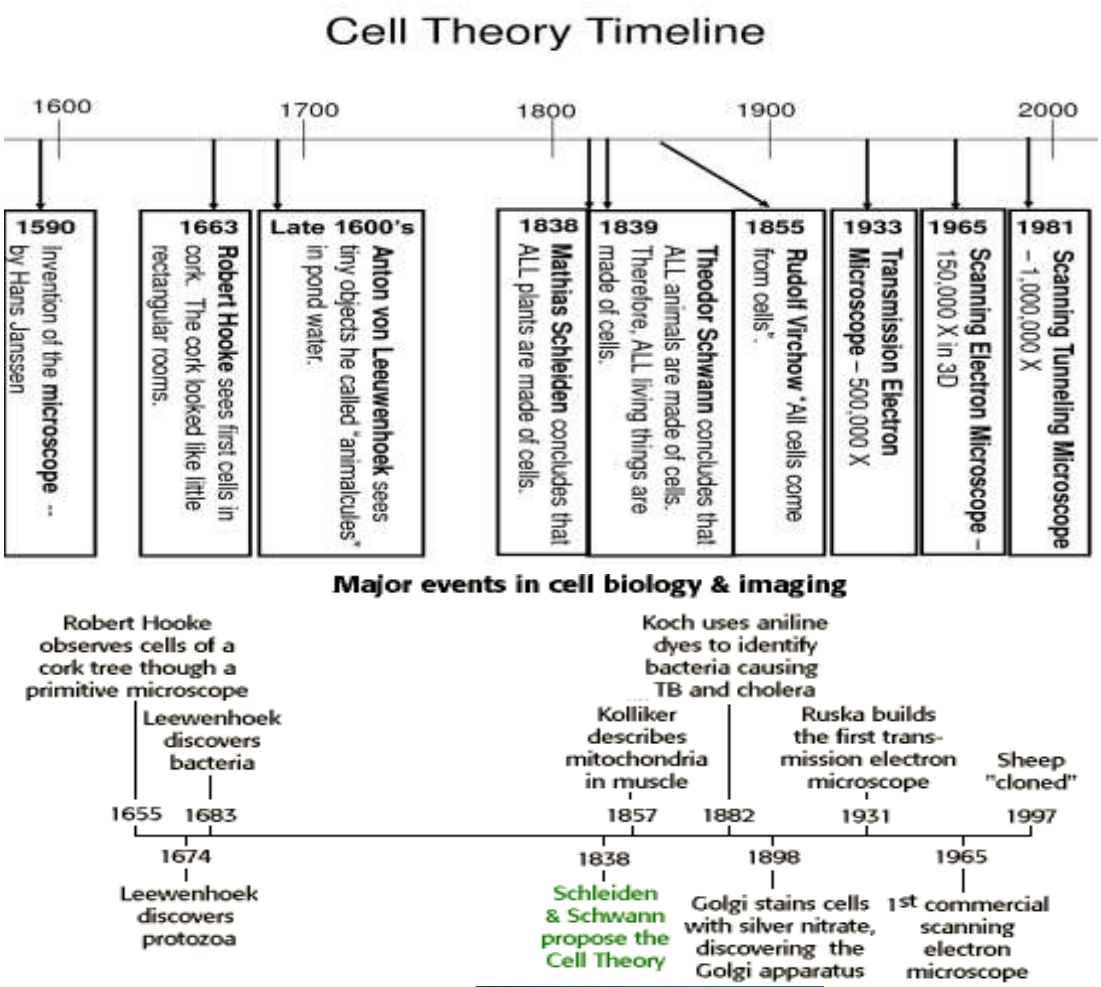
- Basics of cell structure
- Basics of Cell Biology (structure & function) – Discovery of cell and Cell Theory
- Structure of Prokaryotic and Eukaryotic cells
- Cell wall, plasma Membrane, Cytoplasm
- Comparison between plant and animal cells

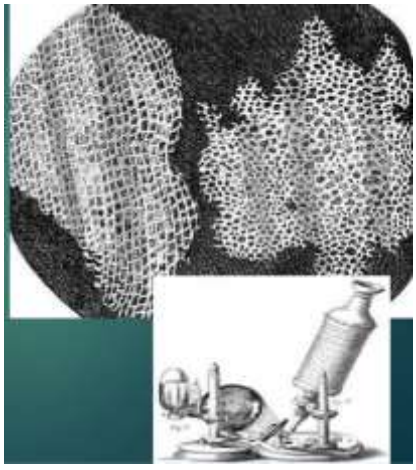
- As a sub-discipline of biology, cell biology is concerned with the study of the structure and function of cells.
- As such, it can explain the structure of different types of cells, types of cell components, the metabolic processes of a cell, cell life cycle and signaling pathways to name a few.
- Here, we shall look at some of the major areas of cell biology including some of the tools used.The cell is defined as the fundamental, functional unit of life.
- Some organisms are comprised of only one cell whereas others have many cells that are organized into tissues, organs, and systems.
- The scientific study of the cell is called cell biology.
- This field deals with the cell structure and function in detail.
- It covers topics such as DNA replication, protein synthesis, and cell defence.

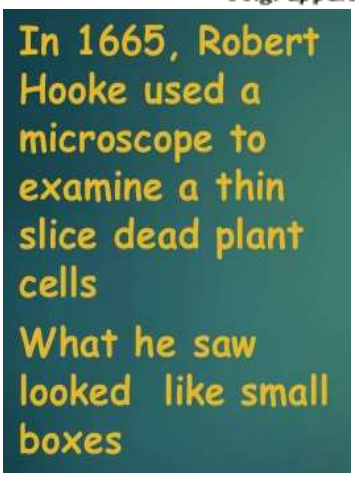


Cell Theory

Cell Theory is a basic principle in biology that was formulated by Thodor Schwann, Matthias Schleiden and Rudolph Virchow







- Hooke's most important publication was Micrographia, a 1665 volume documenting experiments he had made with a microscope.
- In this groundbreaking study, he coined the term "cell" while discussing the structure of cork.

- He also described flies, feathers and snowflakes, and correctly identified fossils as remnants of once-living things.
- The 1678 publication of Hooke's Lectures of Spring shared his theory of elasticity; in what came to be known as "Hooke's Law," he stated that the force required to extend or compress a spring is proportional to the distance of that extension or compression.
- In an ongoing, related project, Hooke worked for many years on the invention of a spring-regulated watch.
- A true polymath, the topics Hooke covered during his career include comets, the motion of light, the rotation of Jupiter, gravity, human memory, and the properties of air.
- In all of his studies and demonstrations, he adhered to the scientific method of experimentation and observation.
- Hooke also utilized the most up-to-date instruments in his many projects.

Antonie Van Leeuwenhoek

- Known For: Improvements to the microscope, discovery of bacteria, discovery of sperm, descriptions of all manner of microscopic cell structures (plant and animal), yeasts, molds, and more
- Also Known As: Antonie Van Leeuwenhoek, Antony Van Leeuwenhoek

- Anton van Leeuwenhoek (October 24, 1632–August 30, 1723) invented the first practical microscopes and used them to become the first person to see and describe bacteria, among other microscopic discoveries.
- Indeed, van Leeuwenhoek's work effectively refuted the doctrine of spontaneous generation, the theory that living organisms could spontaneously emerge from nonliving matter.
- His studies also led to the development of the sciences of bacteriology and protozoology.

Cell Theory-Introduction

- It wasn ' t until the 1830s that the widespread importance of cells was realized.
- In 1838, Matthias Schleiden, a German lawyer turned botanist, concluded that, despite differences in the structure of various tissues, plants were made of cells and that the plant embryo arose from a single cell.

- In 1839, Theodor Schwann, a German zoologist and colleague of Schleiden ' s, published a comprehensive report on the cellular basis of animal life.
- Schwann concluded that the cells of plants and animals are similar structures and proposed these two tenets of the cell theory :
- All organisms are composed of one or more cells.
- The cell is the structural unit of life.
- Schleiden and Schwann ' s ideas on the origin of cells proved to be less insightful; both agreed that cells could arise from noncellular materials.
- Given the prominence that these two scientists held in the scientific world, it took a number of years before observations by other biologists were accepted as demonstrating that cells did not arise in
- this manner any more than organisms arose by spontaneous generation.
- By 1855, Rudolf Virchow, a German pathologist, had made a convincing case for the third tenet of the cell theory:
- ● Cells can arise only by division from a preexisting cell.
- Cell Theory is a basic principle in biology that was formulated by Thodor Schwann, Matthias Schleiden and Rudolph Virchow.
- Cell Theory, was composed of the first three statements shown:

1. All living things are made up of cells.

2. The cell is structural & functional unit of all living things.

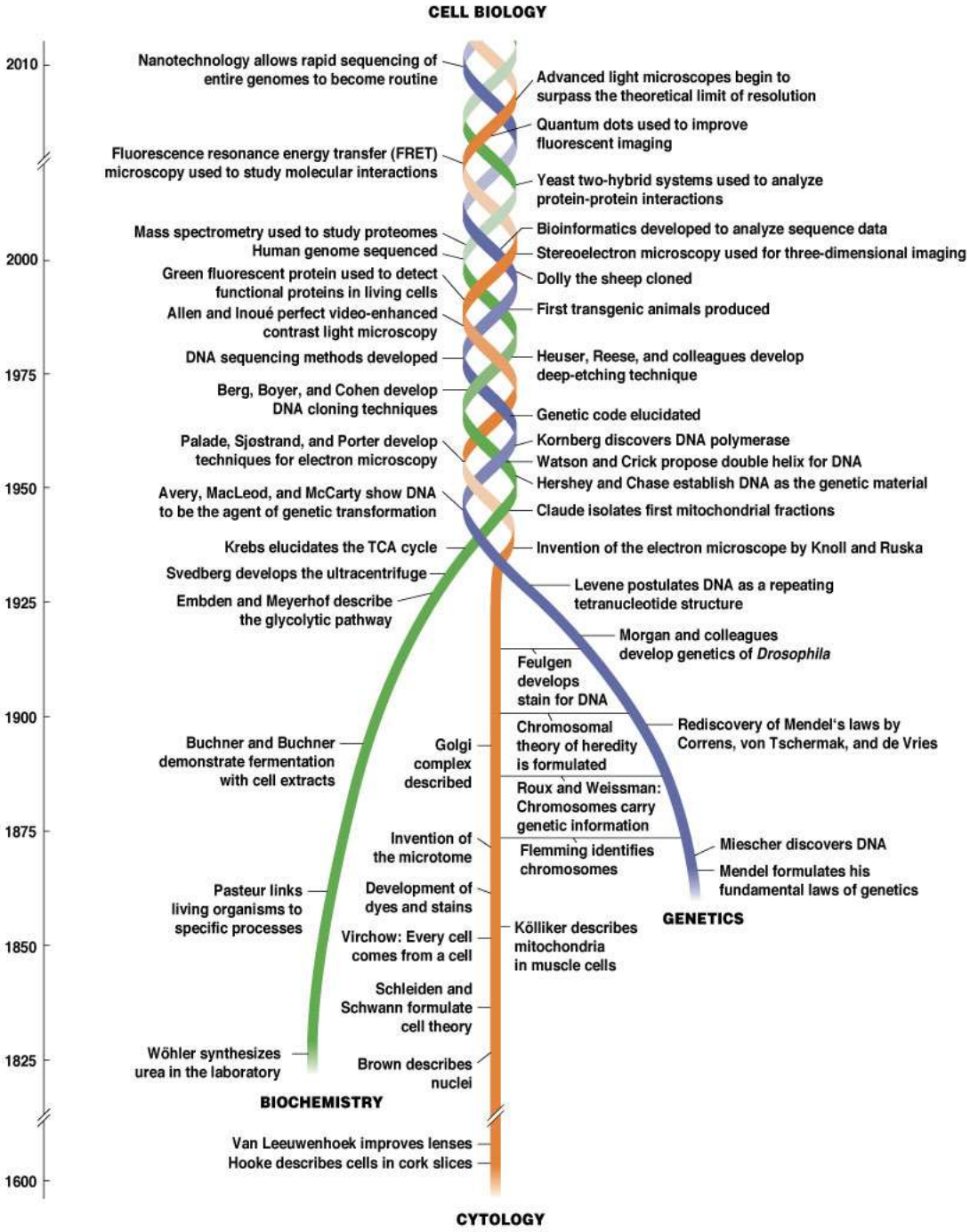
3. All cells come from pre-existing cells.

4. Cells contain inheritable information which is passed from cell to cell during cell division.

5. Cells are basically the same in chemical composition.

6. All energy flow (metabolism & biochemistry) of life occurs within cells.

Several additional facts have been added to the cell theory since then. The "Modern Cell Theory" also includes the last three statements as shown.

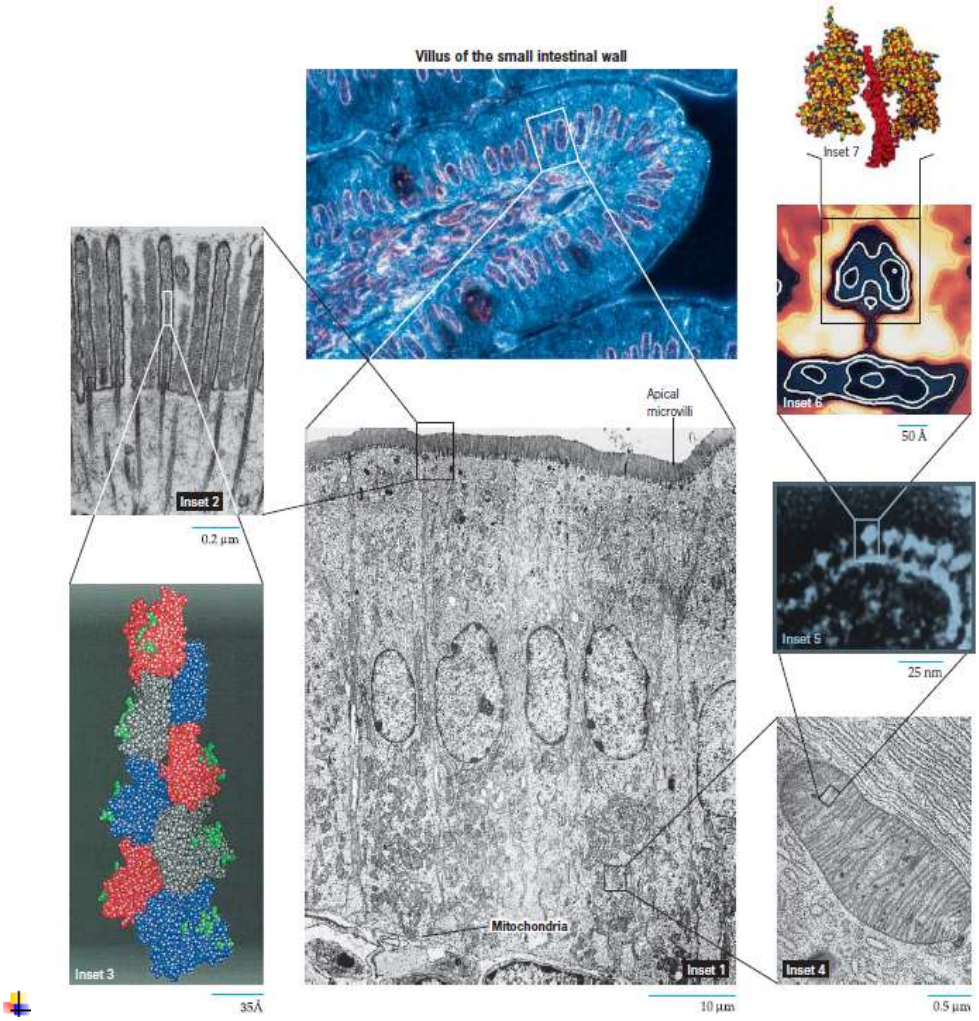


Basic Properties of Cells

1.Cells Are Highly Complex and Organized:

- Cellular activities can be remarkably precise. DNA duplication,for example, occurs with an error rate of less than one mistake every ten million nucleotides incorporated—and most of these are quickly corrected by an elaborate repair mechanism that recognizes the defect.

- Organization of atoms into small-sized molecules; the organization of these molecules into giant polymers; and the organization of different types of polymeric molecules into complexes, which in turn are organized into subcellular organelles and finally into cells.
- Each type of cell has a consistent appearance when viewed under a high-powered electron microscope; that is, its organelles have a particular shape and location, from one individual of a species to another. Similarly, each type of organelle has a consistent composition of macromolecules, which are arranged in a predictable pattern.
- Consider the cells lining your intestine that are responsible for removing nutrients from your digestive tract.
- Inset 1 shows an electron micrograph of the epithelial layer of cells that lines
- the inner intestinal wall. The apical surface of each cell, which faces the channel of the intestine, contains a large number of microvilli involved in nutrient absorption. The basal region of each cell contains large numbers of mitochondria, where energy is made available to the cell.
- Inset 2 shows the apical microvilli; each microvillus contains a bundle of actin filaments.
- Inset 3 shows the actin protein subunits that make up each filament.
- Inset 4 shows an individual mitochondrion similar to those found in the basal region of the epithelial cells.
- Inset 5 shows a portion of an inner membrane of a mitochondrion including the stalked particles that project from the membrane and correspond to the sites where ATP is synthesized.
- Insets 6 and 7 show molecular models of the ATP- synthesizing machinery

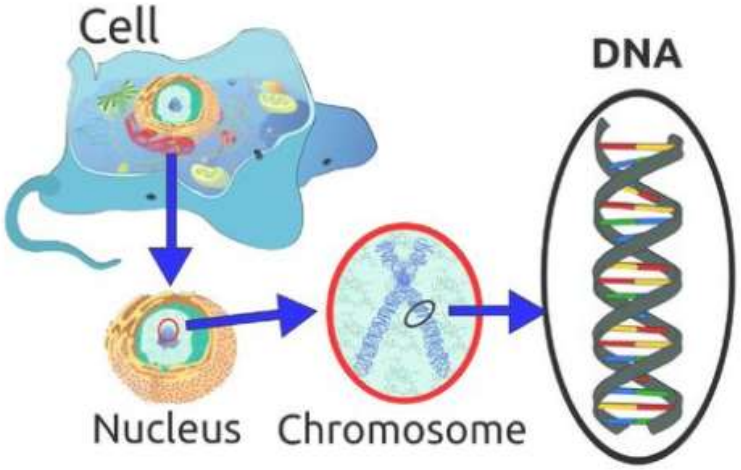


2.Cells Possess a Genetic Program and the Means to Use It

Organisms are built according to information encoded in a collection of genes, which are constructed of DNA.

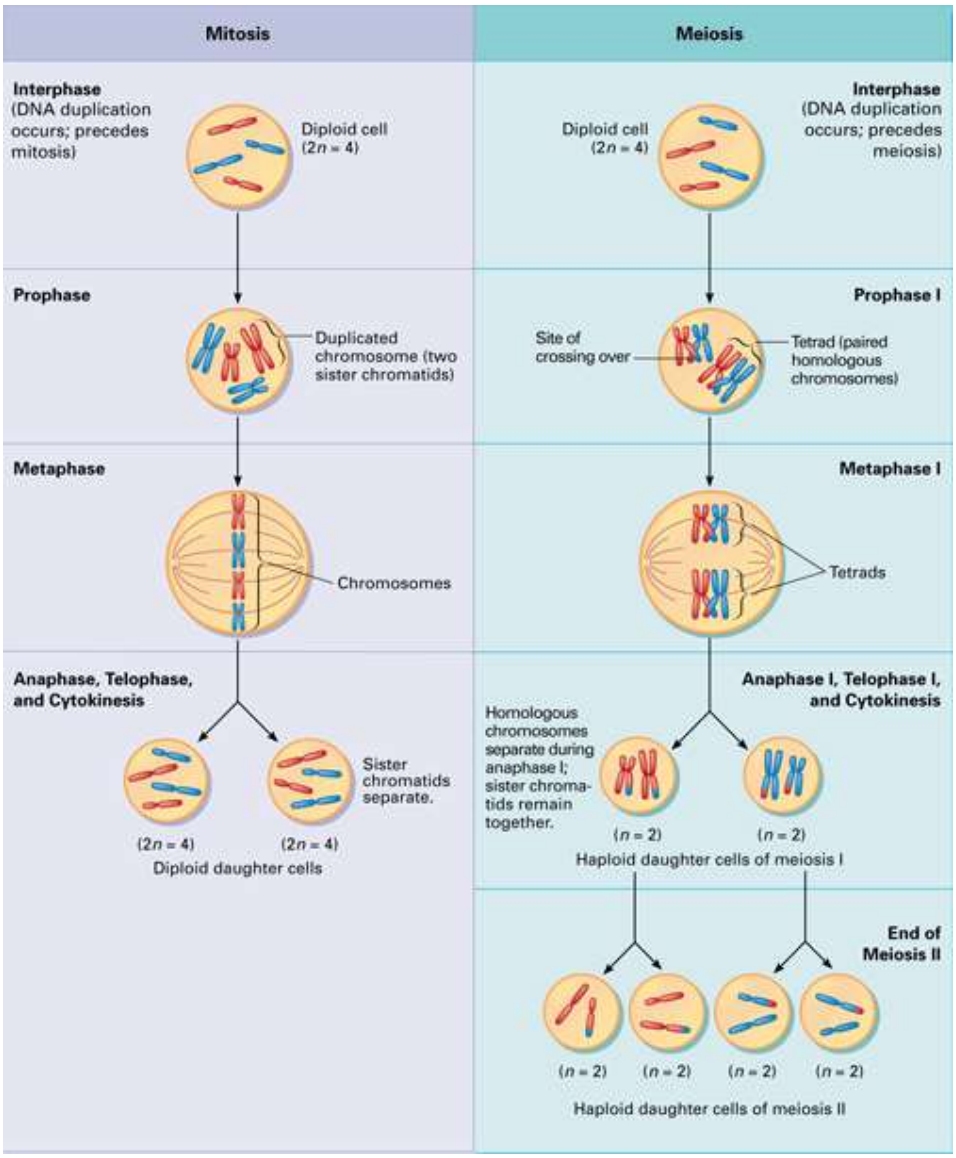
Genes are more than storage lockers for information: They constitute the recipes for constructing cellular structures, the directions for running cellular activities, and the program for making more of themselves.

The molecular structure of genes allows for changes in genetic information (mutations) that lead to variation among individuals, which forms the basis of biological evolution.



3. Cells Are Capable of Producing More of themselves

- Cells reproduce by division, a process in which the contents of a “mother” cell are distributed into two “daughter” cells.



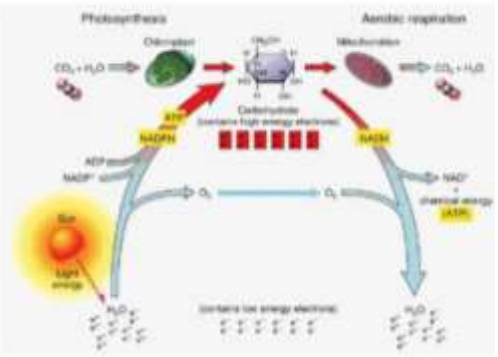
4.Cells Acquire and Utilize Energy

- Cells Acquire and Utilize Energy
  - Plant cells derive energy from the products of photosynthesis, mainly in the form of glucose.
  - Cell can convert glucose into ATP—a substance with readily available energy.

5.Cells Carry Out a Variety of Chemical Reactions

- Cells function like miniaturized chemical plants. Even the simplest bacterial cell is capable of hundreds of different chemical transformations, none of which occurs at any significant rate in the inanimate world.
- Virtually all chemical changes that take place in cells require *enzymes* —molecules that greatly increase the rate at which a chemical reaction occurs. The sum total of the chemical reactions in a cell ' s metabolism .

- Cells Acquire and Utilize Energy
- Cells Carry Out a Variety of Chemical Reactions
- Cells Engage in Mechanical Activities
- Cells Are Able to Respond to Stimuli



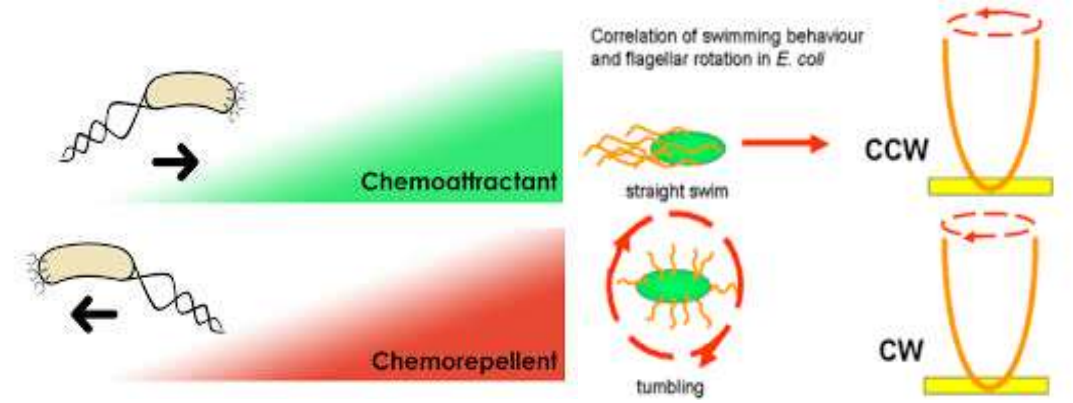
6.Cells Engage in Mechanical Activities

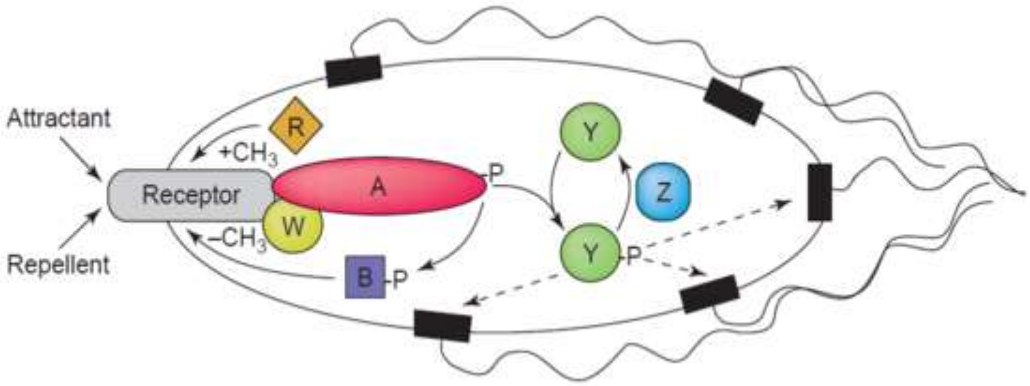
- Cells are sites of bustling activity. Materials are transported from place to place, structures are assembled and then rapidly disassembled, and, in many cases, the entire cell moves itself from one site to another.
- These types of activities are based on dynamic, mechanical changes within cells, many of which are initiated by changes in the shape of "motor" proteins. Motor proteins are just one of many types of molecular "machines" employed by cells to carry out mechanical activities.

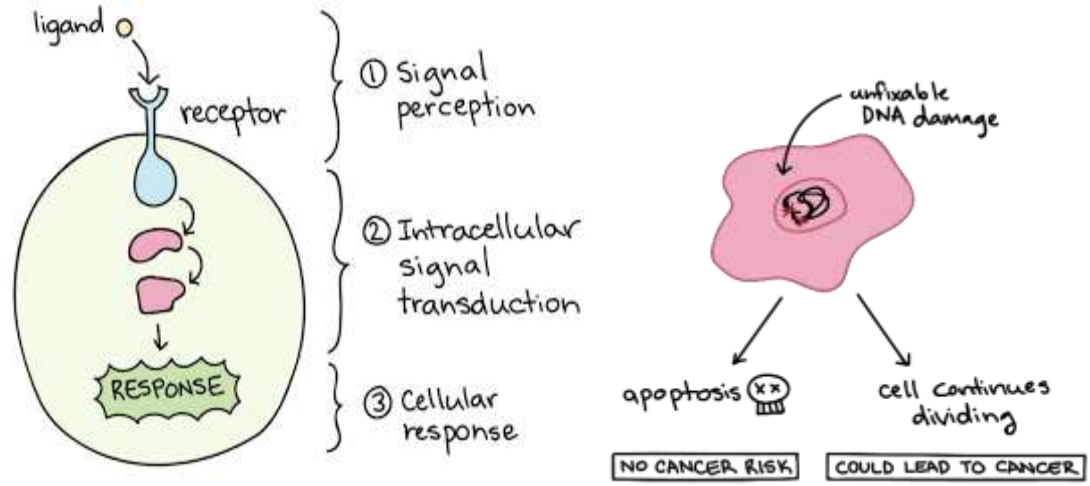
7. Cells Are Able to Respond to Stimuli

- Some cells respond to stimuli in obvious ways; a single-celled protist, for example, moves away from an object in its path or moves toward a source of nutrients.
- Cells within a multicellular plant or animal respond to stimuli less obviously.

- Most cells are covered with receptors that interact with substances in the environment in highly specific ways.
- Cells possess receptors to hormones, growth factors, and extracellular materials, as well as to substances on the surfaces of other cells.
- A cell ' s receptors provide pathways through which external stimuli can evoke specific responses in target cells.
- Cells may respond to specific stimuli by altering their metabolic activities, moving from one place to another, or even committing suicide.



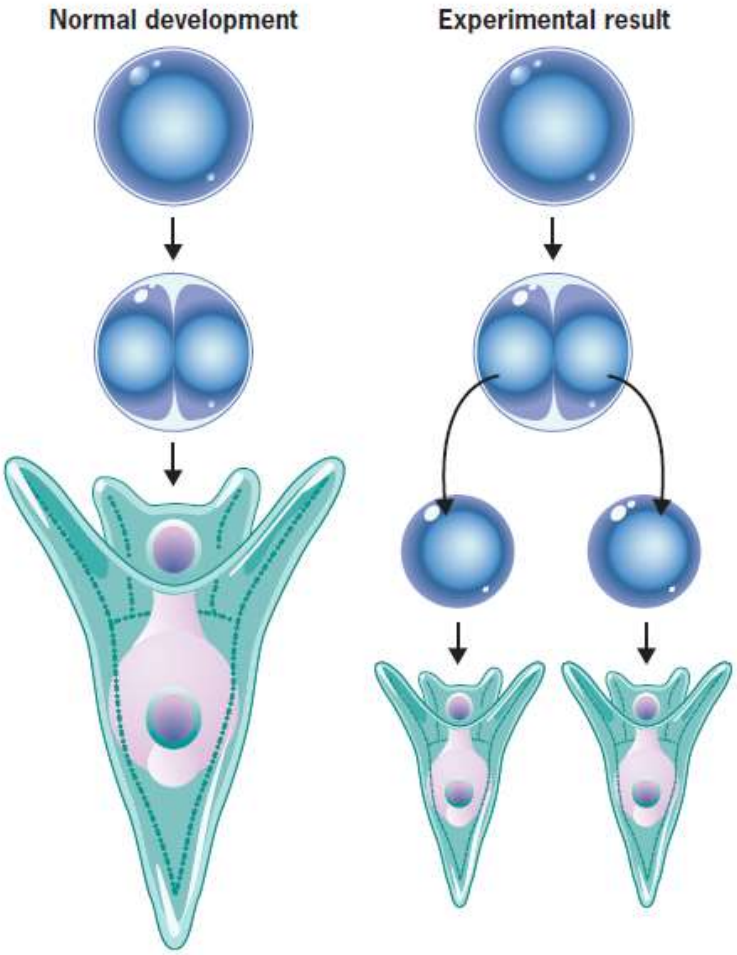




8. Cells Are Capable of Self-Regulation

- 1891 by Hans Driesch, a German embryologist. Driesch found that he could completely separate the first two or four cells of a sea urchin embryo and each of the isolated cells would proceed to develop into a normal embryo
- The left panel depicts the normal development of a sea urchin in which a fertilized egg gives rise to a single embryo.
- The right panel depicts an experiment in which the cells of an early embryo are separated from one another after the first division, and each cell is allowed to develop in isolation.
- Rather than developing into half of an embryo, as it would if left undisturbed, each isolated cell recognizes the absence of its neighbor, regulating its development to form a complete (although smaller) embryo.


9.Cells Evolve



9.Cells Evolve

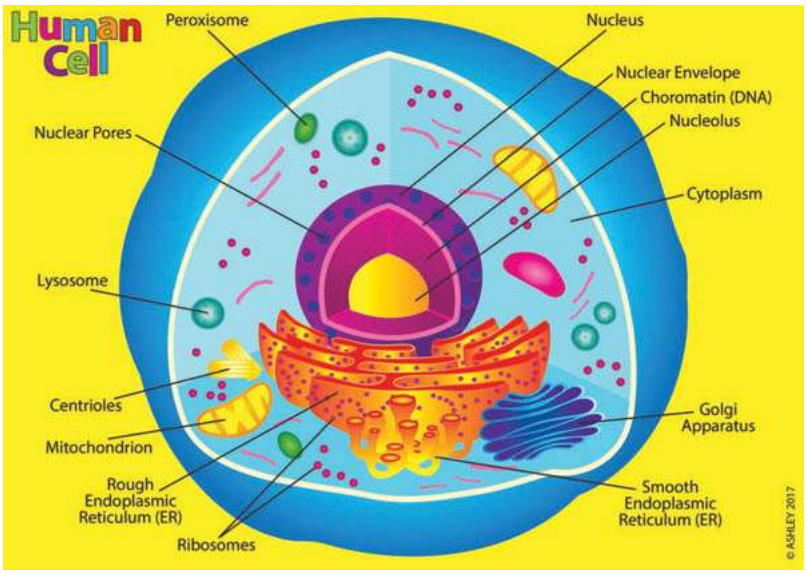
- According to one of the tenets of modern biology, all living organisms have evolved from a single, common ancestral cell that lived more than three billion years ago.
- Because it gave rise to all the living organisms that we know of, this ancient cell is often referred to as the last universal common ancestor (or LUCA).

Structure of Prokaryotic and Eukaryotic cells

The cell

The cell is the structural and functional unit of life. It may be also regarded as the *basic unit of biological activity.*

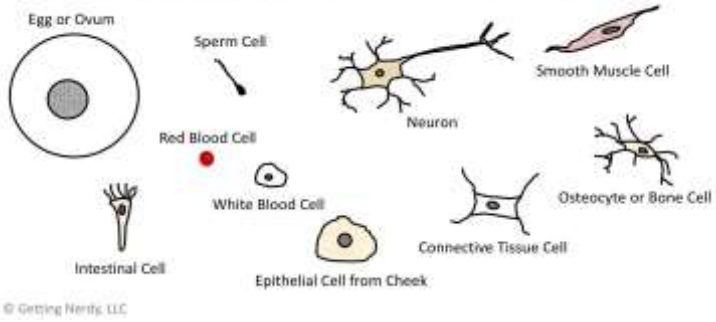
The concept of cell originated from the contributions of Schleiden and Schwann (1838). However, it was only after 1940, the complexities of cell structure were exposed.



What is a Cell?

A cell is the smallest unit that is capable of performing life functions – i.e. has all of the characteristics of living things.

Notice how the shape of the cell determines what its function is...



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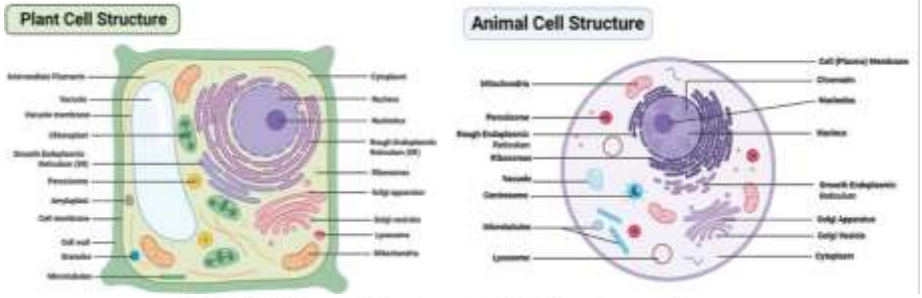
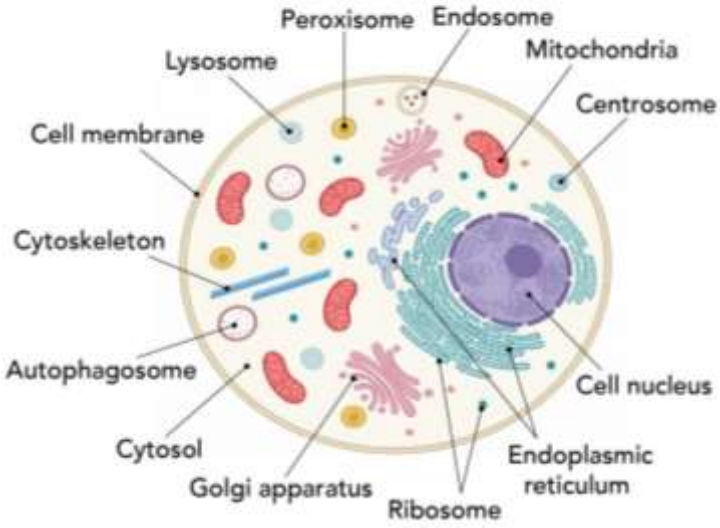
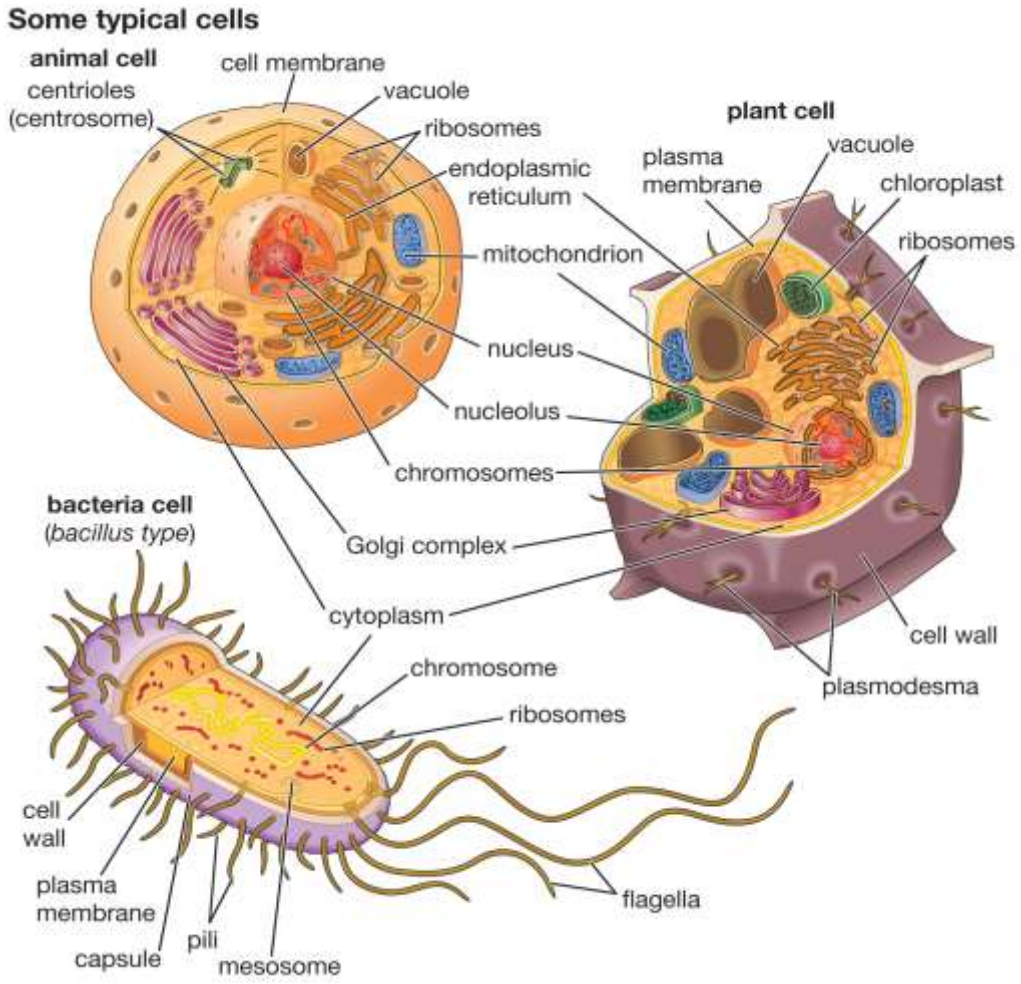
Cell Organelles

Structure and Functions with diagram

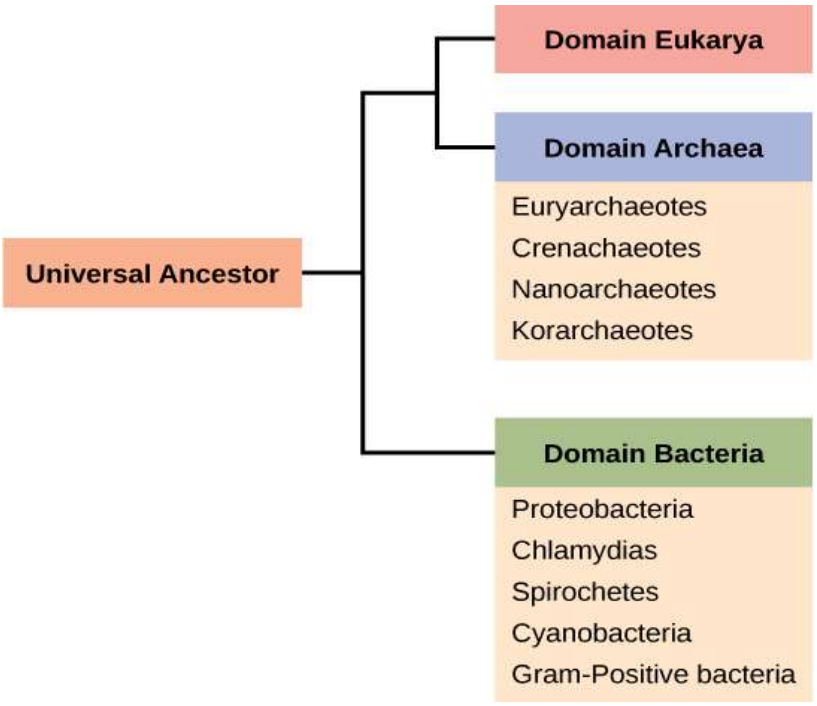


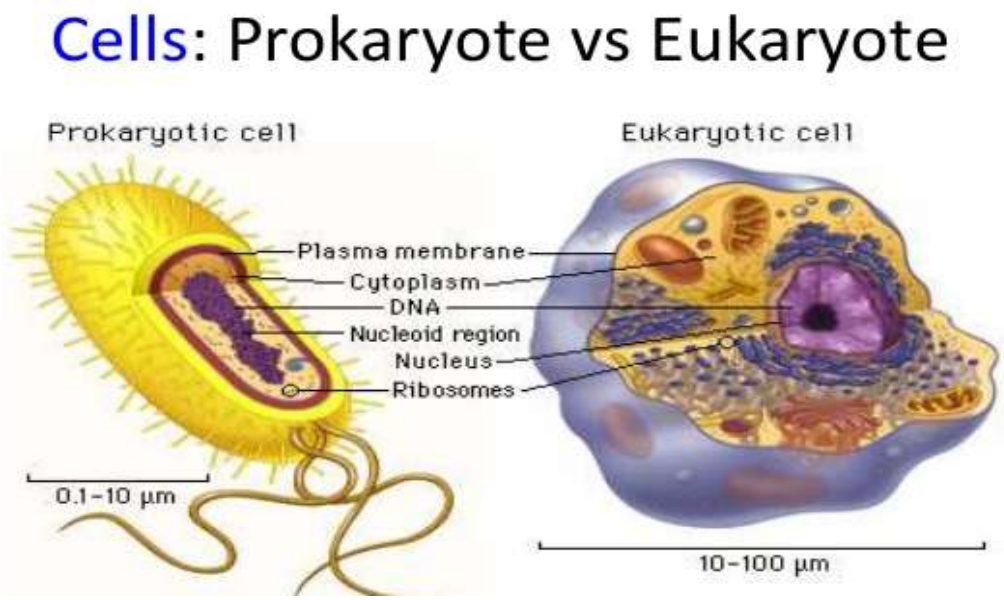
Cell Structure and Organelles



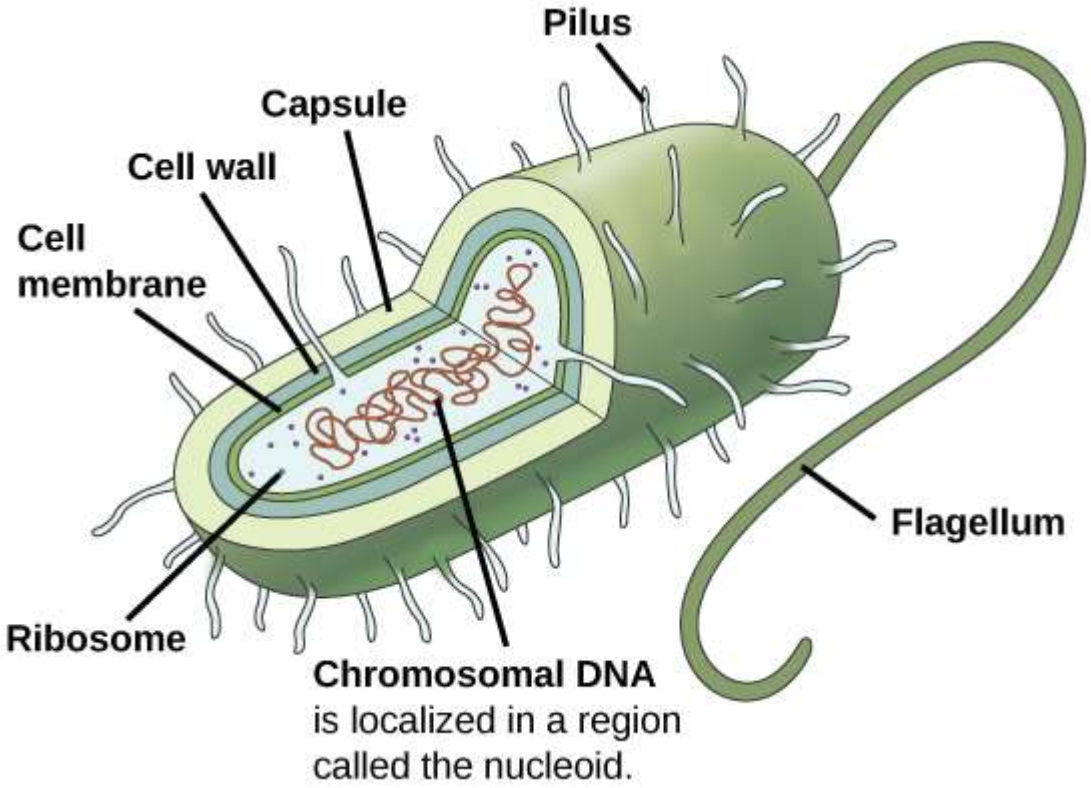


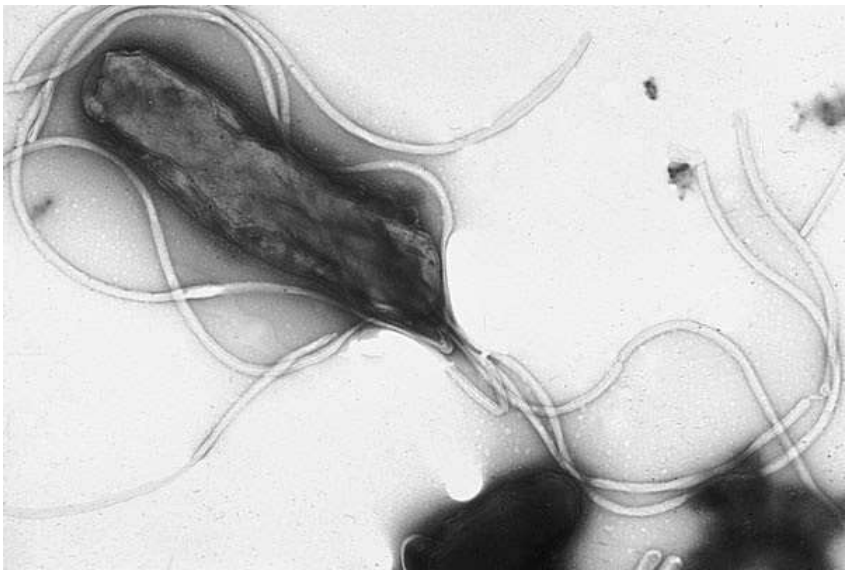
- Bacteria and Archaea are both prokaryotes but differ enough to be placed in separate domains.
- An ancestor of modern Archaea is believed to have given rise to Eukarya, the third domain of life.
- Archaeal and bacterial phyla are shown; the evolutionary relationship between these phyla is still open to debate.





- Prokaryotes are organisms whose cells lack a nucleus and other organelles.
- Prokaryotes are divided into two distinct groups: the bacteria and the archaea, which scientists believe have unique evolutionary lineages.
- Most prokaryotes are small, single-celled organisms that have a relatively simple structure.
- Prokaryotic cells are surrounded by a plasma membrane, but they have no internal membrane-bound organelles within their cytoplasm.
- The absence of a nucleus and other membrane-bound organelles differentiates prokaryotes from another class of organisms called eukaryotes.



- 

- Most prokaryotes carry a small amount of genetic material in the form of a single molecule, or chromosome, of circular DNA.
- The DNA in prokaryotes is contained in a central area of the cell called the nucleoid, which is not surrounded by a nuclear membrane.
- Many prokaryotes also carry small, circular DNA molecules called plasmids, which are distinct from the chromosomal DNA and can provide genetic advantages in specific environments.

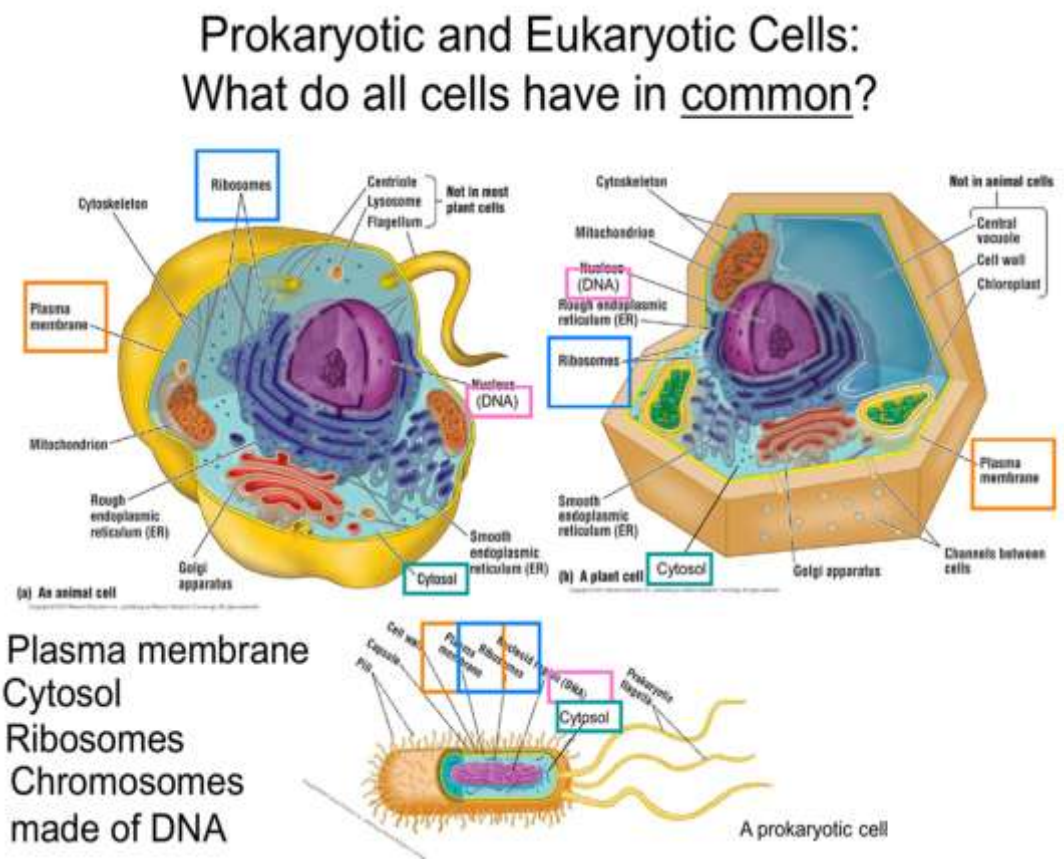
- Key Points
- Prokaryotes lack an organized nucleus and other membrane-bound organelles.
- Prokaryotic DNA is found in a central part of the cell called the nucleoid.
- The cell wall of a prokaryote acts as an extra layer of protection, helps maintain cell shape, and prevents dehydration.
- Prokaryotic cell size ranges from 0.1 to 5.0 μm in diameter.
- The small size of prokaryotes allows quick entry and diffusion of ions and molecules to other parts of the cell while also allowing fast removal of waste products out of the cell.
- Key Terms
- Nucleoid: the irregularly-shaped region within a prokaryote cell where the genetic material is localized

Features held in common by the two types of cells:

- Plasma membrane of similar construction
- Genetic information encoded in DNA using identical genetic code
- Similar mechanisms for transcription and translation of genetic information, including similar ribosomes
- Shared metabolic pathways (e.g., glycolysis and TCA cycle)
- Similar apparatus for conservation of chemical energy as ATP (located in the plasma membrane of prokaryotes and the mitochondrial membrane of eukaryotes)
- Similar mechanism of photosynthesis (between cyanobacteria and green plants)
- Similar mechanism for synthesizing and inserting membrane proteins
- Proteasomes (protein digesting structures) of similar construction (between archaebacteria and eukaryotes)
- Cytoskeletal filaments built of proteins similar to actin and tubulin

Features of eukaryotic cells not found in prokaryotes:

- Division of cells into nucleus and cytoplasm, separated by a nuclear envelope containing complex pore structures
- Complex chromosomes composed of DNA and associated proteins that are capable of compacting into mitotic structures
- Complex membranous cytoplasmic organelles (includes endoplasmic reticulum, Golgi complex, lysosomes, endosomes, peroxisomes, and glyoxisomes)
- Specialized cytoplasmic organelles for aerobic respiration (mitochondria) and photosynthesis (chloroplasts)
- Complex cytoskeletal system (including actin filaments, intermediate filaments, and microtubules) and associated motor proteins
- Complex flagella and cilia
- Ability to ingest particulate material by enclosure within plasma membrane vesicles (phagocytosis)
- Cellulose-containing cell walls (in plants)
- Cell division using a microtubule-containing mitotic spindle that separates chromosomes
- Presence of two copies of genes per cell (diploidy), one from each parent
- Presence of three different RNA synthesizing enzymes (RNA polymerases)
- Sexual reproduction requiring meiosis and fertilization



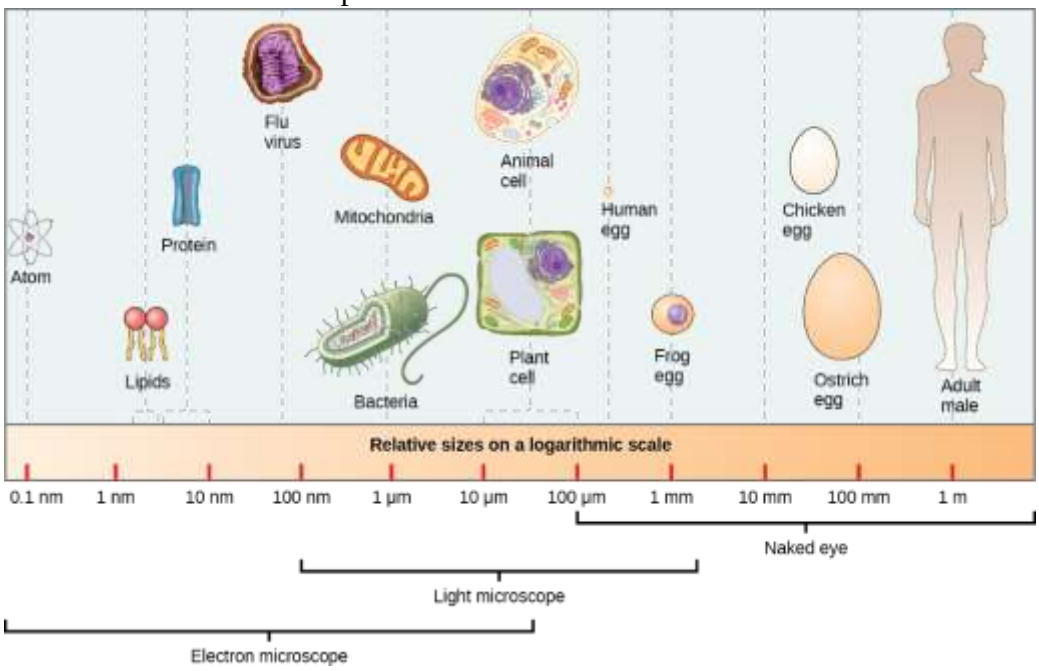
- ❑ Prokaryotic cells are single-celled entities that are primitive in structure and function as they lack a membrane-bound nucleus and other organelles.
- ❑ The term "prokaryote" is derived from two Greek words, 'pro' meaning 'before' and 'karyon' meaning 'nucleus'.
- ❑ Prokaryotes are considered to be the first living organisms of the earth as they are the simplest form of life.
- ❑ Eukaryotes are organisms whose cells have a nucleus and other organelles enclosed by a plasma membrane.
- ❑ Organelles are internal structures responsible for a variety of functions, such as energy production and protein synthesis.

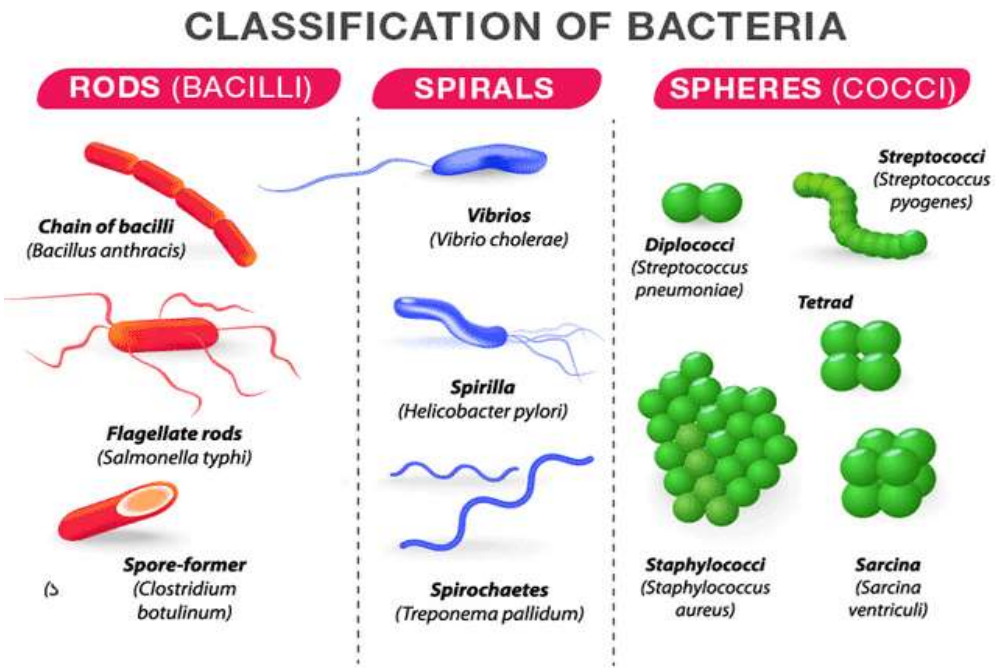
Cell Size

- At 0.1 to 5.0 µm in diameter, prokaryotic cells are significantly smaller than eukaryotic cells, which have diameters ranging from 10 to 100 µm.

- The prokaryotes' small size allows ions and organic molecules that enter them to quickly diffuse to other parts of the cell.

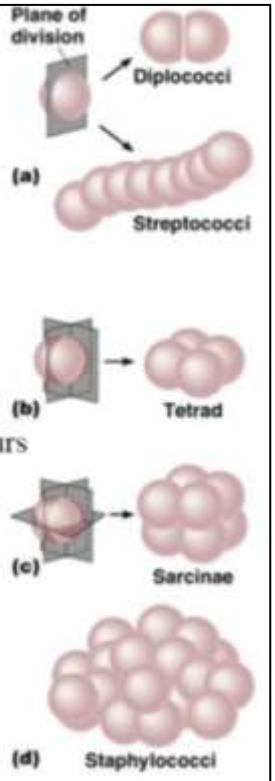
- Similarly, any wastes produced within a prokaryotic cell can quickly diffuse. This is not the case in eukaryotic cells, which have developed different structural adaptations to enhance intracellular transport.





Cocci

-single coccus: daughter cells separate
-diplococcus: 2, flat on adjacent sides
-streptococci: chain, all cells divide in same plane
-tetrad: 4, division occurs in two planes
-sarcinae: 8, division occurs in three planes
-staphylococci: group, cluster, cells divide in random planes

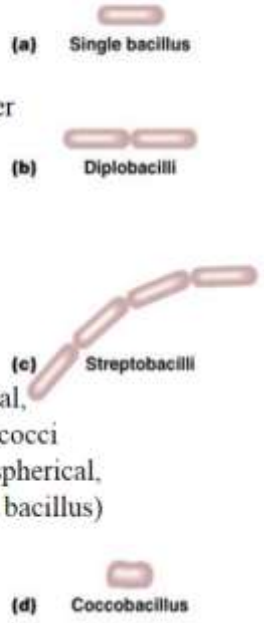


Bacilli

-rods of various length: oval to "hot dog"
-rods divide only along the short axis

-single bacillus: daughter cells separate
-diplobacilli: 2
-streptobacilli: chain

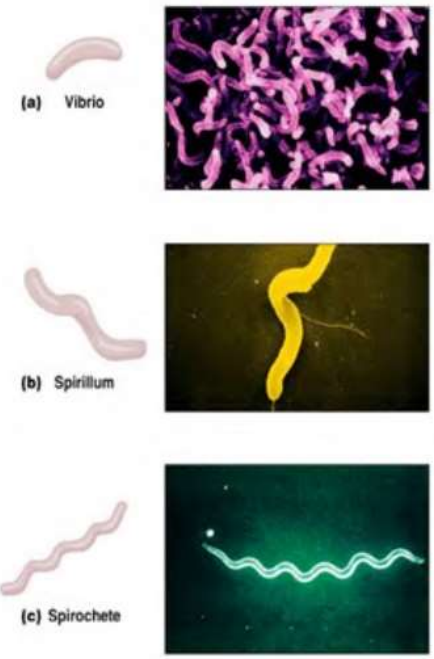
-coccobacillus: short oval, often confused with cocci (cocci are perfectly spherical, any ovalish shape = bacillus)



- **Spiral**

one or more twists
I. vibrio: curved rod
II.spirillum: rigid helical shape, like corkscrew
III. spirochete: flexible helical shape,

❖ Most bacteria are **monomorphic**: always one shape
❖ Some are genetically **pleomorphic**: have varied shapes within the population of a single species



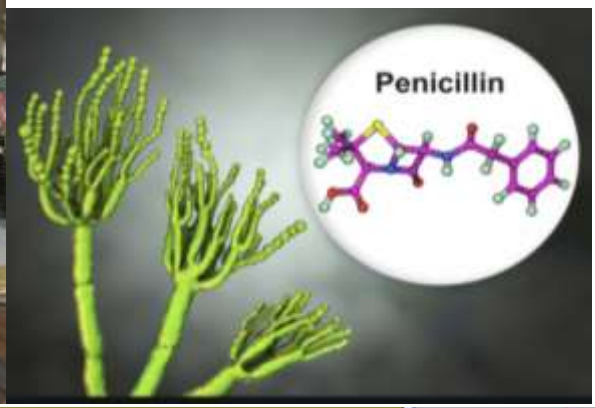
Penicillin was first isolated by the Scottish Scientist Alexander Fleming from samples of mold (*Penicillium notatum*) that contaminated a culture dish of Staphylococcus, producing a clear ring (lack of bacterial growth) around the mold.

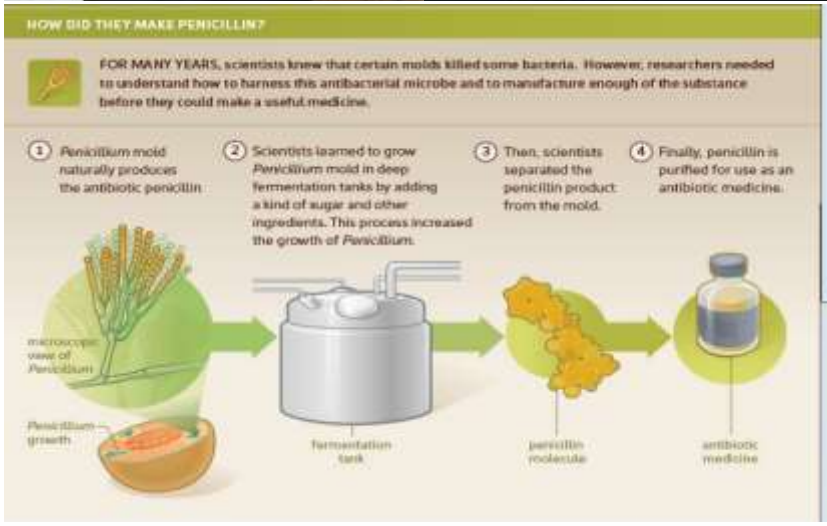
He subsequently purified the active ingredient from "mold juice", and found that it could kill a wide range of harmful bacterial, including *streptococcus, meningococcus and the diphtheria bacillus*.

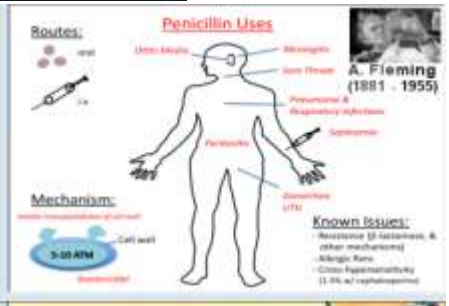
However, Fleming did not extend his work to clinical study because he was not able to purify enough penicillin for the experiments.

The use of penicillin as a therapeutic agent to treat infections did not happen until the 1940s when Howard Walter Florey and Ernst Chain developed the biochemical methodologies.

Penicillin G (intravenous use), penicillin V (use by mouth), procaine penicillin, and benzathine penicillin (intramuscular use)



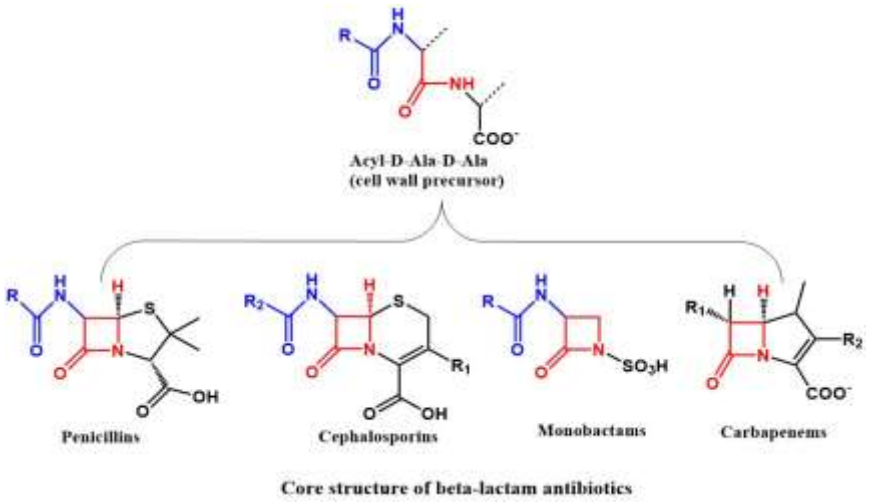




Antibiotics are medicines that are used to fight bacterial infections. These medicines kill prokaryotic cells without harming human cells.

What part or parts of the bacterial cell do you think antibiotics target? Why?

- Most bacteria produce a cell wall that is composed partly of a macromolecule called peptidoglycan, itself made up of amino sugars and short peptides.
- Human cells do not make or need peptidoglycan.
- Penicillin, one of the first antibiotics to be used widely, prevents the final cross-linking step, or transpeptidation, in assembly of this macromolecule.
- The result is a very fragile cell wall that bursts, killing the bacterium.
- No harm comes to the human host because penicillin does not inhibit any biochemical process that goes on within us.



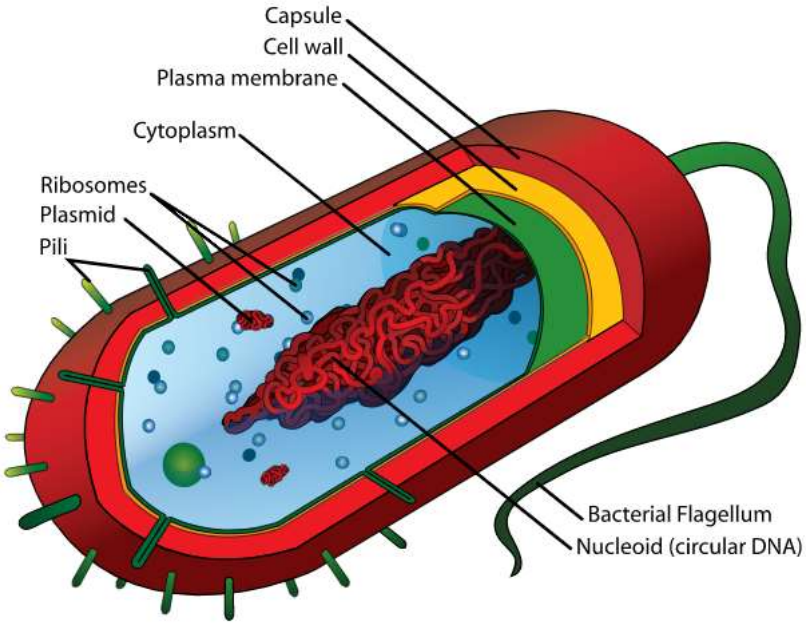
Core structure of beta-lactam antibiotics

- All beta-lactam antibiotics contain the same core 4-member "beta-lactam" ring (red). This ring mimics the shape of the terminal D-Ala-D-Ala peptide sequence that serves as the substrate for cell wall transpeptidases that form covalent bonds between different peptidoglycan chains during periods of cell growth.
- The 4 ring structure and associated side groups result in tight binding to the active site of transpeptidases (also known as Penicillin Binding Proteins).
- Tight binding inhibits enzyme activity, and consequent cell wall formation.

Antibiotics types	Category	Agents
Penicillins	Natural Penicillins	Penicillin G, Penicillin V
	Antistaphylococcal Penicillins	Nafcillin, Oxacillin, (Methicillin*), Dicloxacillin
	Aminopenicillins	Amoxicillin, Ampicillin
	Aminopenicillins + β-lactamase inhibitors	Ampicillin-sulbactam, Amoxicillin-clavulanate
	Extended-spectrum Penicillins	Piperacillin, ticarcillin
	Extended-spectrum + β-lactamase inhibitors	Piperacillin-tazobactam, Ticarcillin-clavulanate
Cephalosporins	First Generation	Cefazolin, Cephalexin
	Second Generation	Cefotetan, Cefoxitin, Cefuroxime, axetil, Cefaclor
	Third Generation	Cefotaxime, Ceftazidime, Ceftriaxone, Cefixime, Cefdinir
	Fourth Generation	Cefepime
	Fifth Generation	Ceftaroline
Monobactams	Monobactams	Aztreonam
Carbapenems	Carbapenems	Imipenem/cilastatin, Meropenem, Doripenem, Ertapenem

Bacterial Cell Walls

- A wall located outside the cell membrane provides the cell support, and protection against mechanical stress or damage from osmotic rupture and lysis.
- The major component of the bacterial cell wall is peptidoglycan or murein. This rigid structure of peptidoglycan, specific only to prokaryotes, gives the cell shape and surrounds the cytoplasmic membrane.

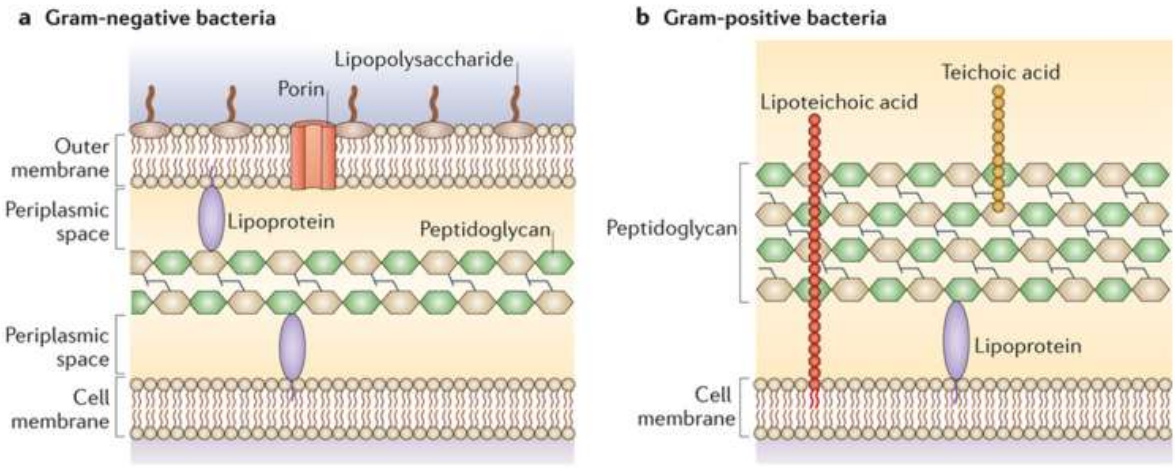


- The bacterial cell wall performs several functions

1. Providing overall strength to the cell.
2. It also helps maintain the cell shape, which is important for how the cell will grow, reproduce, obtain nutrients, and move.
3. It protects the cell from osmotic lysis, as the cell moves from one environment to another or transports in nutrients from its surroundings. Since water can freely move across both the cell membrane and the cell wall, the cell is at risk for an osmotic imbalance, which could put pressure on the relatively weak plasma membrane.
4. Studies have actually shown that the internal pressure of a cell is similar to the pressure found inside a fully inflated car tire. That is a lot of pressure for the plasma membrane to withstand! The cell wall can keep out certain molecules, such as toxins, particularly for gram negative bacteria.
5. And lastly, the bacterial cell wall can contribute to the pathogenicity or disease –causing ability of the cell for certain bacterial pathogens.

Gram positive cell wall & Gram-negative cell wall

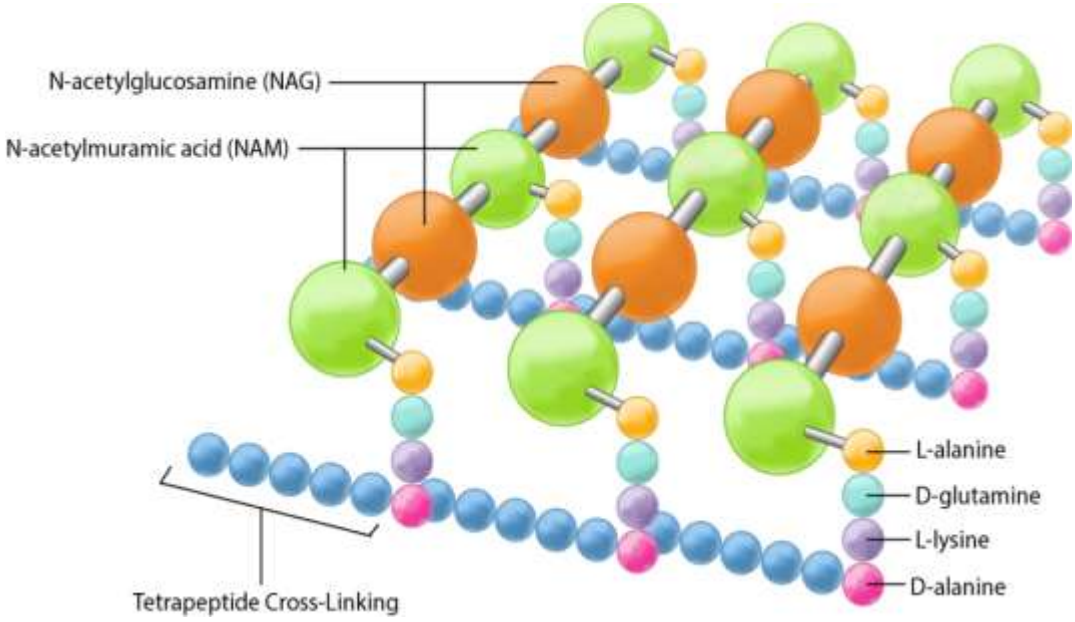
- ❑ The two different cell wall types can be identified in the lab by a differential stain known as the Gram stain.
- ❑ Developed in 1884, it's been in use ever since.
- ❑ Once the electron microscope was invented in the 1940s, it was found that the staining difference correlated with differences in the cell walls.



Peptidoglycan is a polysaccharide made of two glucose derivatives, N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM), alternated in long chains.

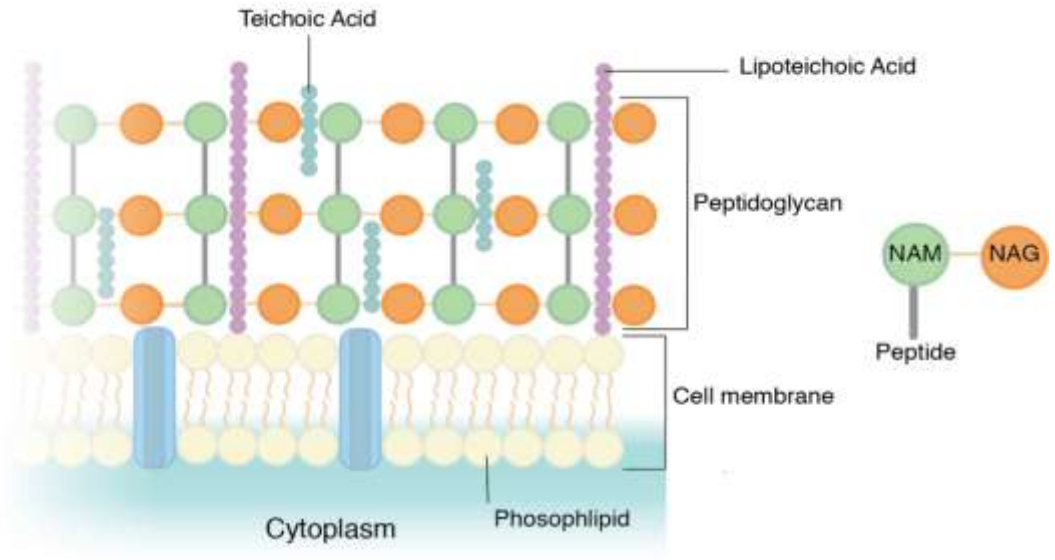
- The chains are cross-linked to one another by a tetrapeptide that extends off the NAM sugar unit, allowing a lattice-like structure to form.
- The four amino acids that compose the tetrapeptide are: L-alanine, D-glutamine, L-lysine or meso-diaminopimelic acid (DPA), and D-alanine.

- The tetrapeptides can be directly cross-linked to one another, with the D-alanine on one tetrapeptide binding to the L-lysine/ DPA on another tetrapeptide.
- In many gram positive bacteria there is a cross-bridge of five amino acids such as glycine (peptide interbridge) that serves to connect one tetrapeptide to another.
- In either case the cross-linking serves to increase the strength of the overall structure, with more strength derived from complete cross-linking, where every tetrapeptide is bound in some way to a tetrapeptide on another NAG-NAM chain.



Gram Positive Cell walls

- ❑ The cell walls of gram positive bacteria are composed predominantly of peptidoglycan.
- ❑ In fact, peptidoglycan can represent up to 90% of the cell wall, with layer after layer forming around the cell membrane.
- ❑ The NAM tetrapeptides are typically cross-linked with a peptide interbridge and complete cross-linking is common.
- ❑ The additional component in a gram positive cell wall is teichoic acid, a glycopolymer, which is embedded within the peptidoglycan layers.



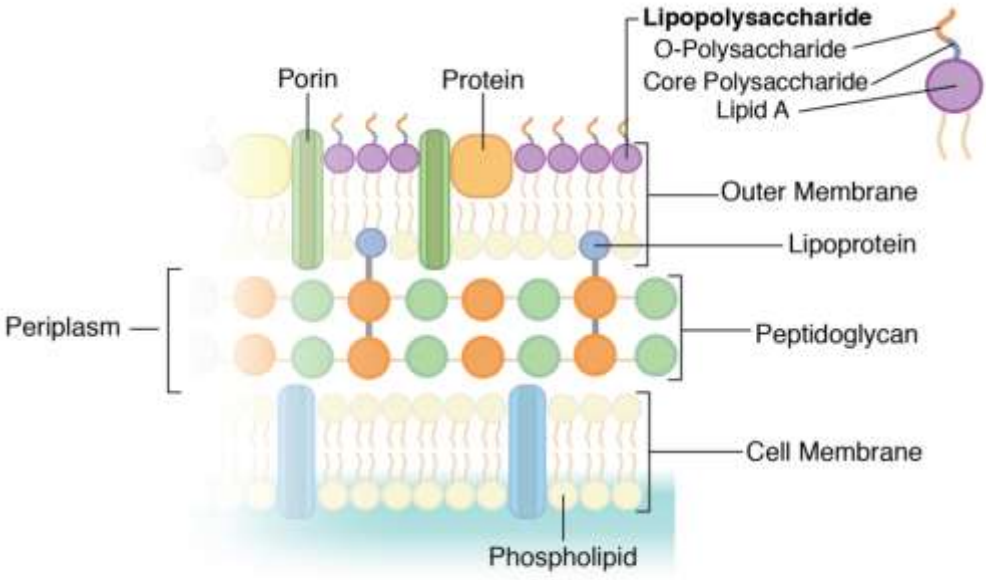
Gram Positive Bacteria Cell Wall

Teichoic acid

- Teichoic acid is believed to play several important roles for the cell, such as generation of the net negative charge of the cell, which is essential for development of a proton motive force.
- Teichoic acid contributes to the overall rigidity of the cell wall, which is important for the maintenance of the cell shape, particularly in rod-shaped organisms.
- There is also evidence that teichoic acids participate in cell division, by interacting with the peptidoglycan biosynthesis machinery.
- Lastly, teichoic acids appear to play a role in resistance to adverse conditions such as high temperatures and high salt concentrations, as well as to β-lactam antibiotics.
- Teichoic acids can either be covalently linked to peptidoglycan (wall teichoic acids or WTA) or connected to the cell membrane via a lipid anchor, in which case it is referred to as lipoteichoic acid.
- Since peptidoglycan is relatively porous, most substances can pass through the gram positive cell wall with little difficulty.
- But some nutrients are too large, requiring the cell to rely on the use of exoenzymes.
- These extracellular enzymes are made within the cell's cytoplasm and then secreted past the cell membrane, through the cell wall, where they function outside of the cell to break down large macromolecules into smaller components.

Gram Negative Cell Walls

- The cell walls of gram negative bacteria are more complex than that of gram positive bacteria, with more ingredients overall.
- They do contain peptidoglycan as well, although only a couple of layers, representing 5-10% of the total cell wall.
- What is most notable about the gram negative cell wall is the presence of a plasma membrane located outside of the peptidoglycan layers, known as the outer membrane.
- This makes up the bulk of the gram negative cell wall.
- The outer membrane is composed of a lipid bilayer, very similar in composition to the cell membrane with polar heads, fatty acid tails, and integral proteins.
- It differs from the cell membrane by the presence of large molecules known as lipopolysaccharide (LPS), which are anchored into the outer membrane and project from the cell into the environment.



Gram Negative Bacteria Cell Wall

- LPS is made up of three different components:
- O-antigen or O-polysaccharide, which represents the outermost part of the structure ,
- Core polysaccharide,
- Lipid A, which anchors the LPS into the outer membrane.

- LPS is known to serve many different functions for the cell, such as contributing to the net negative charge for the cell, helping to stabilize the outer membrane, and providing

protection from certain chemical substances by physically blocking access to other parts of the cell wall.

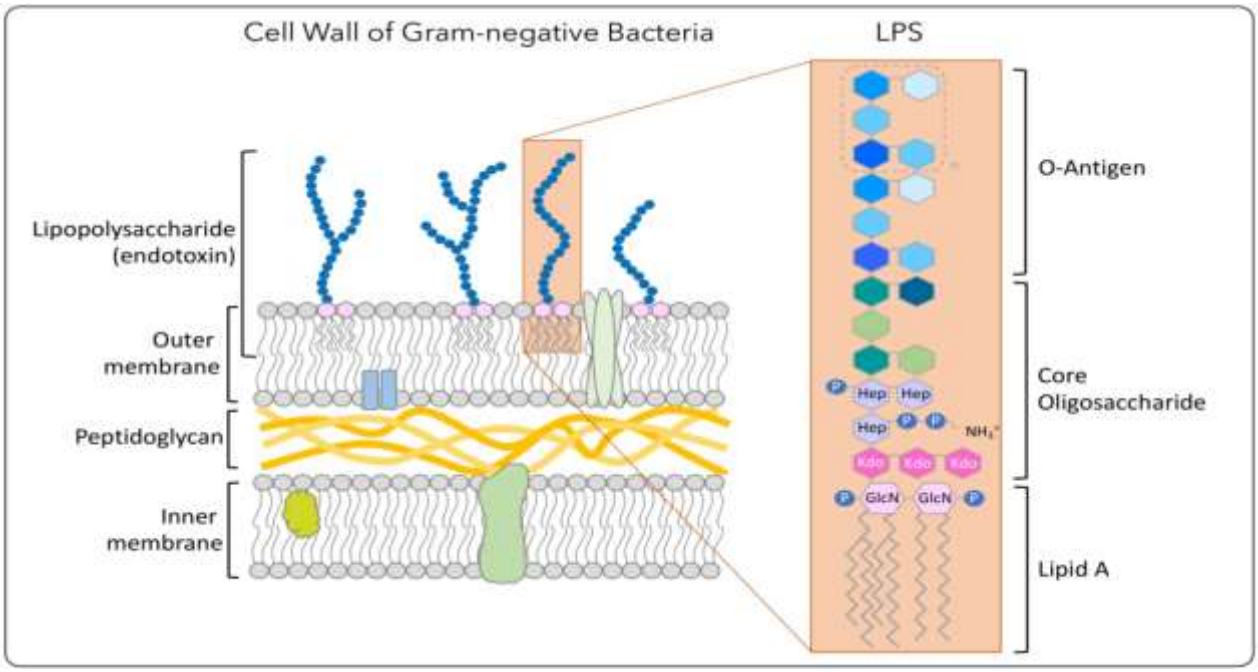
- In addition, LPS plays a role in the host response to pathogenic gram negative bacteria.

- The O-antigen triggers an immune response in an infected host, causing the generation of antibodies specific to that part of LPS (think of E. coli O157).

- Lipid A acts as a toxin, specifically an endotoxin, causing general symptoms of illness such as fever and diarrhea.

- A large amount of lipid A released into the bloodstream can trigger endotoxic shock, a body-wide inflammatory response which can be life-threatening.

- A phospholipid called Lipid A;
- It embeds Lipolysaccharide layer in the outer leaflet.
- Also known as endotoxin, it is responsible for toxic effects (fever and shock).
- Generally it is not released until death of cell.
- Exception: Neisseria meningitidis, which over-produces outer membrane fragments.



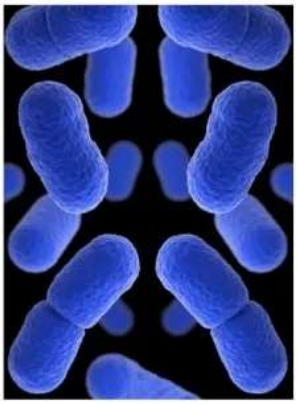
A core polysaccharide of fiver sugars linked through ketodeoxyoctulonate (KDO) to lipid A.

- Exception: Only one Gram positive bacteria, i.e. *Listeria monocyotogenes* has been found to contain an authentic lipopolysaccharide.

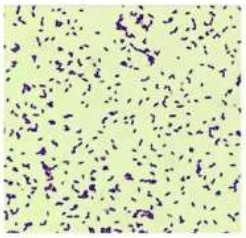
Listeria monocytogenes is a facultative intracellular Gram-positive coccobacilli responsible for listeriosis, one of the serious food-borne infections

Listeria monocytogenes

microbeonline



Beta-hemolytic colonies



Gram positive coccobacilli

	2 tetrapeptides of adjacent chains of NAM, NAG are linked by peptide bridges (which contain 5 Glycine)	2 tetrapeptides of NAM, NAG are directly linked between D-Alanine and DAG within 2 tetrapeptides
Teichoic acid	10% of cell wall Polyribitol/polyglycerol phosphate linked to peptidoglycan	None
Lipoteichoic acid	Lipid linked teichoic acid	None
Periplasmic space	Small or none	Contains enzymes for transport, degradation and synthesis
Outer membrane	None	Phospholipids with saturated fatty acids. Embedded porins, lipoproteins, transport proteins
Lipopolysaccharide	None	Lipid A (endotoxin), core polysaccharide, O antigen

Structure	Chemical Composition	Function
Essential components		
Cell wall		
Peptidoglycan	Glycan (sugar) backbone with peptide side chains that are cross-linked	Gives rigid support, protects against osmotic pressure, is the site of action of penicillins and cephalosporins, and is degraded by lysozyme
Outer membrane of gram-negative bacteria	Lipid A	Toxic component of endotoxin
	Polysaccharide	Major surface antigen used frequently in laboratory diagnosis
Surface fibers of gram-positive bacteria	Teichoic acid	Major surface antigen but rarely used in laboratory diagnosis
Plasma membrane	Lipoprotein bilayer without sterols	Site of oxidative and transport enzymes
Ribosome	RNA and protein in 50S and 30S subunits	Protein synthesis; site of action of aminoglycosides, erythromycin, tetracyclines, and chloramphenicol
Nucleoid	DNA	Genetic material
Mesosome	Invagination of plasma membrane	Participates in cell division and secretion
Periplasm	Space between plasma membrane and outer membrane	Contains many hydrolytic enzymes, including β-lactamases
Nonessential components		
Capsule	Polysaccharide[1]	Protects against phagocytosis
Pilus or fimbria	Glycoprotein	Two types: (1) mediates attachment to cell surfaces; (2) sex pilus mediates attachment of two bacteria during conjugation
Flagellum	Protein	Motility
Spore	Keratinlike coat, dipicolinic acid	Provides resistance to dehydration, heat, and chemicals
Plasmid	DNA	Contains a variety of genes for antibiotic resistance and toxins
Granule	Glycogen, lipids, polyphosphates	Site of nutrients in cytoplasm
Glycocalyx	Polysaccharide	Mediates adherence to surfaces

[1]Except in *Bacillus anthracis*, in which it is a polypeptide of D-glutamic acid.

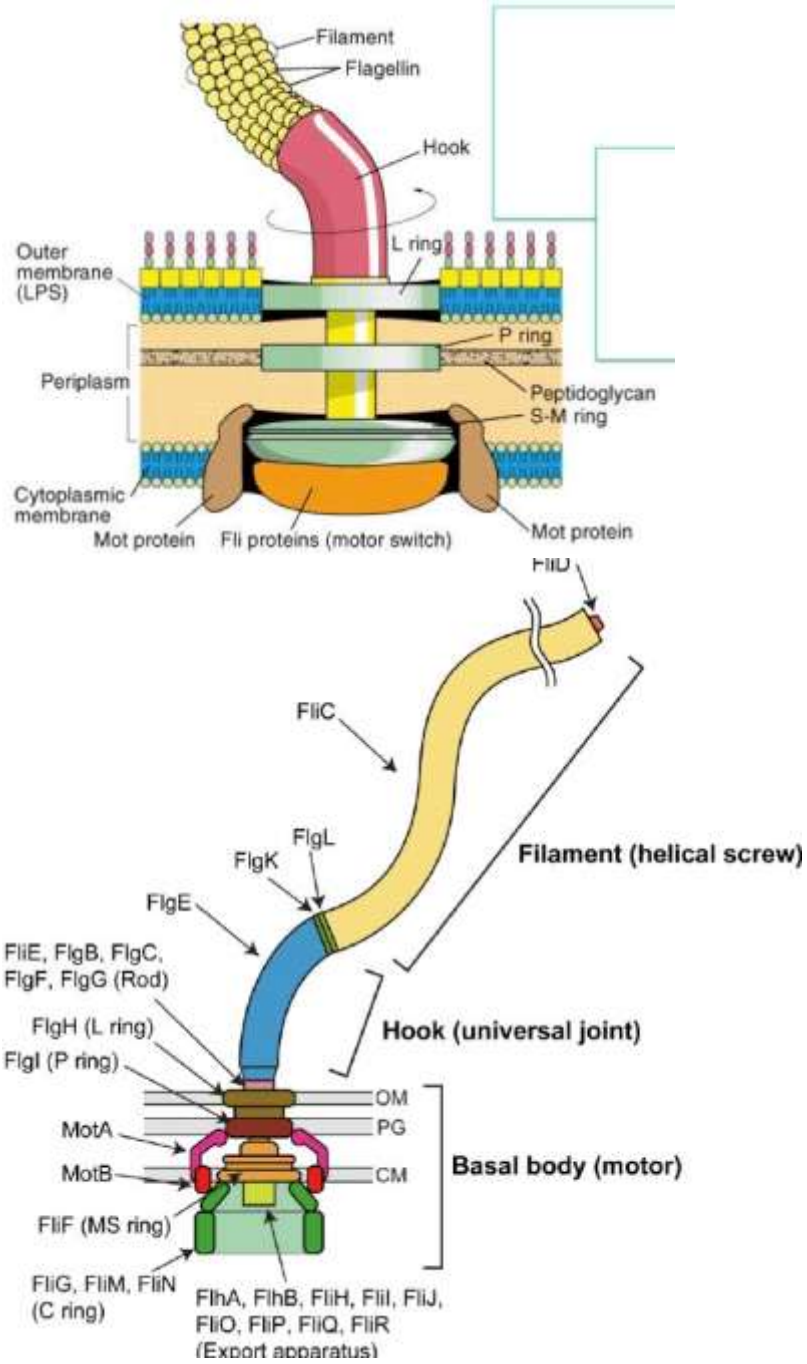
	Prokaryote	Eukaryote
Nucleus	Absent	Present
Membrane-bound organelles	Absent	Present
Cell structure	Unicellular	Mostly multicellular; some unicellular
Cell size	Smaller (0.1-5 µm)	Larger (10-100 µm)
Complexity	Simpler	More complex
DNA Form	Circular	Linear
Examples	Bacteria, archaea	Animals, plants, fungi, protists

Surface Structures

Flagella:

- The flagella of motile bacteria differ in structure from eukaryotic flagella.

- A basal body anchored in the plasma membrane and cell wall gives rise to a cylindrical protein filament.
- The flagellum moves by whirling about its long axis.
- The number and arrangement of flagella on the cell are diagnostically useful.

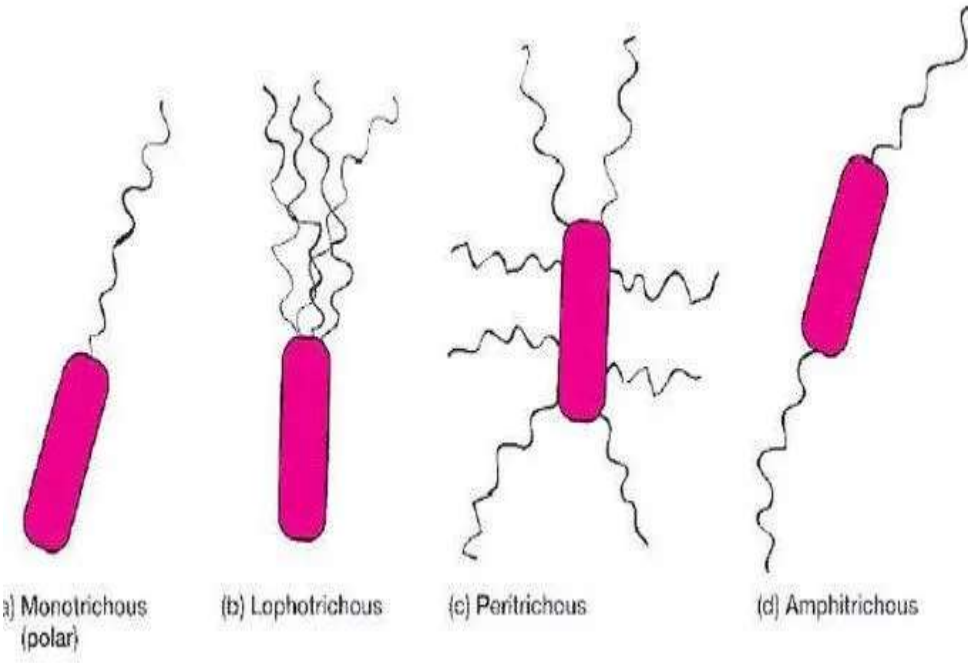


Bacterial flagella are long, thin (about 20 nm),

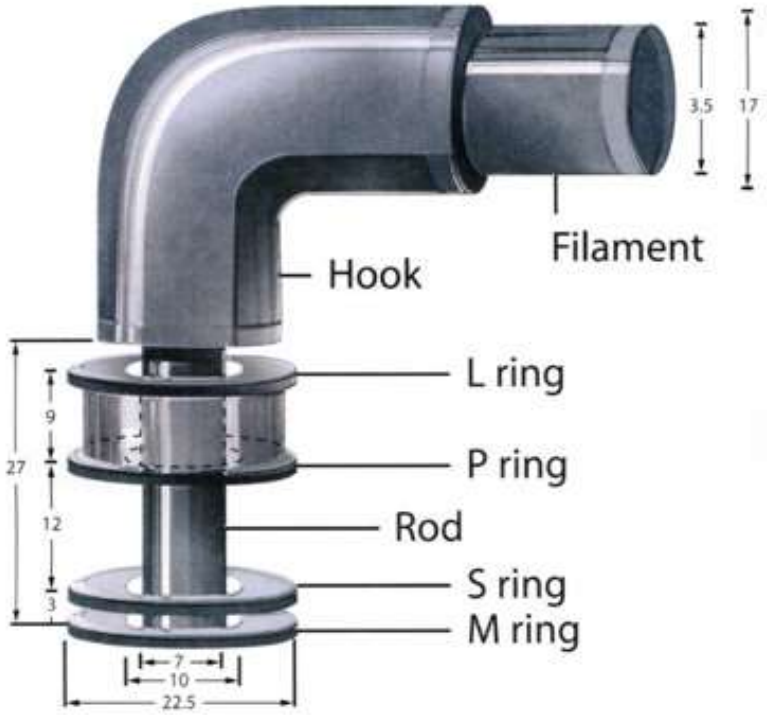
whip-like appendages that move the bacteria towards nutrients and other attractants.

Flagella are free at one end and attached to the cell at the other end.

Flagellum can never be seen directly with the light microscope but only after staining with special flagella stains that increase their diameter.



- Monotrichous (Mono means one): Single polar flagellum e.g. Vibrio cholerae, Campylobacter spp. (polar flagella often in pairs to give a “seagull” appearance).
- Amphitrichous: Single flagellum at both ends e.g. Alcaligenes faecalis (Note: amphibians live both on land and in water). flagellar arrangement of bacteria
- Lophotrichous: Tuft of flagella at one or both ends e.g. Spirilla spp
- Peritrichous (flagella in periphery): Flagella surrounding the bacterial cell. All the members of family Enterobacteriaceae, if motile have peritrichous flagella. e.g. Salmonella Typhi, Escherichia coli, Proteus spp (highly motile organism; shows swarming motility)



The ultrastructure of the flagellum of E. coli -illustrated in Figure (after Dr. Julius Adler of the University of Wisconsin).

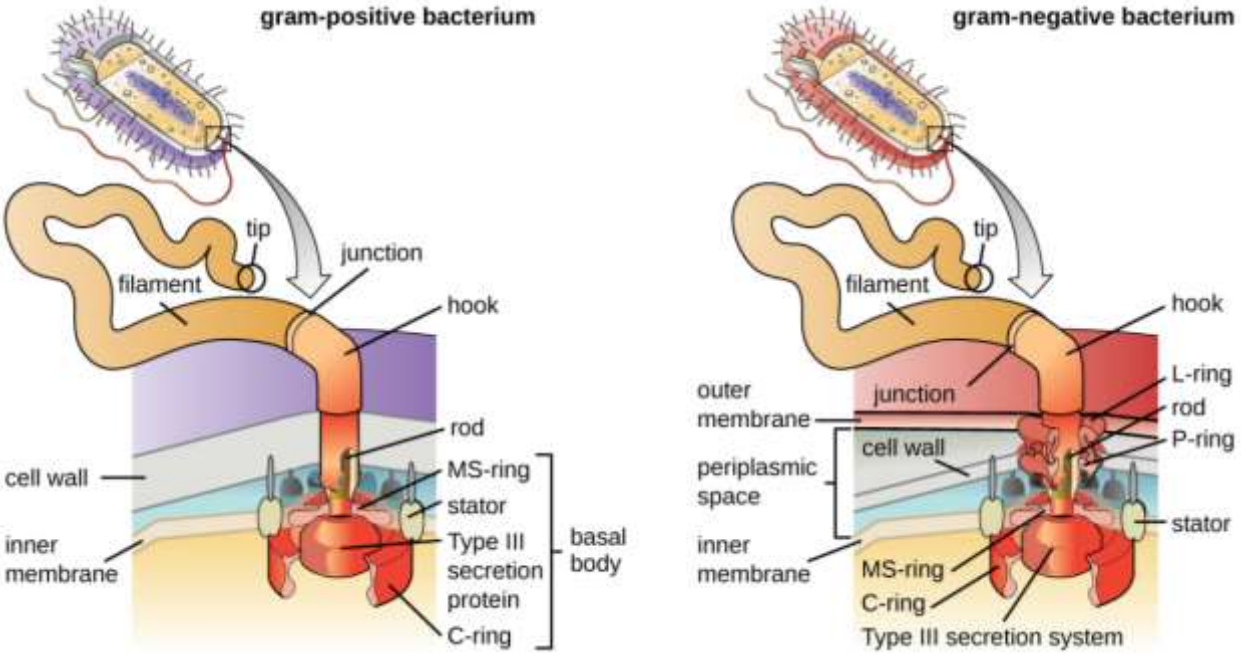
- About 50 genes are required for flagellar synthesis and function.

- The flagellar apparatus consists of several distinct proteins:
- A system of rings embedded in the cell envelope (the basal body),
- A hook-like structure near the cell surface,
- And the flagellar filament.

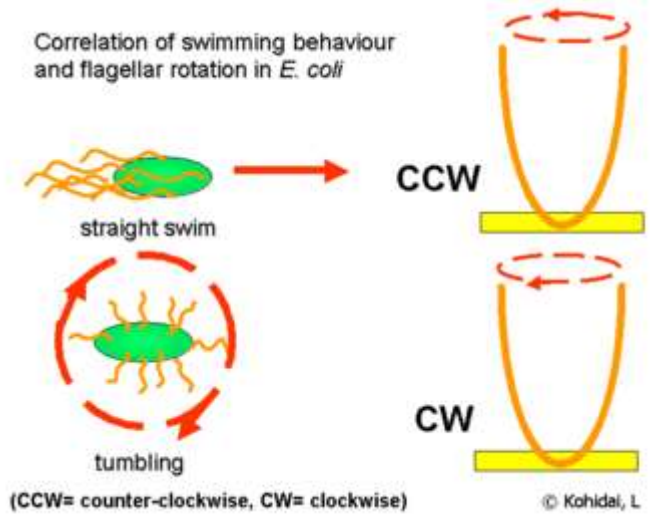
- The innermost rings, the M and S rings, located in the plasma membrane, comprise the motor apparatus.

- The outermost rings, the P and L rings, located in the periplasm and the outer membrane respectively, function as bushings to support the rod where it is joined to the hook of the filament on the cell surface.

- As the M ring turns, powered by an influx of protons, the rotary motion is transferred to the filament which turns to propel the bacterium.



- The basic structure of a bacterial flagellum consists of a basal body, hook, and filament. The basal body composition and arrangement differ between gram-positive and gram-negative bacteria.
- Procaryotes are known to exhibit a variety of types of tactic behavior, i.e., the ability to move (swim) in response to environmental stimuli.
- For example, during chemotaxis a bacterium can sense the quality and quantity of certain chemicals in its environment and swim towards them (if they are useful nutrients) or away from them (if they are harmful substances).
- Other types of tactic response in procaryotes include phototaxis, aerotaxis and magnetotaxis.
- The occurrence of tactic behavior provides evidence for the ecological (survival) advantage of flagella in bacteria and other procaryotes.



Pili (Fimbriae):

- Pili are slender, hairlike, proteinaceous appendages on the surface of many (particularly Gram-negative) bacteria.
- They are important in adhesion to host surfaces.
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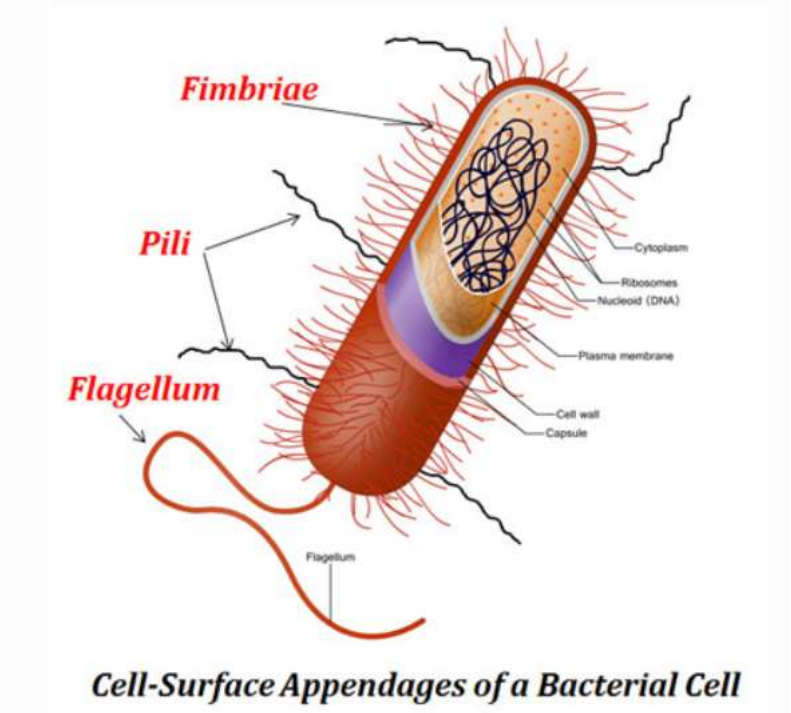


Cell-Surface Appendages of a Bacterial Cell

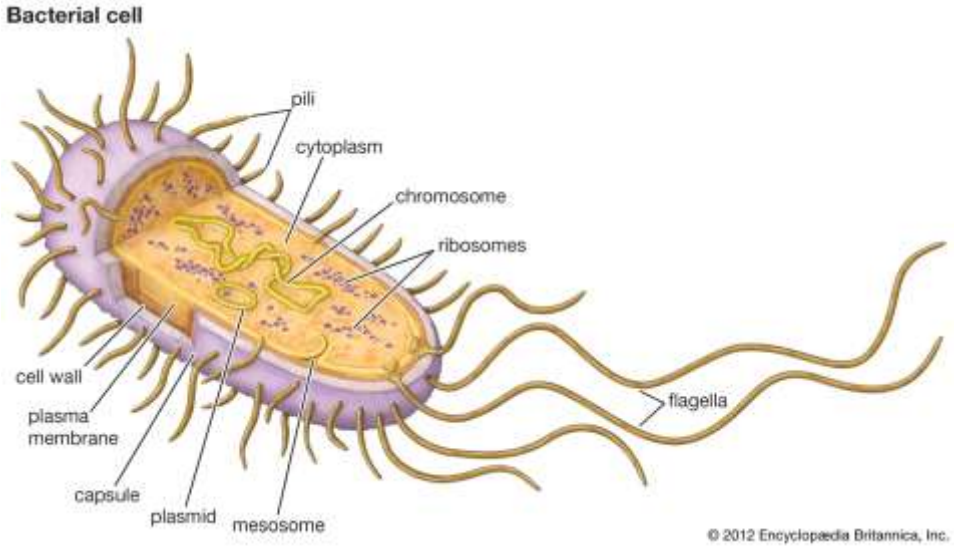
- Major determinants of bacterial virulence because they allow pathogens to attach to (colonize) tissues and/or to resist attack by phagocytic white blood cells.

- For example, pathogenic *Neisseria gonorrhoeae* adheres specifically to the human cervical or urethral epithelium by means of its fimbriae;
- enterotoxigenic strains of *E. coli* adhere to the mucosal epithelium of the intestine by means of specific fimbriae;
- the M-protein and associated fimbriae of *Streptococcus pyogenes* are involved in adherence and to resistance to engulfment by phagocytes.

Characteristics	Fimbriae	Pili
Definition	Fimbriae are tiny bristle-like fibers arising from the surface of bacterial cells.	Pili are hair like microfibers that are thick tubular structure made up of pilin.
Length	Shorter than pili	Longer than fimbriae.
Diameter	Thin	Thicker than fimbriae.
Number	No. of fimbriae are 200-400 per cell.	No of pili are less 1-10 per cell.
Made up of	Fimbrillin protein.	Pilin protein.
Rigidity	Less rigid.	More rigid than fimbriae.
Found in	Both gram positive and gram negative bacteria.	Only gram negative bacteria.
Formation	Is governed by bacterial genes in the nucleoid region.	Is governed by plasmid genes.
Function	Responsible for cell to surface attachment. Specialized for attachment i.e. enable the cell to adhere the surfaces of other bacteria.	Responsible for bacterial conjugation. Two basic function of pili. They are gene transfer and attachment.
Motility	Do not function in active motility.	Type IV pili shows twitching type of motility.
Receptors	No receptors of other.	Serve as receptor for certain viruses.
Examples	*Salmonella typhimurium*, *Shigella dysenteriae*. *Shigella dysenteriae* uses its fimbriae to attach to the intestine and then produces a toxin that causes diarrhea.	*Escherichia coli*, *Neisseria gonorrhoeae*. *Neisseria gonorrhoeae*, the cause of gonorrhea, uses pili to attach to the urogenital and cervical epithelium when it causes disease.

Capsules/ Glycocalyx: Some bacteria form a thick outer capsule of high-molecular-weight, viscous polysaccharide gel; others have more amorphous slime layers.

- Capsules confer resistance to phagocytosis.



Bacterium	Capsule composition	Structural subunits
Gram-positive Bacteria		
Bacillus anthracis	polypeptide (polyglutamic acid)	D-glutamic acid
Bacillus megaterium	polypeptide and polysaccharide	D-glutamic acid, amino sugars, sugars
Streptococcus mutans	polysaccharide	(dextran) glucose
Streptococcus pneumoniae	polysaccharides	sugars, amino sugars, uronic acids
Streptococcus pyogenes	polysaccharide (hyaluronic acid)	N-acetyl-glucosamine and glucuronic acid
Gram-negative Bacteria		
Acetobacter xylinum	polysaccharide	(cellulose) glucose
Escherichia coli	polysaccharide (colonic acid)	glucose, galactose, fucose glucuronic acid
Pseudomonas aeruginosa	polysaccharide	mannuronic acid
Azotobacter vinelandii	polysaccharide	glucuronic acid
Agrobacterium tumefaciens	polysaccharide	(glucan) glucose

- Capsules have several functions and often have multiple functions in a particular organism.
- Like fimbriae, capsules, slime layers, and glycocalyx often mediate adherence of cells to surfaces.
- Capsules also protect bacterial cells from engulfment by predatory protozoa or white blood cells (phagocytes), or from attack by antimicrobial agents of plant or animal origin.
- Capsules in certain soil bacteria protect cells from perennial effects of drying or desiccation.
- Capsular materials (e.g. dextrans) may be overproduced when bacteria are fed sugars to become reserves of carbohydrate for subsequent metabolism.

Slime layer

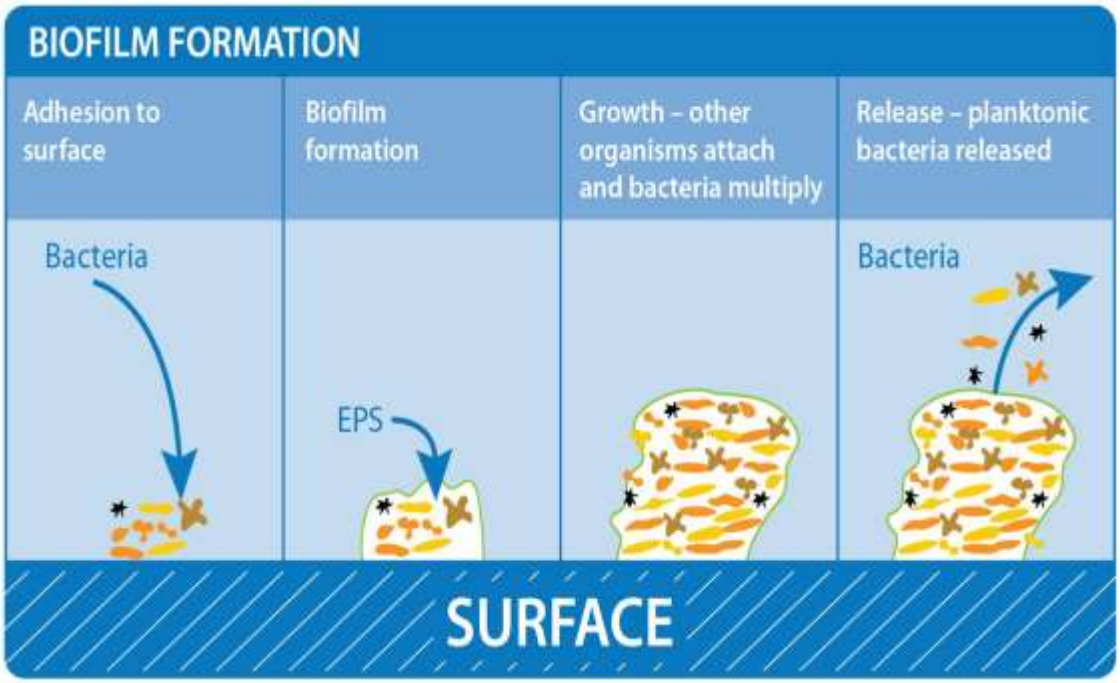
- A slime layer is a less tightly organized layer that is only loosely attached to the cell wall and can be more easily washed off.

- Slime layers may be composed of polysaccharides, glycoproteins, or glycolipids.

- Glycocalyces allows cells to adhere to surfaces, aiding in the formation of biofilms (colonies of microbes that form in layers on surfaces).

- In nature, most microbes live in mixed communities within biofilms, partly because the biofilm affords them some level of protection.

- Biofilms generally hold water like a sponge, preventing desiccation. They also protect cells from predation and hinder the action of antibiotics and disinfectants. All of these properties are advantageous to the microbes living in a biofilm, but they present challenges in a clinical setting, where the goal is often to eliminate microbes.



- For bacteria, the advantages of biofilm formation are numerous:
- Protection (from antibiotics, disinfectants and dynamic environments).
- Intercellular communications within a biofilm and rapidly enabling temporal adaptation.
- The ability to survive in nutrient deficient conditions.

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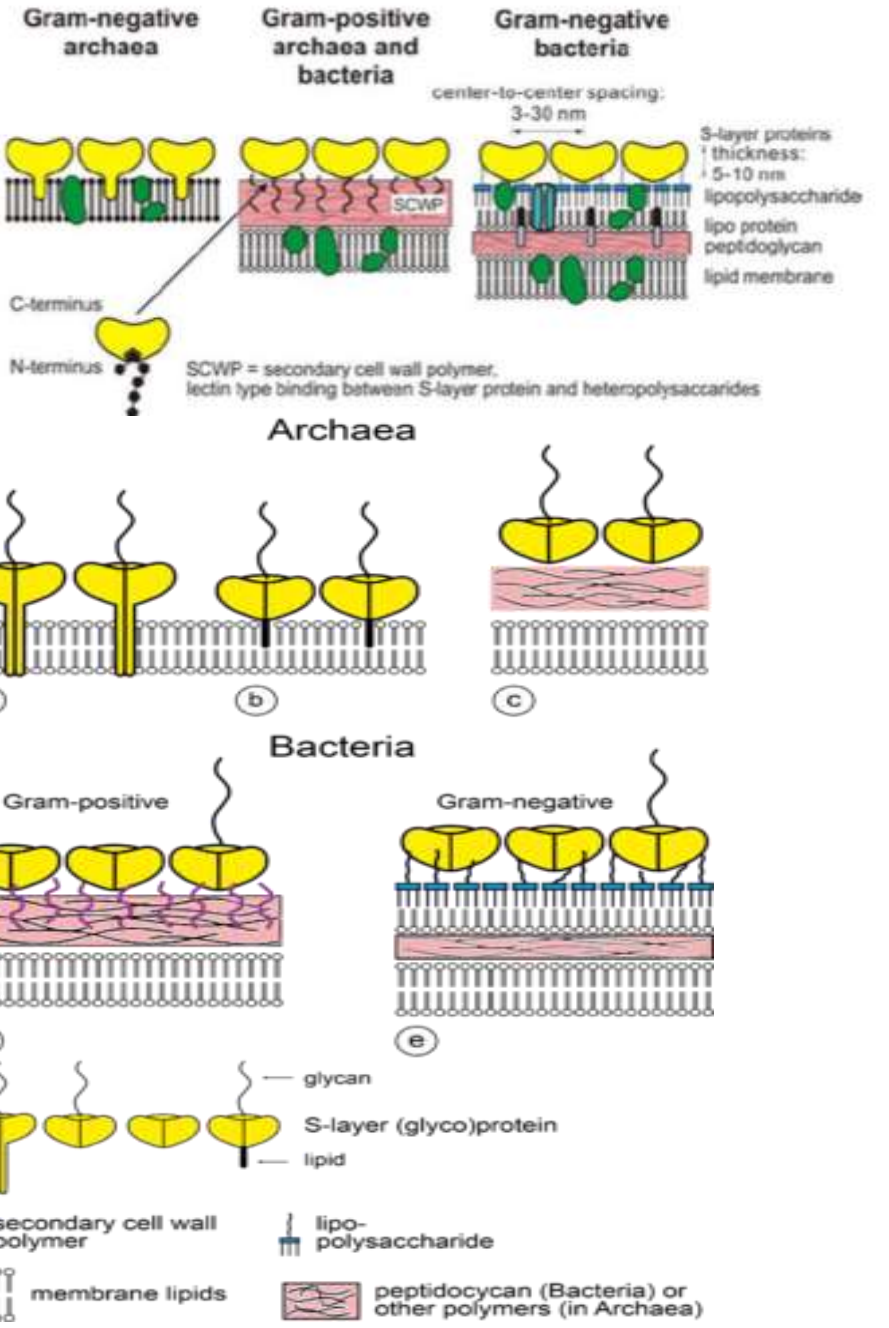
CAPSULE VERSUS SLIME LAYER

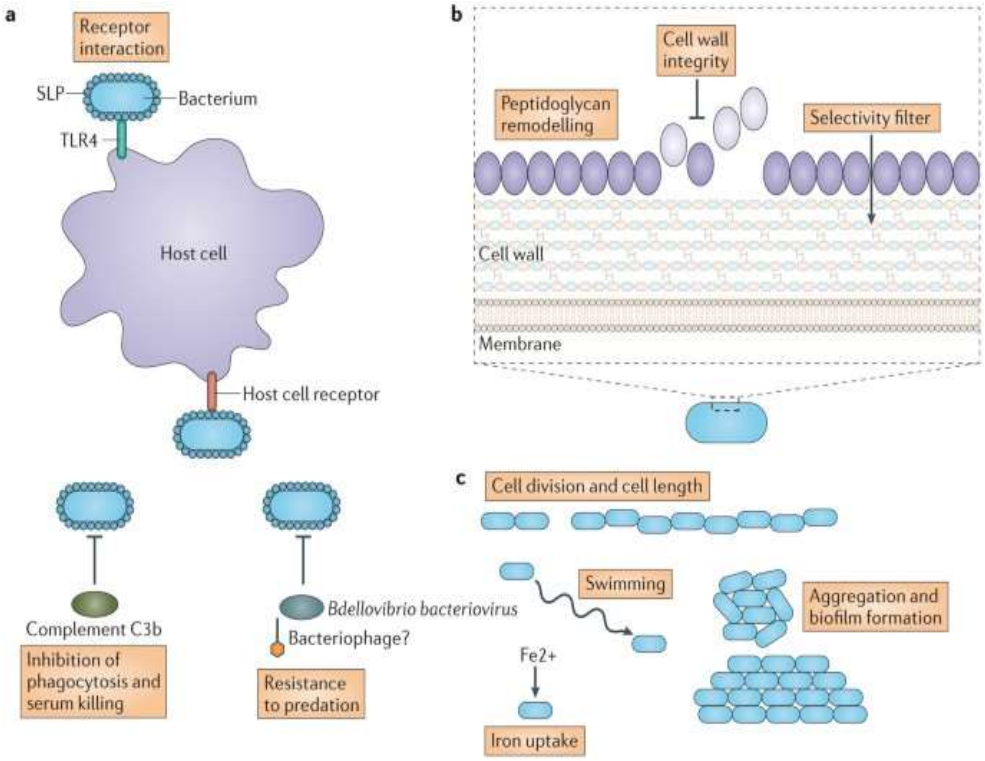
CAPSULE	SLIME LAYER
Capsule is a glycocalyx layer, consisting of firmly associated polysaccharide molecules with the cell wall	Slime layer is a glycocalyx layer that consists of loosely associated glycoprotein molecules
Composed of polysaccharides	Composed of exopolysaccharides, glycoproteins, and glycolipids
Thicker than the slime layer	A thin glycocalyx layer
Tightly bound to the cell wall	Loosely bound to the cell wall
Well organized layer; difficult to be washed off	Unorganized layer and can be easily washed off
Acts as a virulence factor that helps to evade phagocytosis	Mainly aids in the adherence; also protects the cell from dehydration and nutrient loss

S-layer proteins

- 

- Probable roles of S-layer proteins in infection (part a) include adhesin activity

- SLPs have roles in the maintenance of cell envelope integrity



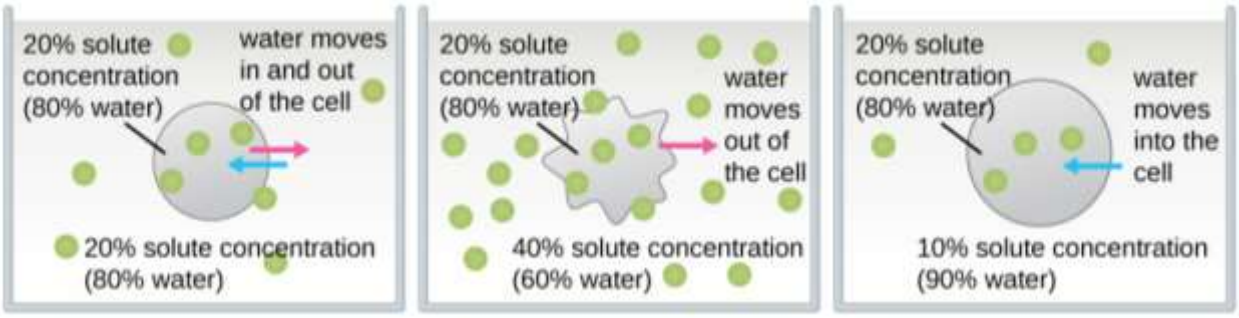
- S-layer- associated protein A (BslA) of Bacillus anthracis binds to HeLa cells and mutants are attenuated in models of infection79.

- Binding of surface layer proteins (SLPs) to enteric cells has been observed in Clostridium difficile.
- The external environment of a cell can be described as an isotonic, hypertonic, or hypotonic medium.

- In an isotonic medium, the solute concentrations inside and outside the cell are approximately equal, so there is no net movement of water across the cell membrane.

- In a hypertonic medium, the solute concentration outside the cell exceeds that inside the cell, so water diffuses out of the cell and into the external medium.

- In a hypotonic medium, the solute concentration inside the cell exceeds that outside of the cell, so water will move by osmosis into the cell. This causes the cell to swell and potentially lyse, or burst.



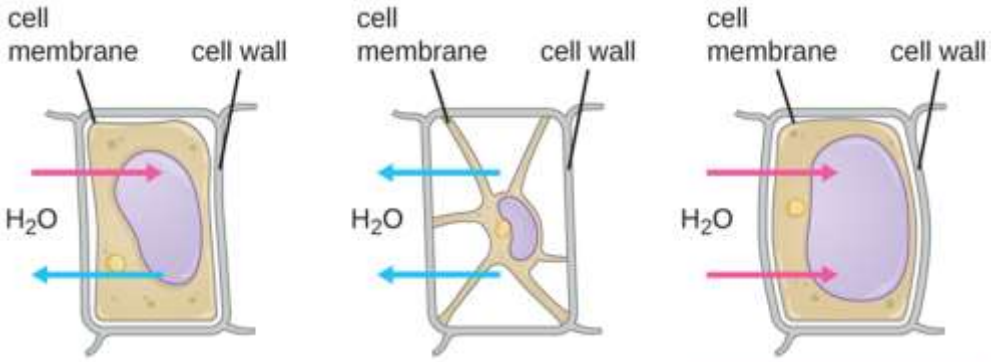
a Isotonic solution
A solution that has the *same* solute concentration as another solution. There is no net movement of water particles, and the overall concentration on both sides of the cell membrane remains constant.

b Hypertonic solution
A solution that has a *higher* solute concentration than another solution. Water particles will move out of the cell, causing crenation.

c Hypotonic solution
A solution that has a *lower* solute concentration than another solution. Water particles will move into the cell, causing the cell to expand and eventually lyse.

In cells that lack a cell wall, changes in osmotic pressure can lead to crenation in hypertonic environments or cell lysis in hypotonic environments.

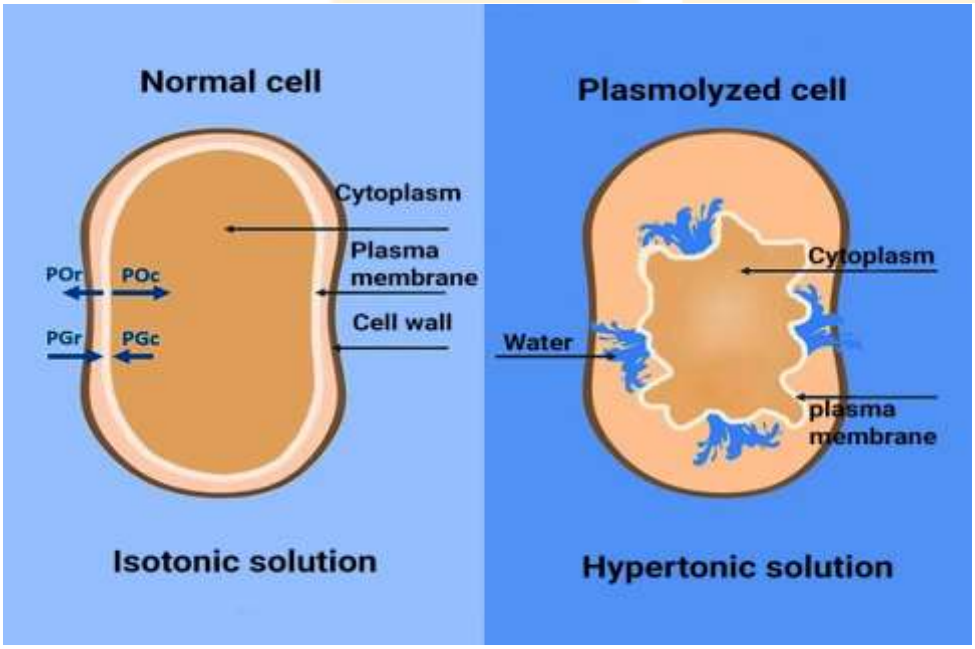
- The degree to which a particular cell is able to withstand changes in osmotic pressure is called tonicity.
- Cells that have a cell wall are better able to withstand subtle changes in osmotic pressure and maintain their shape.
- In hypertonic environments, cells that lack a cell wall can become dehydrated, causing crenation, or shriveling of the cell; the plasma membrane contracts and appears scalloped or notched .
- By contrast, cells that possess a cell wall undergo plasmolysis rather than crenation.
- In plasmolysis, the plasma membrane contracts and detaches from the cell wall, and there is a decrease in interior volume, but the cell wall remains intact, thus allowing the cell to maintain some shape and integrity for a period of time
- Likewise, cells that lack a cell wall are more prone to lysis in hypotonic environments. The presence of a cell wall allows the cell to maintain its shape and integrity for a longer time before lysing.



a Isotonic solution
No net movement of water particles. Cell membrane is attached to cell wall.

b Hypertonic solution
Water particles move out of the cell. Cell membrane shrinks and detaches from cell wall (plasmolysis).

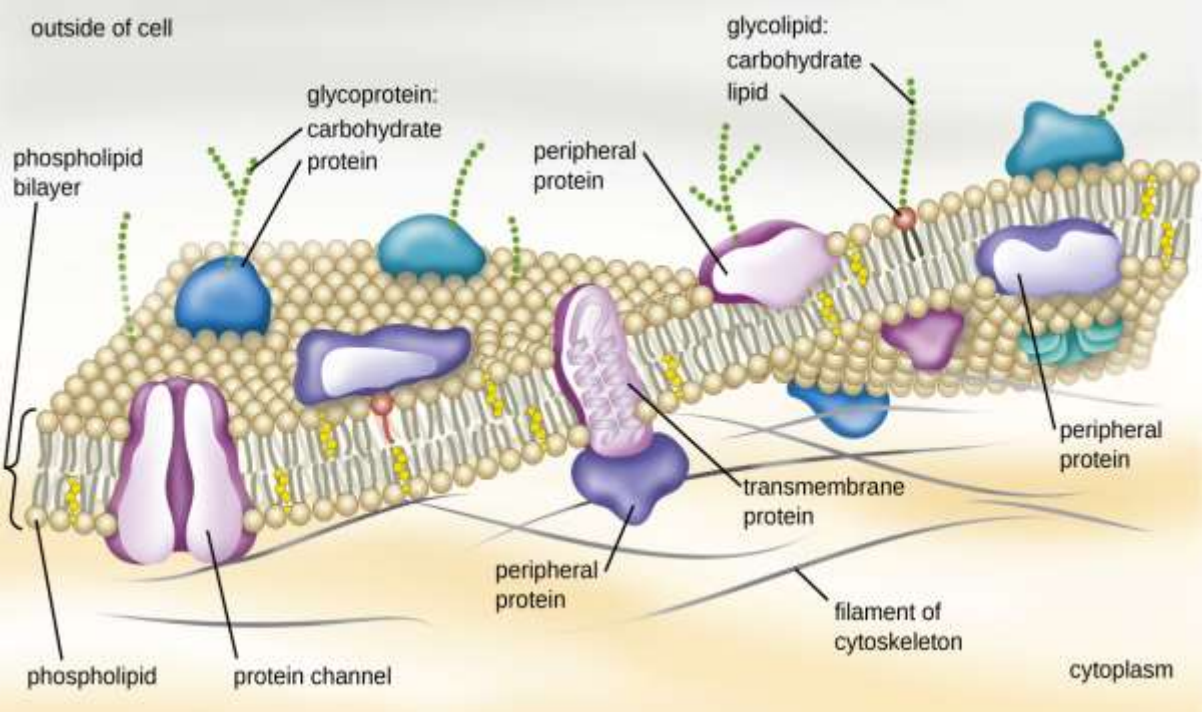
c Hypotonic solution
Water particles move into the cell. Cell wall counteracts osmotic pressure to prevent swelling and lysis.



The cytoplasmic membrane, also called a cell membrane or plasma membrane

- Structures that enclose the cytoplasm and internal structures of the cell are known collectively as the cell envelope.
- In prokaryotic cells, the structures of the cell envelope vary depending on the type of cell and organism.
- Most (but not all) prokaryotic cells have a cell wall, but the makeup of this cell wall varies.

- All cells (prokaryotic and eukaryotic) have a plasma membrane (also called cytoplasmic membrane or cell membrane) that exhibits selective permeability, allowing some molecules to enter or leave the cell while restricting the passage of others.



- ❑ The structure of the plasma membrane is often described in terms of the fluid mosaic model, which refers to the ability of membrane components to move fluidly within the plane of the membrane, as well as the mosaic-like composition of the components, which include a diverse array of lipid and protein components.
- ❑ The plasma membrane structure of most bacterial and eukaryotic cell types is a bilayer composed mainly of phospholipids formed with ester linkages and proteins.
- ❑ These phospholipids and proteins have the ability to move laterally within the plane of the membranes as well as between the two phospholipid layers.

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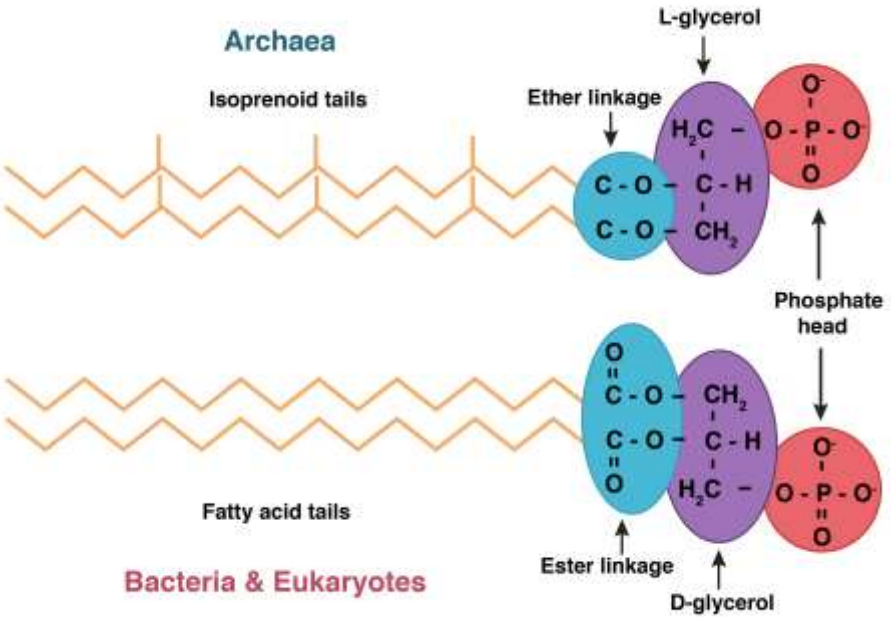
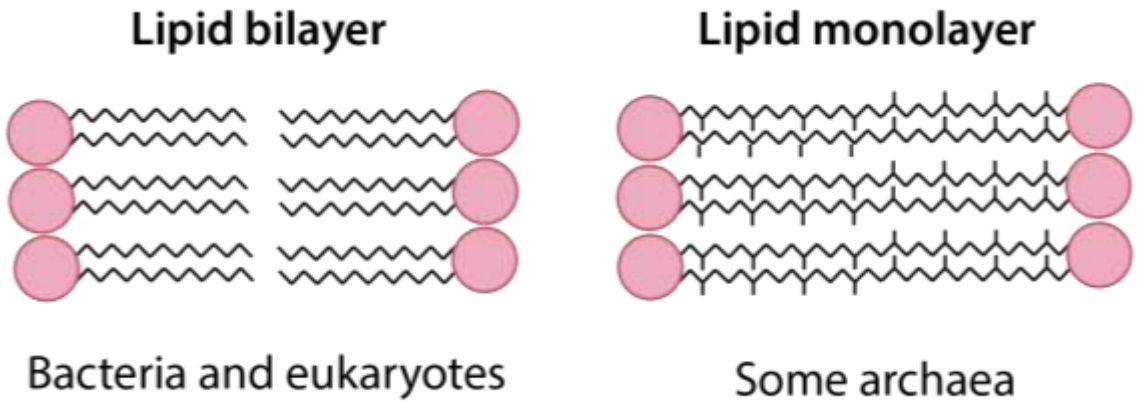
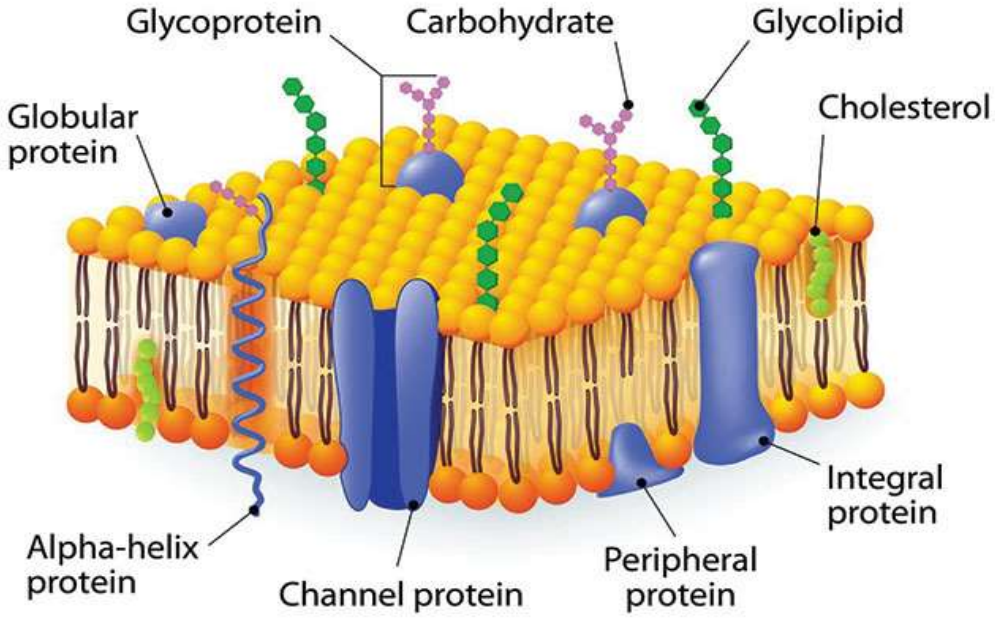




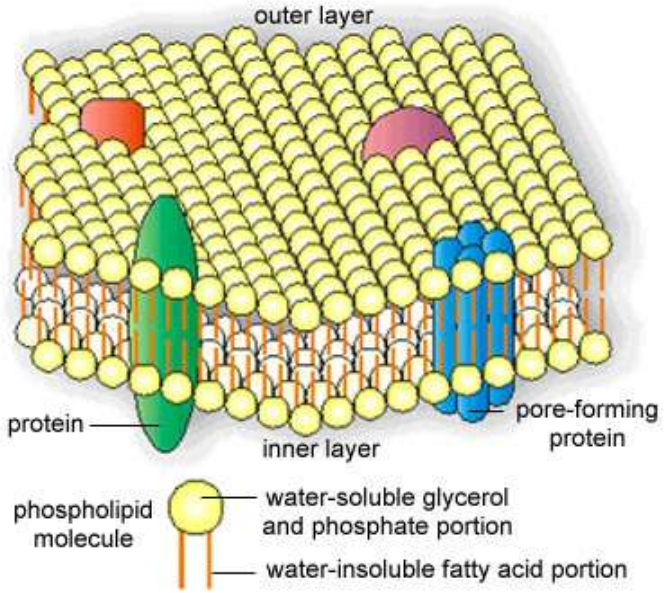
- Proteins on the cell's surface are important for a variety of functions, including cell-to-cell communication, and sensing environmental conditions and pathogenic virulence factors.
- Membrane proteins and phospholipids may have carbohydrates (sugars) associated with them and are called glycoproteins or glycolipids, respectively.
- These glycoprotein and glycolipid complexes extend out from the surface of the cell, allowing the cell to interact with the external environment.
- Glycoproteins and glycolipids in the plasma membrane can vary considerably in chemical composition among archaea, bacteria, and eukaryotes, allowing scientists to use them to characterize unique species.
- In Biochemistry to Identify Microorganisms, phospholipid-derived fatty acid analysis (PLFA) profiles can be used to identify unique types of cells based on differences in fatty acids. Archaea, bacteria, and eukaryotes each have a unique PFLA profile.



The cytoplasmic membrane-Bacteria

The cytoplasmic membrane, also called a cell membrane or plasma membrane, is about 7 nanometers (nm; 1/1,000,000,000 m) thick. It lies internal to the cell wall and encloses the cytoplasm of the bacterium

- Like all biological membranes in nature, the bacterial cytoplasmic membrane is composed of phospholipid and protein molecules.
- In electron micrographs, it appears as 2 dark bands separated by a light band and is actually a fluid phospholipid bilayer imbedded with proteins .
- With the exception of the mycoplasmas, the only bacteria that lack a cell wall, prokaryotic membranes lack sterols.
- Many bacteria, however, do contain sterol-like molecules called hopanoids.
- Like the sterols found in eukaryotic cell membranes, the hopanoids most likely stabilize the bacterial cytoplasmic membrane.



- The phospholipid bilayer is arranged so that the polar ends of the molecules (the phosphate and glycerol portion of the phospholipid that is soluble in water) form the outermost and innermost surface of the membrane while the non-polar ends (the fatty acid portions of the phospholipids that are insoluble in water) form the center of the membrane

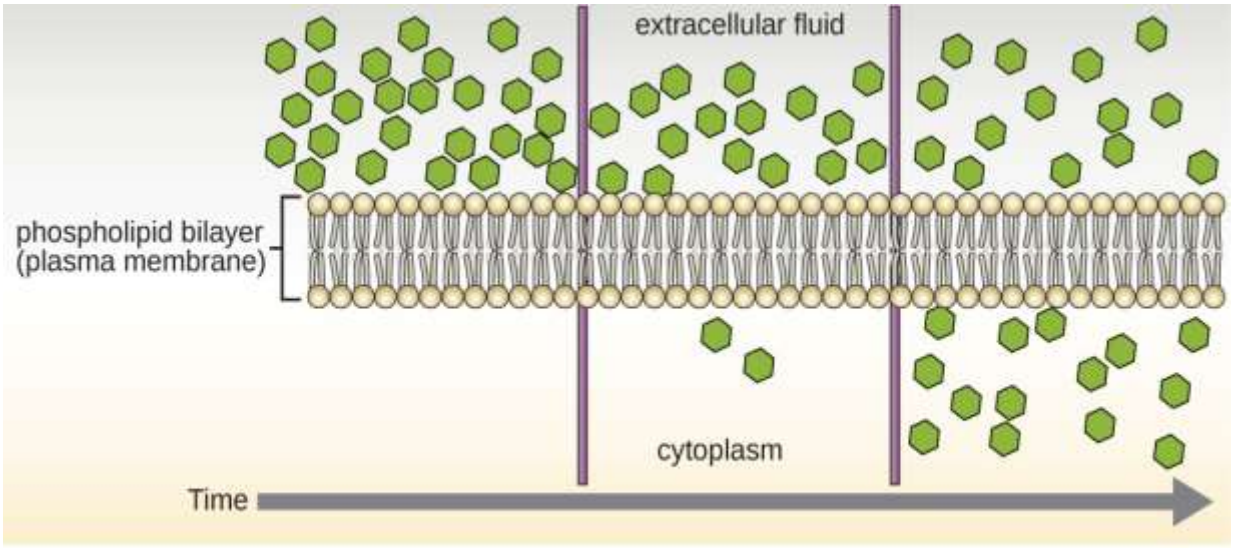
Functions

- The cytoplasmic membrane is a selectively permeable membrane that determines what goes in and out of the organism.
- All cells must take in and retain all the various chemicals needed for metabolism.
- Water, dissolved gases such as carbon dioxide and oxygen, and lipid-soluble molecules simply diffuse across the phospholipid bilayer.
- Water-soluble ions generally pass through small pores - less than 0.8 nm in diameter - in the membrane .
- All other molecules require carrier molecules to transport them through the membrane.
- Materials move across the bacterial cytoplasmic membrane by passive diffusion, facilitated diffusion, and active transport.

Membrane Transport Mechanisms

- ❑ One of the most important functions of the plasma membrane is to control the transport of molecules into and out of the cell.

- Internal conditions must be maintained within a certain range despite any changes in the external environment. The transport of substances across the plasma membrane allows cells to do so.

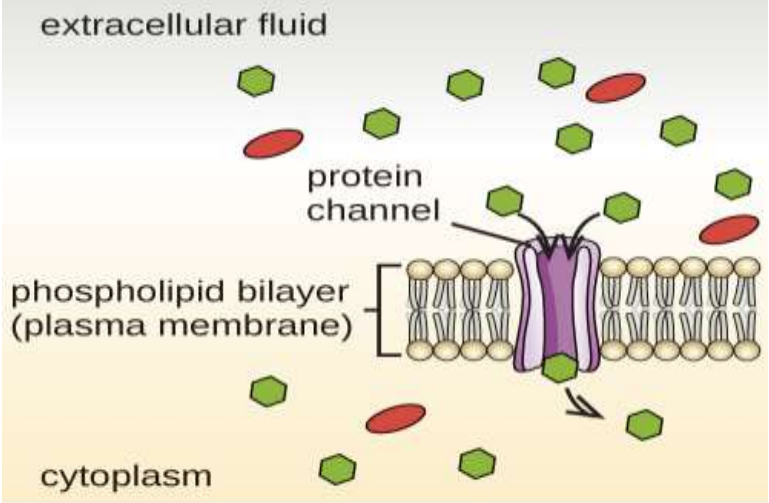


simple diffusion

- Cells use various modes of transport across the plasma membrane.

- For example, molecules moving from a higher concentration to a lower concentration with the concentration gradient are transported by simple diffusion, also known as passive transport

- Some small molecules, like carbon dioxide, may cross the membrane bilayer directly by simple diffusion.
- However, charged molecules, as well as large molecules, need the help of carriers or channels in the membrane.
- These structures ferry molecules across the membrane, a process known as facilitated diffusion



facilitated diffusion

- Active transport occurs when cells move molecules across their membrane against concentration gradients.

- A major difference between passive and active transport is that active transport requires adenosine triphosphate (ATP) or other forms of energy to move molecules "uphill."

Therefore, active transport structures are often called "pumps."

The Nucleoid

- All cellular life has a DNA genome organized into one or more chromosomes.

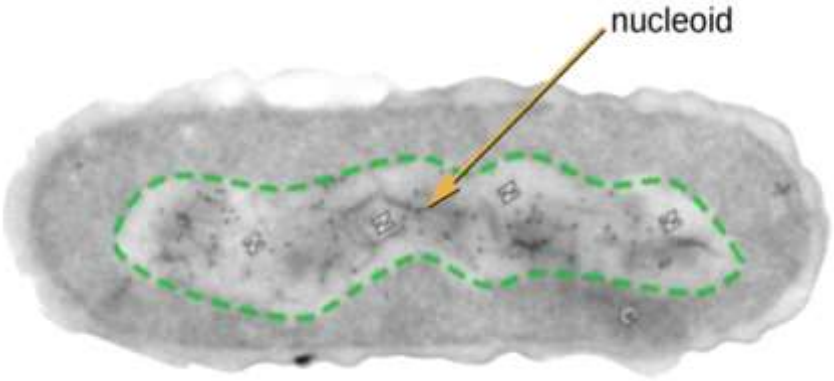
- Prokaryotic chromosomes are typically circular, haploid (unpaired), and not bound by a complex nuclear membrane.

- Prokaryotic DNA and DNA-associated proteins are concentrated within the nucleoid region of the cell .

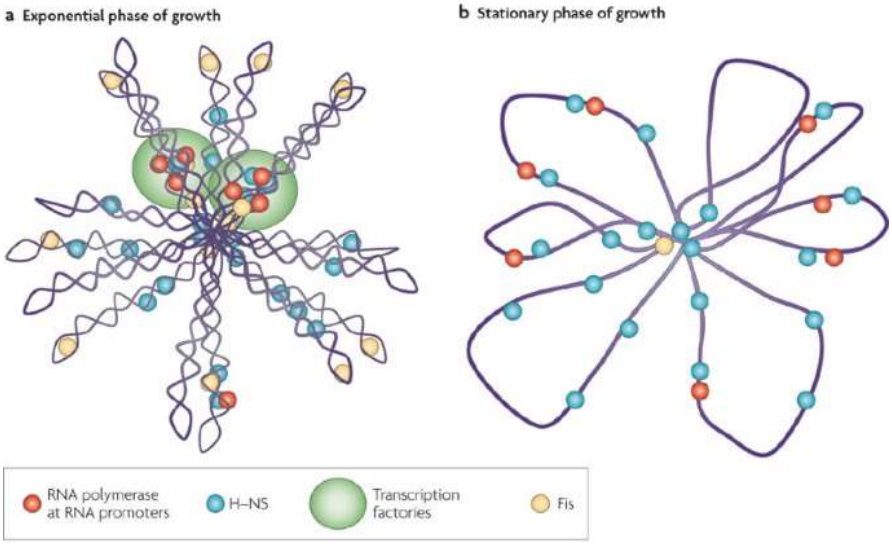
- In general, prokaryotic DNA interacts with nucleoid-associated proteins (NAPs) that assist in the organization and packaging of the chromosome.

- In bacteria, NAPs function similar to histones, which are the DNA-organizing proteins found in eukaryotic cells.

- In archaea, the nucleoid is organized by either NAPs or histone-like DNA organizing proteins.



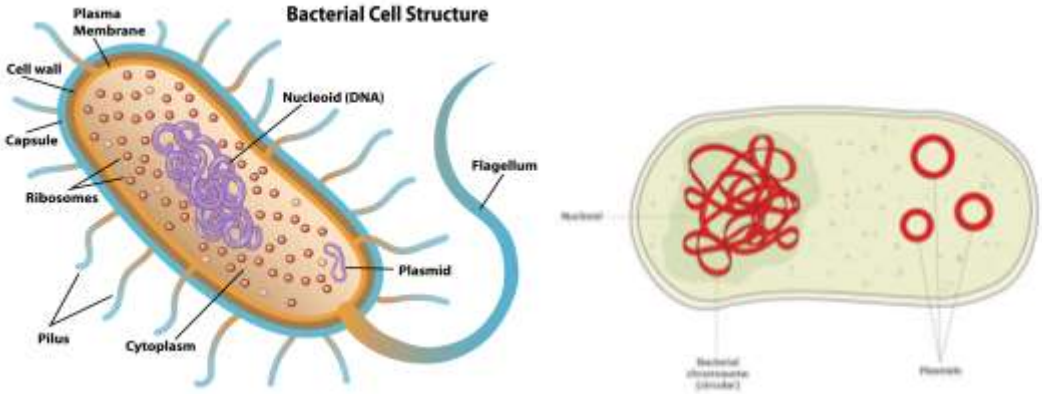
- The nucleoid region (the area enclosed by the green dashed line) is a condensed area of DNA found within prokaryotic cells.
- Because of the density of the area, it does not readily stain and appears lighter in color when viewed with a transmission electron microscope.



Plasmids

- Prokaryotic cells may also contain extrachromosomal DNA, or DNA that is not part of the chromosome.
- This extrachromosomal DNA is found in plasmids, which are small, circular, double-stranded DNA molecules.
- Cells that have plasmids often have hundreds of them within a single cell.
- Plasmids are more commonly found in bacteria; however, plasmids have been found in archaea and eukaryotic organisms.

- Plasmids often carry genes that confer advantageous traits such as antibiotic resistance; thus, they are important to the survival of the organism.



Ribosomes

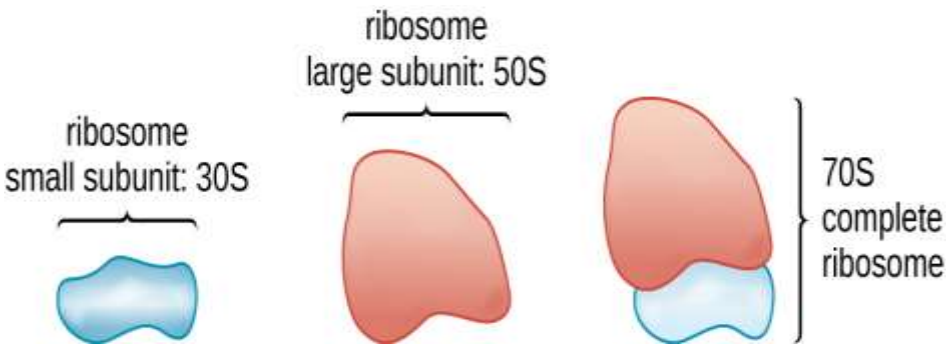
- All cellular life synthesizes proteins, and organisms in all three domains of life possess ribosomes, structures responsible protein synthesis.

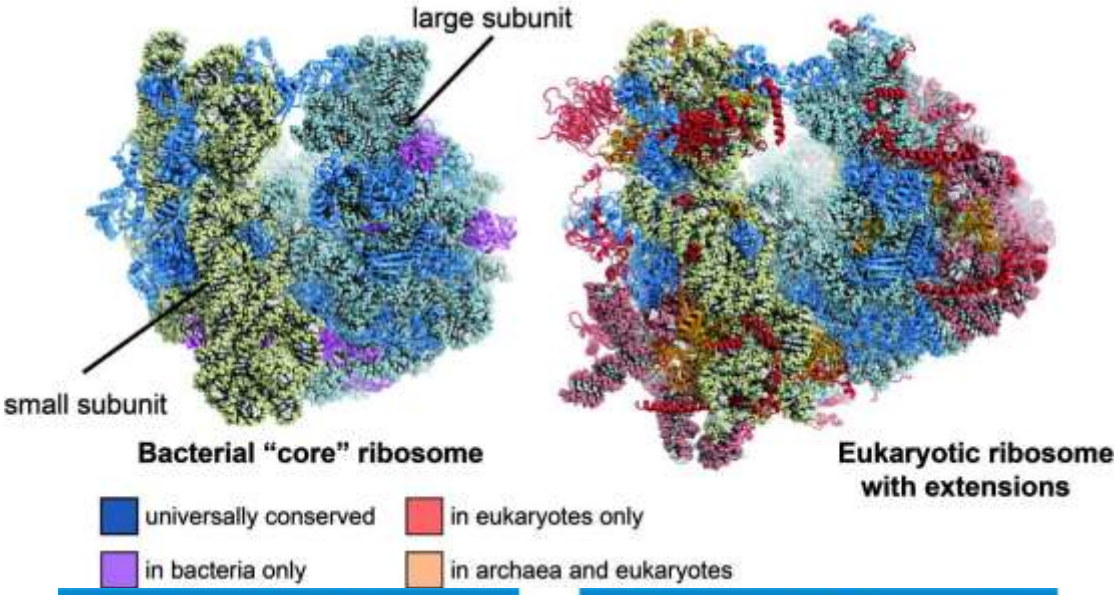
- However, ribosomes in each of the three domains are structurally different.

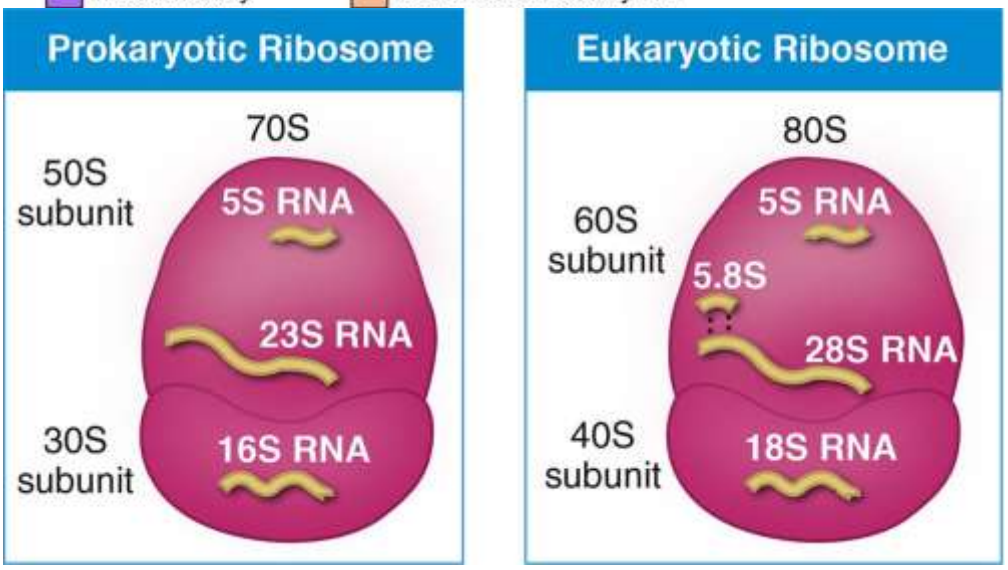
- Ribosomes, themselves, are constructed from proteins, along with ribosomal RNA (rRNA).

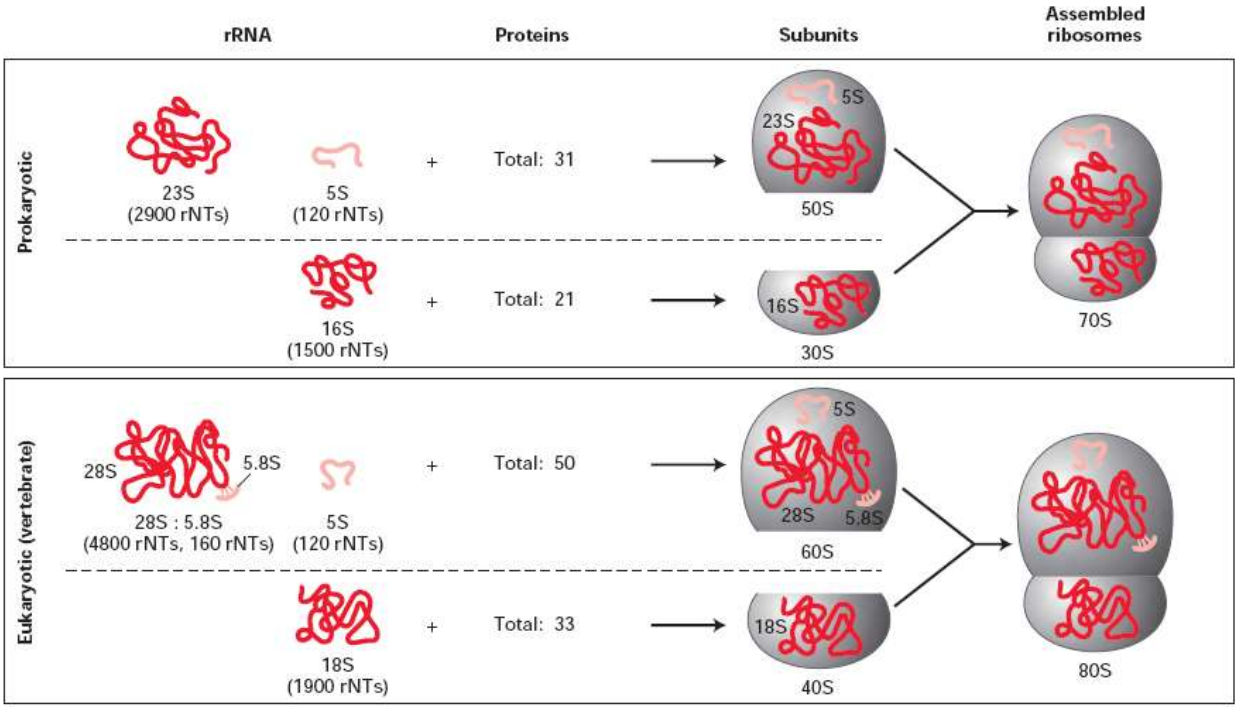
- Prokaryotic ribosomes are found in the cytoplasm. They are called 70S ribosomes because they have a size of 70S, whereas eukaryotic cytoplasmic ribosomes have a size of 80S. (The S stands for Svedberg unit, a measure of sedimentation in an ultracentrifuge, which is based on size, shape, and surface qualities of the structure being analyzed).

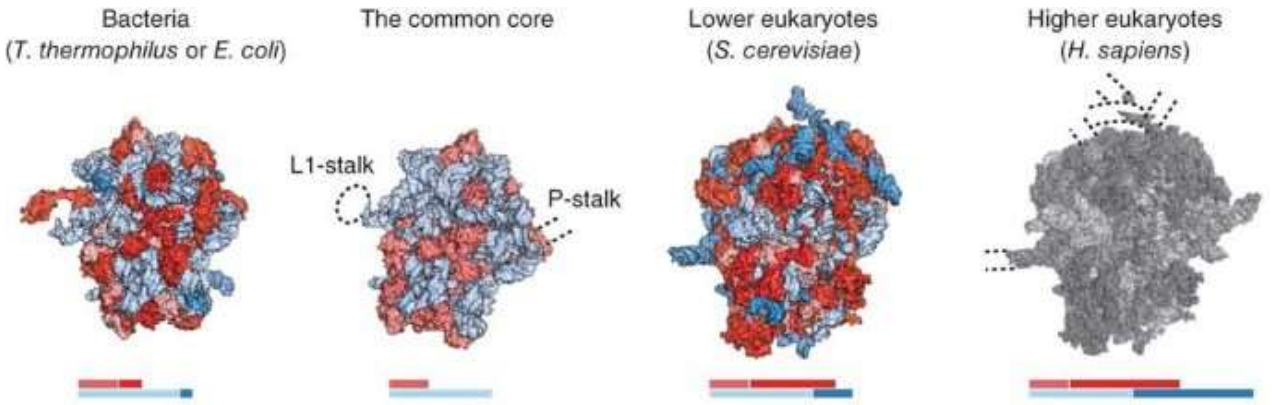
- Although they are the same size, bacterial and archaeal ribosomes have different proteins and rRNA molecules, and the archaeal versions are more similar to their eukaryotic counterparts than to those found in bacteria.




large subunit
small subunit
Bacterial "core" ribosome
Eukaryotic ribosome
with extensions
universally conserved
in eukaryotes only
in bacteria only
in archaea and eukaryotes


Prokaryotic Ribosome
70S
50S
subunit
5S RNA
23S RNA
30S
subunit
16S RNA
Eukaryotic Ribosome
80S
60S
subunit
5S RNA
5.8S
28S RNA
40S
subunit
18S RNA



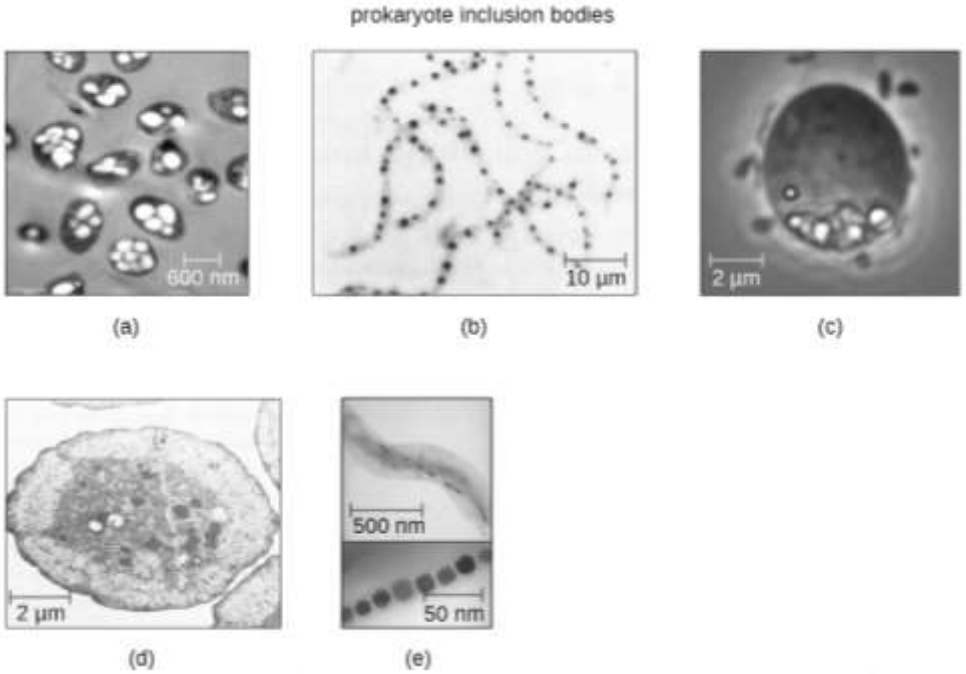


Bacteria (*T. thermophilus* or *E. coli*)	The common core	Lower eukaryotes (*S. cerevisiae*)	Higher eukaryotes (*H. sapiens*)
2.3 MDa	2.0 MDa	3.3 MDa	4.3 MDa
54 proteins 3 rRNA	34 proteins 3 rRNA	79 proteins 4 rRNA	80 proteins: 4 rRNA
Large subunit (50S): 33 proteins 23S rRNA—2,904 bases 5S rRNA—121 bases	Large subunit: 19 proteins 23S rRNA—2,843 bases 5S rRNA—121 bases	Large subunit (60S): 46 proteins 5.8S rRNA—158 bases 25S rRNA—3,396 bases 5S rRNA—121 bases	Large subunit (60S): 47 proteins 5.8S rRNA—156 bases 28S rRNA—5,034 bases 5S rRNA—121 bases
Small subunit (30S): 21 proteins 16S rRNA—1,542 bases	Small subunit: 15 proteins 16S rRNA—1,458 bases	Small subunit (40S): 33 proteins 18S rRNA—1,800 bases	Small subunit (40S): 33 proteins 18S rRNA—1,870 bases

Inclusions

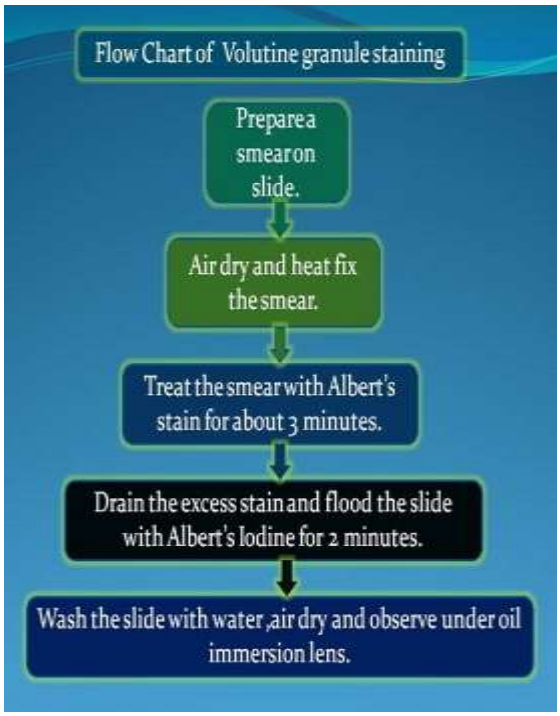
- As single-celled organisms living in unstable environments, some prokaryotic cells have the ability to store excess nutrients within cytoplasmic structures called inclusions.
- Storing nutrients in a polymerized form is advantageous because it reduces the buildup of osmotic pressure that occurs as a cell accumulates solutes.

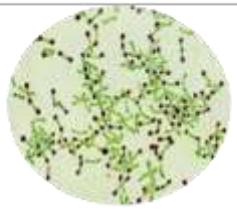
- Various types of inclusions store glycogen and starches, which contain carbon that cells can access for energy.



Prokaryotic cells may have various types of inclusions. (a) A transmission electron micrograph of polyhydroxybutryrate lipid droplets. (b) A light micrograph of volutin granules. (c) A phase-contrast micrograph of sulfur granules. (d) A transmission electron micrograph of magnetosomes. (e) A transmission electron micrograph of gas vacuoles.

Volutin granules, also called metachromatic granules because of their staining characteristics, are inclusions that store polymerized inorganic phosphate that can be used in metabolism and assist in the formation of biofilms. Microbes known to contain volutin granules include the archaea Methanosarcina, the bacterium Corynebacterium diphtheriae, and the unicellular eukaryotic alga Chlamydomonas.



Bacterial Culture	*Corynebacterium diphtheriae*
Metachromatic Granules Staining by Albert's stain Method	
Cell Morphology	
Shape:	Rod shaped bacteria with swollen metachromatic granules
Arrangement:	English L, or V letter or Chinese Letter arrangement
Cell color:	Bluish Black Metachromatic granules with greenish cytoplasm
Presence of Metachromatic Granules or Absence	Metachromatic granules present

Corynebacterium diphtheriae infects the nasopharynx or skin. Toxigenic strains secrete a potent exotoxin which may cause diphtheria. The symptoms of diphtheria include pharyngitis, fever, swelling of the neck or area surrounding the skin lesion. Diphtheritic lesions are covered by a pseudomembrane. The toxin is distributed to distant organs by the circulatory system and may cause paralysis and congestive heart failure.

- Sulfur granules, another type of inclusion, are found in sulfur bacteria of the genus Thiobacillus; these granules store elemental sulfur, which the bacteria use for metabolism.

- Occasionally, certain types of inclusions are surrounded by a phospholipid monolayer embedded with protein. Polyhydroxybutyrate (PHB), which can be produced by species of Bacillus and Pseudomonas, is an example of an inclusion that displays this type of monolayer structure.

- Industrially, PHB has also been used as a source of biodegradable polymers for bioplastics.

- Some prokaryotic cells have other types of inclusions that serve purposes other than nutrient storage.

- For example, some prokaryotic cells produce gas vacuoles, accumulations of small, protein-lined vesicles of gas. These gas vacuoles allow the prokaryotic cells that synthesize them to alter their buoyancy so that they can adjust their location in the water column.

- Magnetotactic bacteria, such as Magnetospirillum magnetotacticum, contain magnetosomes, which are inclusions of magnetic iron oxide or iron sulfide surrounded by a lipid layer. These allow cells to align along a magnetic field, aiding their movement.

- Cyanobacteria such as Anabaena cylindrica and bacteria such as Halothiobacillus neapolitanus produce carboxysome inclusions.

- Carboxysomes are composed of outer shells of thousands of protein subunits.
- Their interior is filled with ribulose-1,5-bisphosphate carboxylase/oxygenase (RuBisCO) and carbonic anhydrase.
- Both of these compounds are used for carbon metabolism.

- Some prokaryotic cells also possess carboxysomes that sequester functionally related enzymes in one location. These structures are considered proto-organelles because they compartmentalize important compounds or chemical reactions, much like many eukaryotic organelles.

Mesosomes

Mesosomes are areas in the cell membrane of prokaryotic (bacterial) cells that fold inward. They play a role in cellular respiration, the process that breaks down food to release energy.

Since Prokaryotes do not contain membrane bound organelles, they need a different approach. Instead, they use the mesosomes as a site for the electron transport chain.
Functions of mesosome in prokaryotic cells are:
1) Involved In Septum Formation During Cell Division.
2) Control The Activity Of Autolytic Enzymes (Enzymes That Aid In Breakdown Of Cells Or Tissue).
3) Site Where Photosynthetic Apparatus In Photosynthetic Bacteria Rest (Photosynthesis Or Respiration).
4) Carry A Site For The Attachment Of Signal Peptides.
5) Have A Specific Attachment Site For DNA During Replication And Contain Enzymes Required During That Process.

In Eukaryotes, most of this process occurs in mitochondria. The third, and final, step of cellular respiration (electron transport chain) occurs in the space between the two membranes of the mitochondria. This step is critical to the cell as most of the energy from food is released during this stage.

The cytoplasm

The cytoplasm refers to the entire region of a cell between the plasma membrane and the nuclear envelope.
It is composed of organelles suspended in the gel-like cytosol, the cytoskeleton, and various chemicals.

Even though the cytoplasm consists of 70 to 80 percent water, it nevertheless has a semisolid consistency. It is crowded in there. Proteins, simple sugars, polysaccharides, amino acids, nucleic acids, fatty acids, ions and many other water-soluble molecules are all competing for space and water.

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DEPARTMENT OF BIOINFORMATICS

UNIT – II - CELL BIOLOGY & BIOCHEMISTRY-SBIA1102

UNIT-2

Eukaryotic cells

- Eukaryotic cells are the cells that are complex in structure and function as they have a membrane-bound well-defined nucleus and other membrane-bound organelles.
- The term "eukaryote" is derived from Greek words, "eu" meaning 'true' and "karyon' meaning 'nucleus.'
- Eukaryotic cells have a more advanced structural composition when compared to prokaryotes.

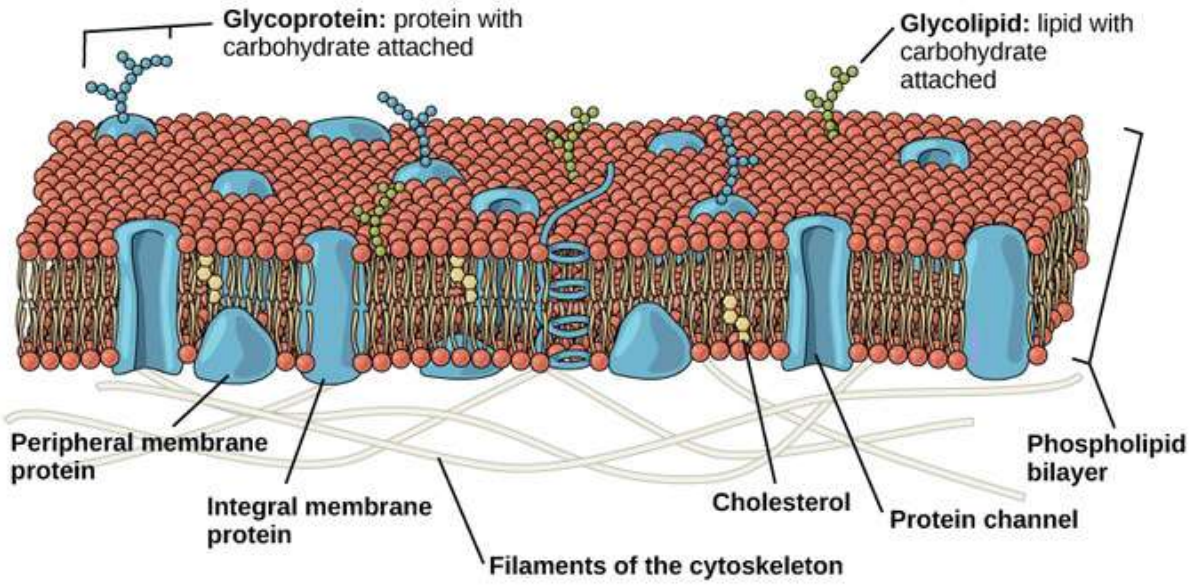
Characteristics of Eukaryotes

1. Cells with nuclei surrounded by a nuclear envelope with nuclear pores. This is the single characteristic that is both necessary and sufficient to define an organism as a eukaryote. All extant eukaryotes have cells with nuclei.
2. Mitochondria. Some extant eukaryotes have very reduced remnants of mitochondria in their cells, whereas other members of their lineages have "typical" mitochondria.
3. A cytoskeleton containing the structural and motility components called actin microfilaments and microtubules. All extant eukaryotes have these cytoskeletal elements.
4. Flagella and cilia, organelles associated with cell motility. Some extant eukaryotes lack flagella and/or cilia, but they are descended from ancestors that possessed them.
5. Chromosomes, each consisting of a linear DNA molecule coiled around basic (alkaline) proteins called histones. The few eukaryotes with chromosomes lacking histones clearly evolved from ancestors that had them.
6. Mitosis, a process of nuclear division wherein replicated chromosomes are divided and separated using elements of the cytoskeleton. Mitosis is universally present in eukaryotes.
7. Sex, a process of genetic recombination unique to eukaryotes in which diploid nuclei at one stage of the life cycle undergo meiosis to yield haploid nuclei and subsequent karyogamy, a stage where two haploid nuclei fuse together to create a diploid zygote nucleus.

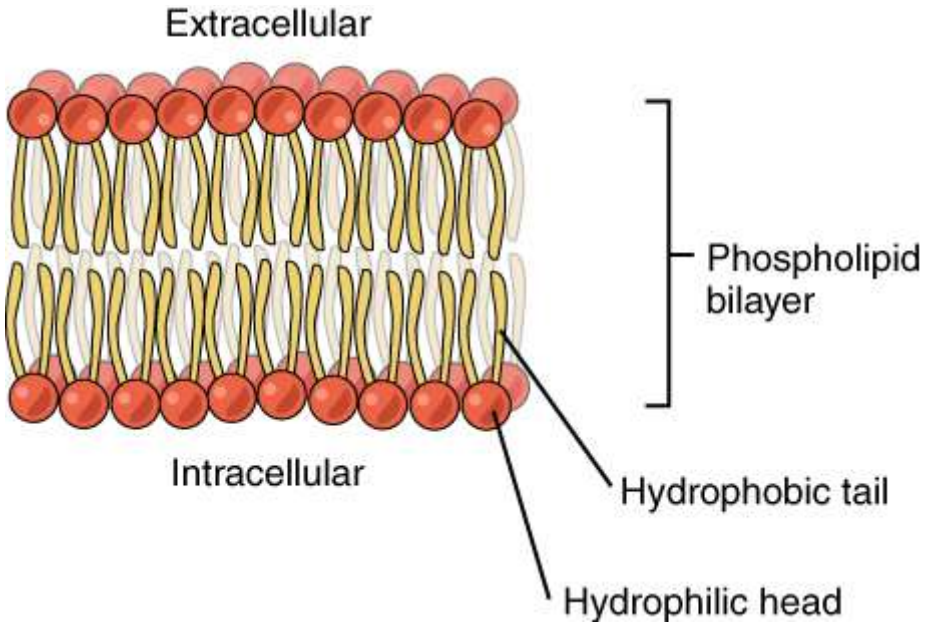
8. Some have cell walls. It might be reasonable to conclude that the last common ancestor could make cell walls during some stage of its life cycle. However, not enough is known about eukaryotes' cell walls and their development to know how much homology exists among them. Homology is the existence of shared ancestry between a pair of structures in different organisms (a similarity that stems from evolution). If the last common ancestor could make cell walls, it is clear that this ability must have been lost in many groups (most obviously animal cells).

Plasma membranes

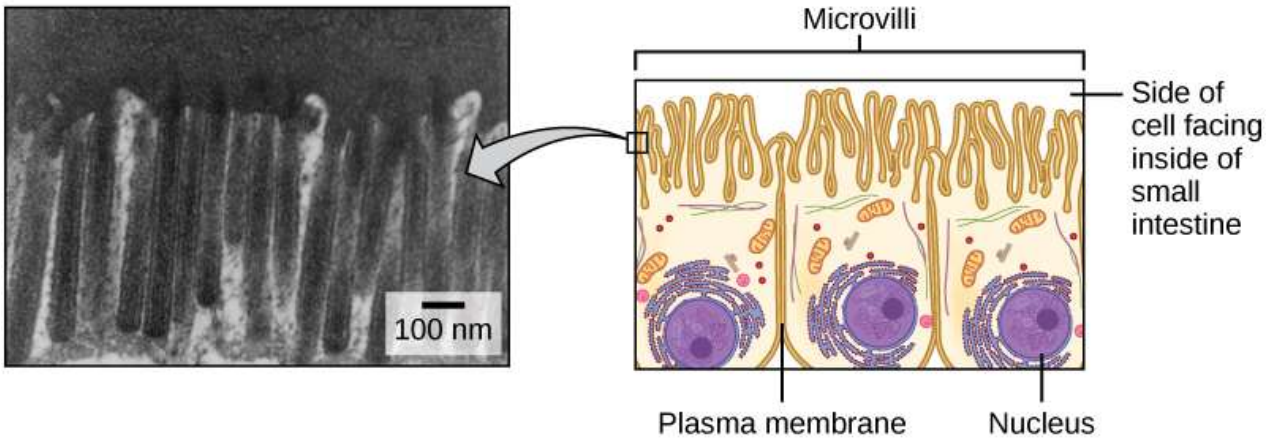
- All eukaryotic cells have a surrounding plasma membrane, which is also known as the cell membrane.
- The plasma membrane is made up by a phospholipid bilayer with embedded proteins that separates the internal contents of the cell from its surrounding environment.
- Only relatively small, non- polar materials can easily move through the lipid bilayer of the plasma membrane.
- Passive transport is the movement of substances across the membrane that does not require the use of energy while active transport is the movement of substances across the membrane using energy.
- Osmosis is the diffusion of water through a semi- permeable membrane down its concentration gradient; this occurs when there is an imbalance of solutes outside of a cell compared to the inside the cell.



- The cell membrane is an extremely pliable structure composed primarily of two adjacent sheets of phospholipids.
- Cholesterol, also present, contributes to the fluidity of the membrane.
- A single phospholipid molecule consists of a polar phosphate “head,” which is hydrophilic, and a non-polar lipid “tail,” which is hydrophobic.
- Unsaturated fatty acids result in kinks in the hydrophobic tails.
- The phospholipid bilayer consists of two phospholipids arranged tail to tail.
- The hydrophobic tails associate with one another, forming the interior of the membrane. The polar heads contact the fluid inside and outside of the cell.

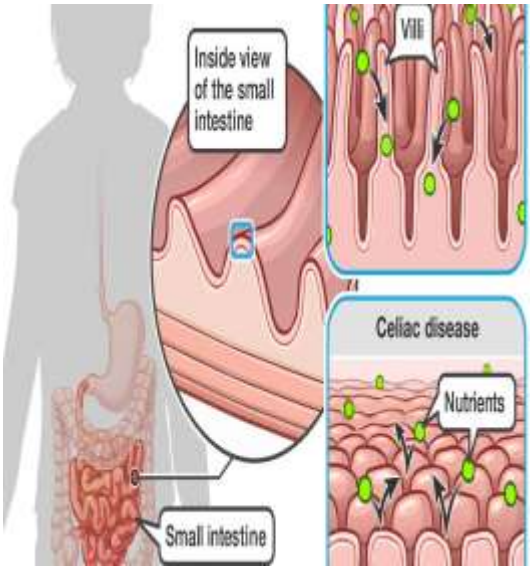


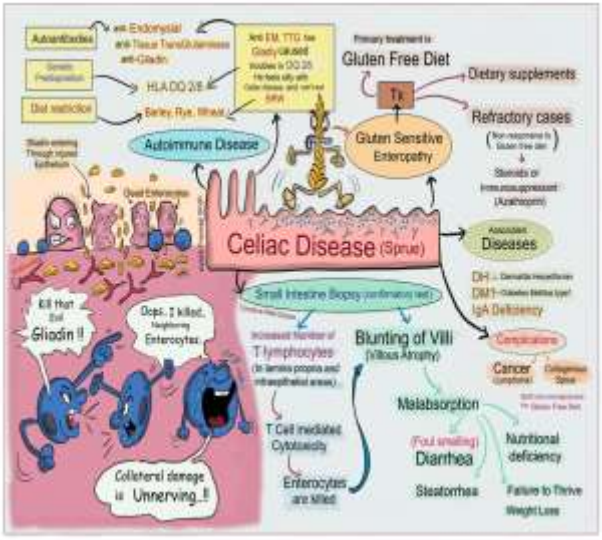
- The plasma membranes of eukaryotic cells may also adopt unique conformations.
- For instance, the plasma membrane of cells that, in multicellular organisms, specialize in absorption are often folded into fingerlike projections called microvilli (singular = microvillus);
- The "folding" of the membrane into microvilli effectively increases the surface area for absorption while minimally impacting the cytosolic volume.
- Such cells can be found lining the small intestine, the organ that absorbs nutrients from digested food.



- An aside: people with celiac disease have an immune response to gluten, a protein found in wheat, barley, and rye.

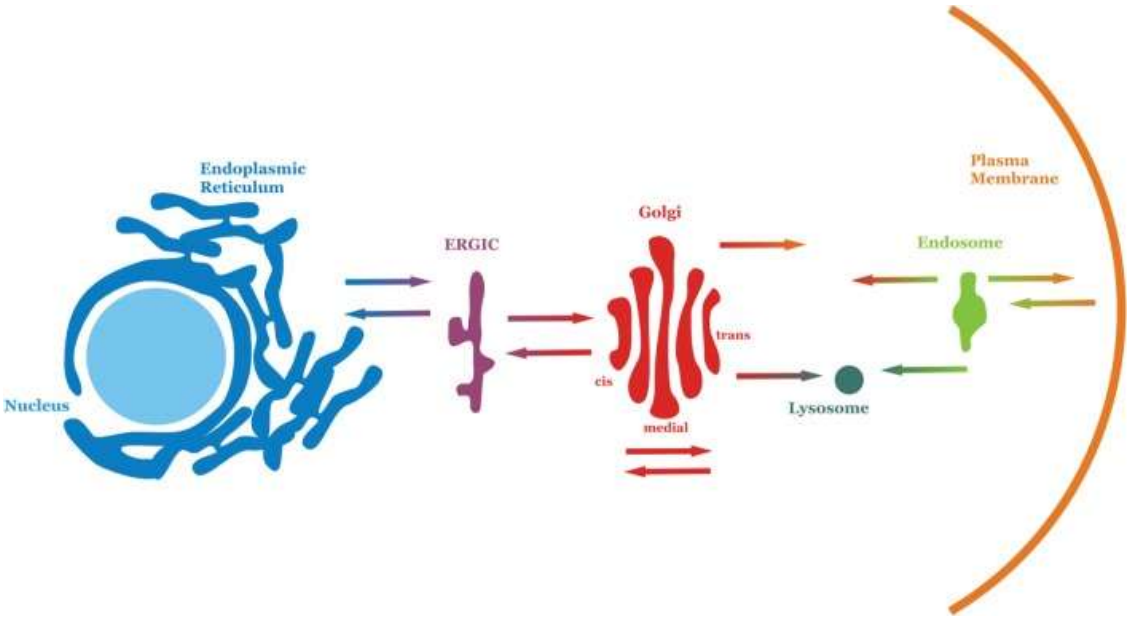
- The immune response damages microvilli. As a consequence, afflicted individuals have an impaired ability to absorb nutrients. This can lead to malnutrition, cramping, and diarrhea.





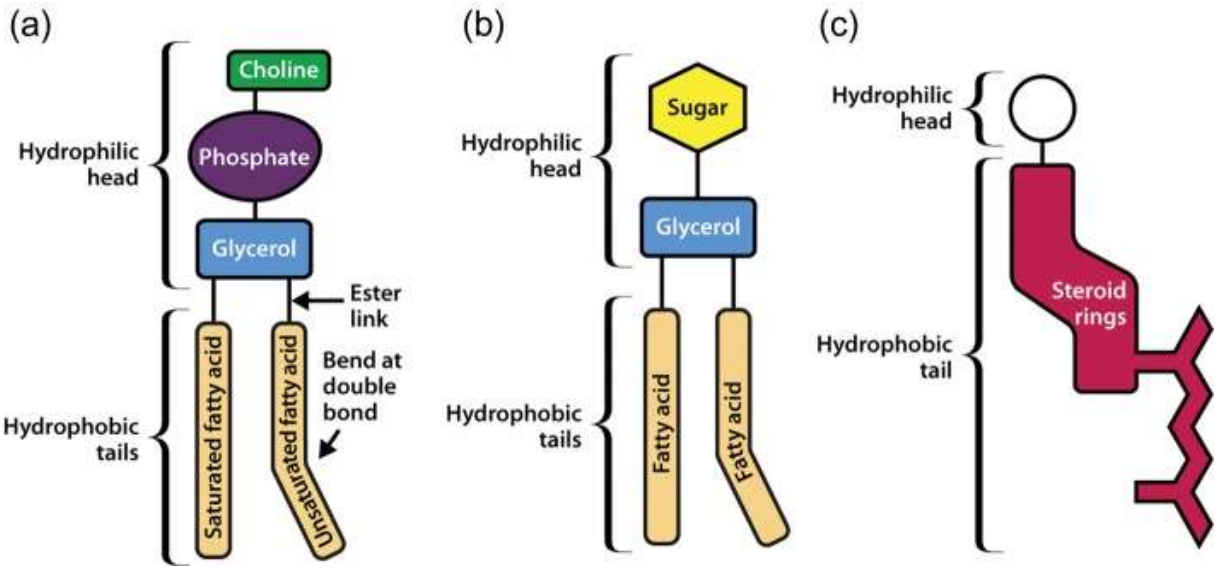
How membranes are made?

- Biological membranes are formed by adding to a pre-existing membrane.
- In prokaryotes this occurs on the inner leaflet of the plasma membrane, facing the cytoplasm.
- In eukaryotes, membrane synthesis takes place at the ER on the cytoplasmic leaflet of the ER membrane (termed the ‘inside’ of the cell).
- Lipids then leave the ER and travel through the secretory pathway for distribution to various subcellular compartments or the plasma membrane.

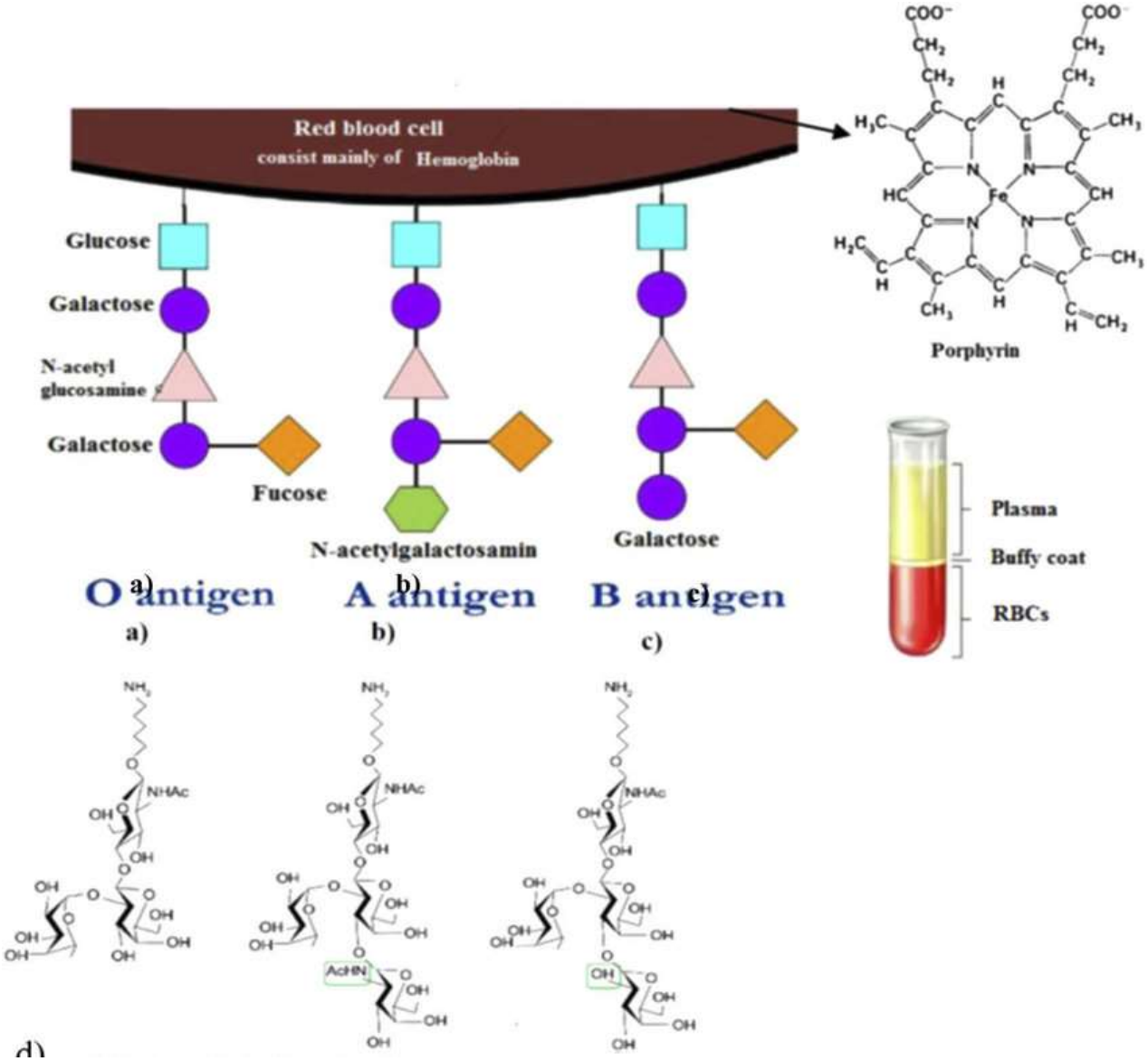


- In eukaryotic cells, enzymes that span the ER catalyse the formation of membrane lipids.
- In the cytoplasmic leaflet of the ER membrane, two fatty acids are bound, one by one, to glycerol phosphate from the cytoplasm.
- This newly formed diacylglycerol phosphate is anchored in the ER membrane by its fatty acid chains.
- The phosphate is then replaced by the head group (e.g. phosphate and choline).
- Flippases in the ER membrane can then move some of these newly formed lipids to the luminal side of the ER membrane. Similarly, flippases in prokaryotes can transfer new lipids from the inner leaflet of the plasma membrane to the outer leaflet.
- These flippases are responsible for adjusting the lipid composition of each layer of the membrane
- In eukaryotes, lipids must then be distributed to the various intracellular membranes.
- The traffic of vesicles between organelles in combination with signals that direct particular lipids to specific locations is required to create the correct lipid composition in all of the cellular membranes .
- Vesicles bud from the ER and travel via the ER–Golgi intermediate compartment (ERGIC) to join with the Golgi, where sorting of lipids takes place.
- The Golgi then sends lipids in vesicles to various destinations, including the plasma membrane and lysosomes.
- Lipids and proteins are internalized from the plasma membrane into endosomes.

- Organelles, such as mitochondria, acquire lipids from the ER by a different mechanism.
- Water-soluble proteins called phospholipid-exchange proteins remove phospholipids from the ER membrane and deposit them in the membranes of the appropriate organelles.
- Three types of lipid are found in biological membranes, namely phospholipids, glycolipids and sterols.
- Phospholipids consist of two fatty acid chains linked to glycerol and a phosphate group. Phospholipids containing glycerol are referred to as glycerophospholipids. An example of a glycerophospholipid that is commonly found in biological membranes is phosphatidylcholine (PC) which has a choline molecule attached to the phosphate group. Serine and ethanolamine can replace the choline in this position, and these lipids are called phosphatidylserine (PS) and phosphatidylethanolamine (PE), respectively. Phospholipids can also be sphingophospholipids (based on sphingosine), such as sphingomyelin.
- Glycolipids can contain either glycerol or sphingosine, and always have a sugar such as glucose in place of the phosphate head found in phospholipids.
- Sterols are absent from most bacterial membranes, but are an important component of animal (typically cholesterol) and plant (mainly stigmasterol) membranes.
- Cholesterol has a quite different structure to that of the phospholipids and glycolipids. It consists of a hydroxyl group (which is the hydrophilic 'head' region), a four-ring steroid structure and a short hydrocarbon side chain



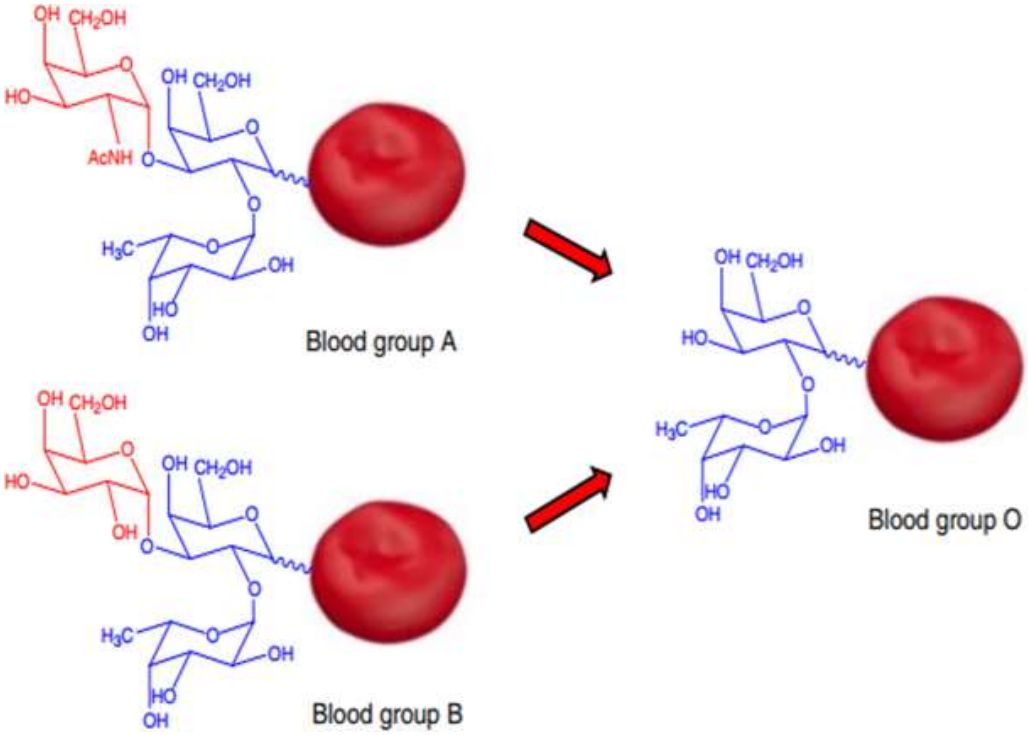
- The sugars attached to lipids and proteins can act as markers due to the structural diversity of sugar chains.
- For example, antigens composed of sugar chains on the surface of red blood cells determine an individual's blood group. These antigens are recognized by antibodies to cause an immune response, which is why matching blood groups must be used in blood transfusions.

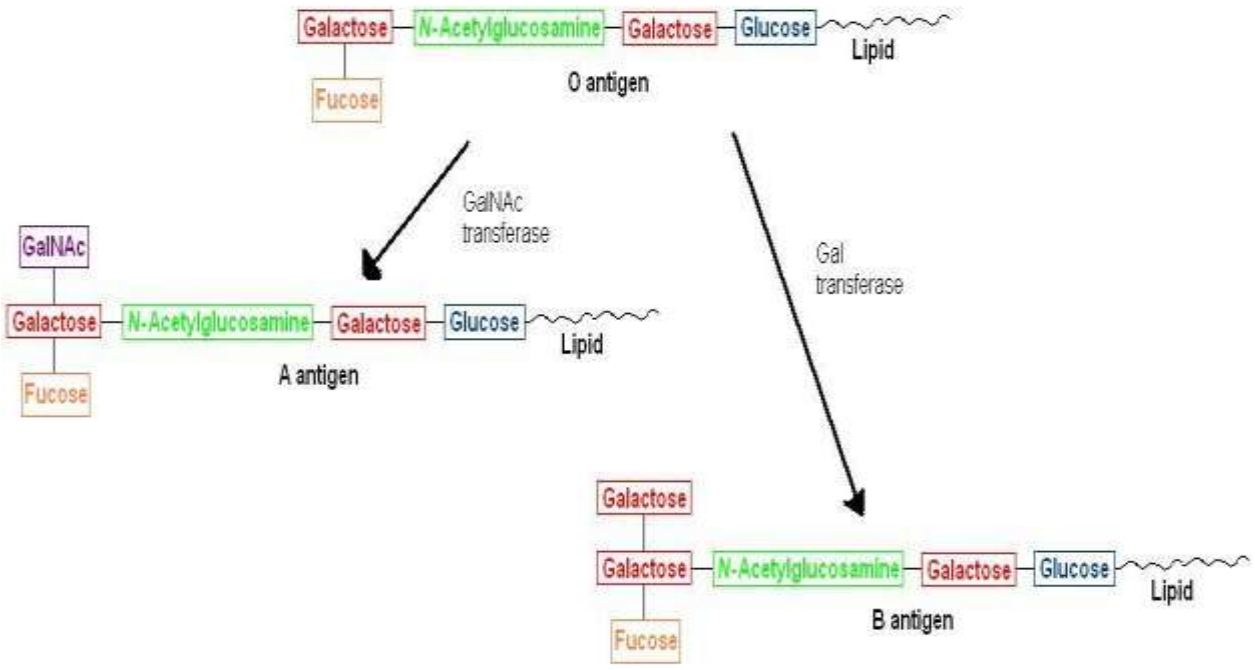


Universal Donors and Universal Recipients

Blood type O is the universal donors due to its versatility of having no molecules on the red blood cell surfaces, which will not trigger any immune response. Therefore type O blood can be donated to any of the other four blood types earning its name.

Blood type AB is the universal recipients due to its lack of antibodies that recognize type A or B surface molecules. AB can receive blood from any of the other four blood types earning its name as the universal receiver. AB however also tends to be the most rare blood type out of the four.

- 



The importance of glycosyltransferases is most prominent when a person needs a blood transfusion.

- It is because of this process that people with type AB blood can accept transfusions of any blood type, since they have all three antigens already present in their bodies. It should be noted that in reality, transfusions are complicated by the Rhesus factor.
- **Distribution of lipids**
- The inner and outer leaflets of bilayers differ in their lipid composition.
- In mammalian cells, the outer leaflet of the plasma membrane contains predominantly **phosphatidylcholine** and sphingomyelin, whereas **phosphatidylserine** and **phosphatidylethanolamine** are found on the inner leaflet.
- During programmed cell death (apoptosis), **phosphatidylserine** is no longer restricted to the inner leaflet of the plasma membrane. It is exposed on the outer leaflet by the action of an enzyme called scramblase which is a type of flippase enzyme.
- **phosphatidylserine** is negatively charged, unlike **phosphatidylcholine**, which has no net charge.
- The movement of **phosphatidylserine** into the outer leaflet therefore changes the charge of the plasma membrane as viewed from the outside of the cell.
- This change in surface charge labels the apoptotic cell for phagocytosis by phagocytic cells such as macrophages.
- Mitochondria play a **critical role in the generation of metabolic energy in eukaryotic cells**.
- They are responsible for most of the useful energy derived from the breakdown of carbohydrates and fatty acids, which is converted to ATP by the process of oxidative phosphorylation.
- Most mitochondrial proteins are translated on free cytosolic ribosomes and imported into the organelle by specific targeting signals.
- In addition, mitochondria are unique among the cytoplasmic organelles already discussed in that they contain their own DNA, which encodes tRNAs, rRNAs, and some mitochondrial proteins.

- The assembly of mitochondria thus involves proteins encoded by their own genomes and translated within the organelle, as well as proteins encoded by the nuclear genome and imported from the cytosol.
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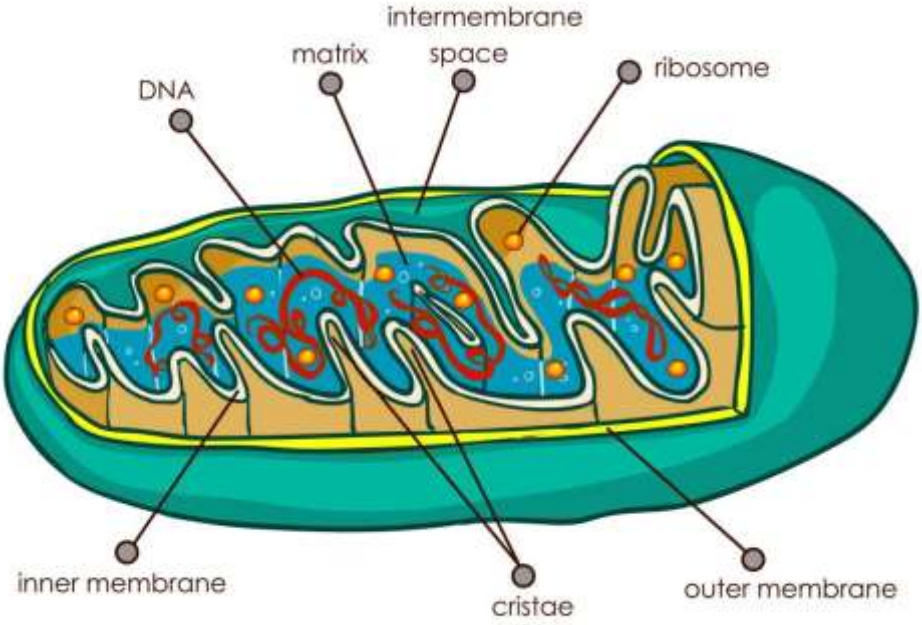
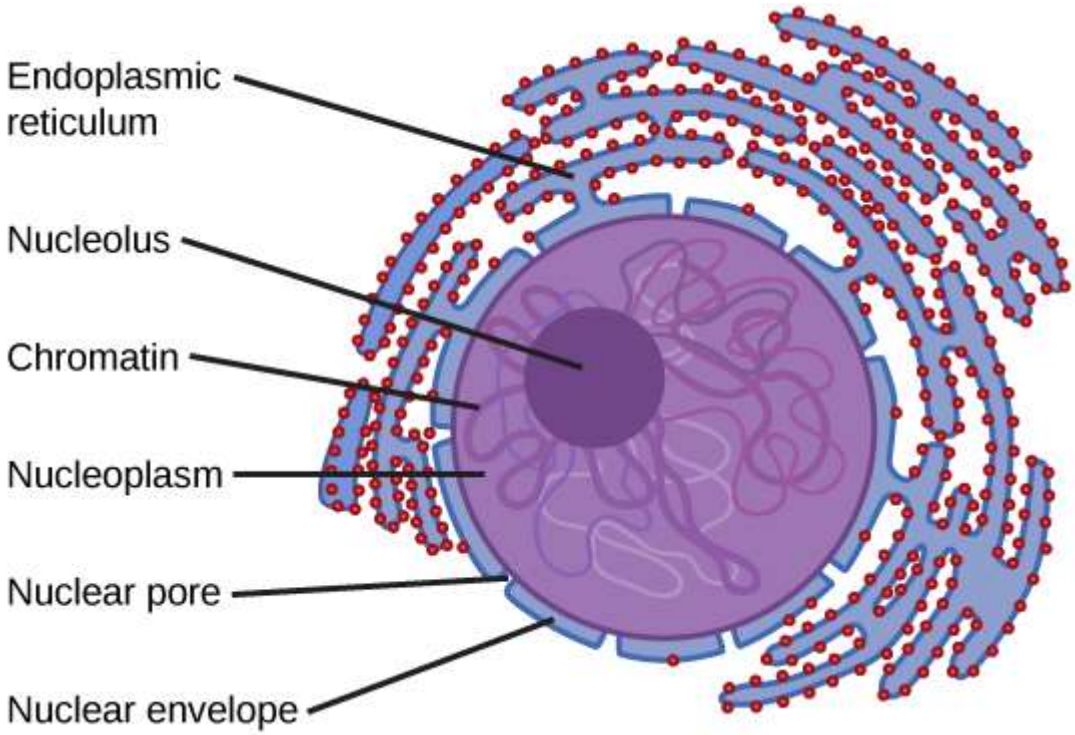


The structure of a nucleus encompasses the

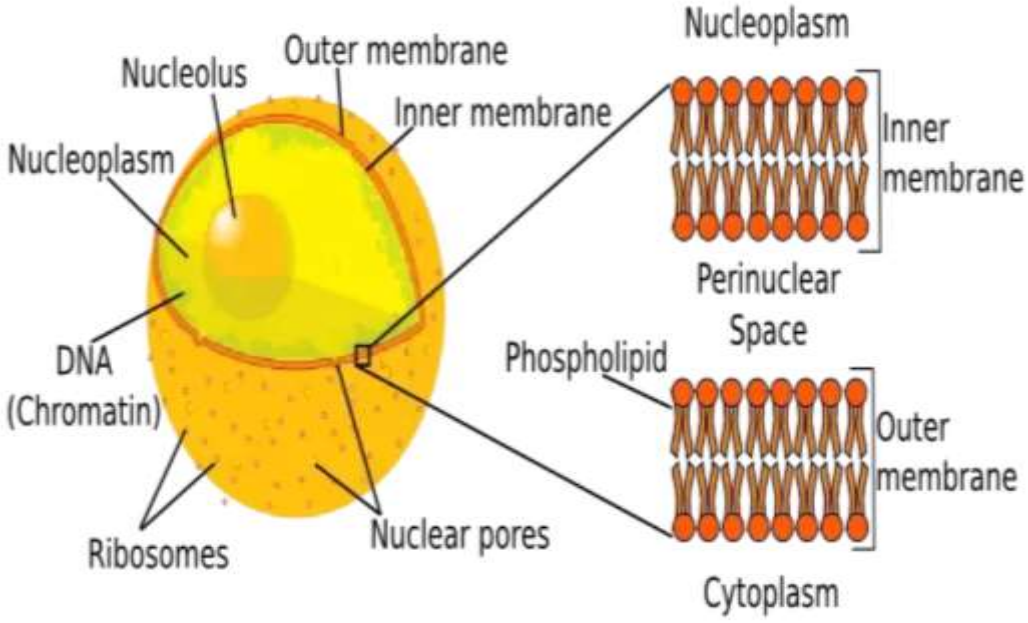
- **Nuclear membrane**
- **Nucleoplasm**
- **Chromosomes, and nucleolus**



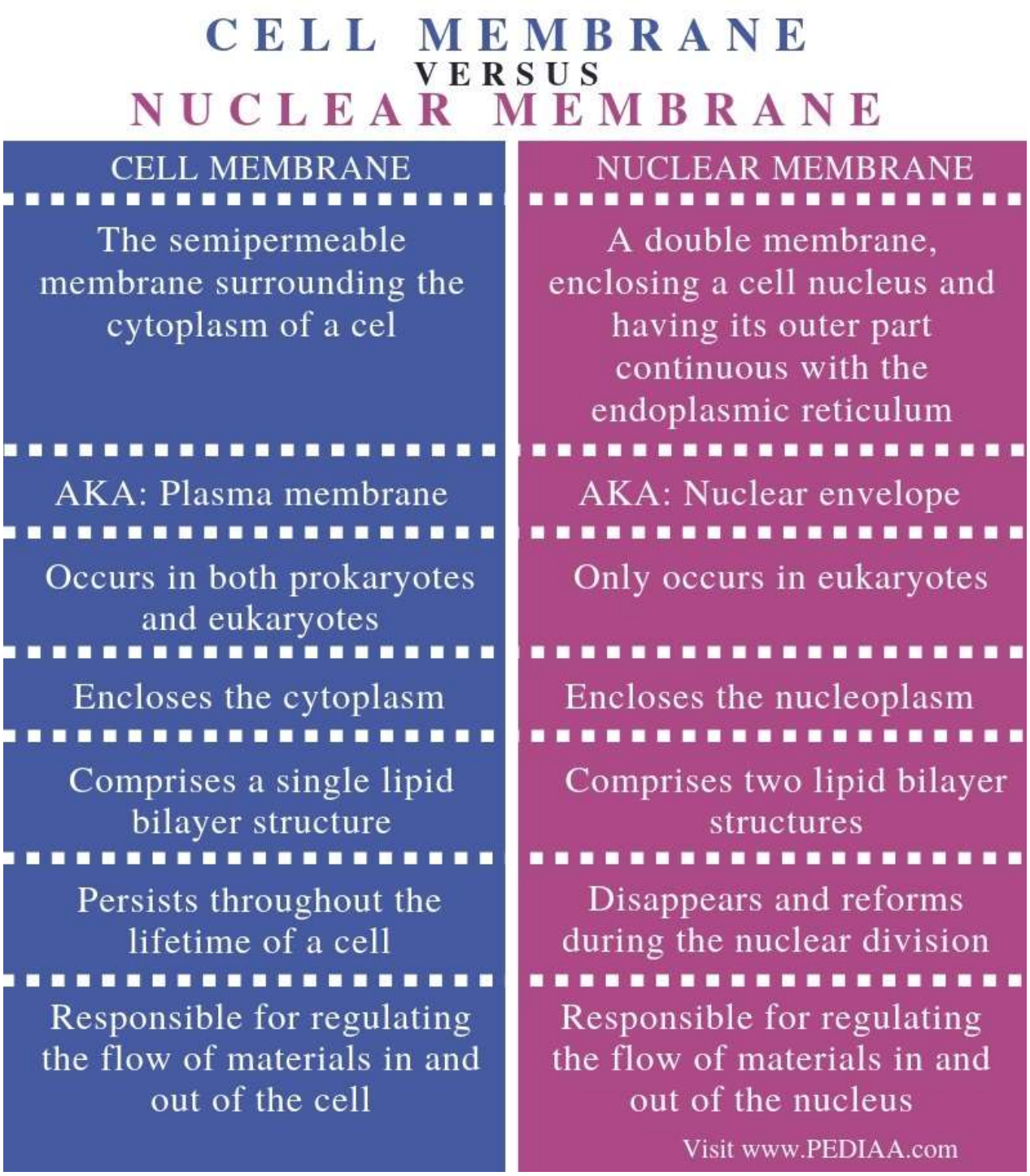
Nuclear Membrane

- The nuclear membrane is a **double-layered structure** that encloses the contents of the nucleus.
- The outer layer of the membrane is connected to the endoplasmic reticulum.
- Like the cell membrane, the nuclear envelope consists of **phospholipids that form a lipid bilayer**.
- The envelope helps to maintain the shape of the nucleus and assists in regulating the flow of molecules into and out of the nucleus through nuclear pores.
- The nucleus communicates with the remaining of the cell or the cytoplasm through several openings called **nuclear pores.**Such nuclear pores are the sites for the exchange of large molecules (proteins and RNA) between the nucleus and cytoplasm.
- A fluid-filled space or perinuclear space is present between the two layers of a nuclear membrane.

Nucleus:

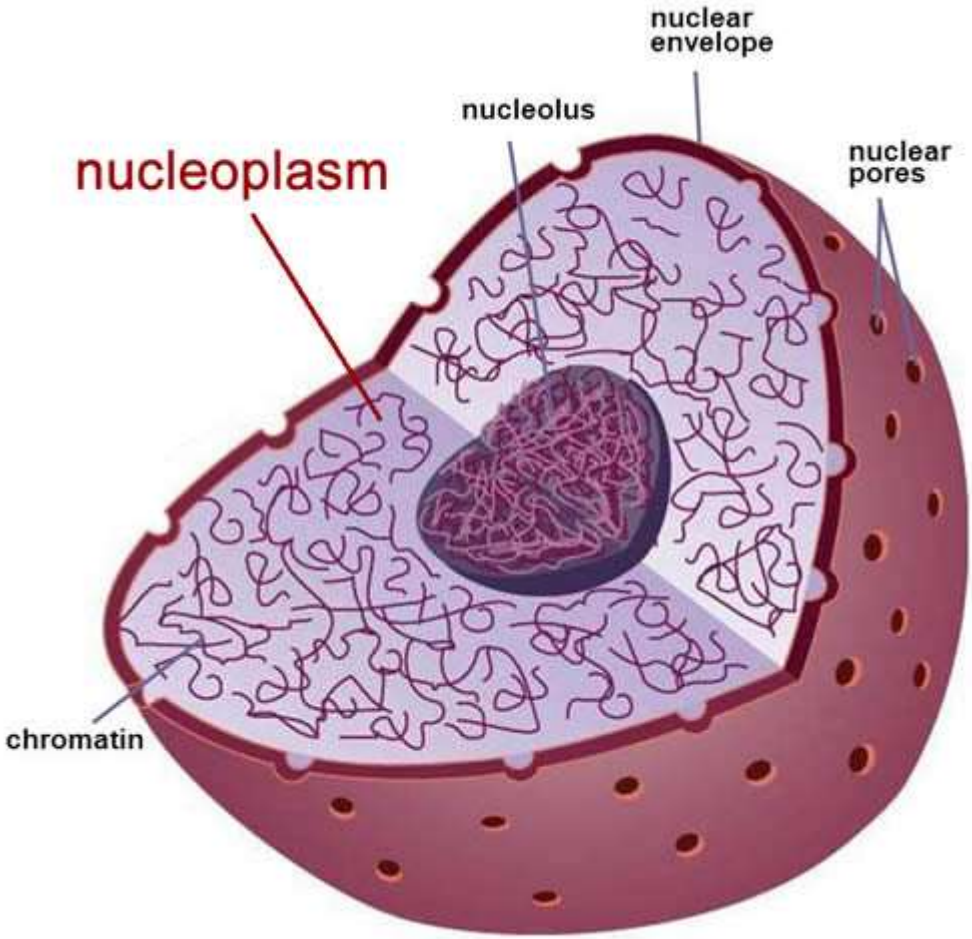


- The nuclear envelope (NE) is a highly regulated membrane barrier that separates the nucleus from the cytoplasm in eukaryotic cells.
- It contains a large number of different proteins that have been implicated in chromatin organization and gene regulation.
- Although the nuclear membrane enables complex levels of gene expression, it also poses a challenge when it comes to cell division.
- To allow access of the mitotic spindle to chromatin, the nucleus of metazoans must completely disassemble during mitosis, generating the need to re-establish the nuclear compartment at the end of each cell division.



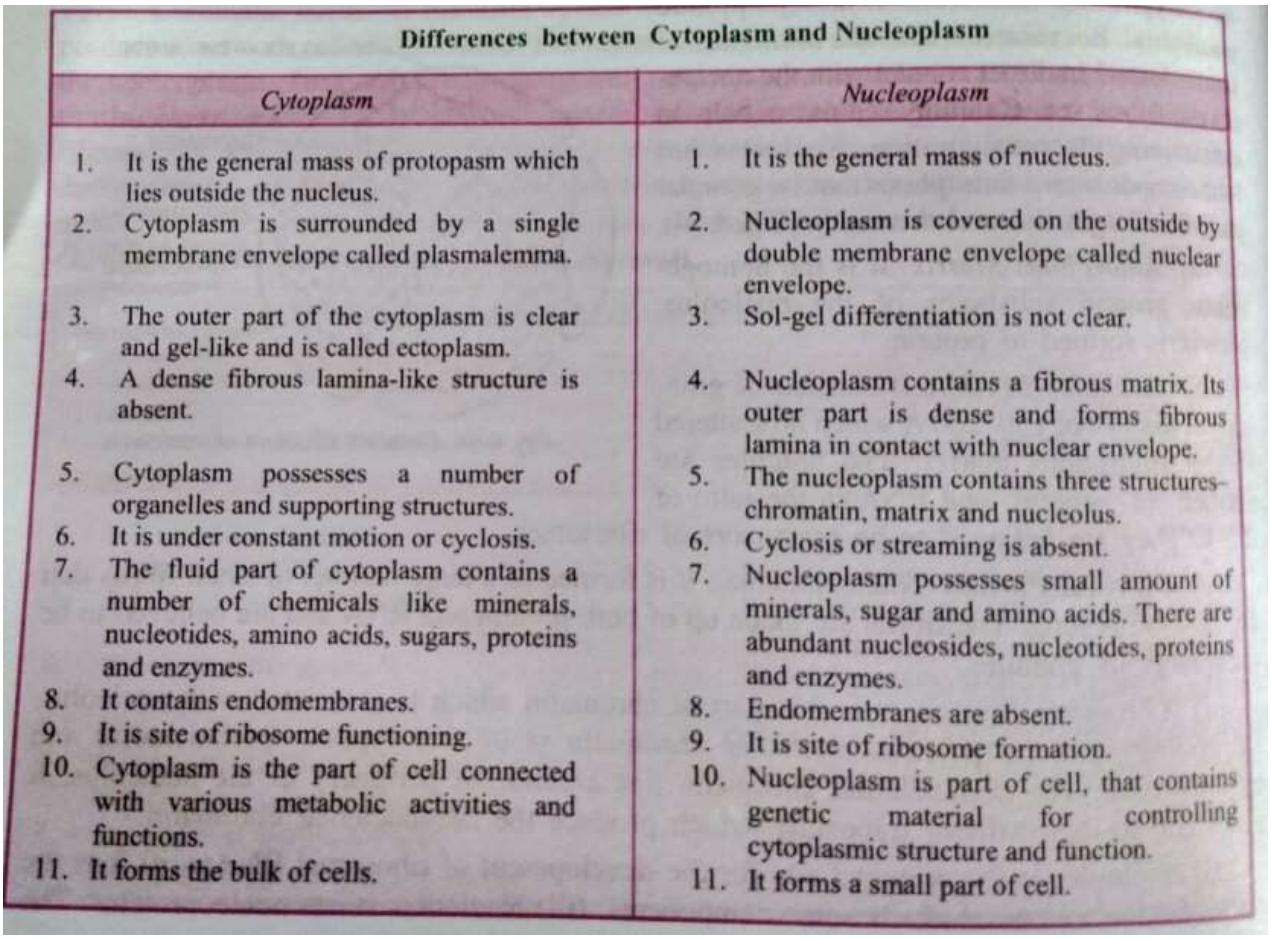
- **Nucleoplasm**
- Nucleoplasm is the gelatinous substance within the nuclear envelope.Also called karyoplasm, this semi-aqueous material is similar to the cytoplasm and is composed mainly of water with dissolved salts, enzymes, and organic molecules suspended within.

- The nucleolus and chromosomes are surrounded by nucleoplasm, which functions to cushion and protect the contents of the nucleus.
- Nucleoplasm also supports the nucleus by helping to maintain its shape.
- Additionally, nucleoplasm provides a medium by which materials, such as enzymes and nucleotides (DNA and RNA subunits), can be transported throughout the nucleus.
- Substances are exchanged between the cytoplasm and nucleoplasm through nuclear pores.



CYTOPLASM VERSUS NUCLEOPLASM

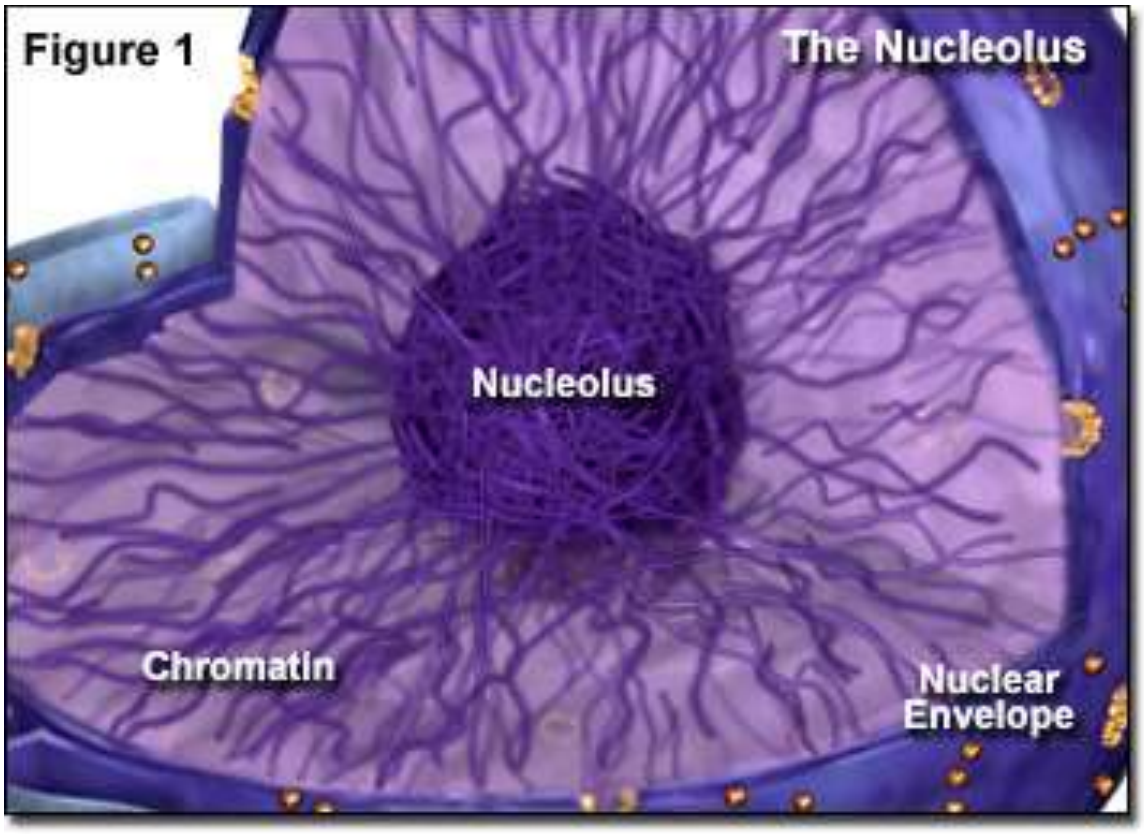
CYTOPLASM	NUCLEOPLASM
Cytoplasm is found inside the cell	Nucleoplasm is found inside the nucleus
Enclosed by the cell membrane	Enclosed by the nuclear envelope
Gelatinous structure	Highly gelatinous structure
Organelles and inclusions are suspended	Nucleolus and chromatin are suspended
A universal feature in all known cells	Only contained by eukaryotic cells
Divided into two cells during cytokinesis	Released during the nuclear division and refilled after the formation of the nuclear envelope



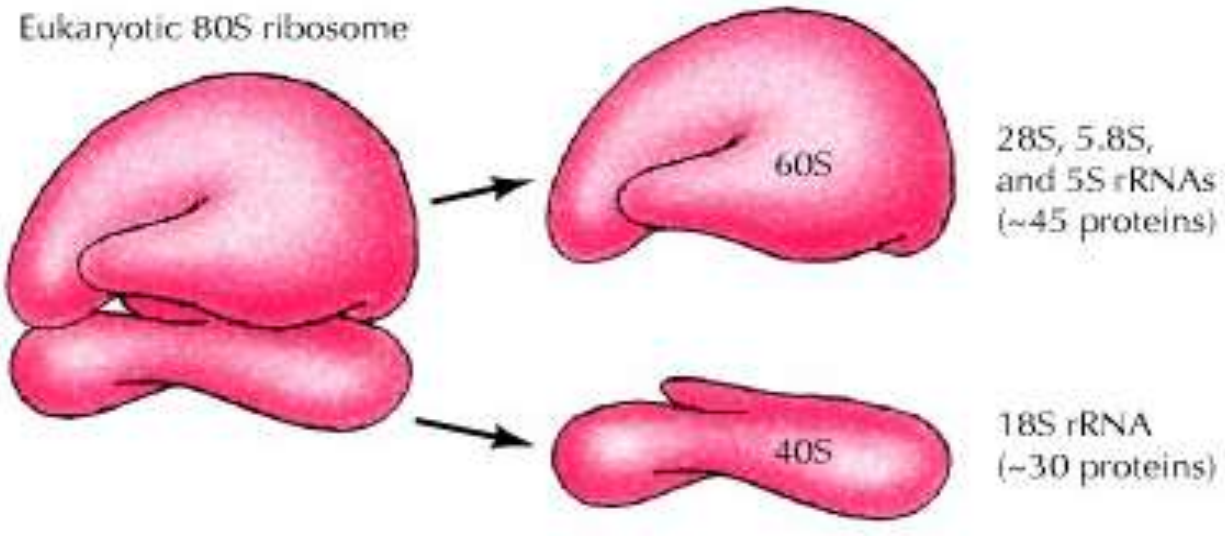
Differences between Cytoplasm and Nucleoplasm

Cytoplasm	*Nucleoplasm*
1. It is the general mass of protopasm which lies outside the nucleus.	1. It is the general mass of nucleus.
2. Cytoplasm is surrounded by a single membrane envelope called plasmalemma.	2. Nucleoplasm is covered on the outside by double membrane envelope called nuclear envelope.
3. The outer part of the cytoplasm is clear and gel-like and is called ectoplasm.	3. Sol-gel differentiation is not clear.
4. A dense fibrous lamina-like structure is absent.	4. Nucleoplasm contains a fibrous matrix. Its outer part is dense and forms fibrous lamina in contact with nuclear envelope.
5. Cytoplasm possesses a number of organelles and supporting structures.	5. The nucleoplasm contains three structures– chromatin, matrix and nucleolus.
6. It is under constant motion or cyclosis.	6. Cyclosis or streaming is absent.
7. The fluid part of cytoplasm contains a number of chemicals like minerals, nucleotides, amino acids, sugars, proteins and enzymes.	7. Nucleoplasm possesses small amount of minerals, sugar and amino acids. There are abundant nucleosides, nucleotides, proteins and enzymes.
8. It contains endomembranes.	8. Endomembranes are absent.
9. It is site of ribosome functioning.	9. It is site of ribosome formation.
10. Cytoplasm is the part of cell connected with various metabolic activities and functions.	10. Nucleoplasm is part of cell, that contains genetic material for controlling cytoplasmic structure and function.
11. It forms the bulk of cells.	11. It forms a small part of cell.

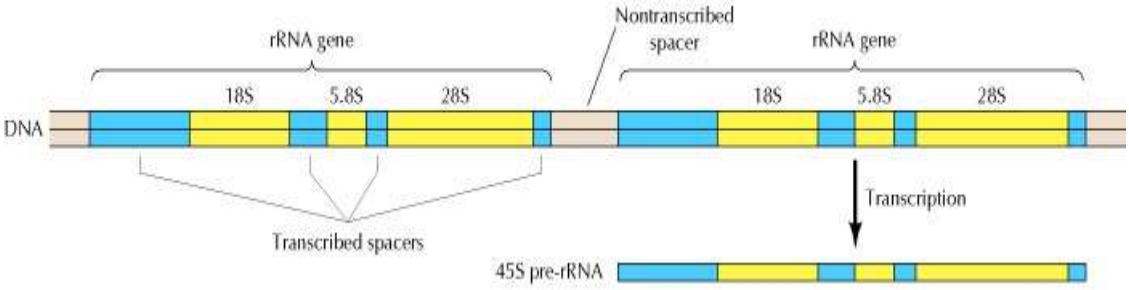
-
- **Nucleolus**
- Contained within the nucleus is a dense, membrane-less structure composed of RNA and proteins called the nucleolus.
- Some of the eukaryotic organisms have a nucleus that contains up to four nucleoli.
- The nucleolus contains nucleolar organizers, which are parts of chromosomes with the genes for ribosome synthesis on them.
- The nucleolus helps to synthesize ribosomes by transcribing and assembling ribosomal RNA subunits. These subunits join together to form a ribosome during protein synthesis.
- The nucleolus disappears when a cell undergoes division and is reformed after the completion of cell division.
- The most prominent substructure within the nucleus is the nucleolus which is the site of rRNA transcription and processing, and of ribosome assembly.

- 

  The nucleolus, which is not surrounded by a membrane, is organized around the chromosomal regions that contain the genes for the 5.8S, 18S, and 28S rRNAs.
- Eukaryotic ribosomes contain four types of RNA, designated the 5S, 5.8S, 18S, and 28S rRNAs



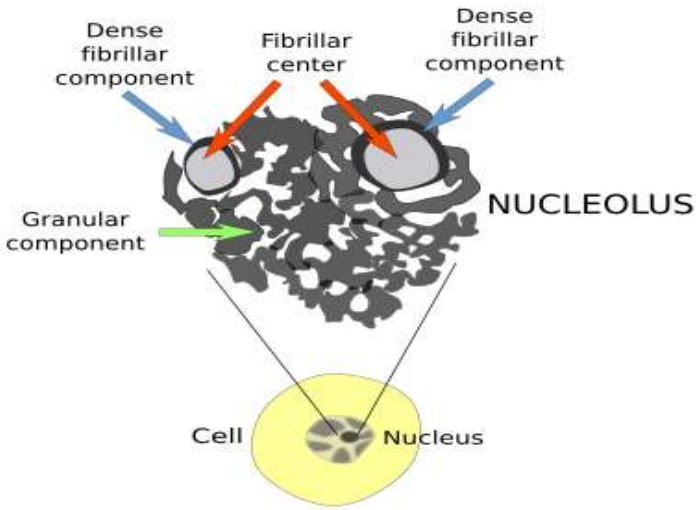
- The 5.8S, 18S, and 28S rRNAs are transcribed as a single unit within the nucleolus by RNA polymerase I, yielding a 45S ribosomal precursor RNA
- The 45S pre-rRNA is processed to the 18S rRNA of the 40S (small) ribosomal subunit and to the 5.8S and 28S rRNAs of the 60S (large) ribosomal subunit.
- Transcription of the 5S rRNA, which is also found in the **60S ribosomal subunit**, takes place outside of the nucleolus and is catalyzed by RNA polymerase III.

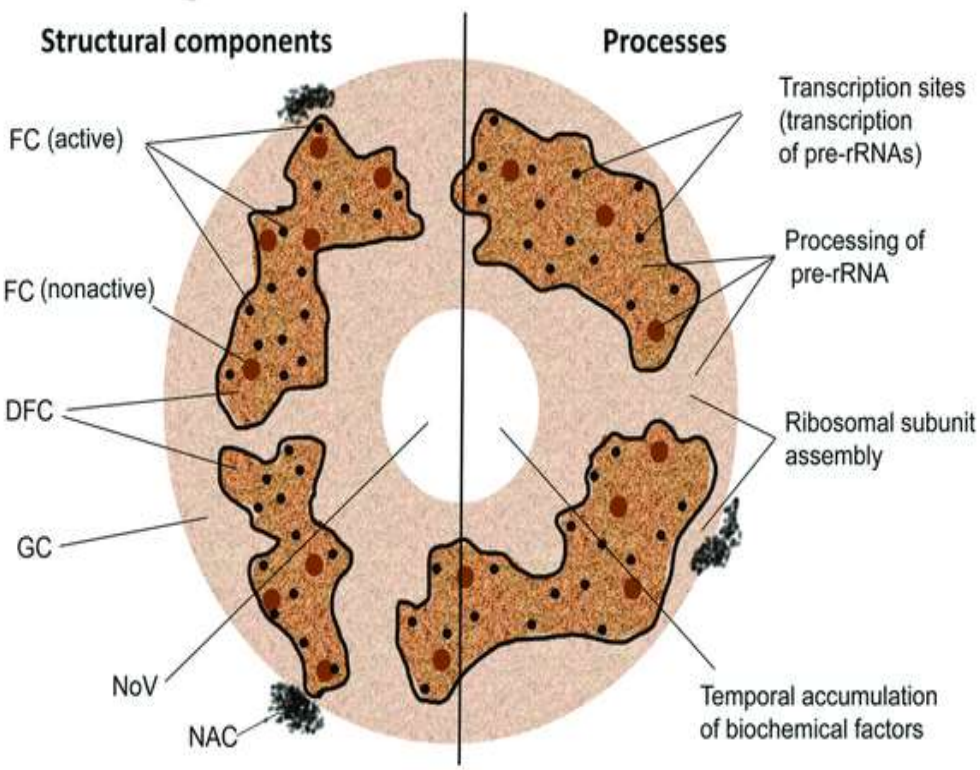


Morphologically, nucleoli consist of three distinguishable regions:

- The fibrillar center(FC)
- Dense fibrillar component(DFC)
- Granular component(GC).
- These different regions are thought to represent the sites of progressive stages of rRNA transcription, processing, and ribosome assembly.
- The rRNA genes are located in the fibrillar centers, with transcription occurring primarily at the boundary of the fibrillar centers and dense fibrillar component.

- Processing of the pre-rRNA is initiated in the dense fibrillar component and continues in the granular component, where the rRNA is assembled with ribosomal proteins to form nearly completed preribosomal subunits, ready for export to the cytoplasm.

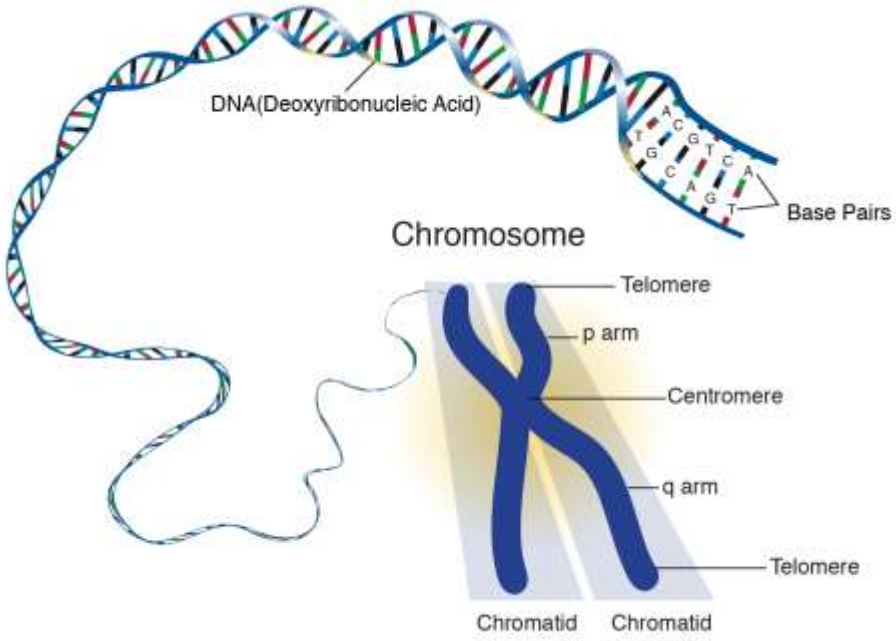


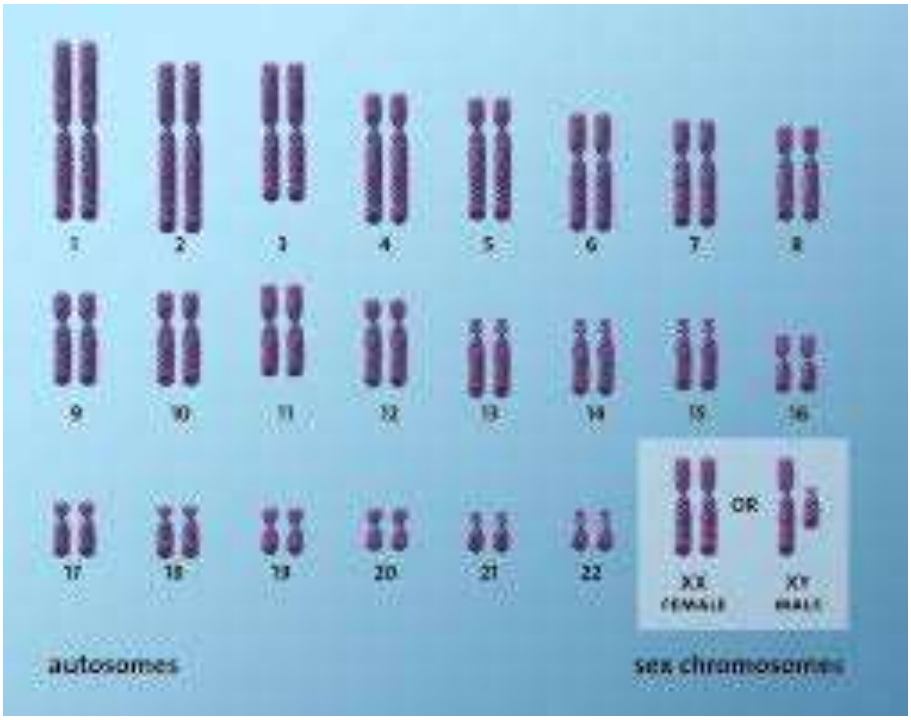
- 

- Following each cell division, nucleoli form around the chromosomal regions that contain the 5.8S, 18S, and 28S rRNA genes, which are therefore called nucleolar organizing regions.

- The formation of nucleoli requires the transcription of 45S pre-rRNA, which appears to lead to the fusion of small prenucleolar bodies that contain processing factors and other components of the nucleolus.
- In most cells, the initially separate nucleoli then fuse to form a single nucleolus.
- The size of the nucleolus depends on the metabolic activity of the cell, with large nucleoli found in cells that are actively engaged in protein synthesis.
- This variation is due primarily to differences in the size of the granular component, reflecting the levels of ribosome synthesis.
- **Functions of Nucleus**
- The nucleus provides a site for genetic transcription that is segregated from the location of translation in the cytoplasm, allowing levels of gene regulation that are not available to prokaryotes. The main function of the cell nucleus is to control gene expression and mediate the replication of DNA during the cell cycle.
- It controls the hereditary characteristics of an organism.
- The organelle is also responsible for protein synthesis, cell division, growth, and differentiation.
- Storage of hereditary material, the genes in the form of long and thin DNA (deoxyribonucleic acid) strands, referred to as chromatin.
- Storage of proteins and RNA (ribonucleic acid) in the nucleolus.
- The nucleus is a site for transcription in which messenger RNA (mRNA) are produced for protein synthesis.
- During the cell division, chromatins are arranged into chromosomes in the nucleus.
- Production of ribosomes (protein factories) in the nucleolus.
- Selective transportation of regulatory factors and energy molecules through nuclear pores.
- **Chromosomes**
- The nucleus is the organelle that **houses chromosomes**.
- Chromosomes consist of DNA, which contains heredity information and instructions for cell growth, development, and reproduction.
- Chromosomes are present in the form of strings of DNA and histones (protein molecules) called **chromatin.**

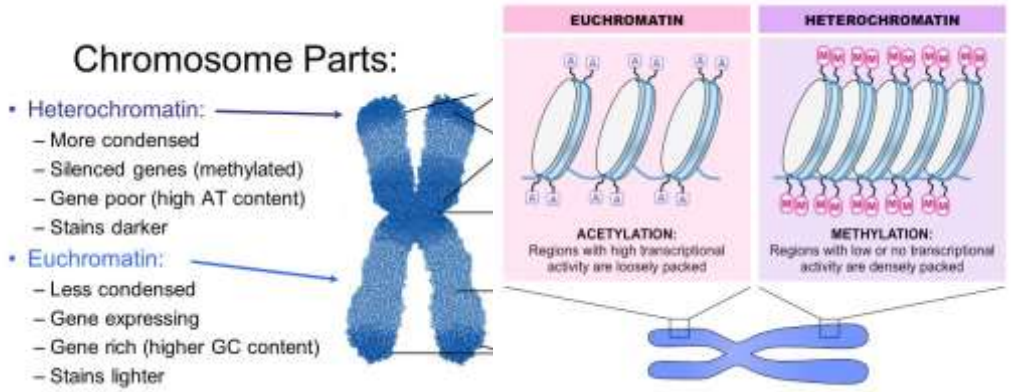
- When a cell is “resting” i.e. not dividing, the chromosomes are organized into long entangled structures called **chromatin.**

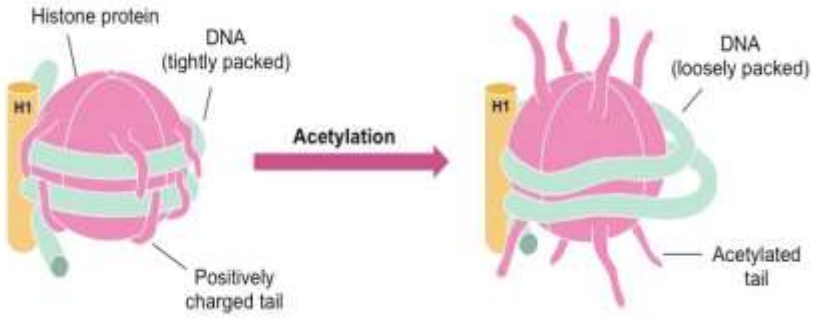


- 

- The chromatin is **further classified** into heterochromatin and euchromatin based on the functions.

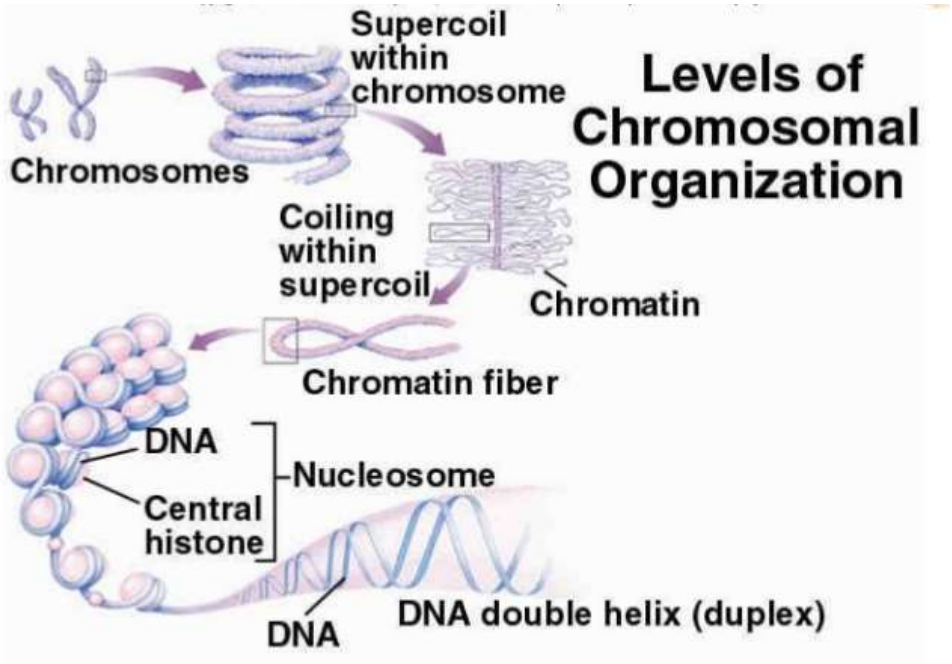
- The former type is a highly condensed, transcriptionally inactive form, mostly present adjacent to the nuclear membrane. On the other hand, euchromatin is a delicate, less condensed organization of chromatin, which is found abundantly in a transcribing cell.
-
- Eukaryotic DNA is wrapped around histone proteins to form compact nucleosomes
- These histone proteins have protruding tails that determine how tightly the DNA is packaged
- Modification of Histone Tails-Typically the histone tails have a positive charge and hence associate tightly with the negatively charged DNA
- Adding an acetyl group to the tail (acetylation) neutralises the charge, making DNA less tightly coiled and increasing transcription
- Adding a methyl group to the tail (methylation) maintains the positive charge, making DNA more coiled and reducing transcription

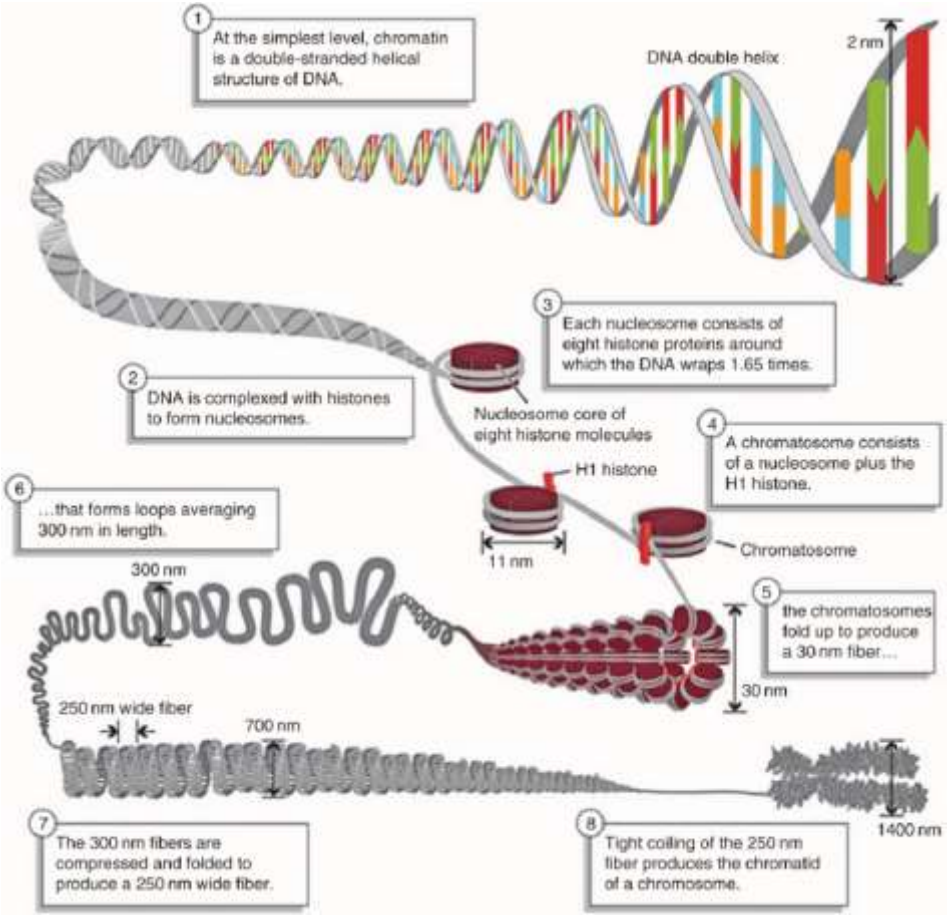




EUCHROMATIN VERSUS HETEROCHROMATIN

	EUCHROMATIN	HETEROCHROMATIN
Location:	Found in the nucleus's inner body.	Found near the edge of the nucleus.
Type:	Only one type is found in the cell's nucleus.	Two types are found in the cell's nucleus: facultative heterochromatin and constitutive he terochromatin.
Presence:	Found in both eukaryotes and prokaryotes.	Found in eukaryotes only.
Function:	Allows genetic changes to take place and the genes to be transcribed.	Allows gene expression to be regulated and maintains the genome's structural integrity.
Condensation or decondensation:	During periods of the cell cycle, condensation and decondensation of the DNA is alternated.	Except when DNA is replicated, heterochromatin stays condensed during each period of the cell cycle.
Stickiness:	Not sticky.	Sticky.
Replication of DNA:	Replicates early	Replicates late
Transcriptional activity:	Consists of regions that are transcriptionally active	Few or none of the regions are transcriptionally active
Genetic activity:	May be exposed to chromosomal crossover so it is genetically active	Prevents chromosomal crossover so it is genetically inactive
Amount of DNA contained:	Contains a low amount of DNA compared to heterochromatin.	Contains a high amount of DNA.
Intensity when stained:	Stained lightly.	Stained dark.
Packaging intensity:	Packaged loosely.	Packaged tightly.





The eukaryotic chromosomal organization. The steps showing the chromosomal organization involved in condensation

Lysosomes

- Lysosomes are found in nearly every animal-like eukaryotic cell.

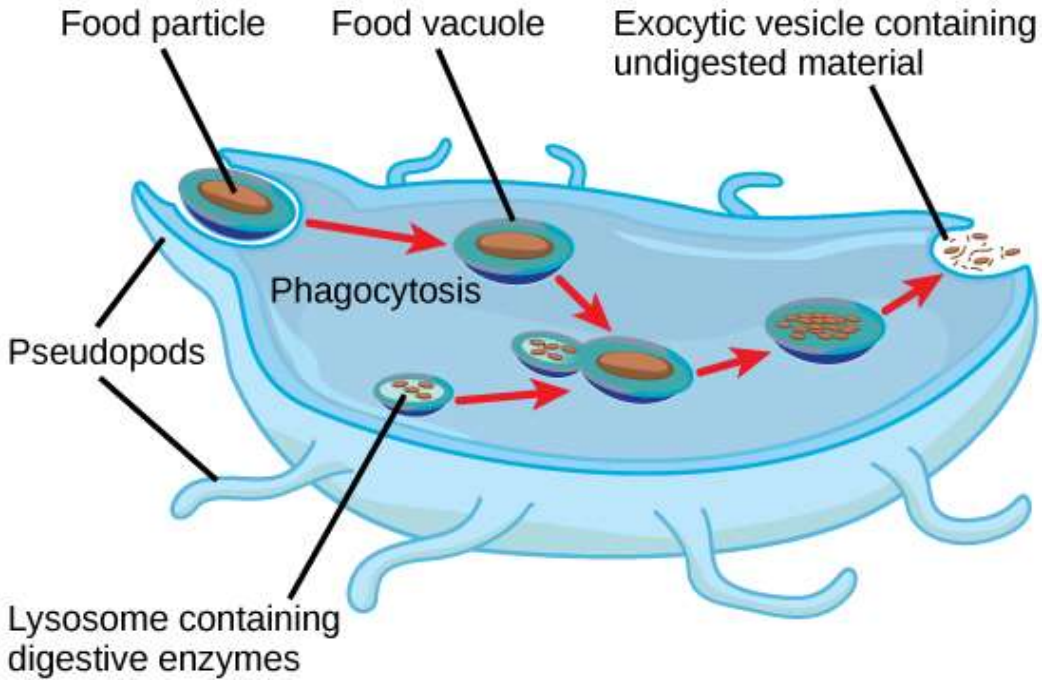
- They are so common in animal cells because, when animal cells take in or absorb food, they need the enzymes found in lysosomes in order to digest and use the food for energy.

- On the other hand, lysosomes are not commonly-found in plant cells.

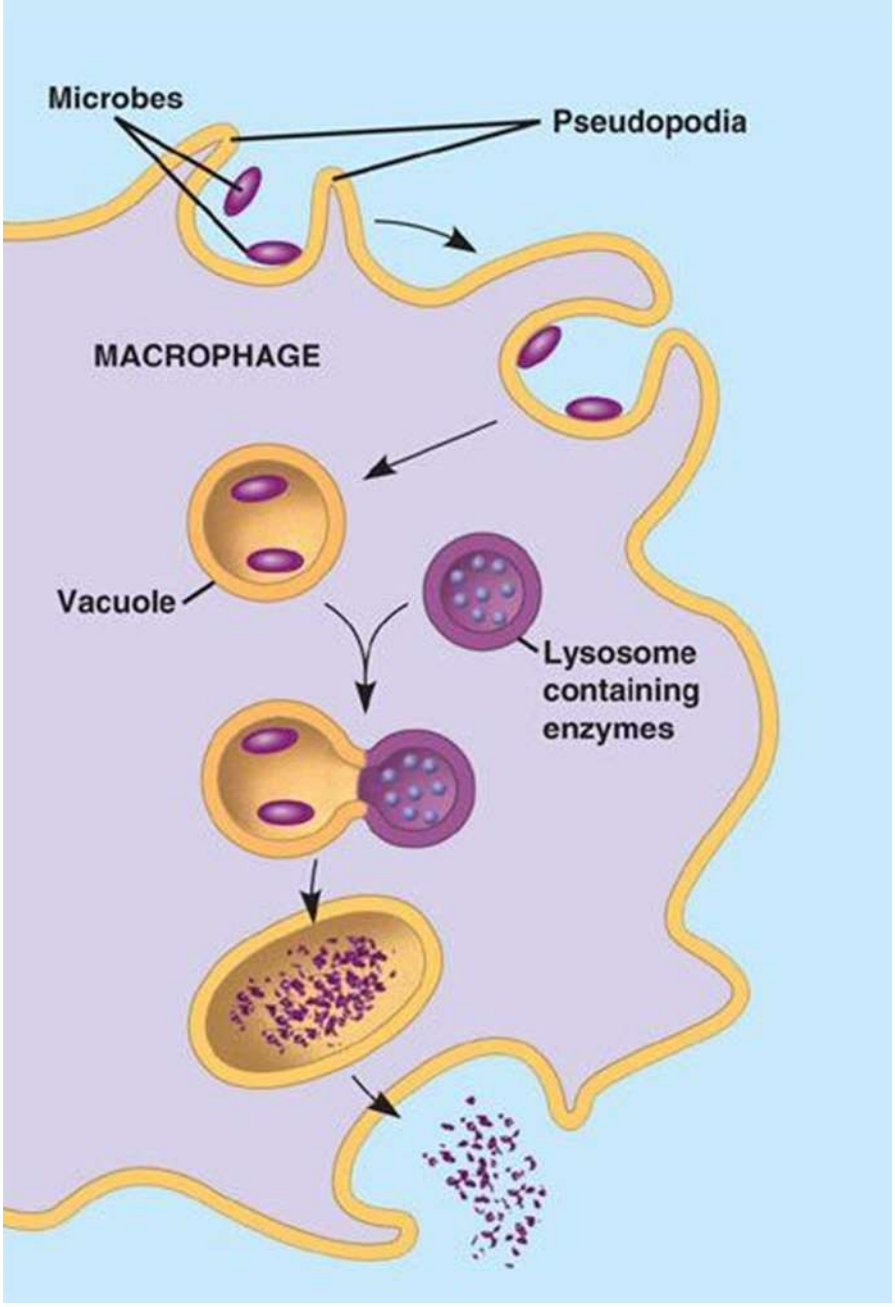
- Lysosomes are not needed in plant cells because they have cell walls that are tough enough to keep the large/foreign substances that lysosomes would usually digest out of the cell.

- **A lysosome has three main functions:**
- The Breakdown/Digestion Of Macromolecules (Carbohydrates, Lipids, Proteins, And Nucleic Acids)
- The Breakdown/Digestion Of Macromolecules (Carbohydrates, Lipids, Proteins, And Nucleic Acids)
- Cell Membrane Repairs
- Responses Against Foreign Substances Such As Bacteria, Viruses And Other Antigens.
- When food is eaten or absorbed by the cell, the lysosome releases its enzymes to break down complex molecules including sugars and proteins into usable energy needed by the cell to survive.
- If no food is provided, the lysosome's enzymes digest other organelles within the cell in order to obtain the necessary nutrients.

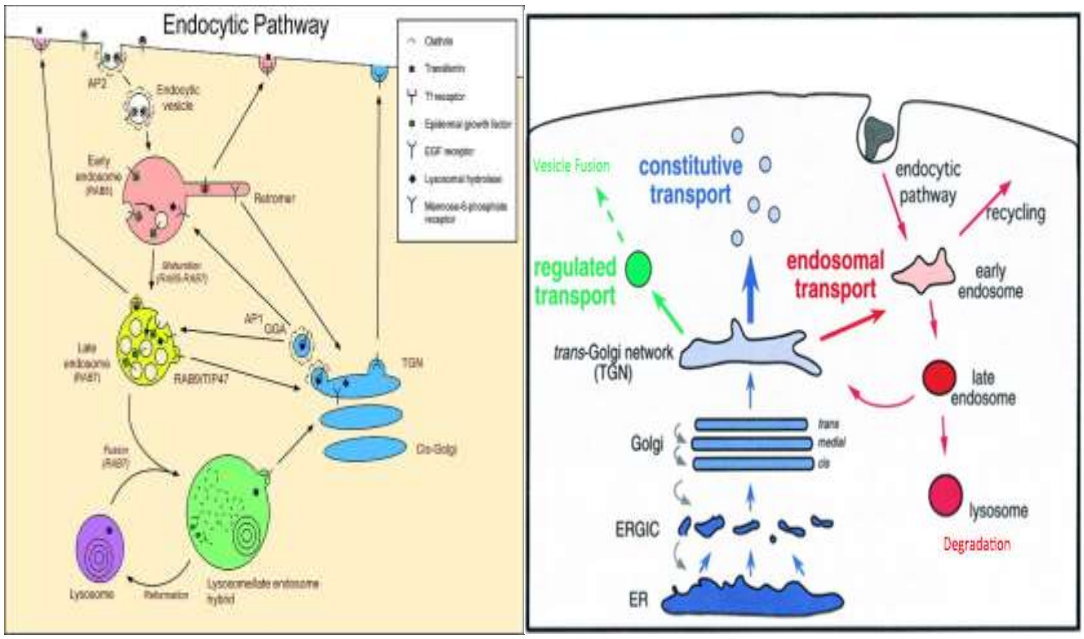
Phagocytosis



- In addition to their role as the digestive component and organelle-recycling facility of animal cells, lysosomes are considered to be parts of the endomembrane system.
- Lysosomes also use their hydrolytic enzymes to destroy pathogens (disease-causing organisms) that might enter the cell.
- A good example of this occurs in a group of white blood cells called macrophages, which are part of your body's immune system.
- In a process known as phagocytosis or endocytosis, a section of the plasma membrane of the macrophage invaginates (folds in) and engulfs a pathogen. The invaginated section, with the pathogen inside, then pinches itself off from the plasma membrane and becomes a vesicle. The vesicle fuses with a lysosome. The lysosome's hydrolytic enzymes then destroy the pathogen.



- Lysosomes are roughly spherical bodies enclosed by a single membrane.
- They are manufactured by the Golgi apparatus and contain over 50 different kinds of hydrolytic enzymes including proteases, lipases, nucleases, and polysaccharidases.
- The pH within the lysosome is about pH 5, substantially less than that of the cytosol (~pH 7.2).
- All the enzymes in the lysosome work best at an acid pH, which reduces the risk of their digesting their own cell if they should escape from the lysosome.



- Materials within the cell scheduled for digestion are first deposited within lysosomes.

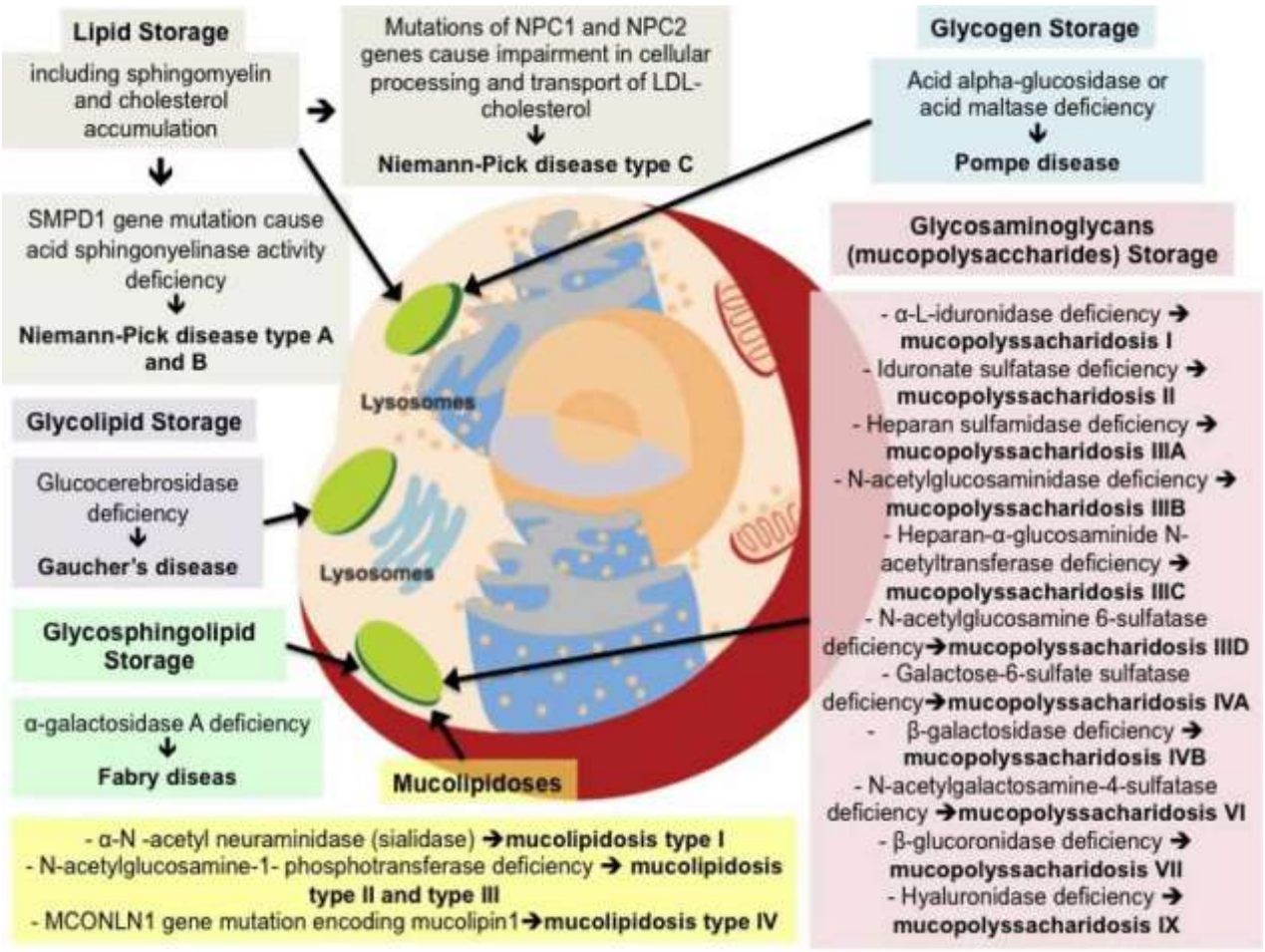
- These may be:
- Other organelles, such as mitochondria, that have ceased functioning properly and have been engulfed in autophagosomes
- Food molecules or, in some cases, food particles taken into the cell by endocytosis
- Foreign particles like bacteria that are engulfed by neutrophils
- Antigens that are taken up by"Professional" antigen-presenting cells like dendritic cells (by phagocytosis) and B cells (by binding to their antigen receptors (bcrs) followed by receptor-mediated endocytosis.

- At one time, it was thought that lysosomes were responsible for killing cells scheduled to be removed from a tissue; for example, the resorption of its tail as the tadpole metamorphoses into a frog. This is incorrect. These examples of programmed cell death (PCD) or apoptosis take place by an entirely different mechanism.

- In some cells, lysosomes have a secretory function — releasing their contents by exocytosis.
- Cytotoxic T cells (CTL) secrete perforin from lysosomes.
- Mast cells secrete some of their many mediators of inflammation from modified lysosomes.
- Melanocytes secrete melanin from modified lysosomes.
- The exocytosis of lysosomes provides the additional membrane needed to quickly seal wounds in the plasma membrane.

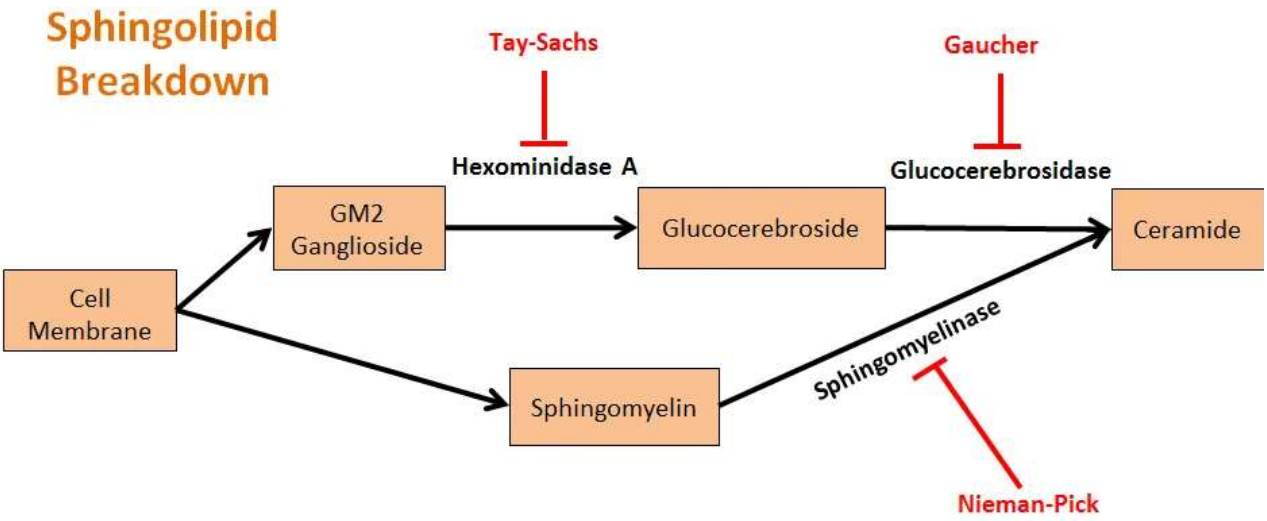
Lysosomes- as a therapeutic target

- Lysosomes are membrane-bound organelles with roles in processes involved in degrading and recycling cellular waste, cellular signalling and energy metabolism.
- Defects in genes encoding lysosomal proteins cause lysosomal storage disorders, in which enzyme replacement therapy has proved successful.
- Growing evidence also implicates roles for lysosomal dysfunction in more common diseases including inflammatory and autoimmune disorders, neurodegenerative diseases, cancer and metabolic disorders.
- With a focus on lysosomal dysfunction in autoimmune disorders and neurodegenerative diseases — including lupus, rheumatoid arthritis, multiple sclerosis, Alzheimer disease and Parkinson disease
- **Lysosomal Storage Diseases**
- Lysosomal storage diseases are caused by the **accumulation of macromolecules (proteins, polysaccharides, lipids) in the lysosomes** because of a genetic failure to manufacture an enzyme needed for their breakdown.
- Neurons of the central nervous system are particularly susceptible to damage.
- Most of these diseases are caused by the inheritance of two defective alleles of the gene encoding one of the hydrolytic enzymes.



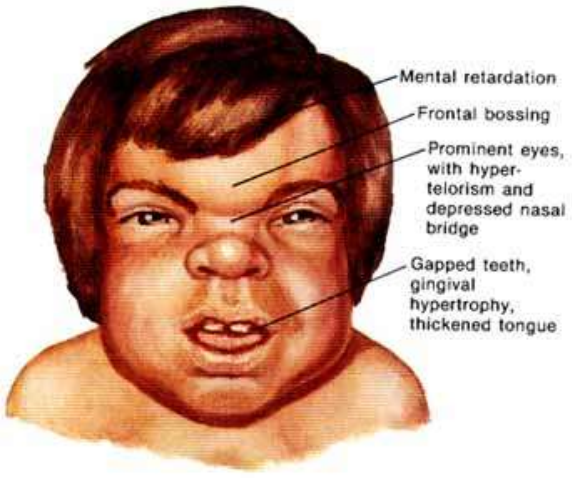
Examples include:

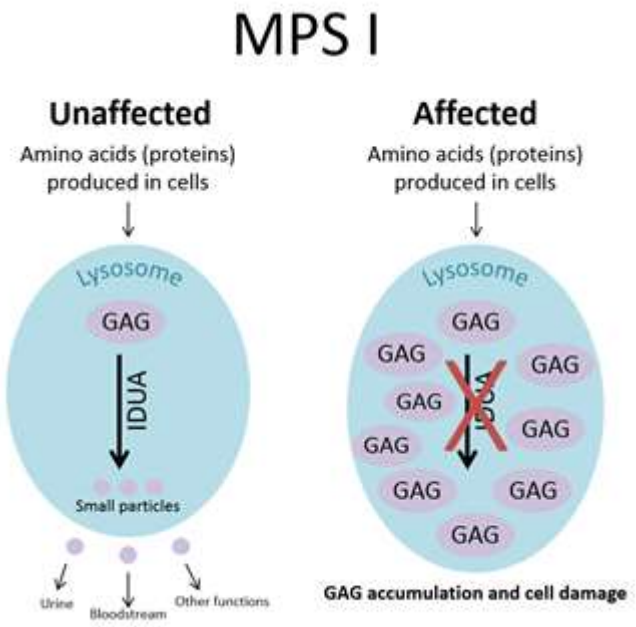
- **Tay-Sachs disease and Gaucher's disease** — both caused by a failure to produce an enzyme needed to break down sphingolipids (fatty acid derivatives found in all cell membranes).



	Deficiency of	Build Up of
Tay-Sachs	Hexominidase A	GM2 Ganglioside
Nieman-Pick	Sphingomyelinase	Sphingomyelin
Gaucher	Glucocerebrosidase	Glucocerebroside

- **Mucopolysaccharidosis I (MPS-I)**-Caused by a failure to synthesize an enzyme (α-L-iduronidase) needed to break down proteoglycans like heparan sulfate.
- In April 2003, the U.S. Food and Drug Administration approved a synthetic version of the enzyme, laronidase (Aldurazyme®), as a possible treatment. This enzyme (containing 628 amino acids) is manufactured by recombinant DNA technology.

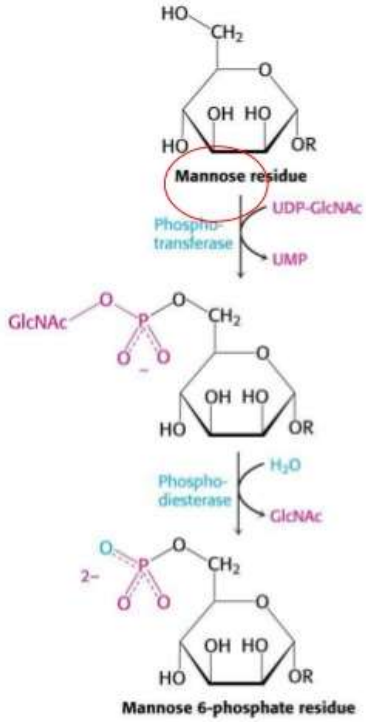




- These are polysaccharides which are formed of more than one type of monosaccharide unit. They include glycosaminoglycans (GAGs) formly called mucopolysaccharides.
- **Glycosaminoglycans (GAGs)**
- Glycosaminoglycans are:
- - Unbranched
- -Long chains (usually >50 sugar units) heteropolysaccharides
- Composed of **repeating disaccharide units,** *usually* made up of **an amino sugar** and a **uronic acid.**
- Glycosaminoglycans are **classified into**:
- **I- Sulfate free glycosaminoglycans:** e.g. hyaluronic Acid
- **II- Sulfate containing glycosaminoglycans:** e.g. chondroitin sulphate, keratan sulphate, dermatan sulphate, heparin and heparan sulphate

Type of GAGs	Constituents	Localization
Hyaluronic acid (HA)	glucuronic acid +N-acetyl-glucosamine	Synovial fluid, skin, ground substance of connective tissue, umbilical cord, vitreous body of the eye, embryonic tissues.
Chondroitin sulfate (CS)	glucuronic acid +N-acetyl-galactosamine sulfate	- Most abundant GAG - Prominent component of cartilage, tendons, ligaments, bone, aorta.
Dermatan sulfate (DS)	L-iduronic acid +N-acetyl-galactosamine sulfate	Skin, blood vessels, heart valves.
Keratan sulfate (KS)	galactose +N-acetyl-glucosamine sulfate (No uronic acid)	Cornea, cartilage, bone
Heparin	L-iduronic (D-glucuronic) acid--sulfate + glucosamine bisulfate	Abundant in granules of mast cells that line blood vessels of liver, lung, skin.
Heparan sulfate	More glucuronic acid and its glucosamine residue contains less sulfate than heparin.	Basement membrane, component of cell surface

- However, one lysosomal storage disease, I-cell disease ("inclusion-cell disease"), is caused by a failure to "tag" (by phosphorylation) all the hydrolytic enzymes that are supposed to be transported from the Golgi apparatus to the lysosomes.
- Lacking the **mannose 6-phosphate (M6P)** tag, they are secreted from the cell instead. The result: all the macromolecules incorporated in lysosomes remain undegraded forming "inclusion bodies" in the cell.



Formation of a mannose 6-phosphate

1. Mannose 6-phosphate is a marker directing certain proteins from the Golgi to lysosomes.

2. Deficient in the phosphotransferase

↓

Can't form mannose 6-phosphate

↓

Mistargeting of essential enzymes

(lysosome → blood and urine)

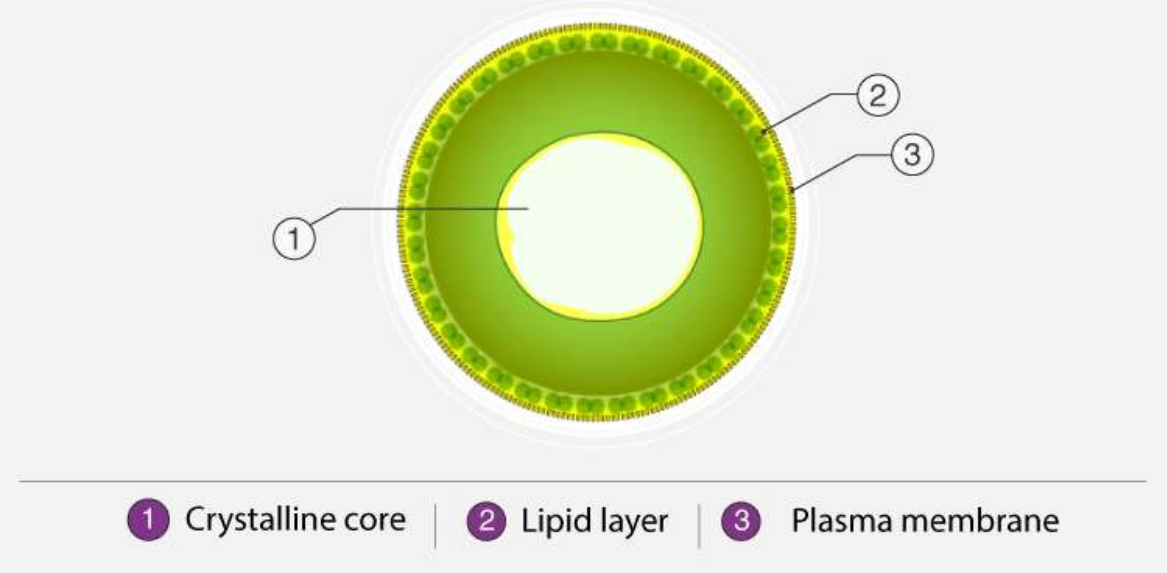
↓

I-cell disease

(psychomotor retardation + skeletal deformities)

- A cell is composed of microbodies (or cytosomes) is a type of organelle that is found in the cells of plants, protozoa, and animals.

- Organelles in the microbody family include **peroxisomes, glyoxysomes, glycosomes and hydrogenosomes**.



	Glyoxysomes	Leaf peroxisomes	Root peroxisomes
Location	oilseed cotyledons, senescent organs	photosynthetic cotyledons, leaves	root nodules
Specialized function	fatty acid metabolism	photorespiration	nitrogen transport
Specialized enzyme system	glyoxylate cycle	glycolate metabolism	ureide metabolism
Representative enzymes	isocitrate lyase, malate synthase	glycolate oxidase, hydroxypyruvate reductase	uricase, allantoinase
Common enzyme systems	peroxide metabolism	peroxide metabolism	peroxide metabolism
Representative enzymes	catalase, oxidases	catalase, oxidases	catalase, oxidases
	fatty acid β-oxidation	fatty acid β-oxidation	fatty acid β-oxidation?
	thiolase, multifunctional enzyme	thiolase, multifunctional enzyme	thiolase, multifunctional enzyme

Three types

Peroxisomes	Sphaerosomes	Glyoxysomes
1. Discovered by De Duve	1. Discovered by Perner	1. Special peroxisomes
2. Found in both plant and animal cell.	2. Found in all the plant cells which involves in the synthesis and storage of lipids.	2. Present in germinating seeds.
3. Contain enzyme for peroxide biosynthesis.	3. These are spherical or oval in shape.	3. Contain enzymes for β-oxidation of fatty acids and Glyoxylate pathway.
4. In plant, they do photorespiration with the help of chloroplast and mitochondria.	4. Function is to help in lipid synthesis and translocation of fats	
5. In animal, cells responsible for detoxification of poisonous substances.		

Peroxisomes

- Peroxisomes, also called microbodies, are about the size of lysosomes (0.5–1.5 µm) and like them are enclosed by a single membrane.
- They also resemble lysosomes in being filled with enzymes.
- However, peroxisomes bud off from the endoplasmic reticulum, not the Golgi apparatus (the source of lysosomes) and the enzymes and other proteins destined for peroxisomes are synthesized in the cytosol.
- Each contains a **p**eroxisomal **t**argeting **s**ignal (**PTS**) that binds to a receptor molecule that takes the protein into the peroxisome and then returns for another load.
- Two peroxisomal targeting signals have been identified:

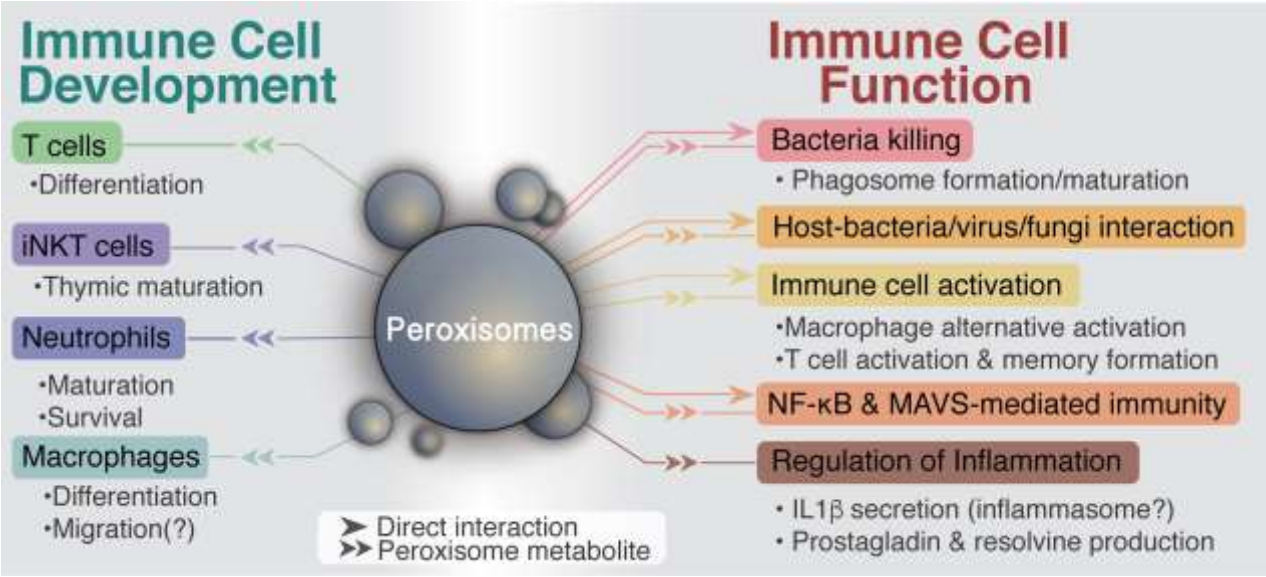
1. **9-amino acid sequence at the N-terminal of the protein**
2. **Tripeptide at the C-terminal.**

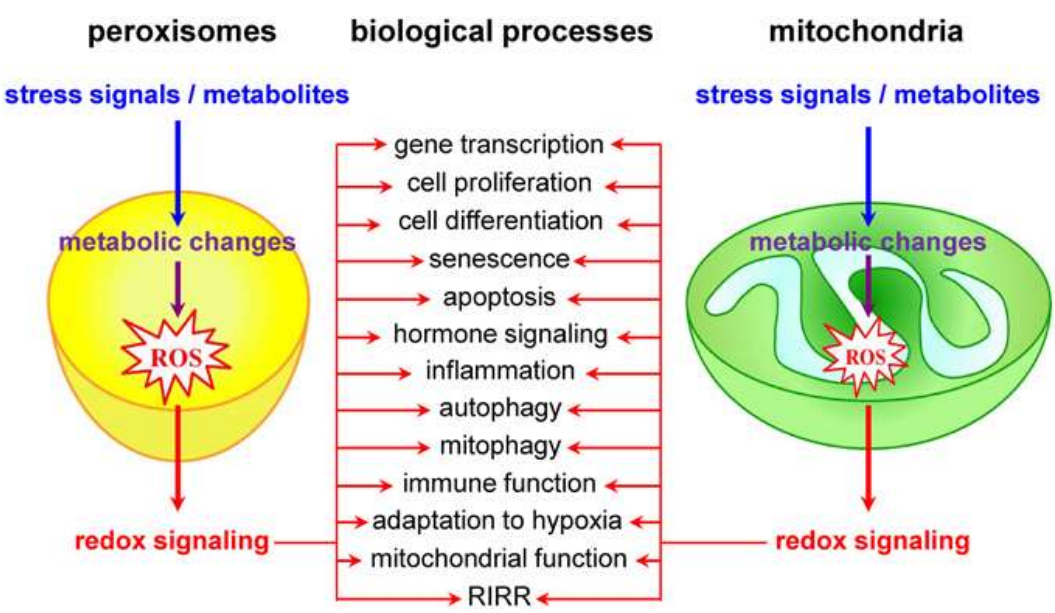
Each has its own receptor to take it to the peroxisome.

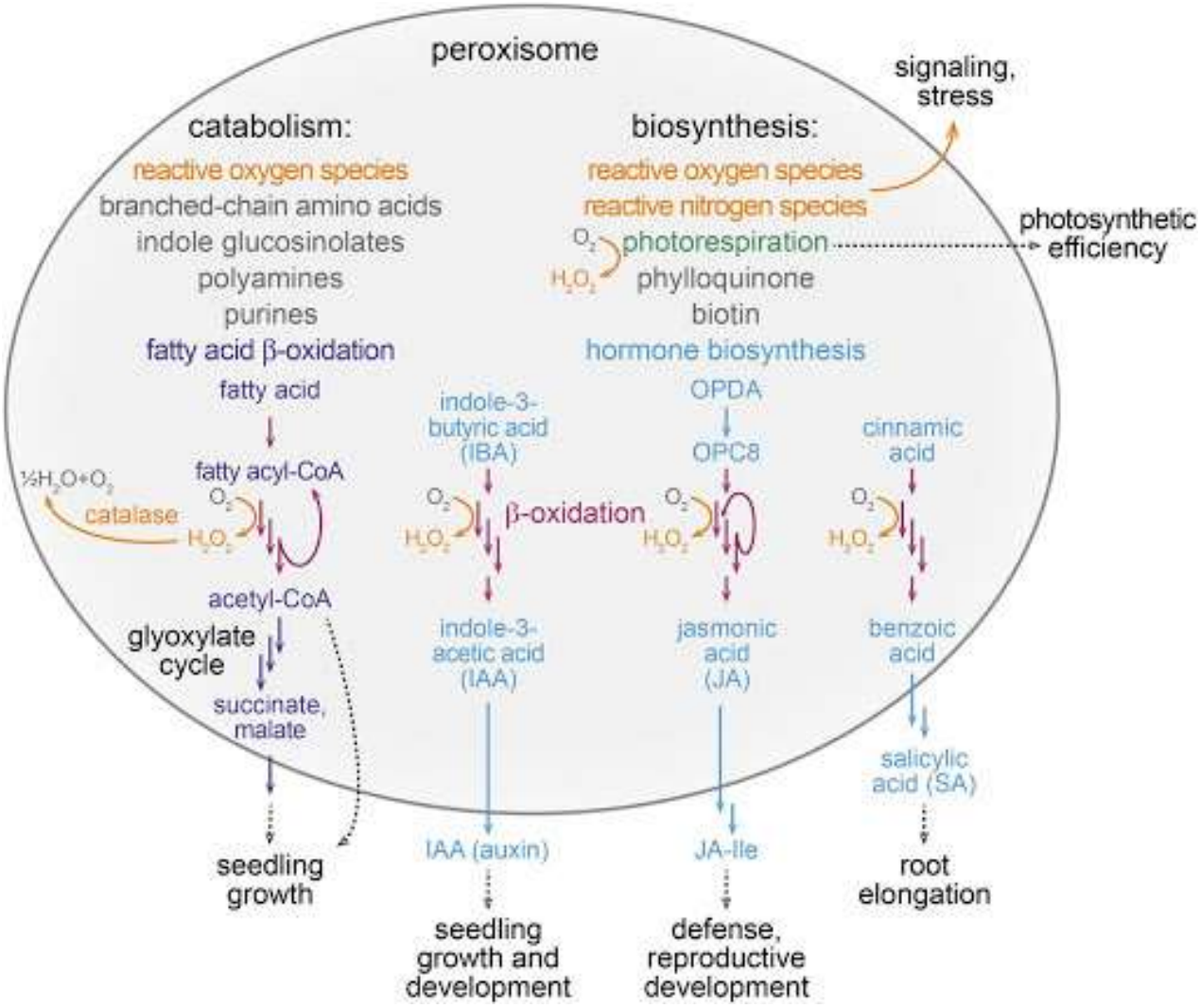
Functions of the **peroxisomes in the human liver include**:

1. Breakdown (by oxidation) of excess fatty acids.
2. Breakdown of hydrogen peroxide (H_2O_2), a potentially dangerous product of fatty-acid oxidation. It is catalyzed by the enzyme catalase.
3. Participates in the synthesis of cholesterol. One of the enzymes involved, HMG-CoA reductase, is the target of the popular cholesterol-lowering "statins".

4. Participates in the synthesis of bile acids.
5. Participates in the **synthesis of the lipids used to make myelin.**
6. Breakdown of **excess purines (AMP, GMP) to uric acid.**
7. Peroxisomes are also present in plant cells where they participate is such functions as symbiotic nitrogen fixation and photorespiration.



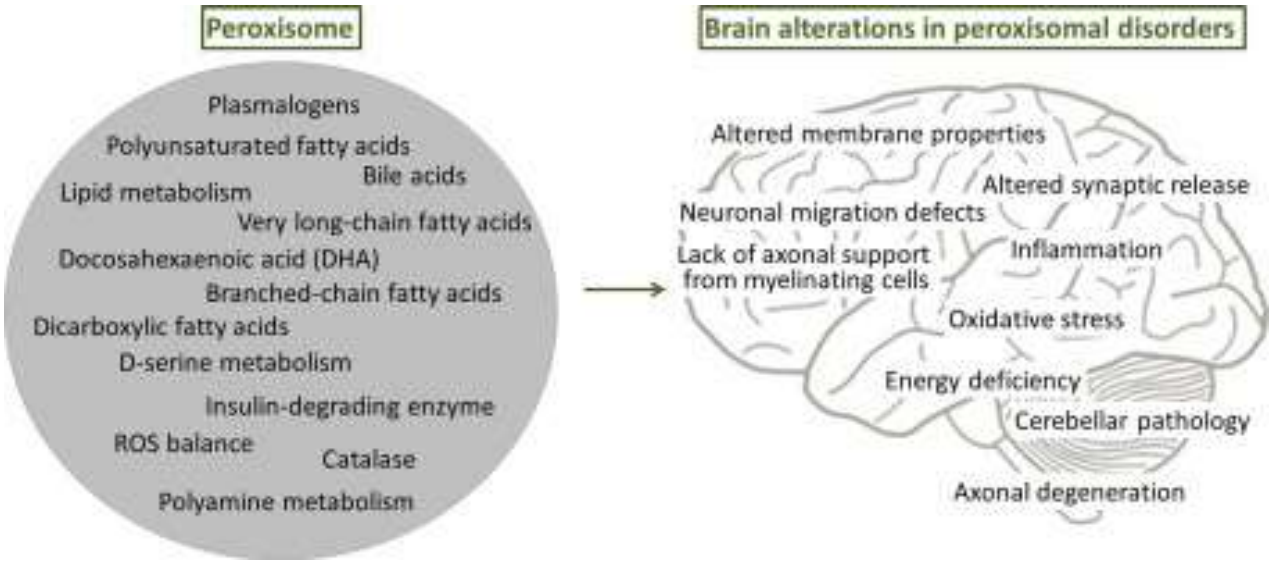




Peroxisome Disorders

- A variety of rare inherited disorders of peroxisome function occur in humans.
- Most involve mutant versions of one or another of the enzymes found within peroxisomes.
- For example: **X-linked adrenoleukodystrophy** (**X-ALD**) results from a **failure to metabolize fatty acids properly**.
- One result is deterioration of the myelin sheaths of neurons.
- The disorder occurs in young boys because the gene is X-linked. An attempt to find an effective treatment was the subject of the 1992 film **Lorenzo's Oil**.
- A few diseases result from **failure to produce functional peroxisomes.**

- For example: **Zellweger syndrome** results from the inheritance of two mutant genes for one of the receptors (PXR1) needed to import proteins into the peroxisome.



Lysosomes

- Membrane bound sacs performing a **digestive** function
- Contains enzymes to digest food, wastes, invading bacteria and breaks down old organelles
- Present in animal cells only
- Golgi apparatus produces lysosomes
- Tay – Sachs disease

Peroxisomes

- Membrane bound sacs performing a digestive function
- Enzymes in peroxisomes are *oxidases* that catalyze redox reactions
- Liver contains many peroxisomes to break down alcohol
- Form by budding off from ER
- Present in animal cells only

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DEPARTMENT OF BIOINFORMATICS

UNIT – III – CELL BIOLOGY AND BIOCHEMISTRY – SBIA1102

Unit -3

Cell Division and Transport
•Cell division - Mitosis & Meiosis,
•Cell cycle ,
•Cell cycle Check points.
•Transport across cell membranes: Passive and active transports, Permeases.
•Basics of cell signalling- autocrine, paracrine and endocrine signalling.

The cell cycle

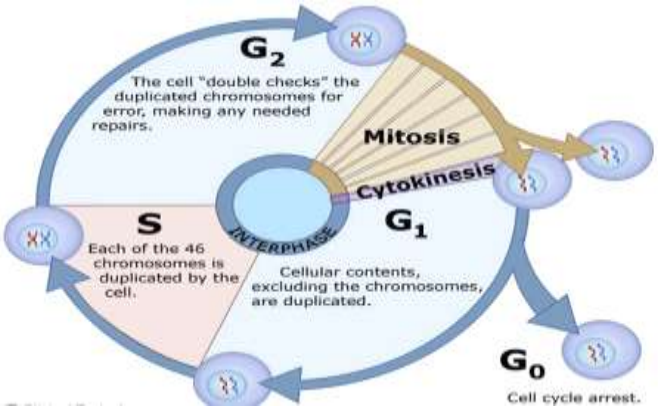
Actively dividing eukaryote cells pass through a series of stagesmknown collectively as the cell cycle: two gap phases (G1 and G2); an S (for synthesis) phase, in which the genetic material is duplicated;and an M phase, in which mitosis partitions the genetic material and the cell divides.

G1 phase.
Metabolic changes prepare the cell for division. At a certain point - the restriction point - the cell is committed to division and moves into the S phase.

S phase. DNA synthesis replicates the genetic material. Each chromosome now consists of two sister chromatids.

G2 phase. Metabolic changes assemble the cytoplasmic materials necessary for mitosis and cytokinesis.

M phase. A nuclear division (mitosis) followed by a cell division (cytokinesis). The period between mitotic divisions - that is, G1, S and G2 - is known as interphase.



Mitosis

•Mitosis is a form of eukaryotic cell division that produces two daughter cells with the same genetic component as the parent cell.

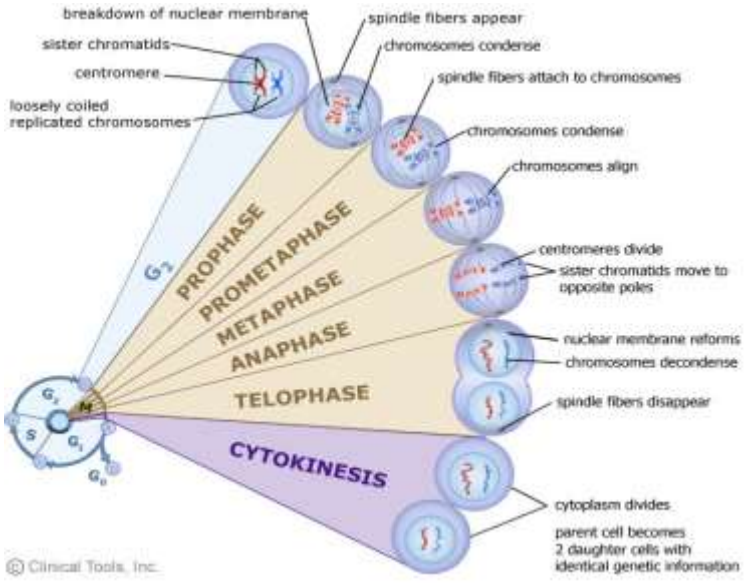
•Chromosomes replicated during the S phase are divided in such a way as to ensure that each daughter cell receives a copy of every chromosome.

•In actively dividing animal cells, the whole process takes about one hour

The replicated chromosomes are attached to a 'mitotic apparatus' that aligns them and then separates the sister chromatids to produce an even partitioning of the genetic material.

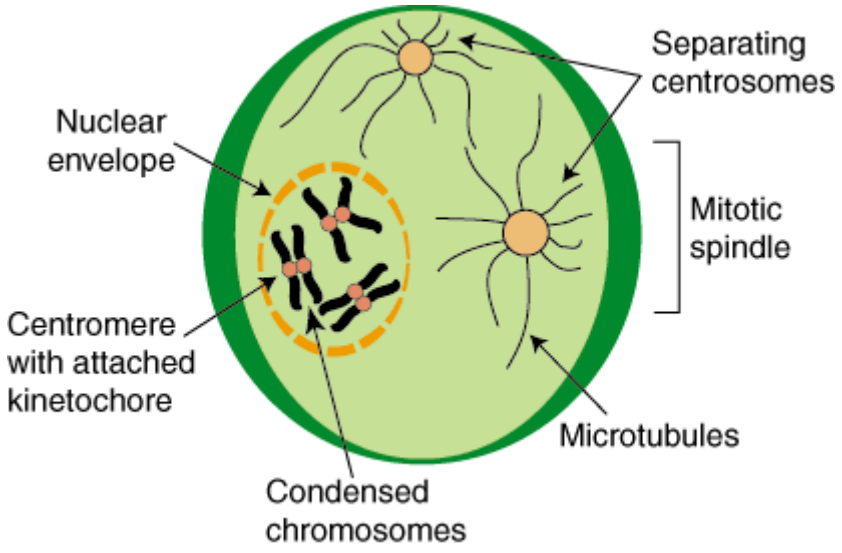
• This separation of the genetic material in a mitotic nuclear division (or karyokinesis) is followed by a separation of the cell cytoplasm in a cellular division (or cytokinesis) to produce two daughter cells.
• In some single-celled organisms mitosis forms the basis of asexual reproduction.
• In diploid multicellular organisms sexual reproduction

Mitosis, continuous although a process, is conventionally divided into five stages:
1. Prophase,
2. Prometaphase, 3. Metaphase,
4. Anaphase 5. Telophase.



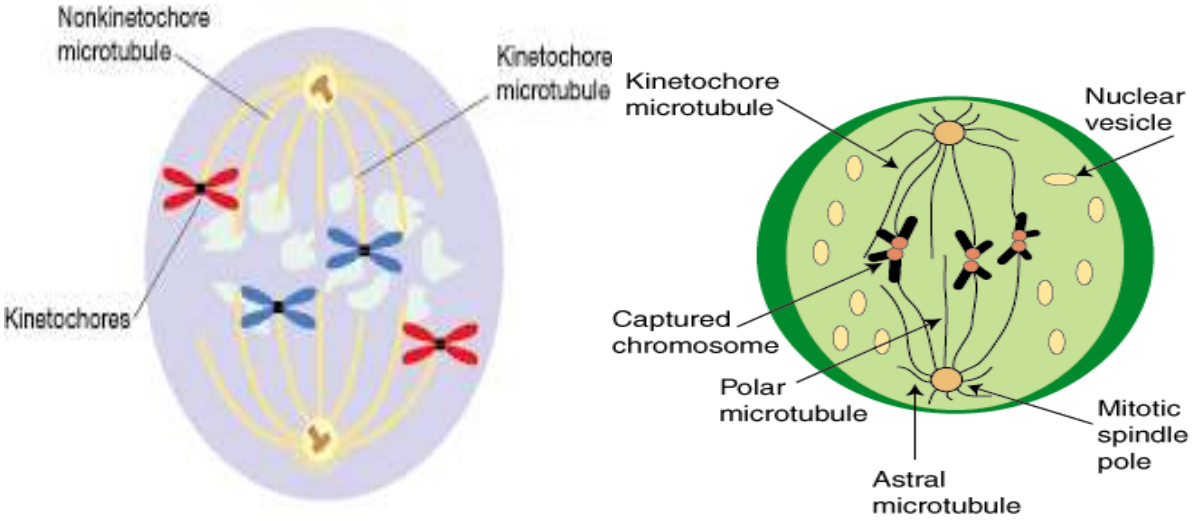
Prophase

• Prophase occupies over half of mitosis.
• The nuclear membrane breaks down to form a number of small vesicles and the nucleolus disintegrates.
• A structure known as the centrosome duplicates itself to form two daughter centrosomes that migrate to opposite ends of the cell.
• The centrosomes organise the production of microtubules that form the spindle fibres that constitute the mitotic spindle.
• The chromosomes condense into compact structures.
• Each replicated chromosome can now be seen to consist of two identical chromatids (or sister chromatids) held together by a structure known as the centromere.



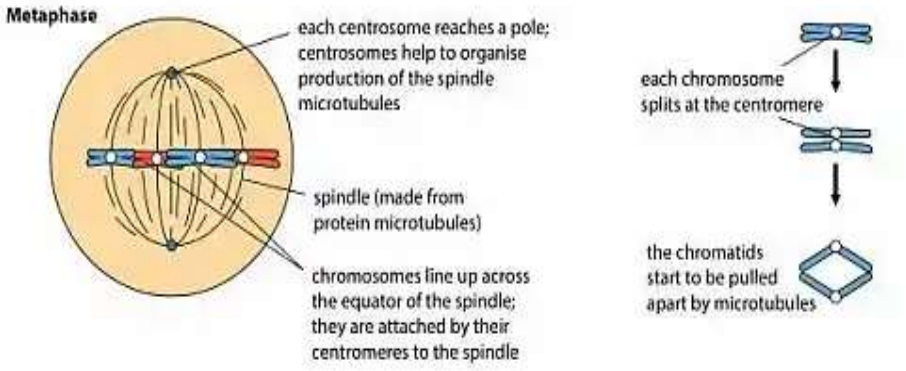
Prometaphase

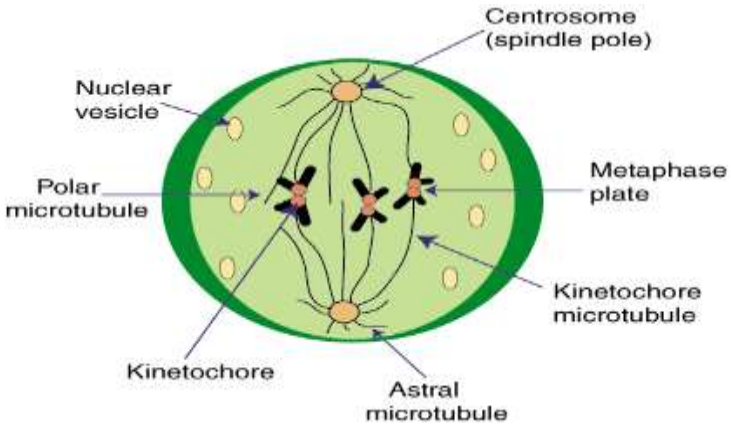
- The chromosomes, led by their centromeres, migrate to the equatorial plane in the mid-line of the cell - at right-angles to the axis formed by the centrosomes.
- This region of the mitotic spindle is known as the **metaphase plate**.
- The spindle fibres bind to a structure associated with the centromere of each chromosome called a **kinetochore.**
- Individual spindle fibres bind to a **kinetochore** structure on each side of the centromere. The chromosomes continue to condense.



Metaphase

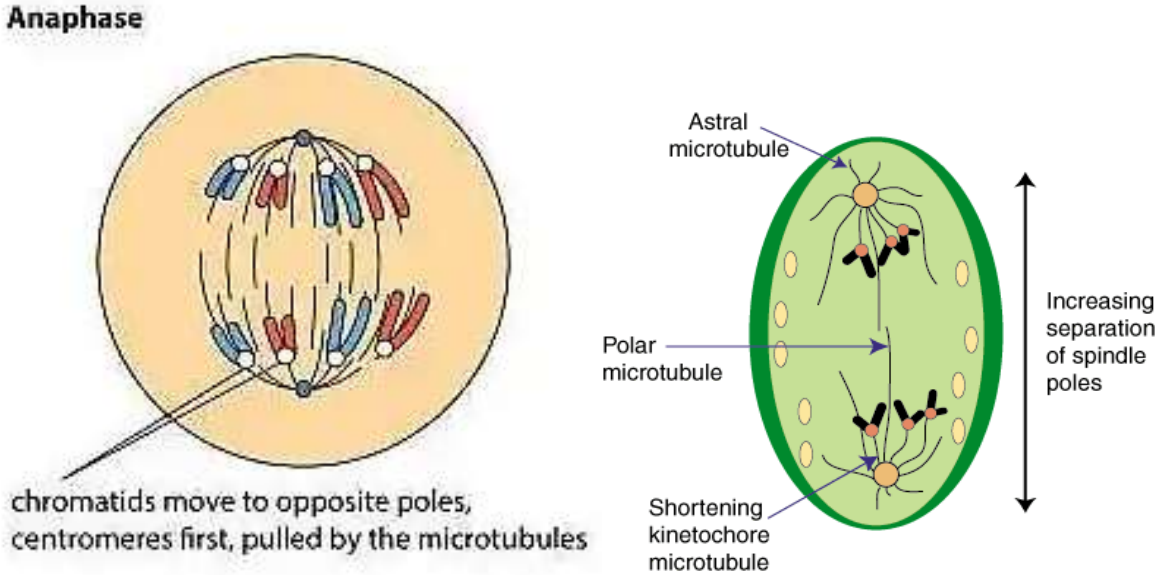
The chromosomes align themselves along the metaphase plate of the spindle apparatus.





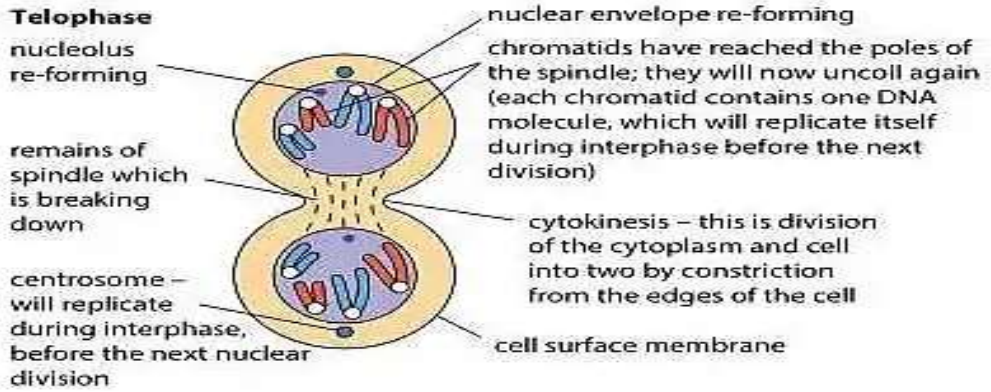
Anaphase

- The shortest stage of mitosis.
- The centromeres divide, and the sister chromatids of each **chromosome are pulled apart - or 'disjoin' -** and move to the opposite ends of the cell, pulled by spindle fibres attached to **the kinetochore regions**.
- The separated sister chromatids are now referred to **as daughter chromosomes**.
- **(It is the alignment and separation in metaphase and anaphase that is important in ensuring that each daughter cell receives a copy of every chromosome.)**



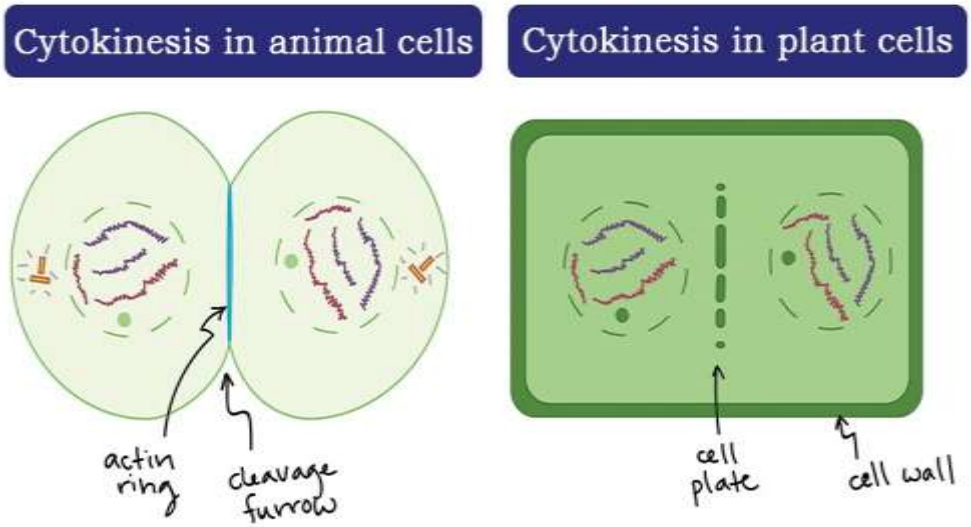
Telophase

- The final stage of mitosis.
- The nuclear membrane reforms around the chromosomes grouped at either pole of the cell, the chromosomes uncoil and become diffuse, and the spindle fibres disappear.



Cytokinesis

- Cytokinesis is a physical process of cell division, that normally takes place after mitosis.
- Cytokinesis is the physical division of the cell cytoplasm, the cell membrane, and cell organelles in eukaryotic cells to produce two distinct cells at the end of the cell cycle in both mitosis and meiosis.



- In most cells, cytokinesis is initiated during the anaphase stage and ends in telophase, a phase where the chromosomes are completely segregated.
- cytokinesis only takes place ones the separation of chromosomes is complete. This ensures that each daughter cell receives a full set of chromosomes along with the complete elements of the cytoplasm and cell organelles.

Cytokinesis takes place in four stages:

Initiation and formation of the cleavage furrow

- During cytokinesis, the initial physical change observed is the appearance of the cleavage furrow on the cell surface.
- The furrow starts to deepen, spreading around the cell until it completely divides into two.

Contraction and constriction

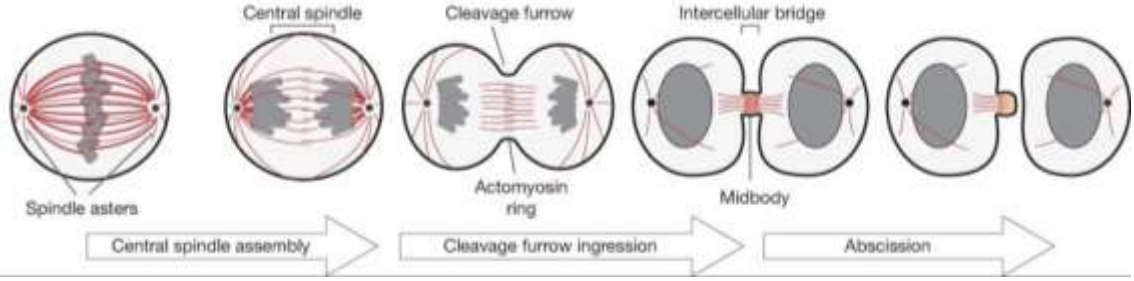
- This is also known as abscission.
- The accomplishment of cytokinesis in animal cells in by the contractile ring, which is a ring that is made up of actin and myosin and regulatory proteins formed under the surface of an animal cell during cell division.

- These rings can contract and constrict the cell pinching it into two.

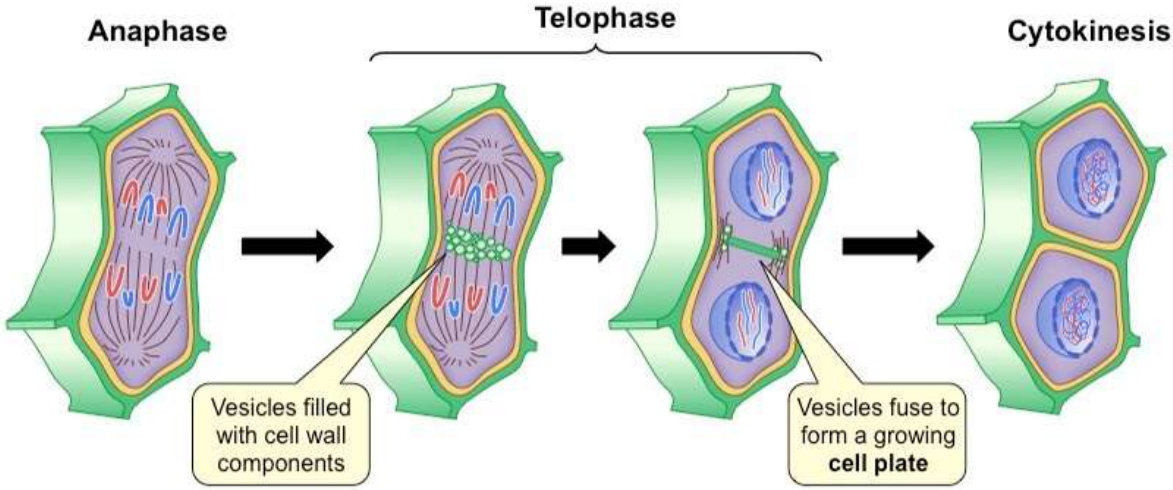
Membrane Insertion

- Concurrently, a new membrane is formed and inserted into the cell membrane, next to the contractile ring through the fusion of the intracellular vesicles.

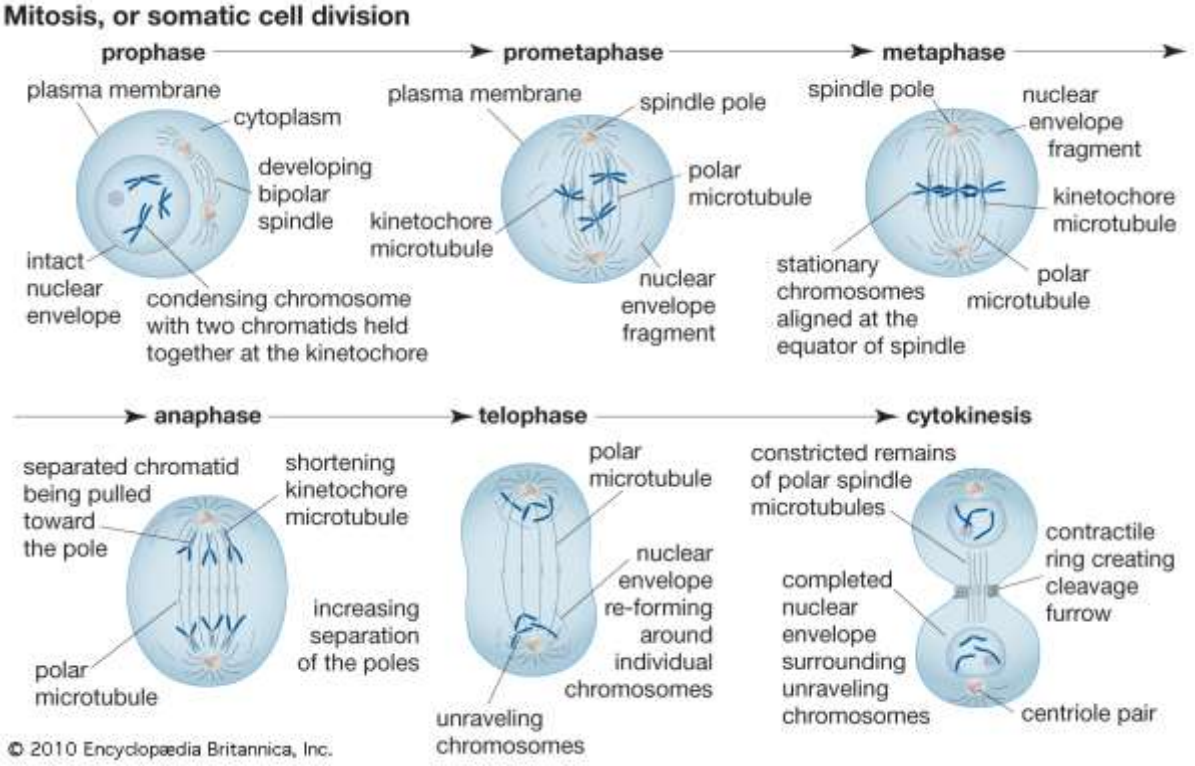
The new membrane enables the cell to increase as the cytoplasmic division takes place.

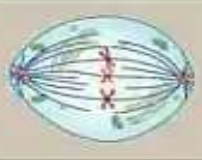
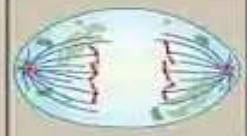
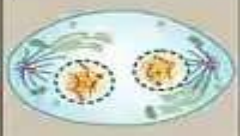


- In animal cells, cytokinesis is achieved when a contractile ring of the cell microtubules form a cleavage furrow that divides the cell membrane into half.
- The microtubules used during cytokinesis are those generated during the initial stages of division and they contribute to the restructuring of the new cell.



In the plant cell, a cell plate is formed that divides the cell into two.



Prophase	Prometaphase	Metaphase	Anaphase	Telophase
				
• Chromosomes condense and become visible • Spindle fibers emerge from the centrosomes • Nuclear envelope breaks down • Centrosomes move toward opposite poles	• Chromosomes continue to condense • Kinetochores appear at the centromeres • Mitotic spindle microtubules attach to kinetochores	• Chromosomes are lined up at the metaphase plate • Each sister chromatid is attached to a spindle fiber originating from opposite poles	• Centromeres split in two • Sister chromatids (now called chromosomes) are pulled toward opposite poles • Certain spindle fibers begin to elongate the cell	• Chromosomes arrive at opposite poles and begin to decondense • Nuclear envelope material surrounds each set of chromosomes • The mitotic spindle breaks down • Spindle fibers continue to push poles apart

Definition of terms used in the explanation of Mitosis

Daughter cells: Daughter cells in mitosis refer to the cells that are formed from the parent cell. A parent cell is a single cell that will divide itself into two to form the daughter cells.

Please note that after mitosis, you have two cells from a single cell. It is not as if the parent cell is different from the two daughter cells formed; it is as if you cut a single orange to form two equal halves and the equal halves now are called daughter cells.

Chromatids: Chromatids are the strands of replicated chromosomes that become the chromosomes when they contract

Microtubules: Microtubules are support fibers for movement of chromosomes during mitosis

Centromeres: Centromeres are needed for the separation of chromatids during mitosis and they are visible as constrictions that serve as sites of attachment of spindle microtubules.

Kinetochore: this helps to bind bundles of microtubules called spindle fibers as they extend from the kinetochores to the poles of the spindle during mitosis

Functions of mitosis

1. ***Mitosis helps in growth***: when the fusion of spermatozoon and ovum occurs, they form a zygote which then starts growing to form a human being or a baby of any animal that has many cells (multicellular organisms). The organisms or human beings grow by the process of mitosis occurring in different parts of the body
2. ***It helps in replacement of cells and tissue repair***: friction occurs as our bodies come in contact with others or hard surfaces and this causes damage to the skin and other parts of the body. Even while we eat, some parts of the intestines slough off, and even when we urinate, the urinary tract slough off. There is a need for the body to replace these damaged parts of the body or repair the worn-out body tissues. The body does this by sending a signal to the cell concerned to start cell division and mitosis. **In fact in some animals, the whole part of the body can be regenerated such as the starfish regenerating a whole arm.**
3. ***The process of mitosis functions in asexual reproduction***: mitosis is the basis of asexual reproduction by unicellular organisms and also the basis of cloning in biotechnology. Budding in multicellular organisms is a form of asexual reproduction and the unicellular organism such as amoeba also reproduces asexually.
4. ***It serves an important function in the immune response***: the cloning of B-lymphocytes and T-lymphocytes during the immune response occurs through the process of mitosis.

Where does mitosis occur?

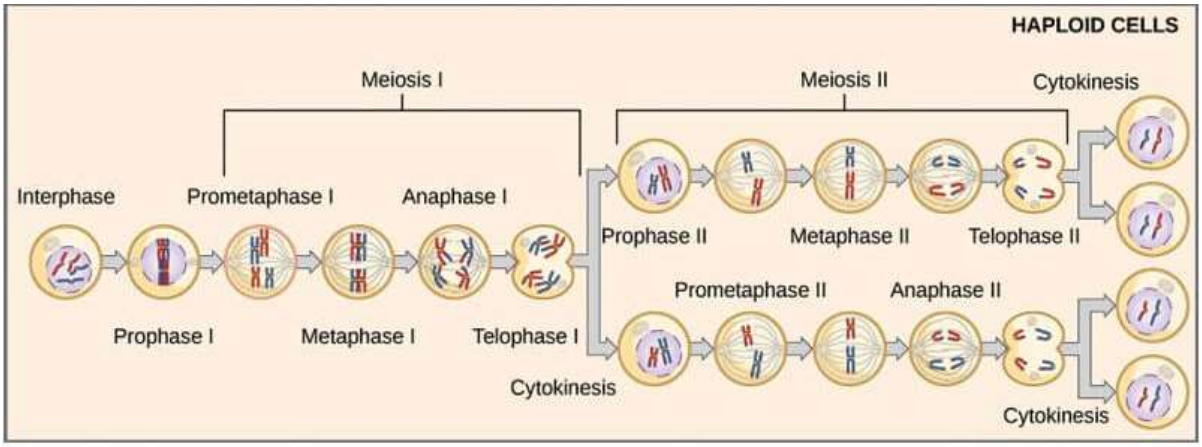
- Mitosis occurs in almost all cells of the body with the exception of the cardiac tissue and nerve tissues (these two tissues do not undergo mitosis because they remain dormant in the G0 phase of the cell cycle).
- The process of **mitosis occurs inside the nucleus of dividing cells**.
- Some of the body tissues take a longer period of time before the cells divide while others take a shorter time and still others do not even divide at all.

- Epithelial tissues such as that of the intestines and that of the skin undergo mitosis within a short period of time (there is rapid cell turnover) this is the reason why an injury to the mouth or skin heals faster than muscles or any other tissue.
- Tissues such as Nerves and cardiac muscles do not divide and this explains why a damaged nerve cannot be repaired again and permanent paralysis of the muscle supplied by the nerve occurs such as in paralysis caused by poliomyelitis. It is also the same reason why heart attack following ischemia leads to heart failure because the heart muscles cannot divide to form new ones again.

Mitosis Overview

- Mitosis is a continuous process of cell division which occurs in all types of living cells.
- Mitosis involves four basic phases – prophase, metaphase, anaphase and telophase.
- Mitosis is the **process where the division of cell occurs by asexual reproduction.**
- In **mitosis,** the **nuclear membrane is broken down, spindle fibres** (microtubules) attach to the chromatids at the centromere and pull apart the chromatids.
- When the chromatids reach separate ends of the cells, the spindle fibres disintegrate and a nuclear membrane rebuilds around the chromosomes making two nuclei.
- Each nucleus is identical to the original nucleus as it was in G1.
- **Meiosis**

- Meiosis is a type of cell division in sexually reproducing eukaryotes, resulting in four daughter cells (gametes), each of which has half the number of chromosomes as compared to the original diploid parent cell.
- The haploid cells become gametes, which by union with another haploid cell during fertilization defines sexual reproduction and formation of a new generation of diploid organisms.
- Meiosis occurs in the germ cells of sexually reproducing organisms.
- In both plants and animals, germ cells are localized in the gonads, but the time at which meiosis takes place varies among different organisms.



Purpose of Meiosis

The process of meiosis is essential for all sexually reproducing organisms for the following reasons:

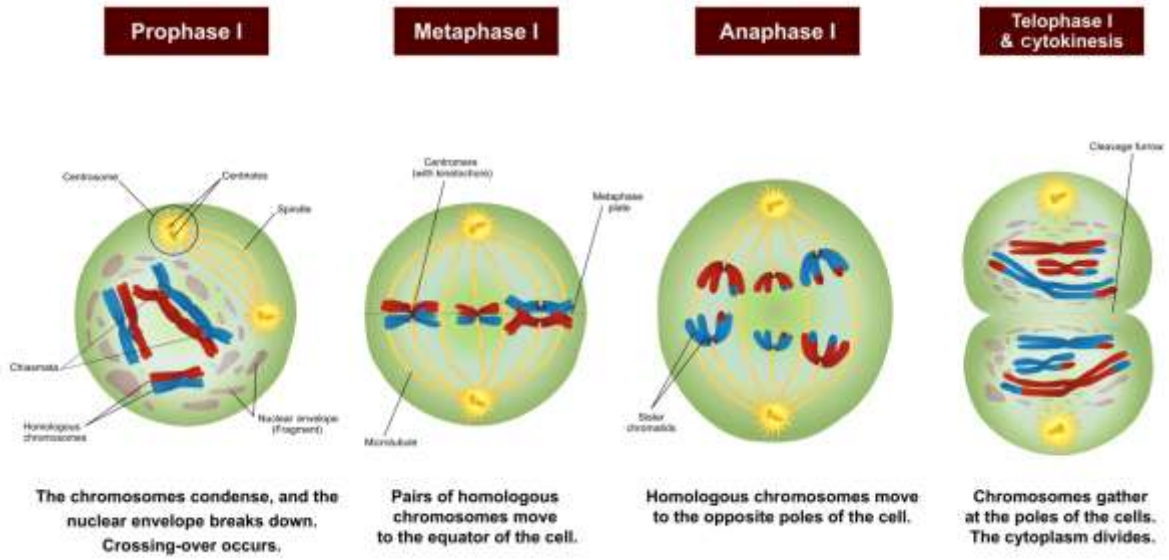
- The meiosis maintains a constant number of chromosomes in sexually reproducing organisms through the formation of gametes.
- By crossing over, the meiosis results in the exchange of the genes and, thus, causes the genetic variations among the species. These variations are the raw materials of the evolutionary process.
- **Stages/Phases of Meiosis**

- Meiosis is composed of two rounds of cell division, namely Meiosis I and Meiosis II.
- Each round of division contains a period of karyokinesis (nuclear division) and cytokinesis (cytoplasmic division).

Meiosis Overview

- Meiosis is the form of nuclear cell division that results in daughter cells that have one half the chromosome numbers as the original cell.
- In organisms that are diploid, the end result is cells that are haploid.
- Each daughter cell gets one complete set of chromosomes, i.e., one of each homologous pair of chromosomes.
- In humans, this means the chromosome number is **reduced from 46 to 23.**
- The only cells that undergo meiosis will become sperm or eggs.
- The joining together of a sperm and egg during fertilization returns the number of the chromosomes to 46.
- Cells that undergo meiosis **go through the cell cycle including the S phase so begin the process with chromosomes that consist of two chromatids just as in mitosis.**
- Meiosis consists of meiosis I and meiosis II.
- In meiosis I homologous chromosomes are separated into different nuclei.

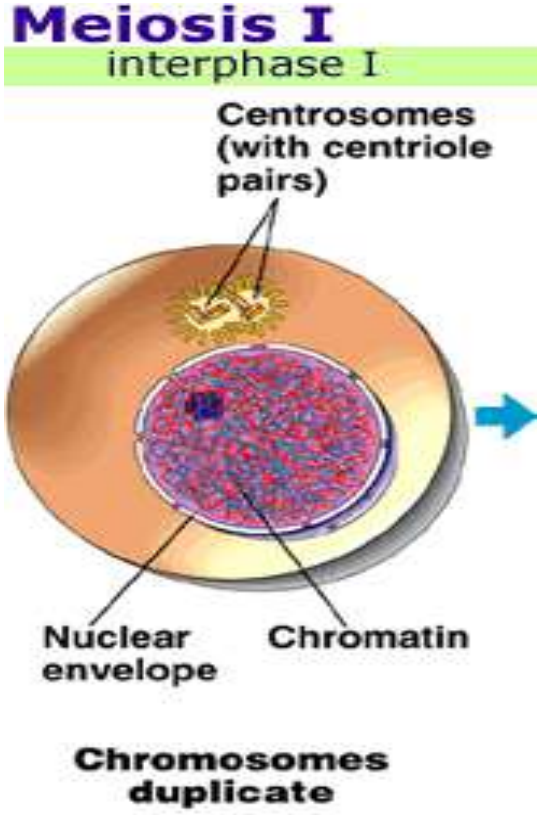
- This is the reduction division; chromosome number is cut in half. Meiosis II is very similar to mitosis; chromatids are separated into separate nuclei.
- As in mitosis, **it is spindle fibres that** "pull" the chromosomes and chromatids apart.
- The end result of meiosis is four cells, each with one complete set of chromosomes instead of two sets of chromosomes.
- The first meiotic division consists of **prolonged prophase in which the homologous chromosomes** come in close contact with each other and exchange hereditary material between them.
- Similarly, in the first meiotic division, the reduction of chromosome number takes place and, thus, two haploid cells are resulted by this division.
- The first meiotic division is also known as the heterotypic division.
- Meiosis I consists of the following steps:



Interphase

- Just like mitosis, meiosis also consists of a preparatory phase called interphase.
- **The interphase is characterized by the following features :**
- The nuclear envelope remains intact, and the chromosomes occur in the form of diffused, long, coiled, and indistinctly visible chromatin fibers.
- The DNA amount becomes double. Due to the accumulation of ribosomal RNA (rRNA) and ribosomal proteins in the nucleolus, the size of the nucleolus is significantly increased.
- In animal cells, a daughter pair of centrioles originates near the already existing centriole and, thus, an interphase cell has two pairs of centrioles.
- In the G2 phase of interphase, there is a decisive change that directs the cell toward meiosis, instead of mitosis.

- At the beginning of the first meiotic division, the nucleus of the dividing cell starts to increase in size by absorbing the water from the cytoplasm, and the nuclear volume increases about three folds.

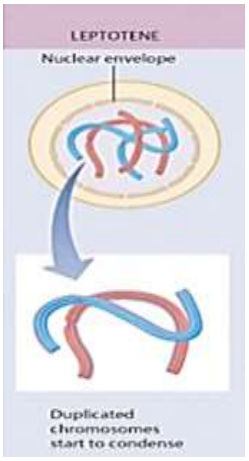


Prophase I

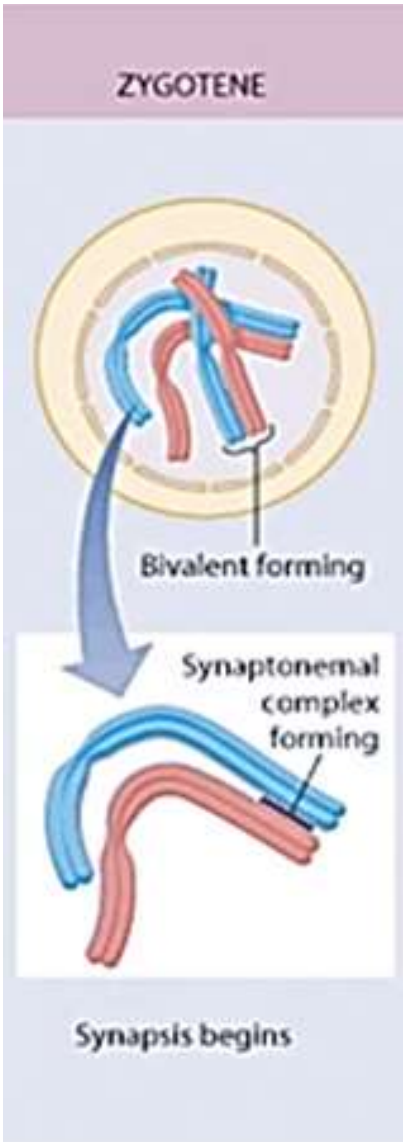
Prophase I is the longest stage of the meiotic division. It includes the following substages:

Leptotene

- In the leptotene stage, the chromosomes become even more uncoiled and resemble a long thread-like shape, and they develop bead-like structures called chromomeres.
- The chromosomes at this stage remain directed towards centrioles, so the chromosomes in the nucleus appear like a bouquet in the animal cell. Therefore, this stage is also called the Bouquet Stage.



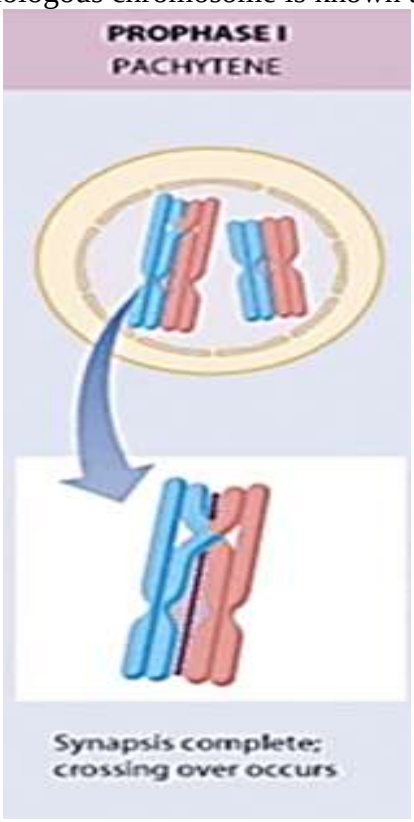
- **Zygotene or Synaptotene**
- The zygotene stage begins with the pairing of homologous chromosomes, which is called synapsis.
- The paired homologous chromosomes are connected by a protein-containing framework called a synaptonemal complex.
- The synaptonemal complex helps to stabilize the pairing of homologous chromosomes and to facilitate recombination or crossing over.
- The synapsis might begin at one or more points along the length of the homologous chromosomes.
- Synapsis might start from the ends of the chromosomes and continues towards their centromeres (proterminal synapsis), or it might start at the centromere and proceed towards the ends (procentric pairing).
- In some cases, the synapsis occurs at various points of the homologous chromosomes (random pairing).



Pachytene

- In this stage, the pair of chromosomes become twisted spirally around each other and cannot be distinguished separately.
- In the middle of the pachytene stage, each homologous chromosome splits lengthwise to form two chromatids, but they continue to be linked together by their common centromere.
- The chromosomes at this point are termed bivalent because it consists of two visible chromosomes, or as a tetrad because of the four visible chromatids.
- This stage is particularly crucial as a critical genetic phenomenon called " crossing over" takes place in this stage.

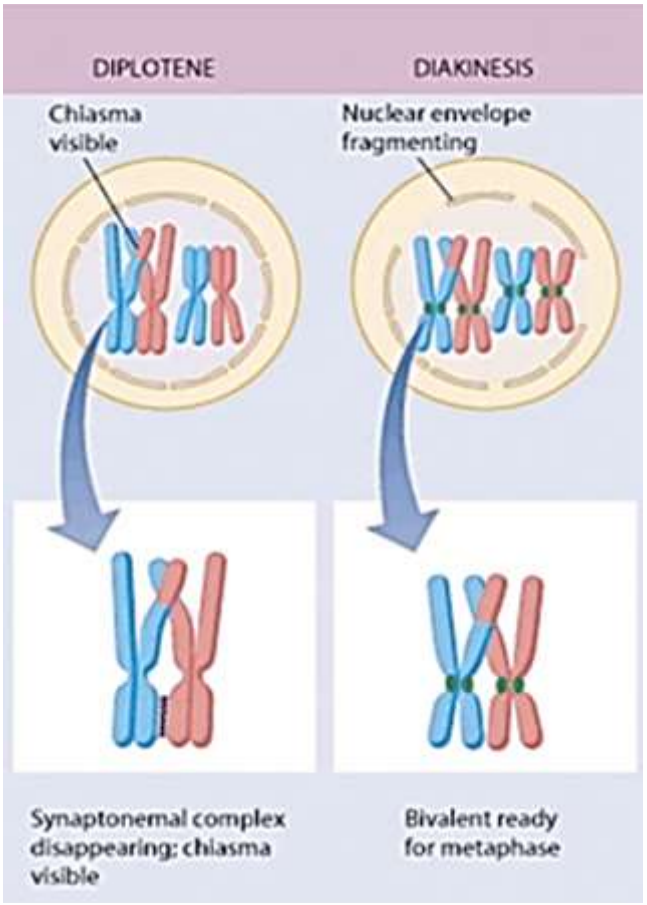
- The crossing over involves redistribution and mutual exchange of hereditary material between two homologous chromosomes.
- The enzyme endonuclease breaks the non-sister chromatids at the place of crossing over.
- After the breaking of chromatids, the interchange of chromatid segments takes place between the non-sister chromatids of the homologous chromosomes.
- Another enzyme, ligase, binds the broken chromatid segments with the non-sister chromatid.
- The process of mutual exchange of chromatin material between one non-sister chromatid of each homologous chromosome is known as the crossing over.



Diplotene

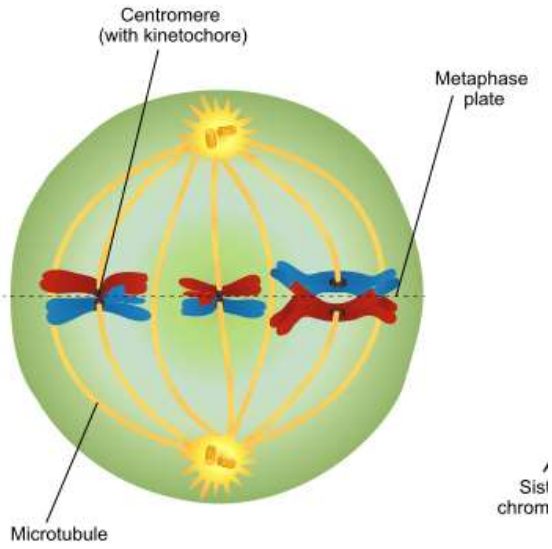
- The synaptonemal complex appears to be dissolved, leaving chromatids of the paired homologous chromosome physically joined at one or more localized points called
- In diplotene, chiasmata move towards the end of chromosomes in a zip like a manner.

Diakinesis



- **Metaphase I**
- Metaphase I consists of spindle fiber attachment to chromosomes and chromosomal alignment at the equator.
- During metaphase I, the spindle fibers are attached with the centromeres of the homologous chromosomes, which are directed towards the opposite poles.

Metaphase I



Pairs of homologous chromosomes move to the equator of the cell.

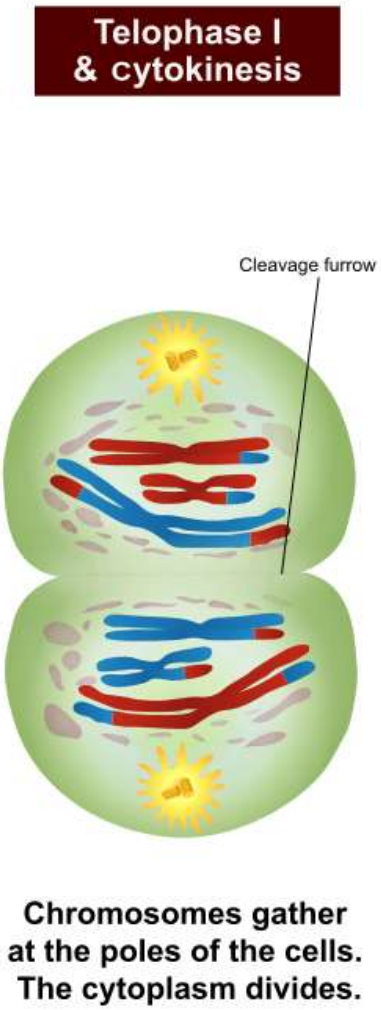
- **Anaphase I**
- At anaphase I homologous chromosomes are separated from each other, and due to the shortening of chromosomal fibers or microtubules, each homologous chromosome with its two chromatids and undivided centromere move towards the opposite poles of the cell.
- Because during the chiasma formation, one of the chromatids has changed its counterpart, therefore, the two chromatids of a chromosome are not genetically identical

Telophase I

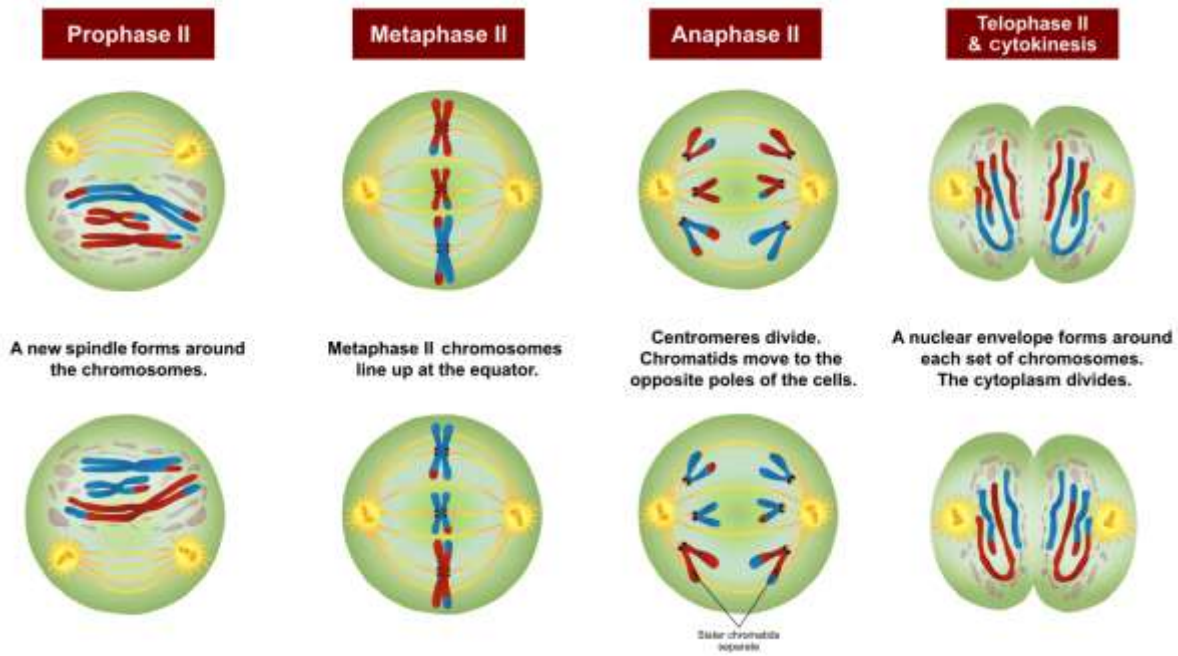
- The onset of telophase I is defined by the movement of a haploid set of chromosomes at each pole.
- The nuclear envelope is formed around the chromosomes, and the chromosomes become uncoiled. The nucleolus reappears and, thus, two daughter nuclei are formed.

Cytokinesis I

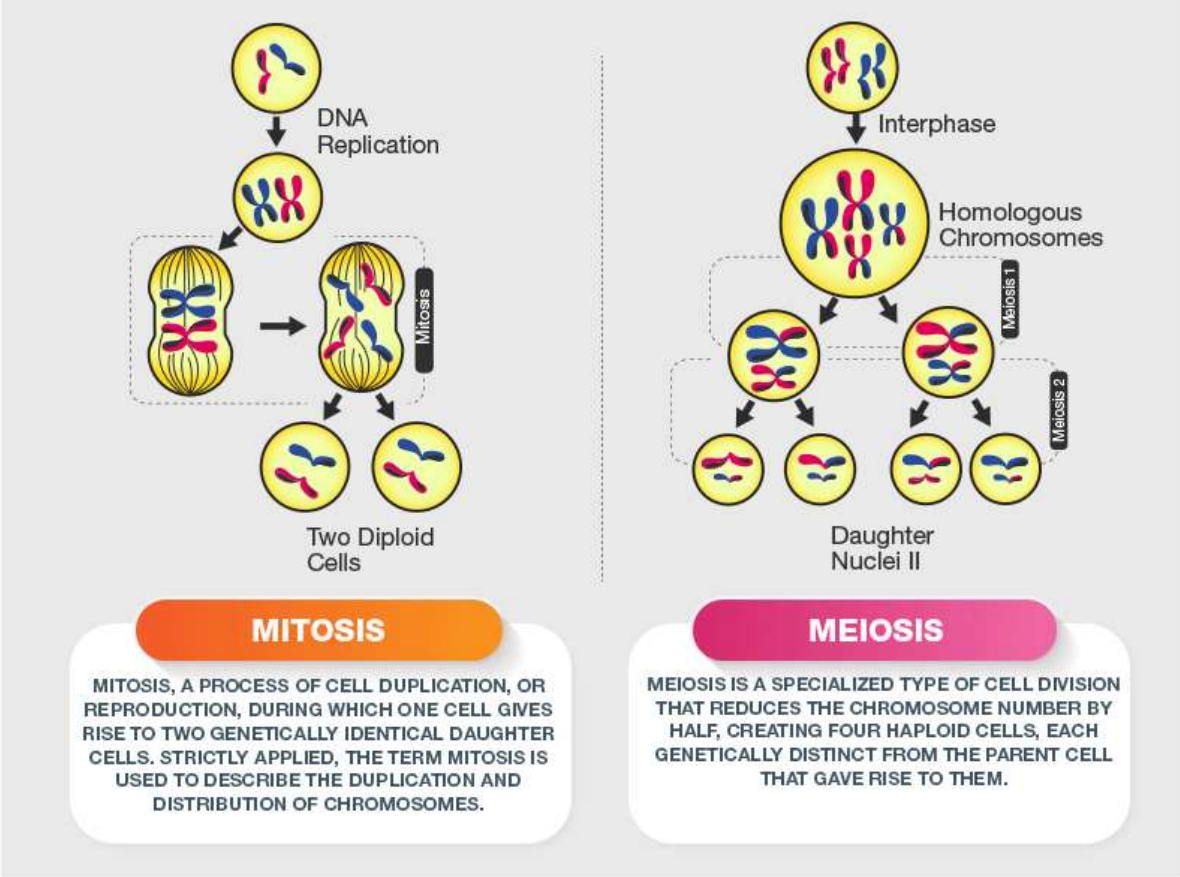
- In animals, cytokinesis occurs by the constriction of the cell membrane while in plants, it occurs through the formation of the cell plate, resulting in the creation of two daughter cells.



Meiosis II



- In the second phase of the meiotic division, the haploid cell divides mitotically and results in four haploid cells. This division is also known as the homotypic division.
- This division does not include the exchange of the genetic material and the reduction of the chromosome number as in the first meiotic division.
- Meiosis II consists of the following steps:

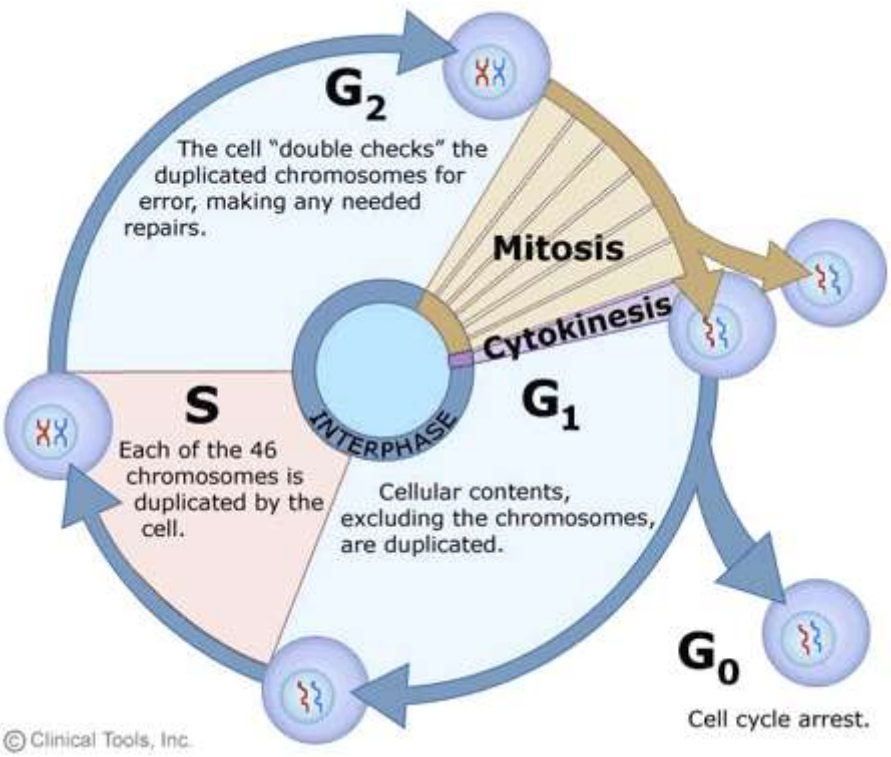

DNA
Replication
Mitosis
Two Diploid
Cells
Interphase
Homologous
Chromosomes
Meiosis 1
Meiosis 2
Daughter
Nuclei II
MITOSIS
MITOSIS, A PROCESS OF CELL DUPLICATION, OR REPRODUCTION, DURING WHICH ONE CELL GIVES RISE TO TWO GENETICALLY IDENTICAL DAUGHTER CELLS. STRICTLY APPLIED, THE TERM MITOSIS IS USED TO DESCRIBE THE DUPLICATION AND DISTRIBUTION OF CHROMOSOMES.
MEIOSIS
MEIOSIS IS A SPECIALIZED TYPE OF CELL DIVISION THAT REDUCES THE CHROMOSOME NUMBER BY HALF, CREATING FOUR HAPLOID CELLS, EACH GENETICALLY DISTINCT FROM THE PARENT CELL THAT GAVE RISE TO THEM.

Difference between Mitosis and Meiosis	
Mitosis	**Meiosis**
Interphase	
Each chromosome replicates. The result is two genetically identical sister chromatids	Chromosomes not yet visible but DNA has been duplicated or replicated
Prophase	
Prophase –Each of the duplicated chromosomes appears as two identical or equal sister chromatids, The mitotic spindle begins to form. Chromosomes condense and thicken	Prophase I – crossing-over recombination – Homologous chromosomes (each consists of two sister chromatids) appear together as pairs. Tetrad is the structure that is formed. Segments of chromosomes are exchanged between non-sister chromatids at crossover points known as chiasmata (crossing-over)
Metaphase	
Metaphase -The chromosomes assemble at the equator at the metaphase plate	Metaphase I Chromosomes adjust on the metaphase plate. Chromosomes are still intact and arranged as pairs of homologues

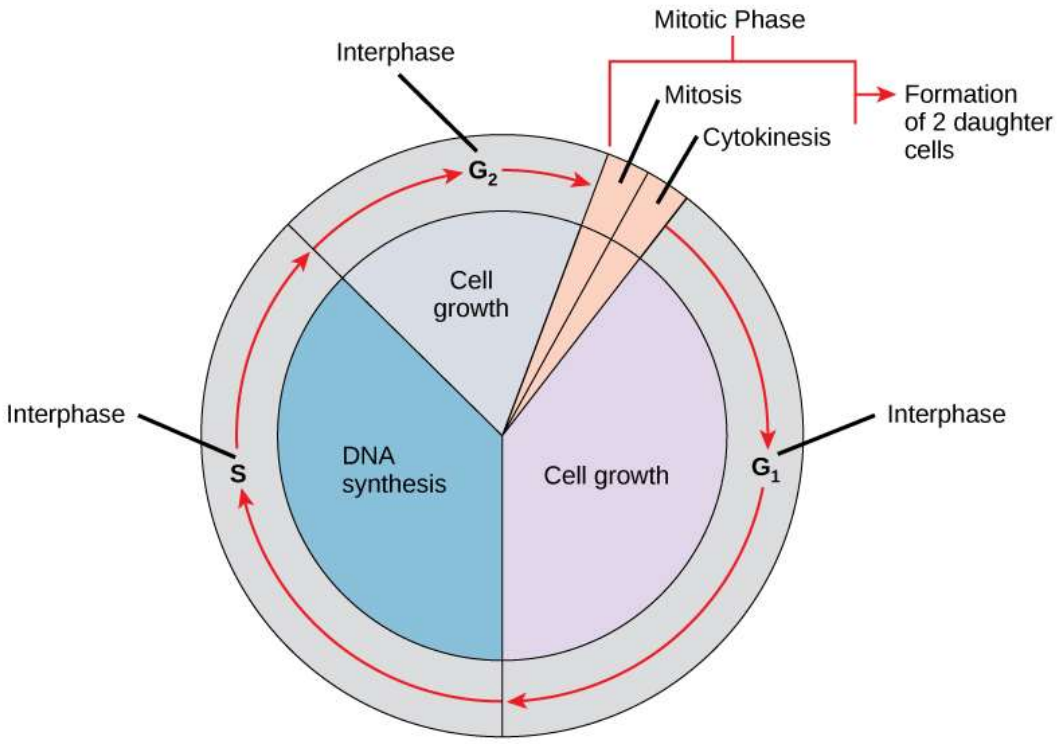
Anaphase	
Anaphase – The spindle fibres begin to contract. This starts to pull the sister chromatids apart. At the end of anaphase, a complete set of daughter chromosomes is found each pole	Anaphase I Sister chromatids stay intact. However, homologous chromosomes drift to the opposite or reverse poles
Mode of Reproduction	
Asexual Reproduction	Sexual Reproduction
Occurrence	
All the cells	Reproductive cells
Function	
General growth and repair, Cell reproduction	Genetic diversity through sexual reproduction
Cytokinesis	
Occurs in Telophase	Occurs in Telophase I and in Telophase II
Discovered by	

The cell cycle

- The cell cycle is the process a cell undertakes to replicate all of its material and divide into two identical cells.
- The cell cycle is an ordered series of events involving cell growth and cell division that produces two new daughter cells.
  The cell cycle has two major phases: interphase and the mitotic phase (Figure).
- During interphase, the cell grows and DNA is replicated.
- During the mitotic phase, the replicated DNA and cytoplasmic contents are separated and the cell divides



1. G1 phase. Metabolic changes prepare the cell for division. At a certain point - the restriction point - the cell is committed to division and moves into the S phase.
2. S phase. DNA synthesis replicates the genetic material. Each chromosome now consists of two sister chromatids.
3. G2 phase. Metabolic changes assemble the cytoplasmic materials necessary for mitosis and cytokinesis.
4. M phase. A nuclear division (mitosis) followed by a cell division (cytokinesis).
5. The period between mitotic divisions - that is, G1, S and G2 - is known as interphase.



Interphase

- During interphase, the cell undergoes normal processes while also preparing for cell division.
- For a cell to move from interphase to the mitotic phase, many internal and external conditions must be met.
- The three stages of interphase are called G1, S, and G2.

G1 Phase

- The first stage of interphase is called the G1 phase, or first gap, because little change is visible. However, during the G1 stage, the cell is quite active at the biochemical level.
- The cell is accumulating the building blocks of chromosomal DNA and the associated proteins, as well as accumulating enough energy reserves to complete the task of replicating each chromosome in the nucleus.
- **S Phase**
- Throughout interphase, nuclear DNA remains in a semi-condensed chromatin configuration. In the S phase(synthesis phase), DNA replication results in the formation of two identical copies of each chromosome—sister chromatids—that are

firmly attached at the centromere region. At this stage, each chromosome is made of two sister chromatids and is a duplicated chromosome. The centrosome is duplicated during the S phase. The two centrosomes will give rise to the mitotic spindle, the apparatus that orchestrates the movement of chromosomes during mitosis. The centrosome consists of a pair of rod-like centrioles at right angles to each other. Centrioles help organize cell division.

- **G2 Phase**
- In the G2 phase, or second gap, the cell replenishes its energy stores and synthesizes the proteins necessary for chromosome manipulation.
- Some cell organelles are duplicated, and the cytoskeleton is dismantled to provide resources for the mitotic spindle. There may be additional cell growth during G2. The final preparations for the mitotic phase must be completed before the cell is able to enter the first stage of mitosis.

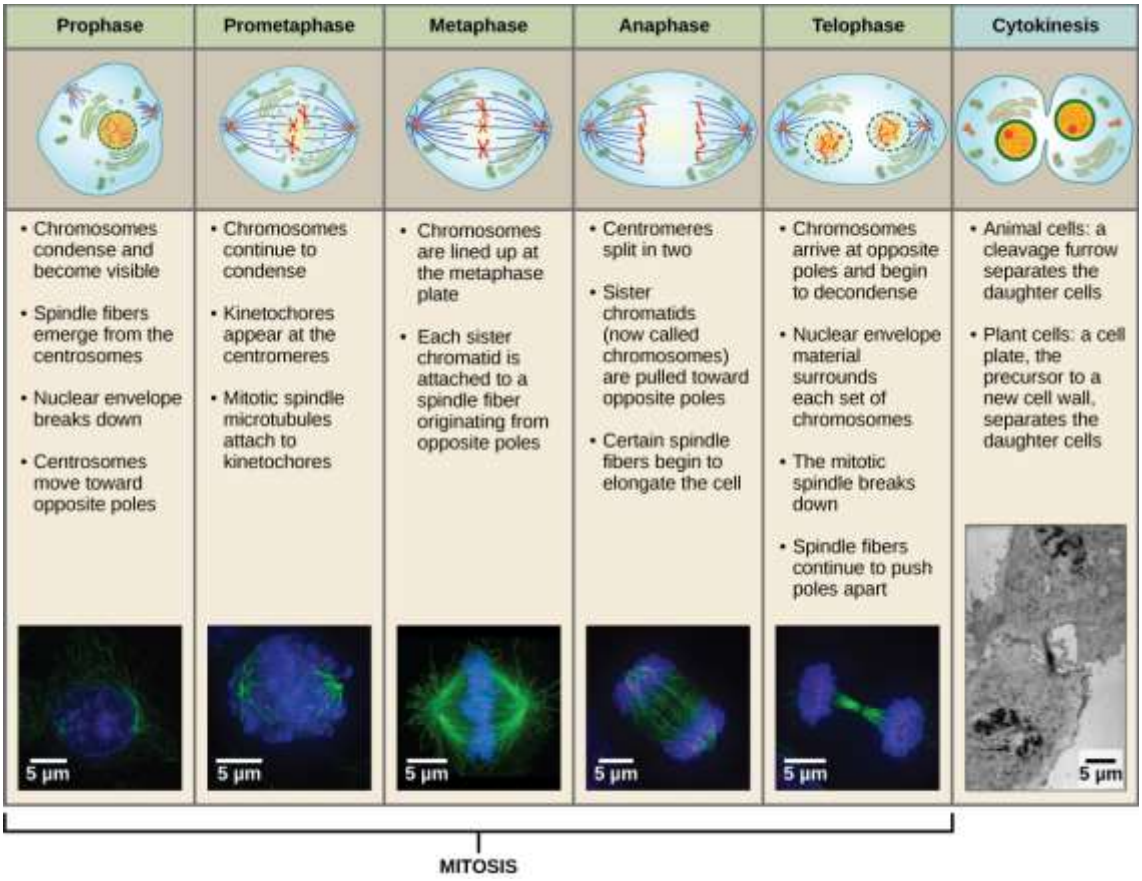
The Mitotic Phase

To make two daughter cells, the contents of the nucleus and the cytoplasm must be divided. The mitotic phase is a multistep process during which the duplicated chromosomes are aligned, separated, and moved to opposite poles of the cell, and then the cell is divided into two new identical daughter cells.

1. The first portion of the mitotic phase, mitosis, is composed of five stages, which accomplish nuclear division.
2. The second portion of the mitotic phase, called cytokinesis, is the physical separation of the cytoplasmic components into two daughter cells.

Mitosis

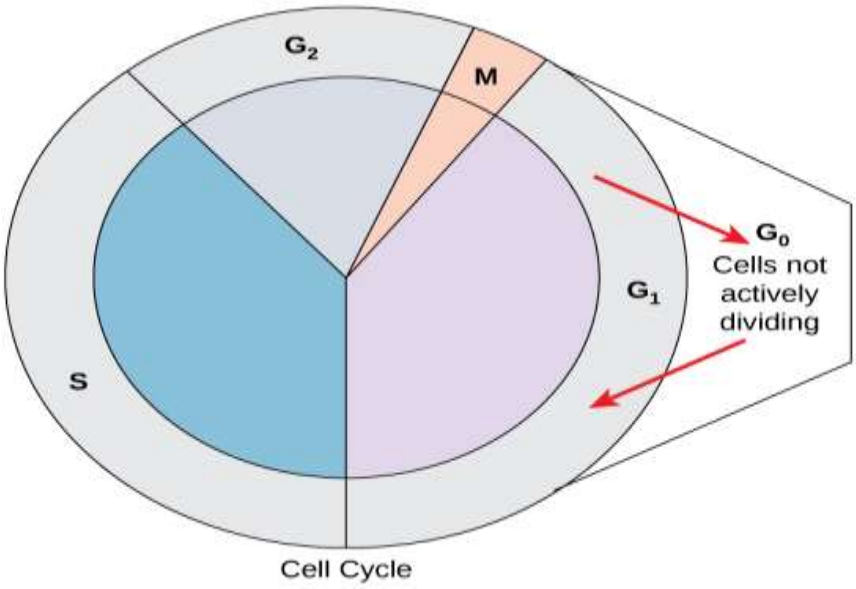
Mitosis is divided into a series of phases—prophase, prometaphase, metaphase, anaphase, and telophase—that result in the division of the cell nucleus



G0 Phase

Not all cells adhere to the classic cell-cycle pattern in which a newly formed daughter cell immediately enters interphase, closely followed by the mitotic phase.

- Cells in the G0 phase are not actively preparing to divide.
- The cell is in a quiescent (inactive) stage, having exited the cell cycle.
- Some cells enter G0 temporarily until an external signal triggers the onset of G1.
- Other cells that never or rarely divide, such as mature cardiac muscle and nerve cells, remain in G0 permanently

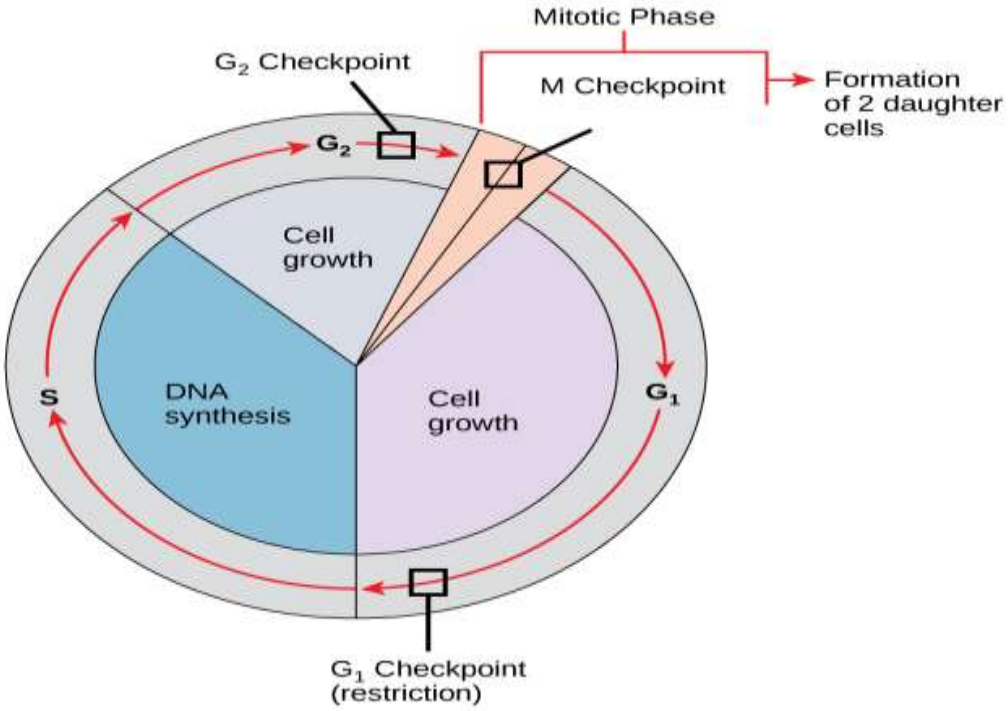


Control of the Cell Cycle

- The length of the cell cycle is highly variable even within the cells of an individual 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, or 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 approximately 24 hours.
- In rapidly dividing human cells with a 24-hour cell cycle, the G_1 phase lasts approximately 11 hours. The timing of events in the cell cycle is controlled by mechanisms that are both internal and external to the cell.

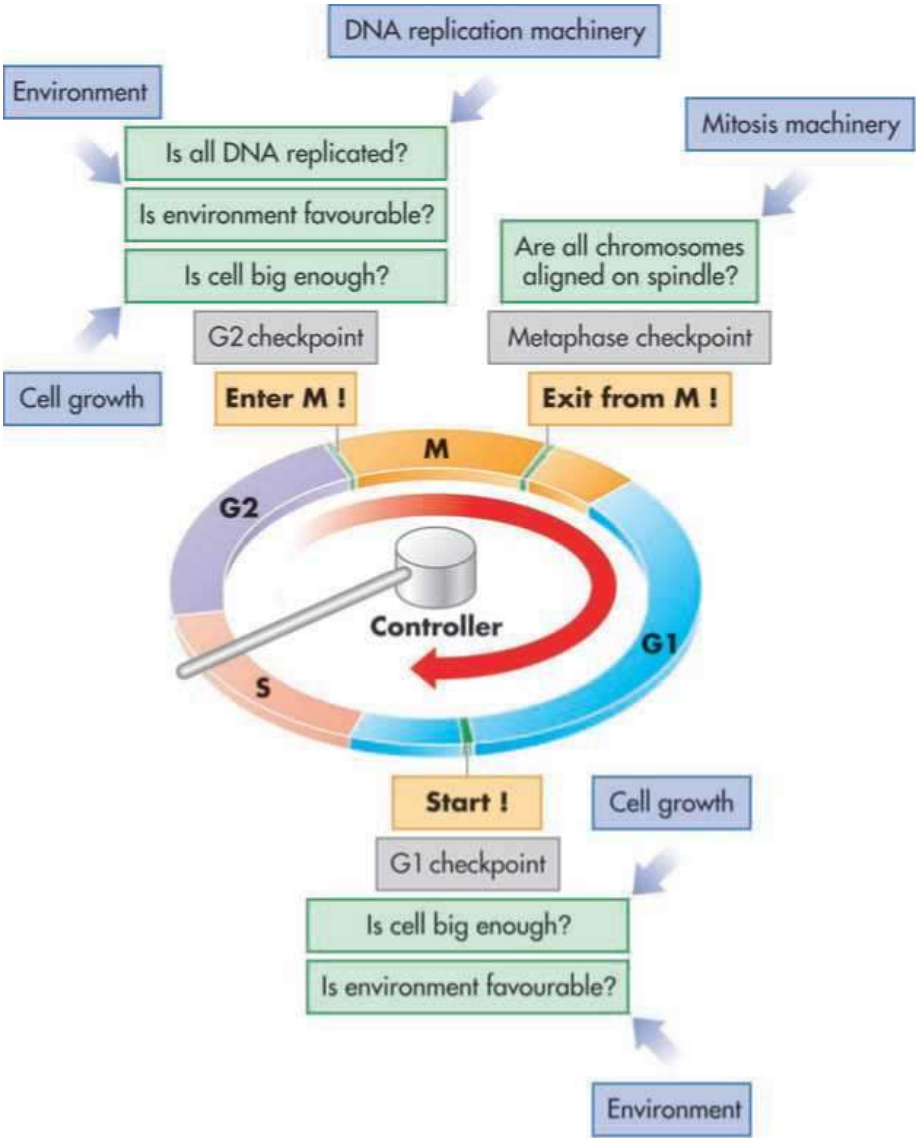
Regulation at Internal Checkpoints

- It is essential that daughter cells 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 the abnormal cell.
- To prevent a compromised cell from continuing to divide, there are internal control mechanisms that operate at three main cell cycle checkpoints at which the cell cycle can be stopped until conditions are favourable.
- These checkpoints occur near the end of G1, at the G2–M transition, and during metaphase



The G1 Checkpoint

- The G1 checkpoint determines whether all conditions are favorable for cell division to proceed.
- The G1checkpoint, also called the restriction point, is the point at which the cell irreversibly commits to the cell-division process.
- In addition to adequate reserves and cell size, there is a check for damage to the genomic DNA at the G1 checkpoint.
- A cell that does not meet all the requirements will not be released into the S phase.
- This transition, as with all of the major checkpoint transitions in the cell cycle, is signaled by cyclins and cyclin dependent kinases (CDKs). **Cyclins are cell-signaling molecules that regulate the cell cycle.**



The G2 Checkpoint

- The G2 checkpoint bars the entry to the mitotic phase if certain conditions are not met.
- As in the G1checkpoint, cell size and protein reserves are assessed.
- However, the most important role of the G2checkpoint is to ensure that all of the chromosomes have been replicated and that the replicated DNA is not damaged.

The M Checkpoint

- The M checkpoint occurs near the end of the metaphase stage of mitosis. The M checkpoint is also known as the spindle checkpoint because it determines if 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 spindle fibers arising from opposite poles of the cell.

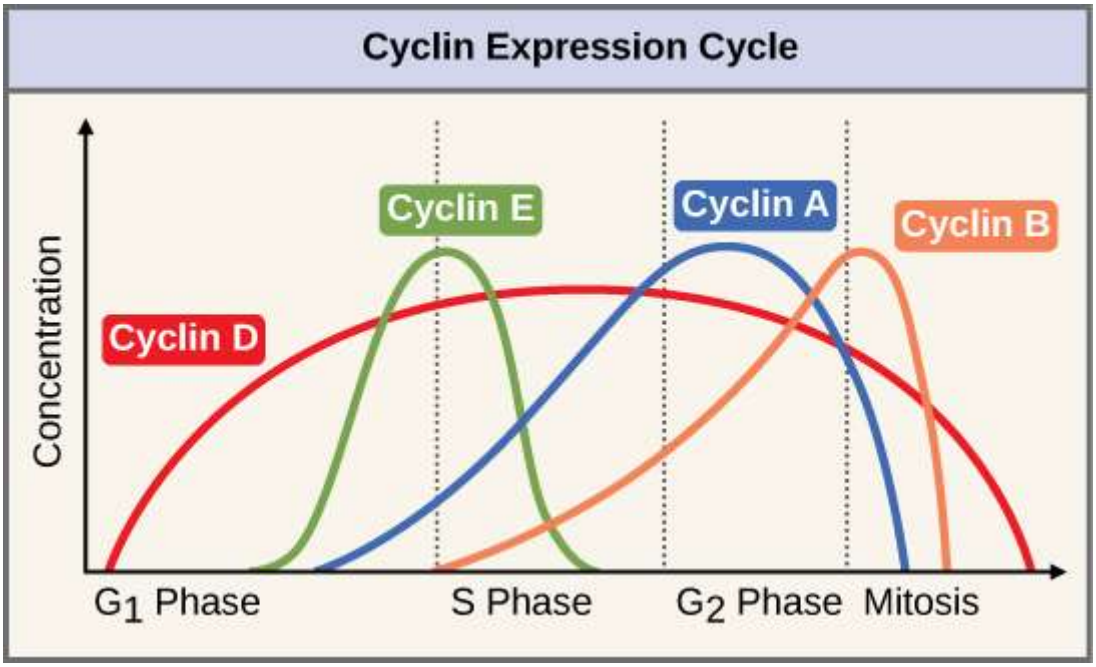
Regulator Molecules of the Cell Cycle

- The cell cycle is controlled by regulator molecules that either promote the process or stop it from progressing.
- 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

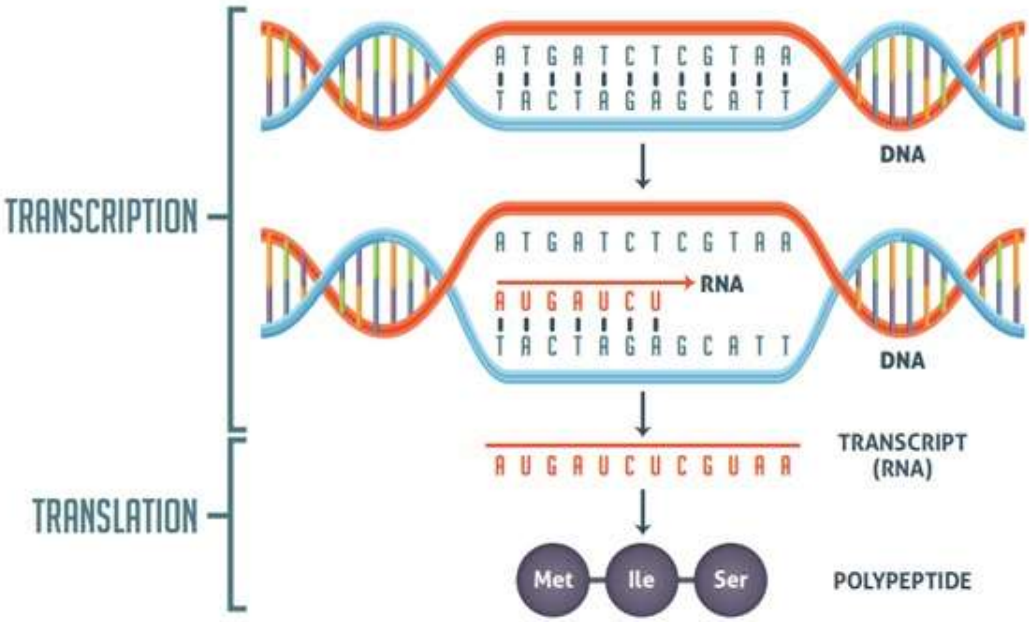
- Two groups of proteins, called cyclins and cyclin-dependent kinases (Cdks), are responsible for the progress of the cell through the various checkpoints.
- The levels of the four cyclin proteins fluctuate throughout the cell cycle in a predictable pattern.
- Increases in the concentration of cyclin 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.

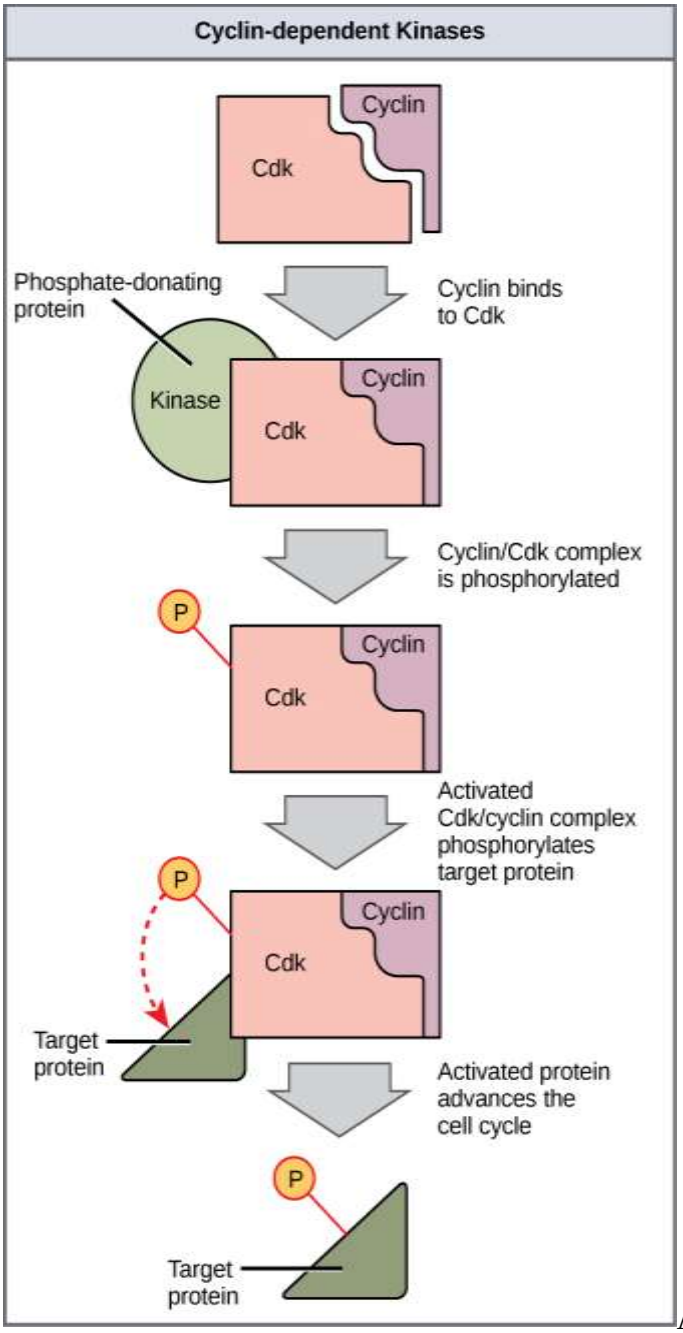


Cyclin Concentrations at Checkpoints:

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.

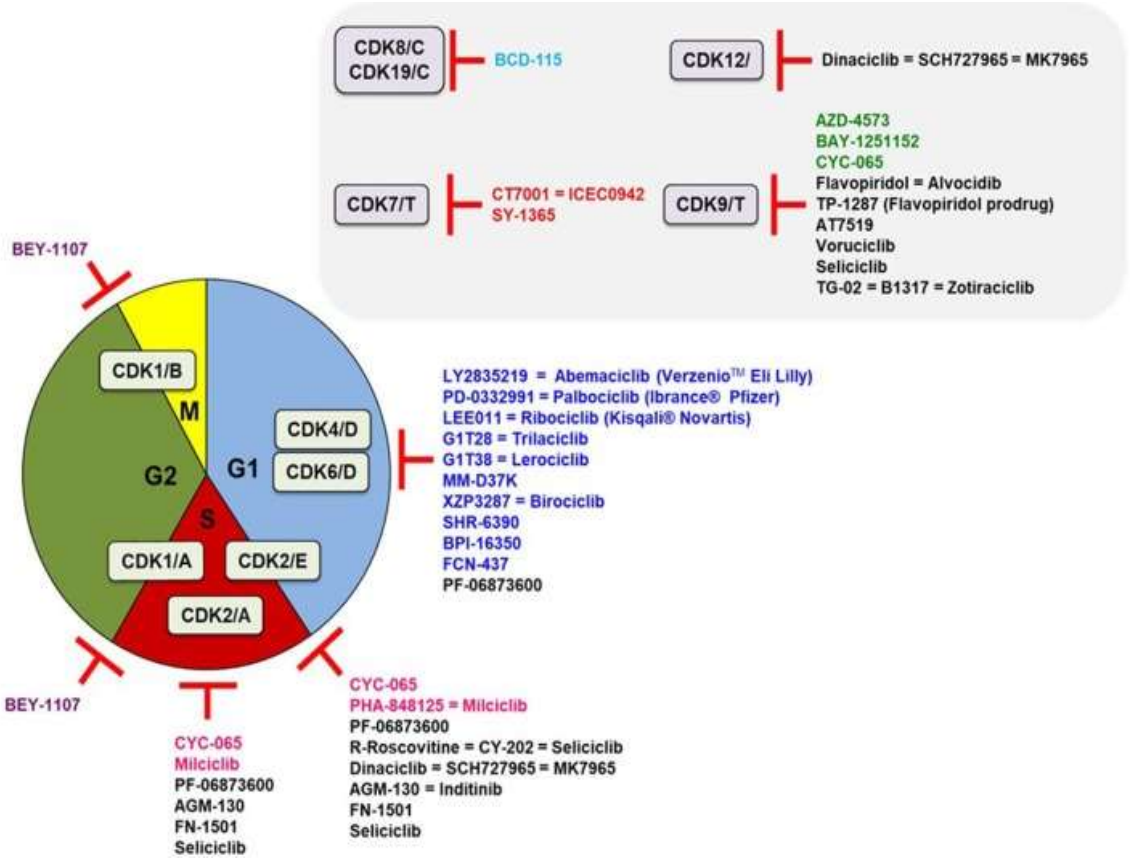


- Cyclins regulate the cell cycle only when they are tightly bound to Cdks.
- To be fully active, the Cdk/cyclin complex must also be phosphorylated in specific locations.
- Like all kinases, Cdks are enzymes (kinases) that phosphorylate other proteins.
- Phosphorylation activates the protein by changing its shape.
- The proteins phosphorylated by Cdks are involved in advancing the cell to the next phase.
- 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.

- 

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 being monitored is completed.


CDK8/C
CDK19/C
BCD-115
CDK12/
Dinaciclib = SCH727965 = MK7965
AZD-4573
BAY-1251152
CYC-065
Flavopiridol = Alvocidib
TP-1287 (Flavopiridol prodrug)
AT7519
Voruciclib
Seliciclib
TG-02 = B1317 = Zotiraciclib
CDK7/T
CT7001 = ICEC0942
SY-1365
CDK9/T
BEY-1107
CDK1/B
M
G2
G1
CDK4/D
CDK6/D
S
CDK1/A
CDK2/E
CDK2/A
LY2835219 = Abemaciclib (Verzenio™ Eli Lilly)
PD-0332991 = Palbociclib (Ibrance® Pfizer)
LEE011 = Ribociclib (Kisqali® Novartis)
G1T28 = Trilaciclib
G1T38 = Lerociclib
MM-D37K
XZP3287 = Birociclib
SHR-6390
BPI-16350
FCN-437
PF-06873600
BEY-1107
CYC-065
PHA-848125 = Milciclib
PF-06873600
R-Roscovitine = CY-202 = Seliciclib
Dinaciclib = SCH727965 = MK7965
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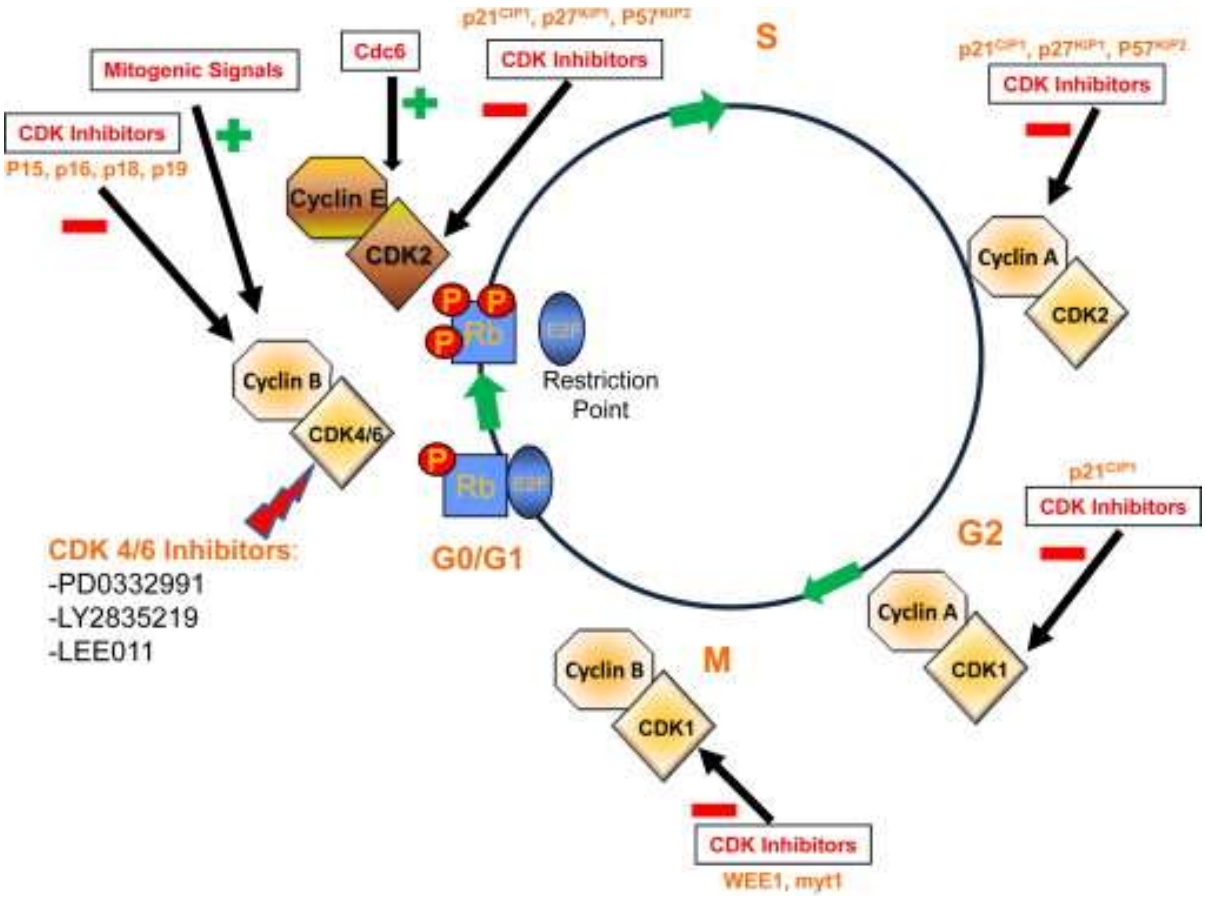
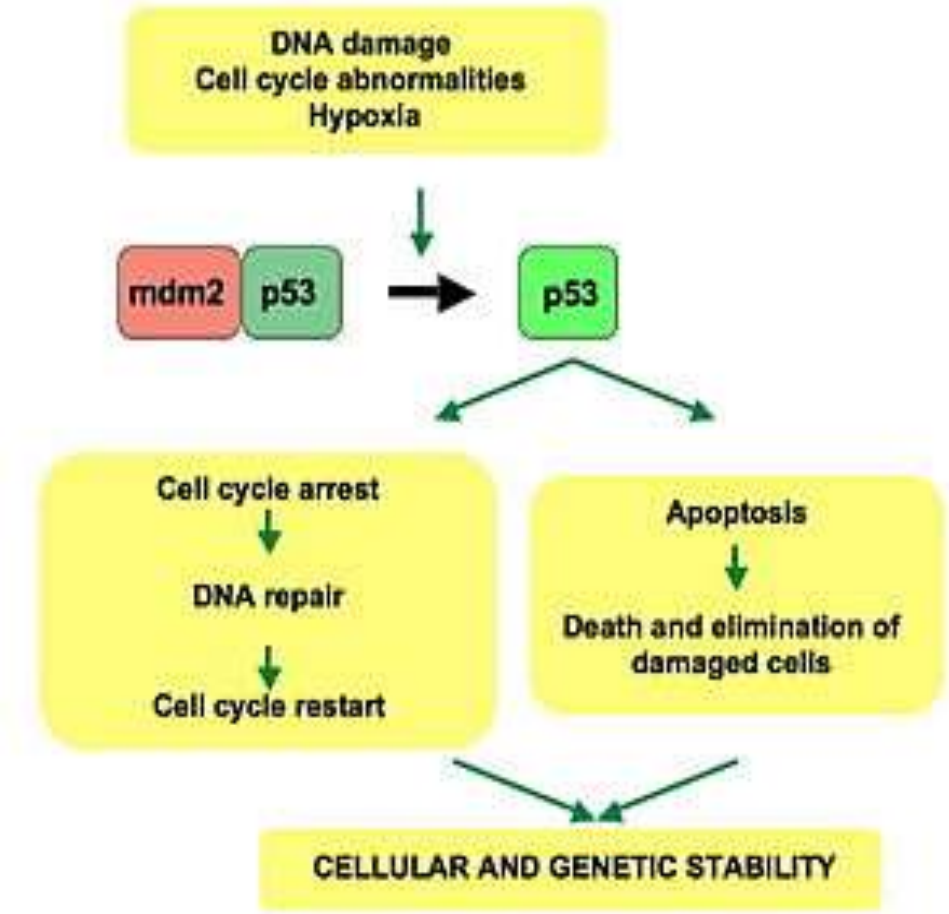


Negative Regulation of the Cell Cycle

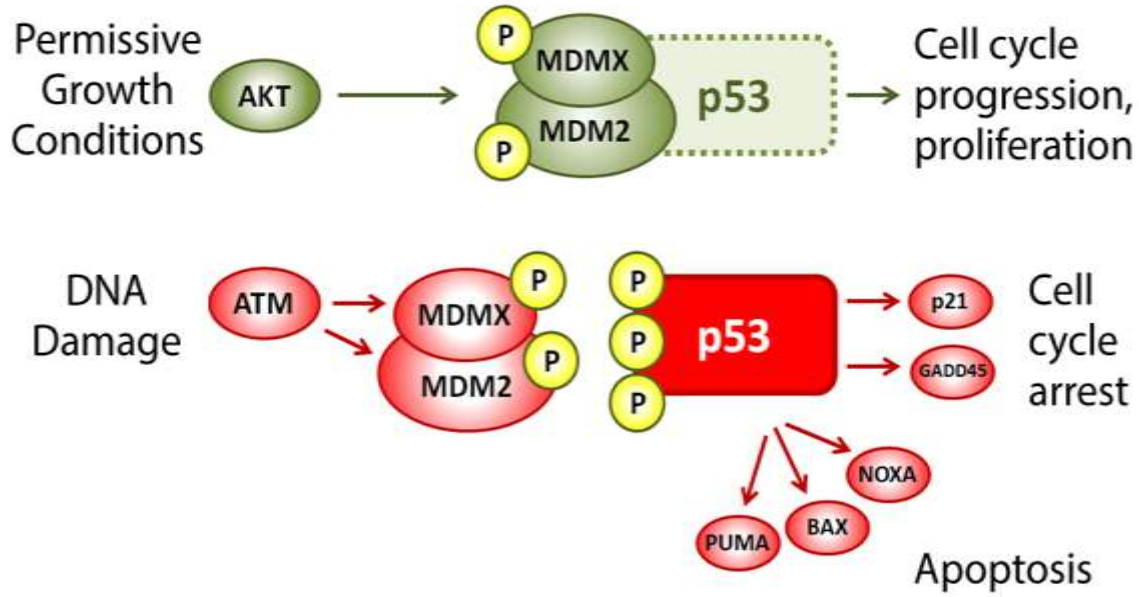
- The second group of cell cycle regulatory molecules are negative regulators.
- Negative regulators halt the cell cycle. Remember that in positive regulation, active molecules cause the cycle to progress.
- The best understood negative regulatory molecules are **retinoblastoma protein (Rb), p53, and p21**. **Rb, p53, and p21 act primarily at the G_1 checkpoint**.
- 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.**
- P53: Guardian of the Genome

- The transcriptional activator and tumor suppressor protein p53 (product of the TP53 gene) was originally discovered as a protein that bound to the SV40 large T-Antigen.
- It was later determined to be a tumor suppressor when it was found that many human tumor cells had mutations in p53, and a high percentage of p53 -/- mice developed tumors.
- The name p53 was given in 1979 describing the apparent molecular mass; SDS-PAGE analysis indicates that it is a 53-kilodalton (kDa) protein. However, the actual mass of the full-length p53 protein (p53α) based on the sum of masses of the amino acid residues is only 43.7 kDa. This difference is due to the high number of proline residues in the protein, which slow its migration on SDS-PAGE, thus making it appear heavier than it actually is.[13] In addition to the full-length protein, the human TP53 gene encodes at least 15 protein isoforms, ranging in size from 3.5 to 43.7 kDa.
- Approximately 50% of all human tumors have a mutation in p53.
- People with Li Fraumeni Syndrome, who carry a mutation in one p53 allele, have a >90% chance of developing cancer in their lifetime.
- P53 earned its reputation as “Guardian of the Genome” by its crucial role in cell cycle arrest, apoptosis, and senescence in response to DNA damage

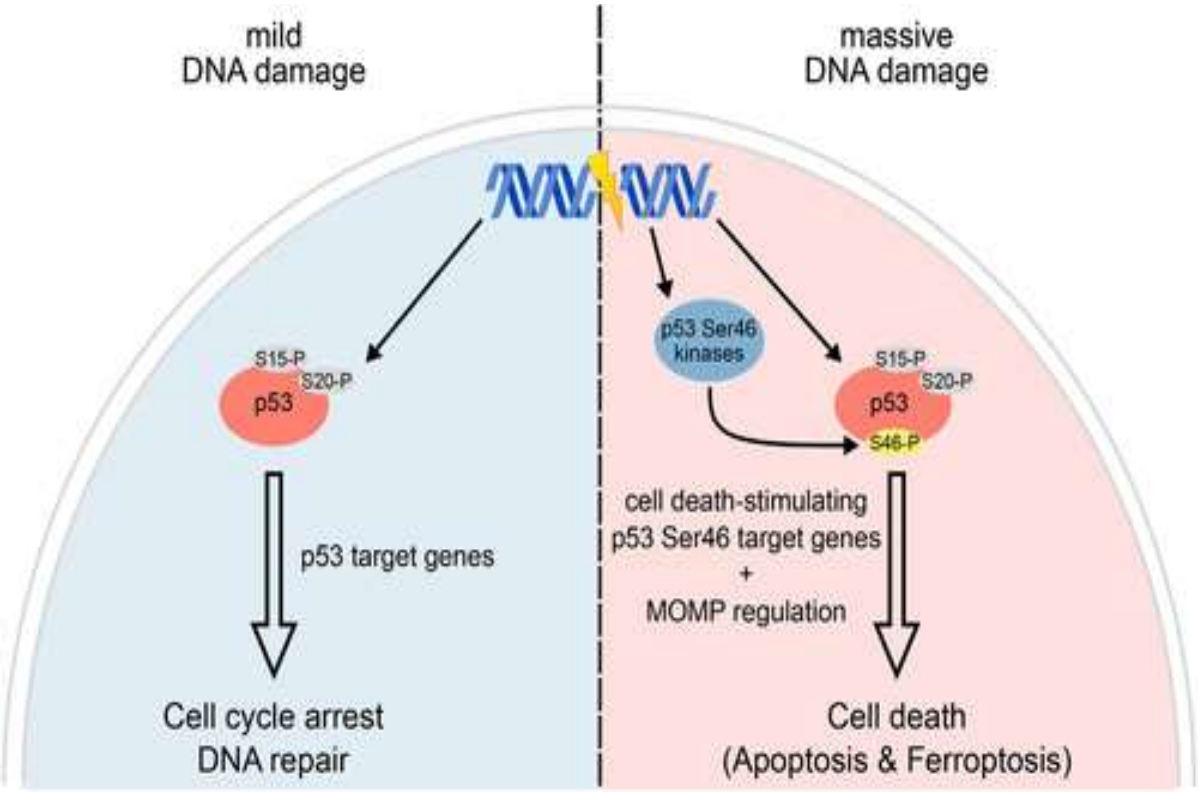


- p53 is a multi-functional protein that has a major impact on the cell's commitment to division; it acts when there is damaged DNA in cells that are undergoing the preparatory processes during G_1.
- If damaged DNA is detected, p53 halts the cell cycle and recruits enzymes to repair the DNA.
- If the DNA cannot be repaired, p53 can trigger apoptosis (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.

- Under permissive growth conditions, growth factor signals act through the kinase AKT to stabilize and activate MDM2 and MDMX, which in turn drive the degradation of p53, leaving cellular levels of p53 low. In the absence of high levels of p53 cells are able to progress through the cell cycle, divide, and proliferate.
- In presence of DNA damage the serine/threonine kinase ATM is activated, which phosphorylates MDM2, MDMX, and p53. Phosphorylation of MDM2 and MDMX results in the stabilization and activation of p53, leading to transcription of downstream genes involved in cell cycle arrest (p21, GADD45) and apoptosis (BAX, PUMA, and NOXA).



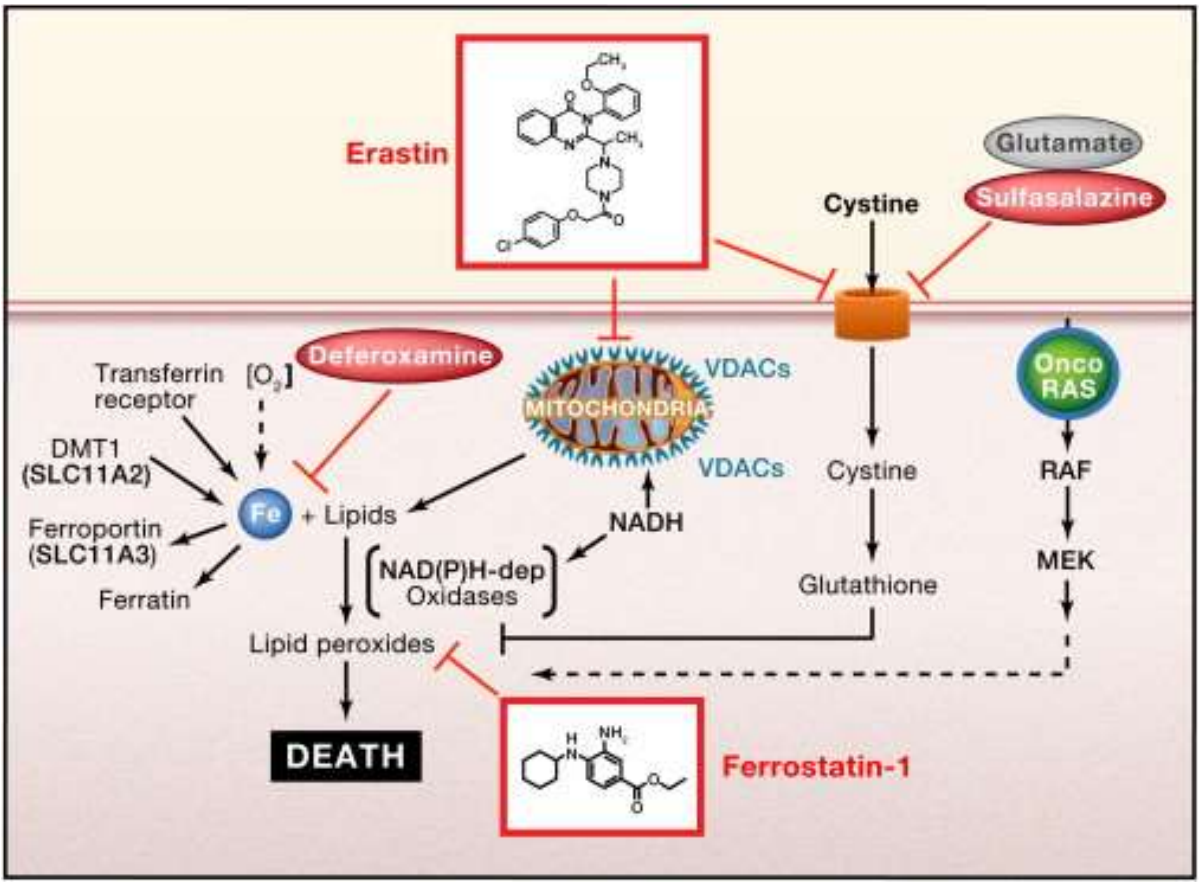
- **Murine double minute X - also known as HDMX in humans, or also MDM4 or HDM4**
- **Mouse double minute 2 homolog (MDM2) also known as E3 ubiquitin-protein ligase**
- **The Growth Arrest and DNA Damage-inducible 45**
- **Noxa (Latin for *damage*) is a pro-apoptotic member of the Bcl-2 protein family**
- **BCL2 Associated X, Apoptosis Regulator**
- **p53 upregulated modulator of apoptosis**

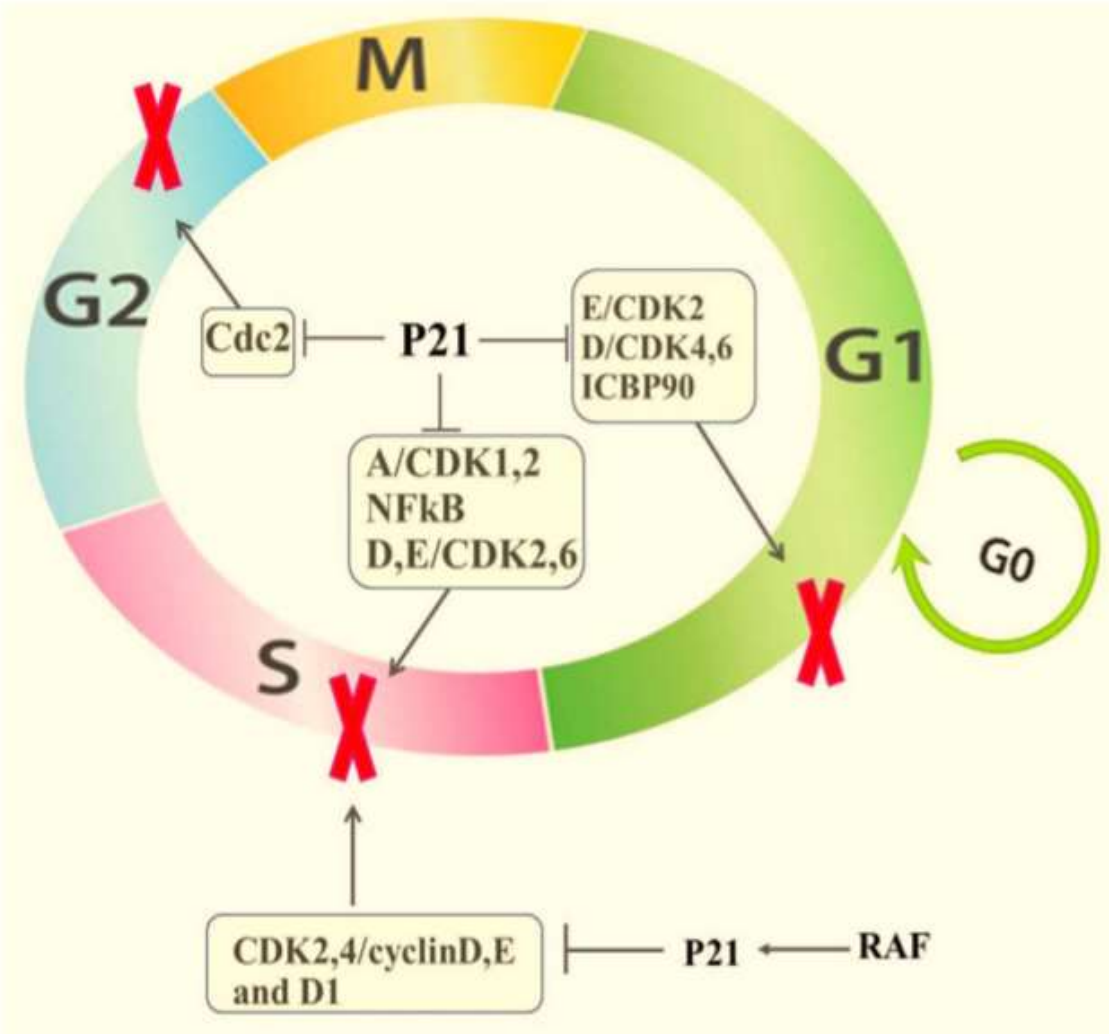


- p53 differentially regulates cell fate decisions in response to mild or severe DNA damage.
- Upon mild damage, p53 is phosphorylated at Ser15 and Ser20 disrupting p53 degradation and thus leading to p53 stabilization and subsequently transactivation of p53 target genes.
- In response to severe DNA damage, the p53 Ser46 kinases additionally phosphorylate p53 at Ser46 resulting in preferential transactivation of cell death-stimulating p53 target genes and p53-dependent induction of mitochondrial outer-membrane permeabilization (MOMP).

Ferroptosis mediated by mitochondrial VDACs

- VDACs are transmembrane channels that transport ions and metabolites and play an important regulatory role in ferroptosis found that erastin acts on VDACs, leading to mitochondrial dysfunction and resulting in a large amount of released oxides, eventually leading to iron-mediated cell death.

- 
Erastin
Glutamate
Sulfasalazine
Cystine
Deferoxamine
Transferrin receptor
[O2]
VDACs
MITOCHONDRIA
VDACs
Onco RAS
DMT1 (SLC11A2)
Fe
+ Lipids
NADH
Cystine
RAF
Ferroportin (SLC11A3)
Ferratin
NAD(P)H-dep Oxidases
Glutathione
MEK
Lipid peroxides
DEATH
Ferrostatin-1


M
G2
G1
S
G0
Cdc2
P21
E/CDK2
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and D1
P21
RAF

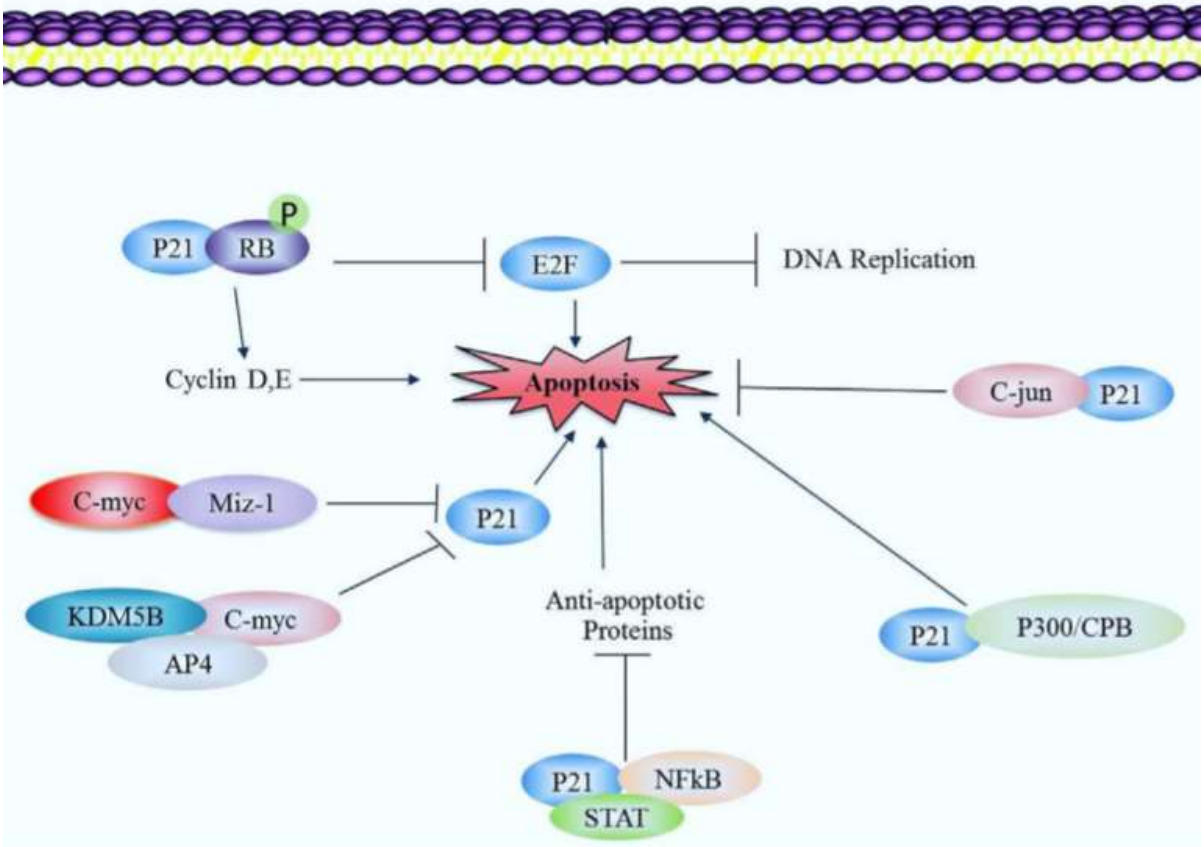
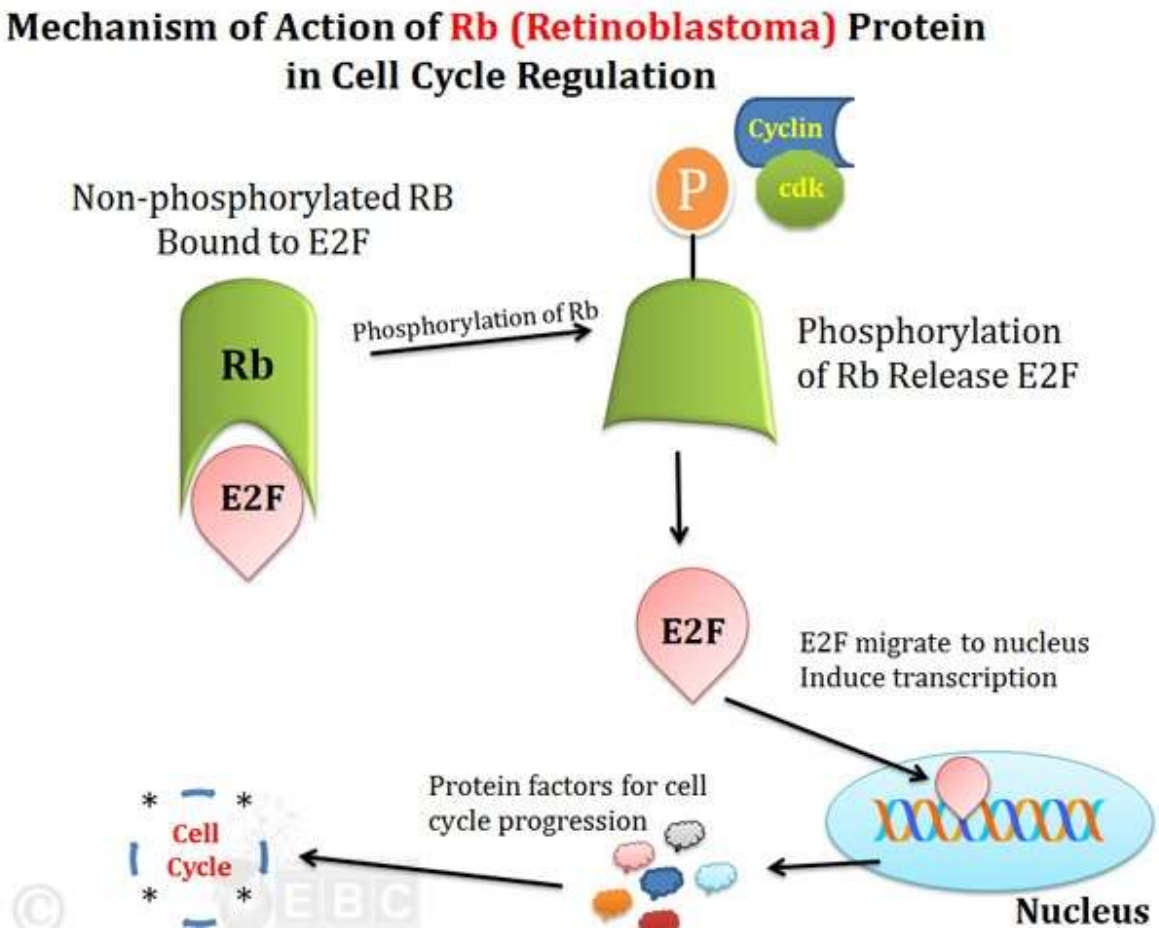


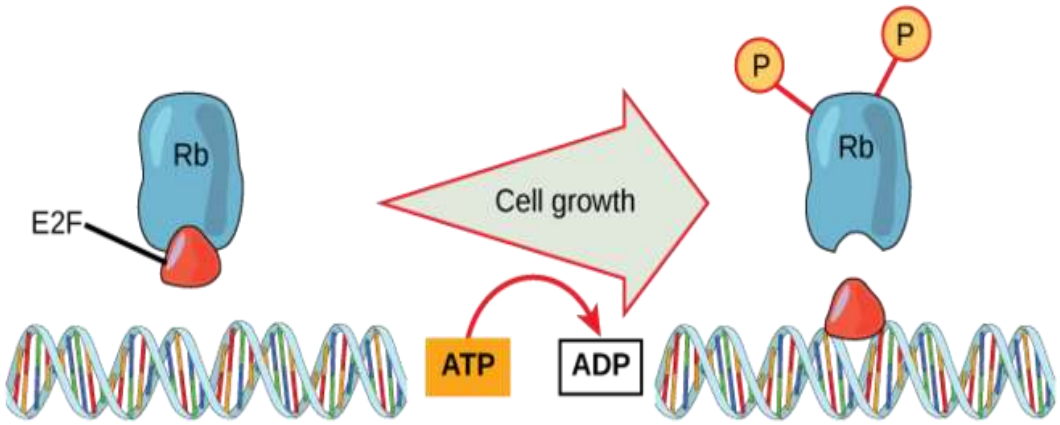
Fig. 3. p21 and apoptosis.

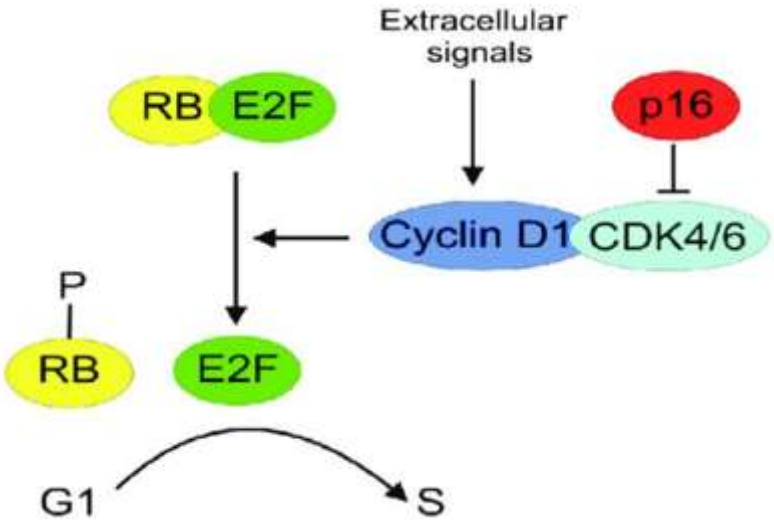


Retinoblastoma proteins are a group of **tumor-suppressor proteins common in many cells.**

- First identified in a malignant tumor of the retina known as retinoblastoma.
- Retinoblastoma is a sporadic or hereditary pediatric neoplasm arising from retinal cells, and ***Knudson (1971***) hypothesized that the tumor phenotype is not apparent unless both copies of the gene are damaged.
- Rb exerts its regulatory influence on other positive regulator proteins. Rb monitors cell size.
- In the active, dephosphorylated state, Rb binds to proteins called transcription factors, most commonly to E2F.

- 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.”





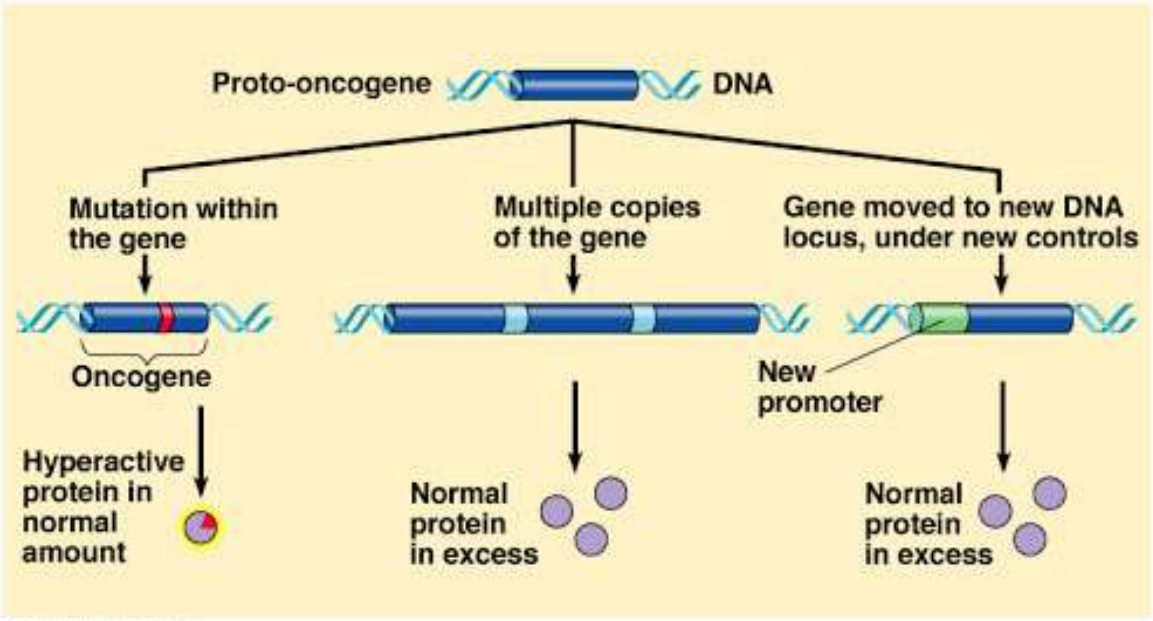
Cancer and the Cell Cycle

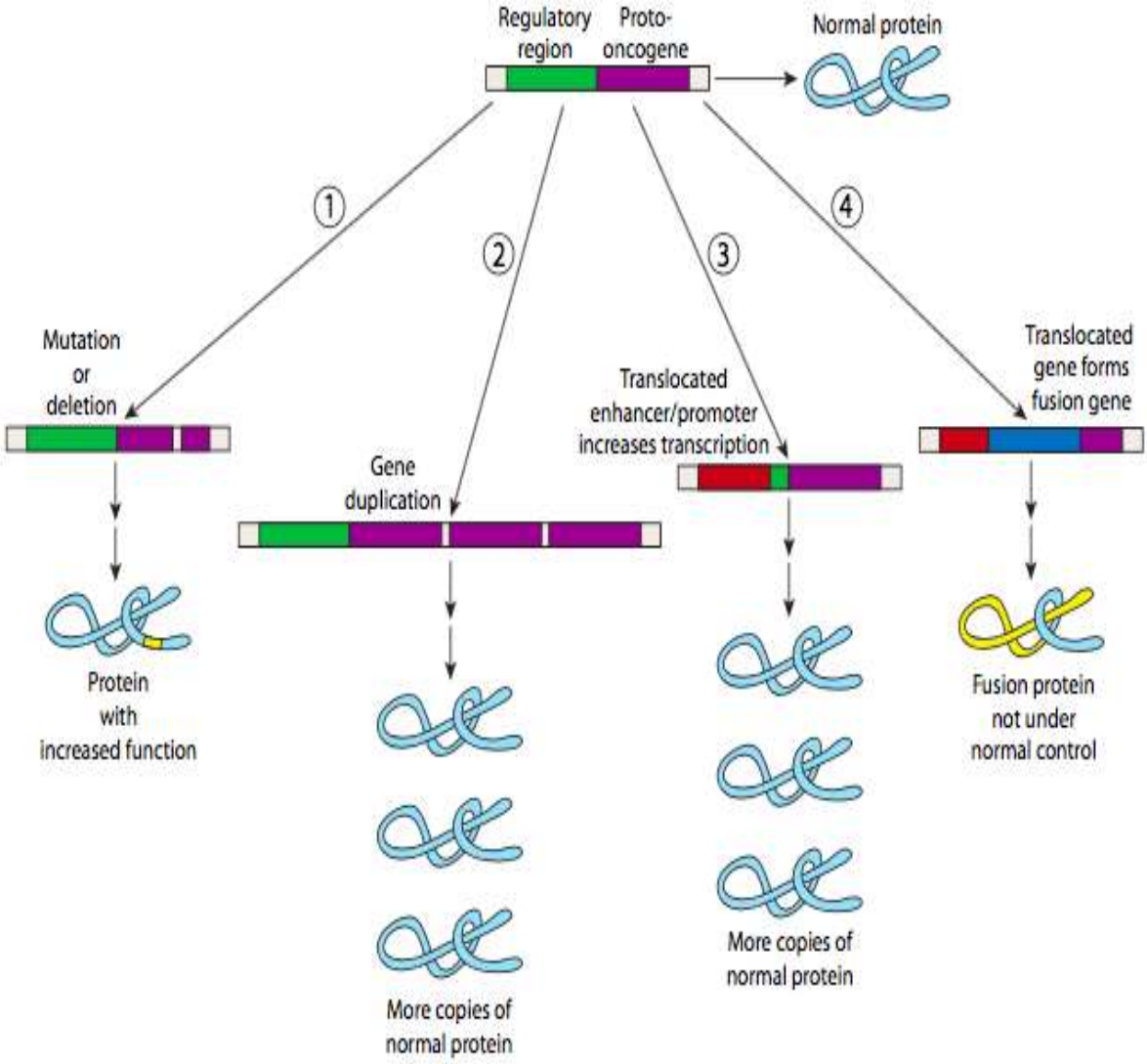
- Cancer is a collective name for many different diseases caused by a common mechanism: uncontrolled cell division.
- Despite the **redundancy and overlapping levels of cell-cycle control, errors occur.**

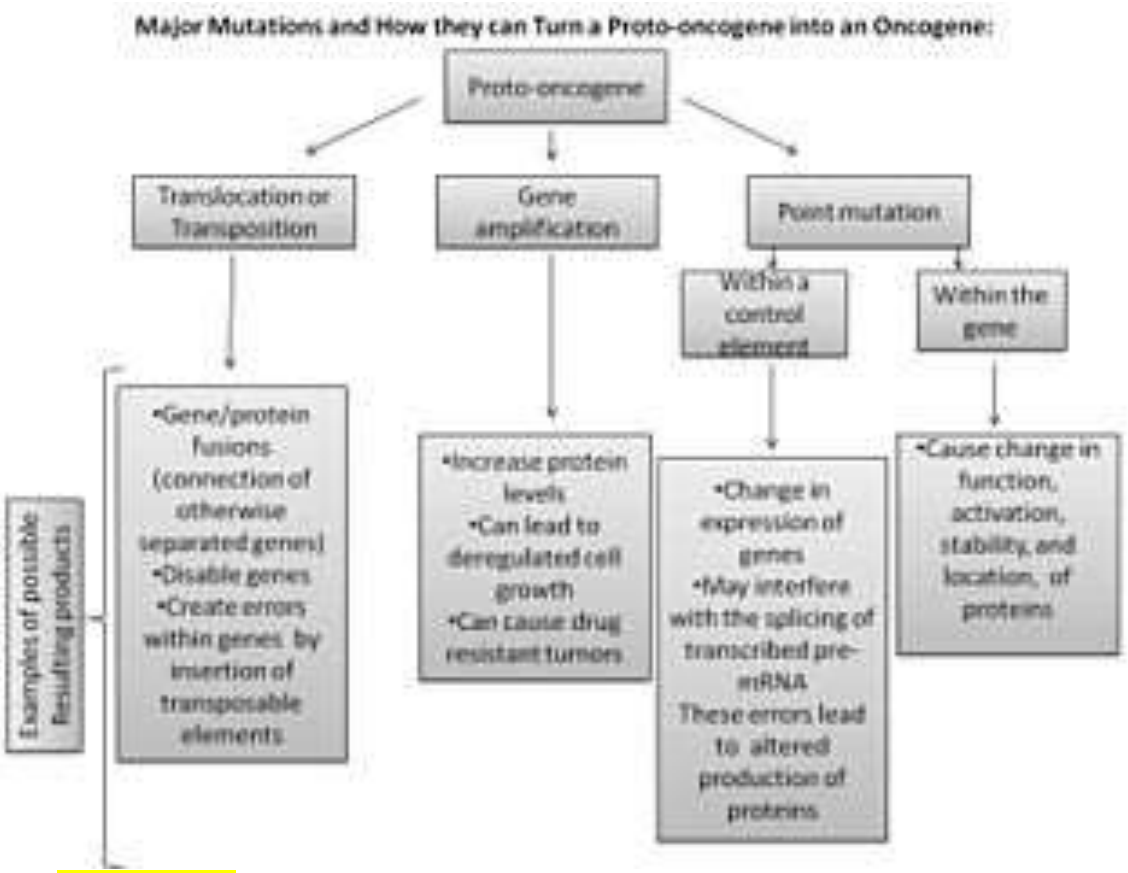
- One of the **critical processes monitored by the cell-cycle checkpoint surveillance mechanism is the proper replication of DNA during the S phase.**
- Even when all of the cell-cycle controls are fully functional, a small percentage of replication errors (mutations) will be passed on to the daughter cells.
- If one of these changes to the DNA nucleotide sequence occurs within a gene, **a gene mutation results**. All cancers begin when a gene mutation gives rise to a faulty protein that participates in the process of cell reproduction.
- The change in the cell that results from the malformed protein may be minor. Even minor mistakes, however, may allow subsequent mistakes to occur more readily.
- Over and over, small, uncorrected errors are passed from parent cell to daughter cells and accumulate as each generation of cells 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 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, **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, a protein involved in cell-cycle regulation**, to be activated before it should be 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 undertake further cell divisions, the mutation would not be propagated and no harm comes to the organism. However, if the atypical daughter cells are able to divide further, the subsequent generation of cells will likely accumulate even more mutations, some possibly in additional genes that regulate the cell cycle.

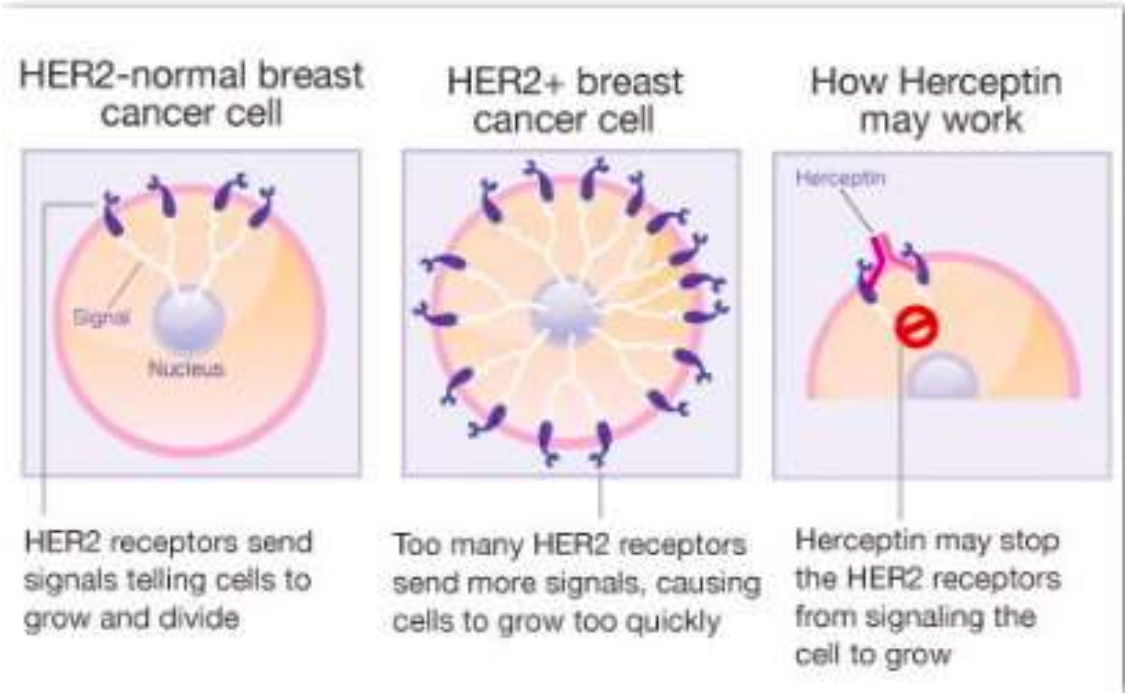

Proto-oncogene
DNA
Mutation within the gene
Multiple copies of the gene
Gene moved to new DNA locus, under new controls
Oncogene
New promoter
Hyperactive protein in normal amount
Normal protein in excess
Normal protein in excess
©Addison Wesley Longman, Inc.


Regulatory region
Proto-oncogene
Normal protein
1
2
3
4
Mutation or deletion
Gene duplication
Translocated enhancer/promoter increases transcription
Translocated gene forms fusion gene
Protein with increased function
More copies of normal protein
More copies of normal protein
Fusion protein not under normal control



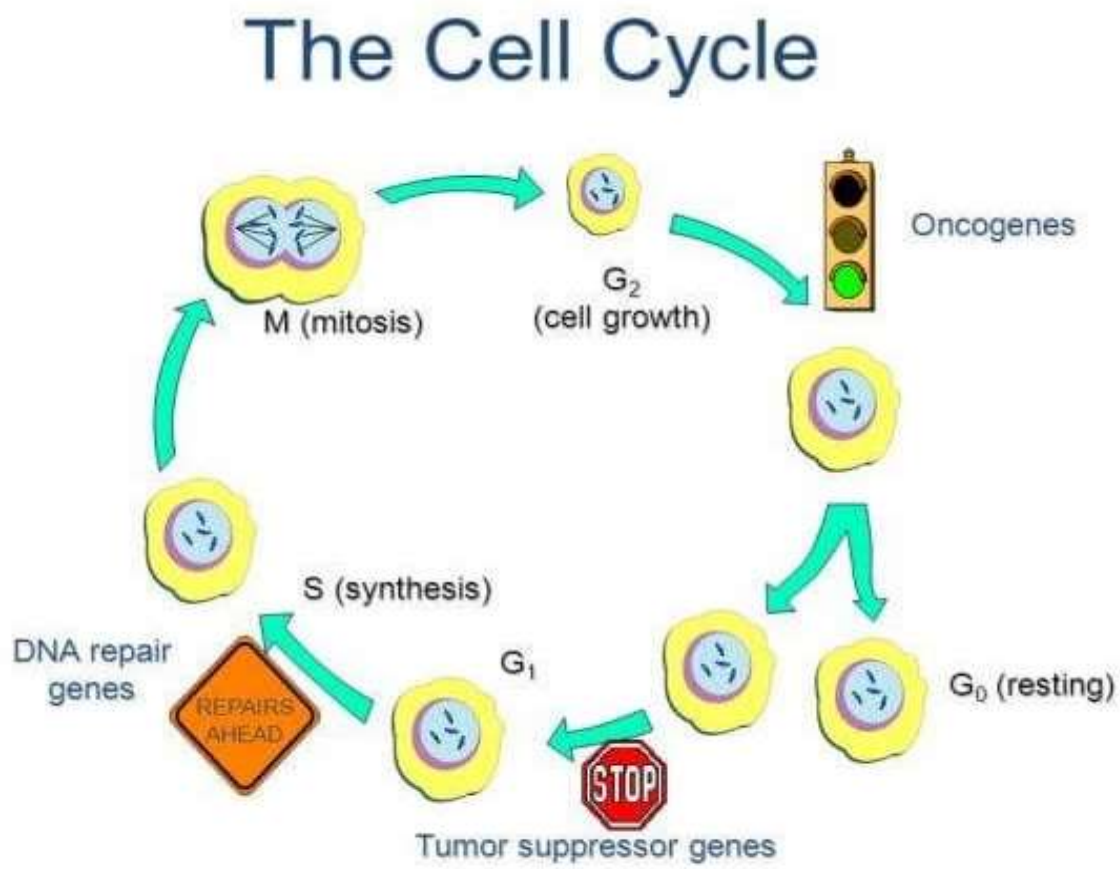
The Cdk example is only one of many genes that are considered proto-oncogenes.

- 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.
- Once a proto-oncogene has been altered such that there is an increase in the rate of the cell cycle, it is then called an oncogene.
- One example of a well known proto-oncogene is the HER2 gene. This gene codes for a transmembrane tyrosine kinase receptor called human epidermal growth factor receptor 2. This protein receptor is involved in the growth, repair and division of cells in the breast.
- In a healthy breast cell, **there are two copies of HER2**, but in some types of breast cancer, the cells contain more than 2 copies, which lead to an excess production of the HER2 protein. This causes the breast cells to grow, divide and proliferate much more quickly than healthy breast cells.

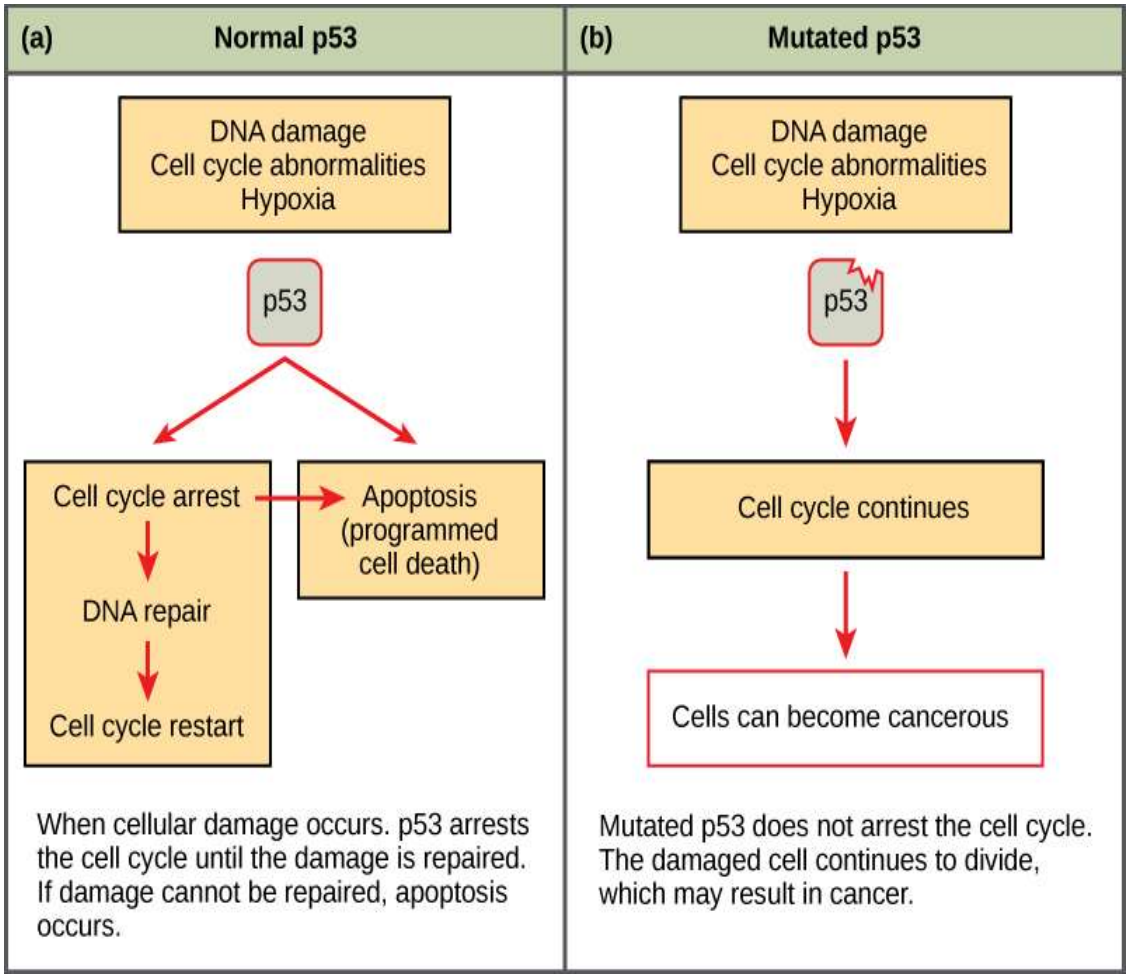


Tumor Suppressor Genes

- Like proto-oncogenes, many of the negative cell-cycle regulatory proteins were discovered in cells that had become cancerous.
- Tumor suppressor genes are genes that code for the negative regulator proteins, the type of regulator that—when activated—can prevent the cell from undergoing uncontrolled division.
- The collective function of the best-understood tumor suppressor gene proteins, retinoblastoma protein (RB1), p53, and p21, is to put up a roadblock to cell-cycle progress 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.



- Mutated p53 genes have been identified in more than 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.
- The p53 protein activates other genes whose products halt the cell cycle (allowing time for DNA repair), activates genes whose products participate in DNA repair, or activates genes that initiate cell death when DNA damage cannot be repaired.
- A damaged p53 gene can result in the cell behaving as if there are no mutations (Figure). This allows cells to divide, propagating the mutation in daughter cells and allowing the accumulation of new mutations. In addition, the damaged version of p53 found in cancer cells cannot trigger cell death.

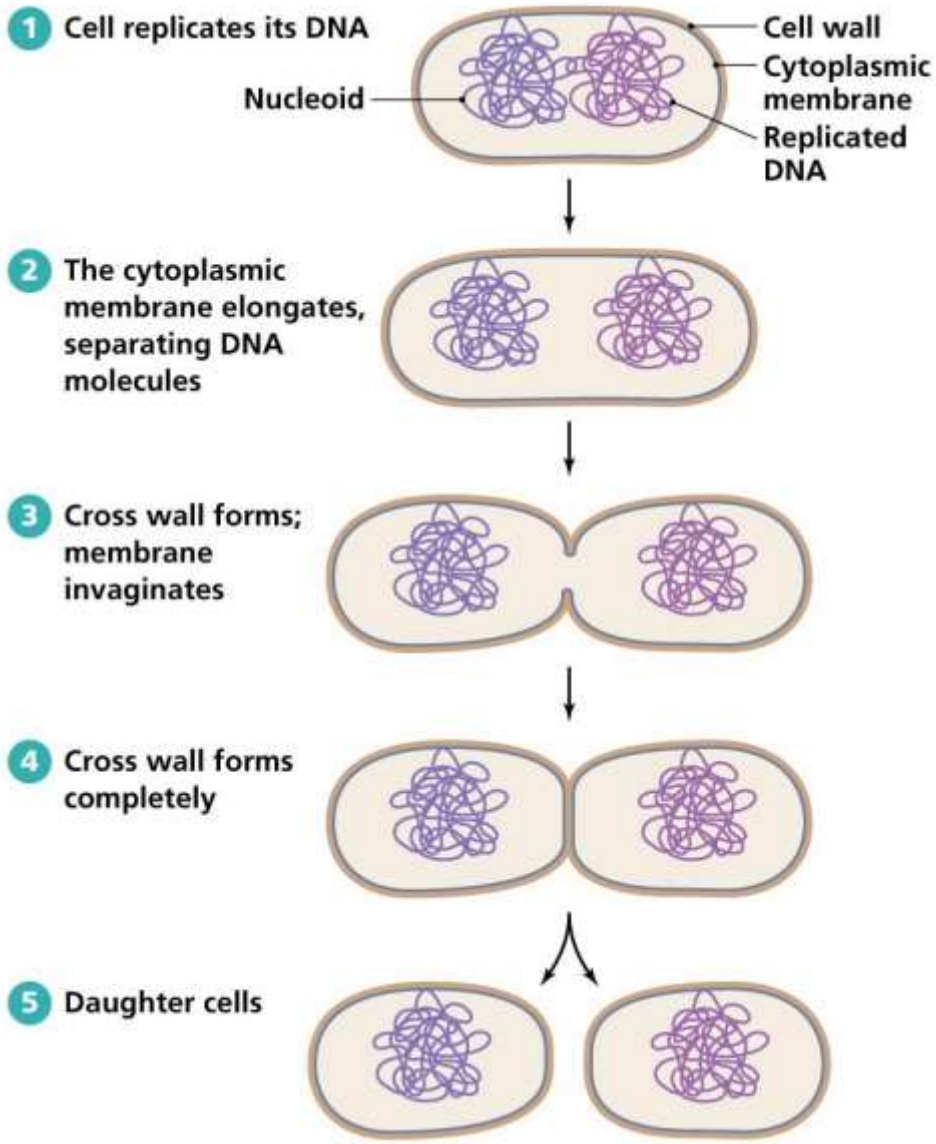


Prokaryotic Cell Division

Binary Fission

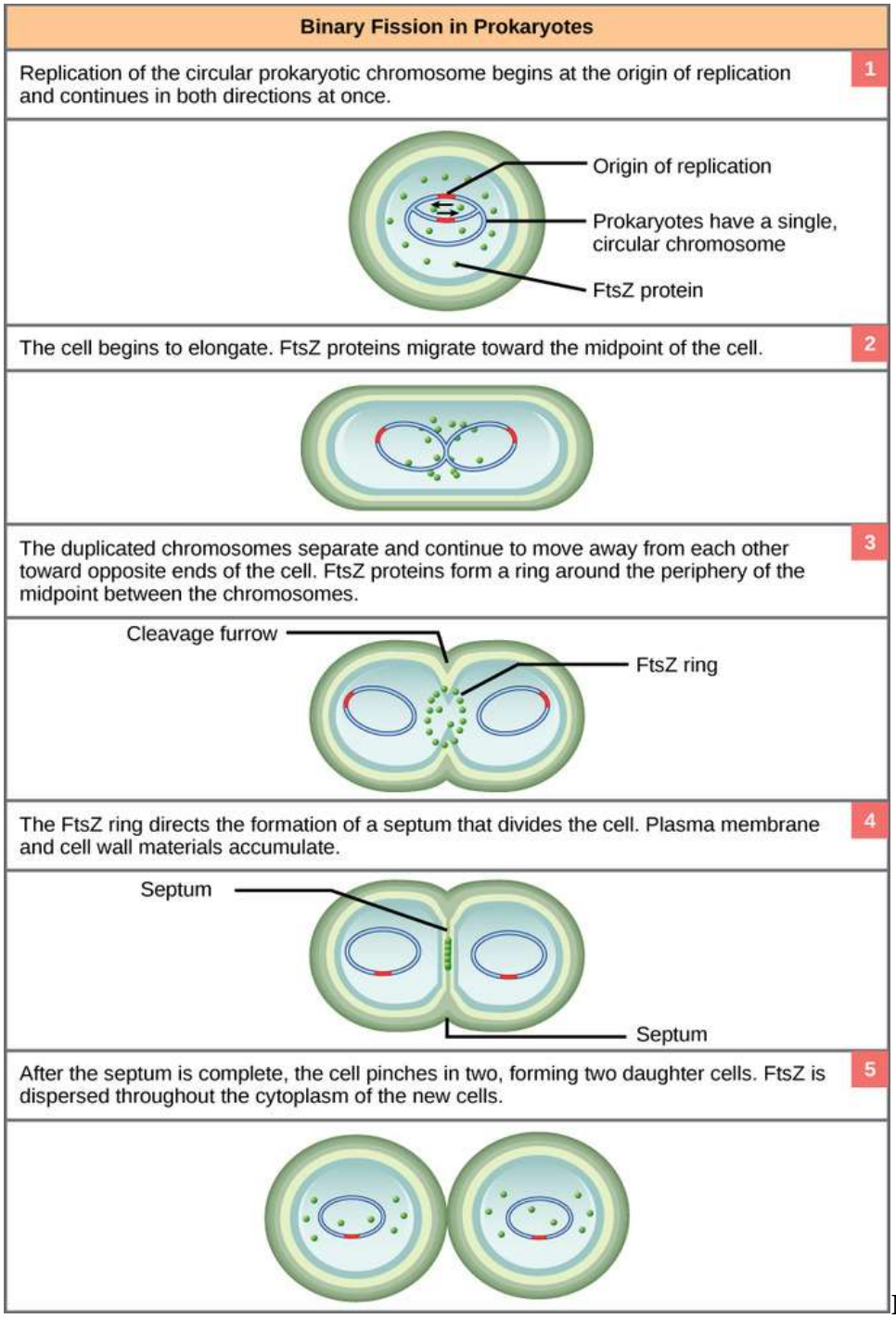
- Binary fission is the method by which prokaryotes produce new individuals that are genetically identical to the parent organism.
- Prokaryotes, **such as bacteria, propagate by binary fission.**
- For unicellular organisms, cell division is the only method used to produce new individuals.
- In both prokaryotic and eukaryotic cells, the outcome of cell reproduction is a pair of daughter cells that are genetically identical to the parent cell.
- In unicellular organisms, daughter cells are individuals.

- Due to the relative simplicity of the prokaryotes, the cell division process, or binary fission, is a less complicated and much more rapid process than cell division in eukaryotes.



- The single, circular DNA chromosome of bacteria is not enclosed in a nucleus, but instead occupies a specific location, the nucleoid, within the cell. Although the DNA of the nucleoid is associated with proteins that aid in packaging the molecule into a compact size, there are no histone proteins and thus, no nucleosomes in prokaryotes.

- The bacterial chromosome is attached to the plasma membrane at about the midpoint of the cell.
- The starting point of replication, the origin, is close to the binding site of the chromosome at the plasma membrane.
- Replication of the DNA is bidirectional, moving away from the origin on both strands of the loop simultaneously.
- As the new double strands are formed, each origin point moves away from the cell wall attachment toward the opposite ends of the cell.
- As the cell elongates, the growing membrane aids in the transport of the chromosomes.
- After the chromosomes have cleared the midpoint of the elongated cell, cytoplasmic separation begins.
- The **formation of a ring composed of repeating units of a protein, FtsZ**, directs the partition between the nucleoids. Formation of the FtsZ ring triggers the accumulation of other proteins that work together to recruit new membrane and cell wall materials to the site. A septum is formed **between the nucleoids, extending gradually from the periphery toward the center of the cell. When the new cell walls are in place, the daughter cells separate.**



Mitotic Spindle Apparatus

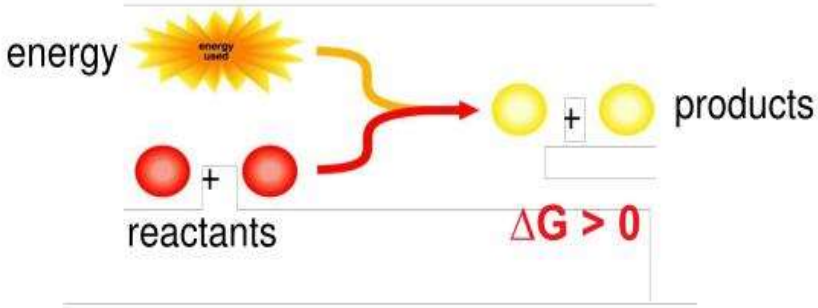
- The precise timing and formation of the mitotic spindle is critical to the success of eukaryotic cell division.
- Prokaryotic cells, on the other hand, do not undergo karyokinesis and, therefore, have no need for a mitotic spindle.
- However, the **FtsZ protein that plays such a vital role in prokaryotic cytokinesis** is structurally and functionally very similar to tubulin, the building block of the microtubules that make up the mitotic spindle fibers that are necessary for eukaryotes.
- FtsZ proteins can form filaments, rings, and other three-dimensional structures that resemble the way tubulin forms microtubules, centrioles, and various cytoskeletal components.
- In addition, both FtsZ and tubulin employ the same energy source, GTP (guanosine triphosphate), to rapidly assemble and disassemble complex structures.
- **FtsZ and tubulin are homologous structures derived from common evolutionary origins**.
- In this example, **FtsZ is the ancestor protein to tubulin (a modern protein).**
- While both **proteins are found in extant organisms, tubulin function has evolved and diversified tremendously since evolving from its FtsZ prokaryotic origin.**
- **Transport across cell membranes: Passive and active transports, Permeases**
- Life depends on a membrane's ability to precisely control the level of solutes in the aqueous compartments, inside and outside, bathing the membrane.
- The membrane determines what solutes enter and leave a cell.
- Transmembrane transport is controlled by complex interactions between membrane lipids, proteins, and carbohydrates.
- A biological membrane is semipermeable, meaning it is permeable to some molecules, **most notably water,** while being very impermeable to most solutes (various biochemicals and salts) found in the bathing solution.
- One of the great wonders of the cell membrane is its ability to regulate the concentration of substances inside the cell.
- These substances **include ions such as Ca^{2+}, Na^{+}, K^{+}, and Cl^{-};** nutrients including sugars, fatty acids, and amino acids; and waste products, particularly carbon dioxide (CO_2), which must leave the cell.

Controlling what enters and exits the cell

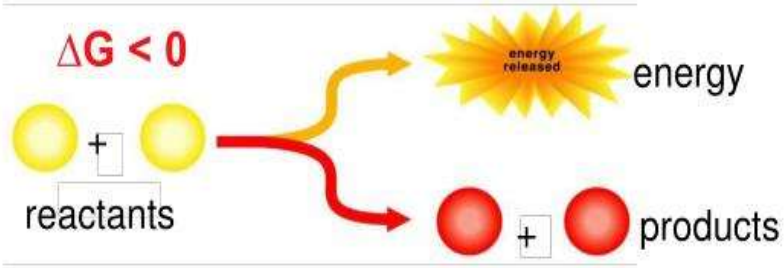
- The membrane's **lipid bilayer structure provides the first level of control**.
- The **phospholipids are tightly packed together, and the membrane has a hydrophobic interior. This structure causes the membrane to be selectively permeable**.
- A membrane that has selective permeability allows only substances meeting certain criteria to pass through it unaided.
- In the case of the cell membrane, only relatively small, nonpolar materials can move through the lipid bilayer at biologically relevant rates (remember, the lipid tails of the membrane are nonpolar).
- All substances that move through the membrane do so by one of two general methods, which are categorized based on whether or not the transport process is exergonic or endergonic.
- Passive transport is the exergonic movement of substances across the membrane.
- In contrast, active transport is the endergonic movement of substances across the membrane that is coupled to an exergonic reaction.

Endergonic and Exergonic Reactions

- Endergonic reaction: requires energy, usually ATP



- Exergonic reaction: releases energy, occurs spontaneously

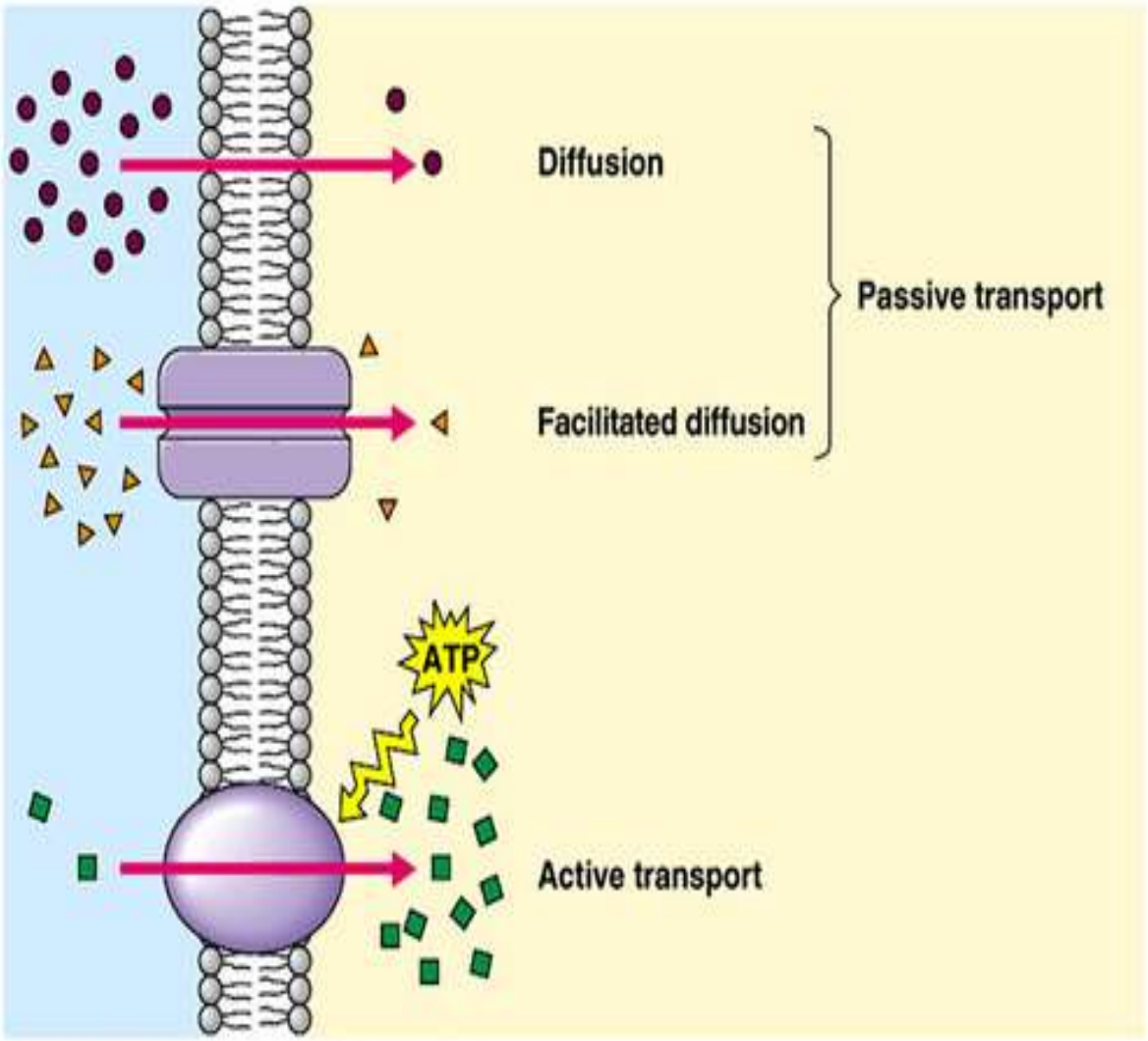


Active Transport

- This is the biological process in which molecules move against the concentration gradient and require chemical energy to move biochemical compounds **from a lower region to the high region**. Therefore, this process uses ATP – Adenosine triphosphate to pump molecules through a concentration gradient.
- Complex **sugar, ions, large cells, proteins**, and other particles are transported in this process.

There are two types of Active transport:

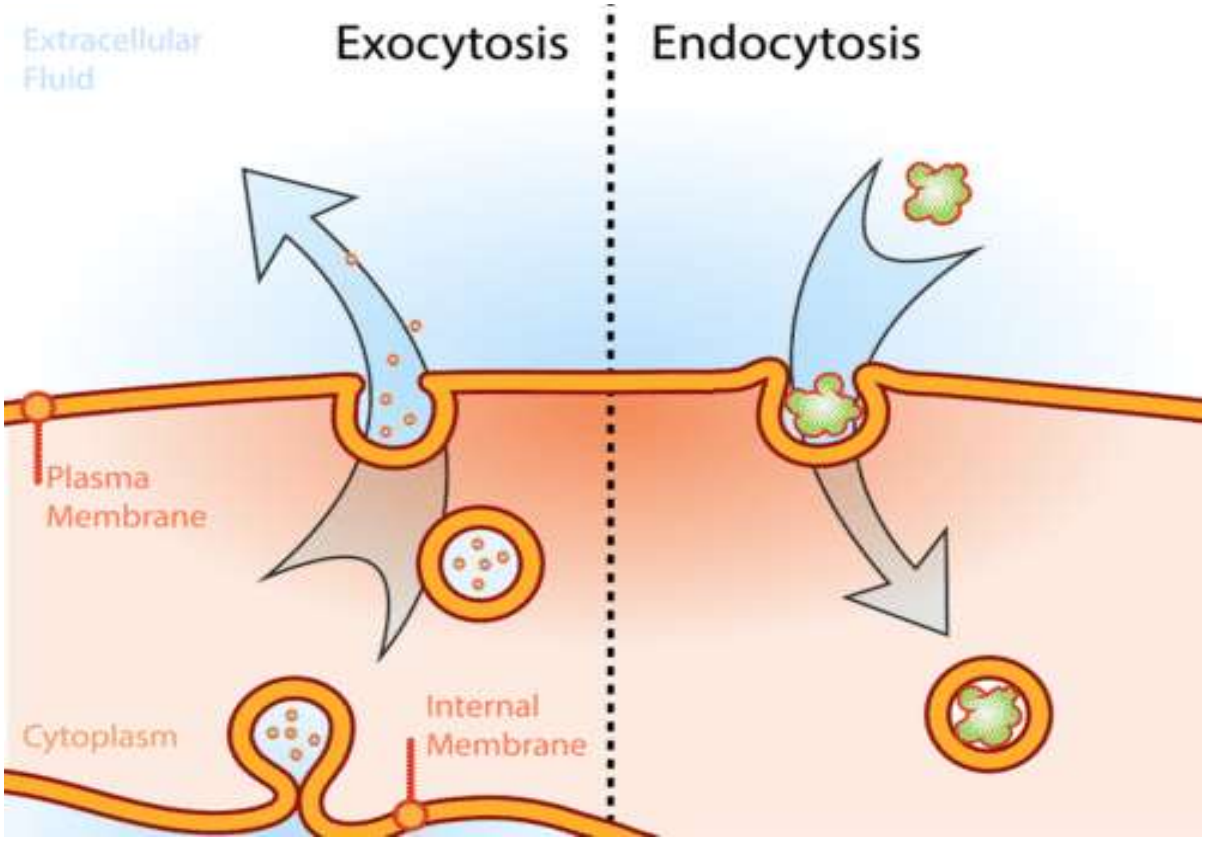
- **Primary Active transport**
- **Secondary Active transport**



- **Exocytosis, endocytosis and sodium-potassium pump are a few examples of active transport**.
- The process of endocytosis and exocytosis are utilized by all the cells for transportation of molecules which cannot passively permeate via the membrane.
- Endocytosis is the process of active transportation of molecules into the cells by the action of engulfing it along with its membrane.
- Exocytosis produces a counter function thereby forcing molecules out of the cell. The process of homeostasis facilitates an equal flow of molecules in and out of a cell

which confers that the number of molecules that enter the cell through endocytosis equates to the number of molecules that exits a cell through the process of exocytosis.

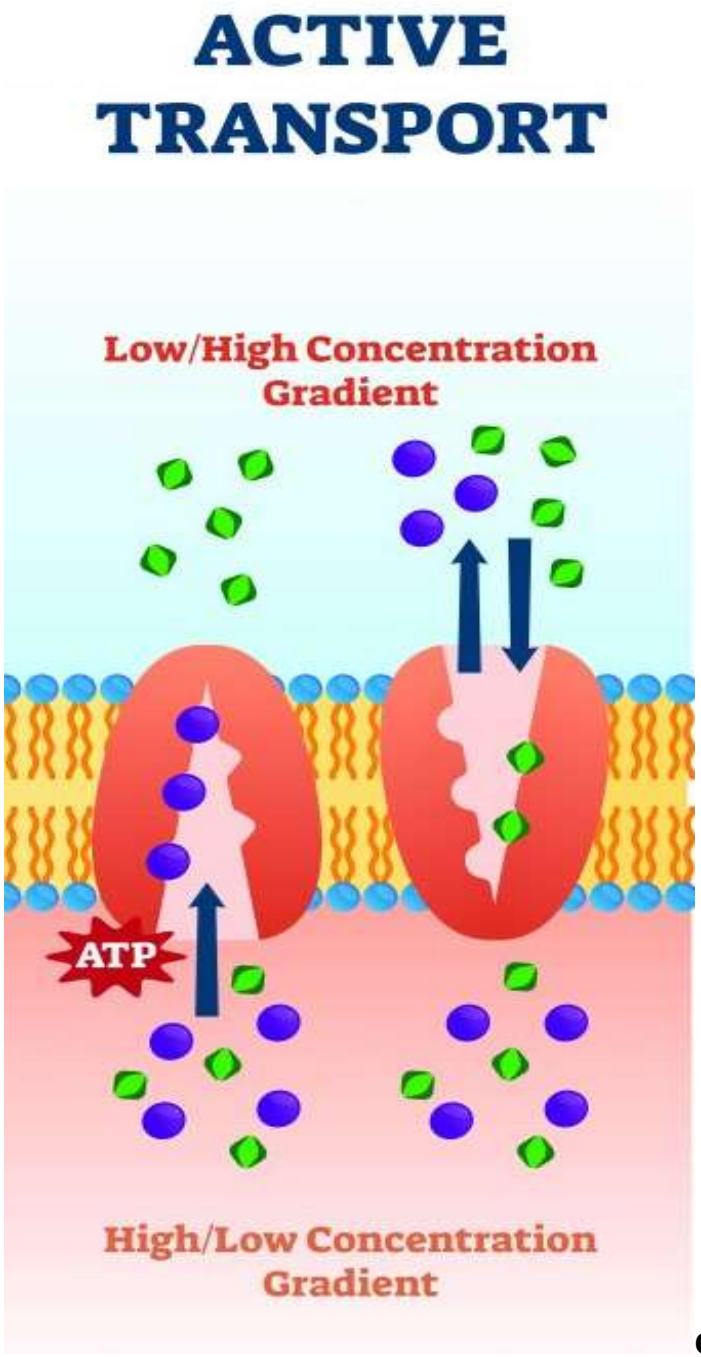
- Both the processes assure that nutrients and wastes are balanced for the smooth functioning of the cells.



Moving Against a Gradient

- To move substances against a concentration or electrochemical gradient, the cell must use energy. This energy is harvested from ATP generated through the cell's metabolism.
- Active transport mechanisms, **collectively called pumps**, work against electrochemical gradients.
- Small substances constantly pass through plasma membranes.
- Active transport maintains concentrations of ions and other substances needed by living cells in the face of these passive movements.

- Much of a cell's supply of metabolic energy may be spent maintaining these processes. (Most of a red blood cell's metabolic energy is used to maintain the imbalance between exterior and interior sodium and potassium levels required by the cell.) Because active transport mechanisms depend on a cell's metabolism for energy, they are sensitive to many metabolic poisons that interfere with the supply of ATP.

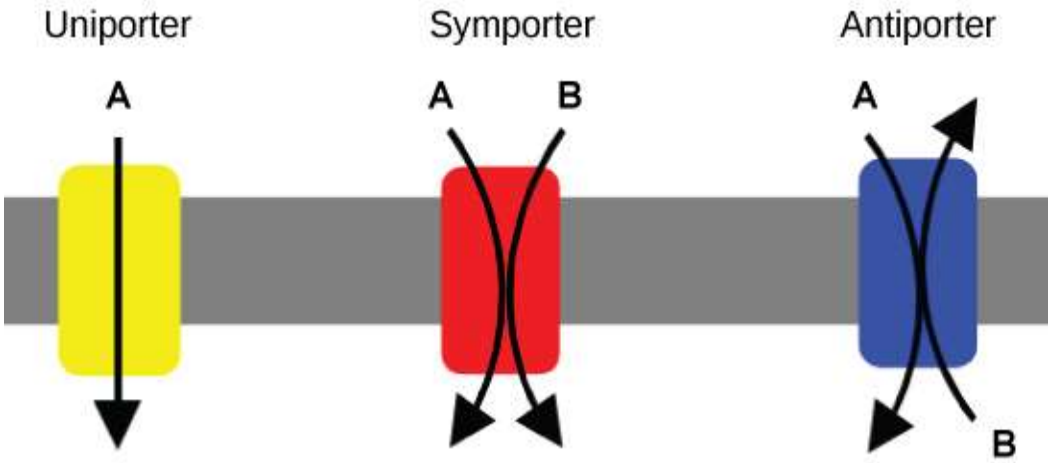


Carrier Proteins for Active Transport

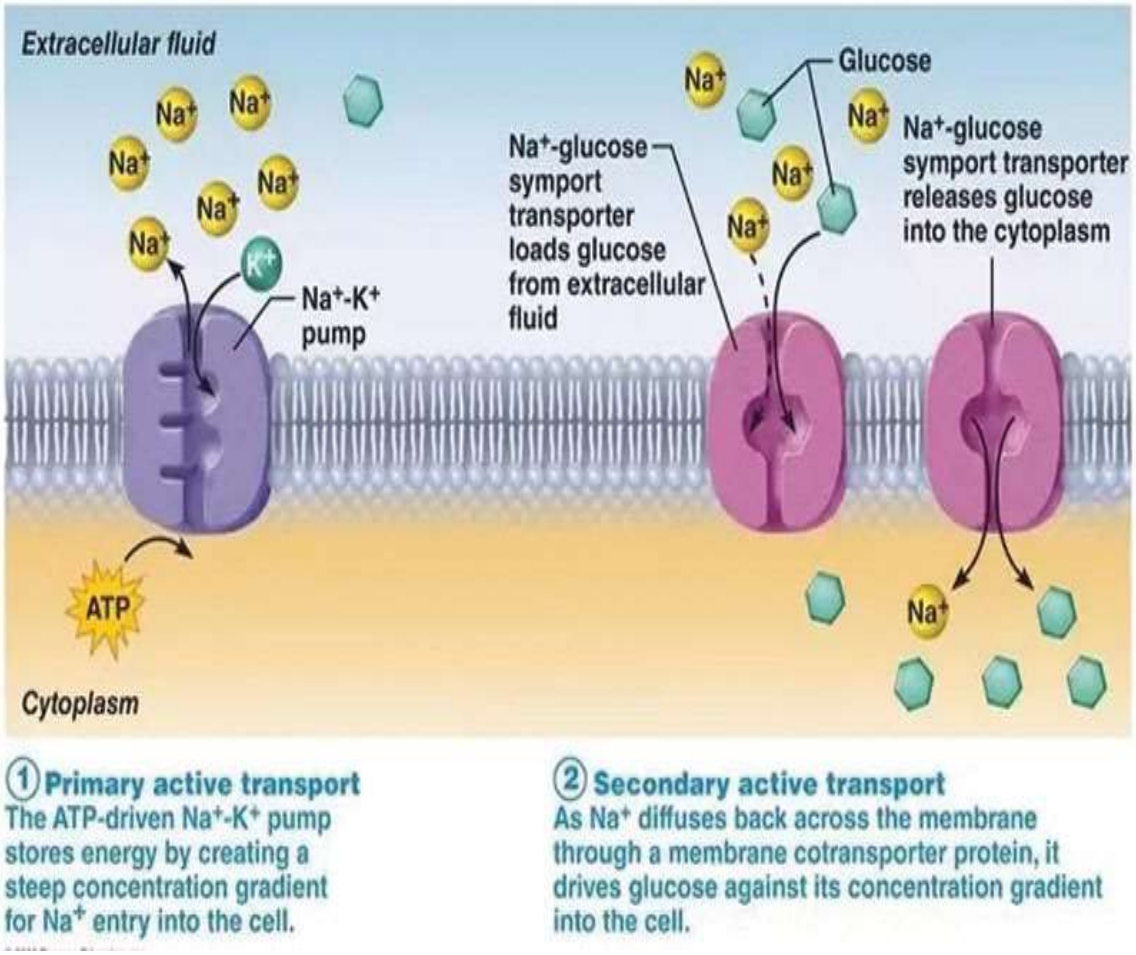
Membrane adaption for active transport is the presence of specific carrier proteins or pumps to facilitate movement:

there are three types of these proteins or **transporters**.

1. A **uniporter** carries **one specific ion or molecule**.
2. A **symporter** carries **two different ions or molecules, both in the same direction.**
3. An **antiporter** also carries **two different ions or molecules, but in different directions.**

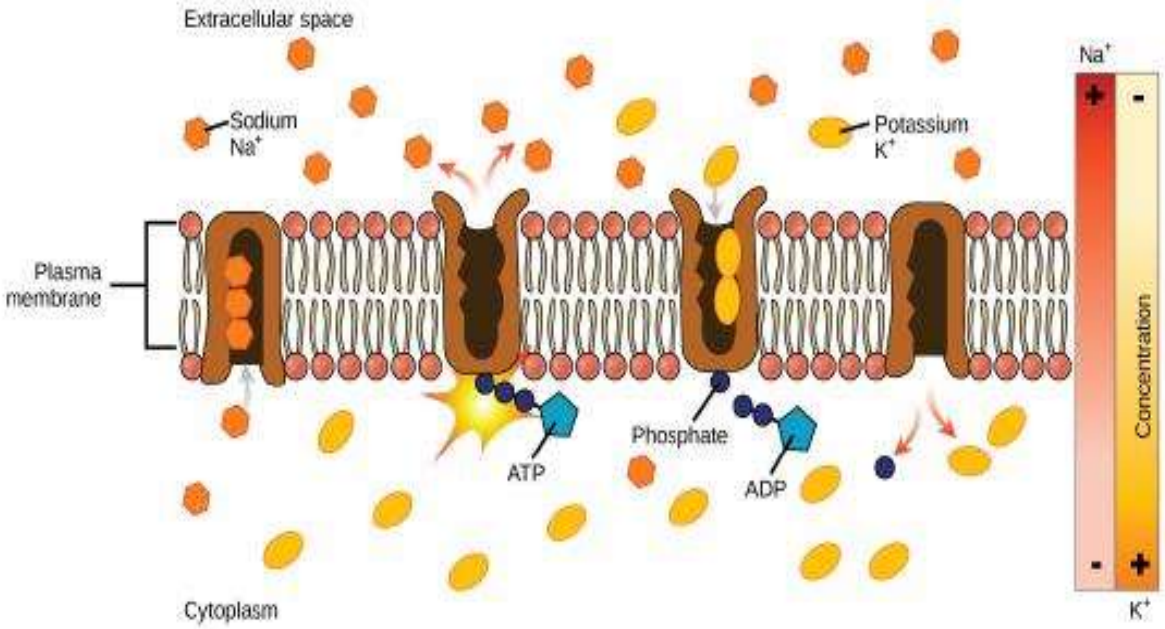


- All of these transporters can also transport small, uncharged organic molecules like glucose.
- These three types of carrier proteins **are also found in facilitated diffusion,** but they **do not require ATP to work in that process**.
- Some examples of pumps for active transport are **Na^+-K^+ ATPase**, which carries sodium and potassium ions, and **H^+-K^+ ATPase,** which carries **hydrogen and potassium ions**. Both of **these are antiporter carrier proteins**.
- **Two other carrier proteins are Ca^{2+} ATPase and H^+ ATPase**, which carry only calcium and only hydrogen ions, respectively. Both are pumps.



- Two mechanisms exist for the transport of small-molecular weight material and small molecules.
- **Primary active transport** moves ions across a membrane and creates a difference in charge across that membrane, **which is directly dependent on ATP.**
- **Secondary active transport** describes the movement of material that is due to the electrochemical gradient established by primary active transport that **does not directly require ATP.**
- **Primary Active Transport**
- One of the most important pumps in animal cells is the sodium-potassium pump (Na+-K+ ATPase), which maintains the electrochemical gradient (and the correct concentrations of Na+ and K+) in living cells.

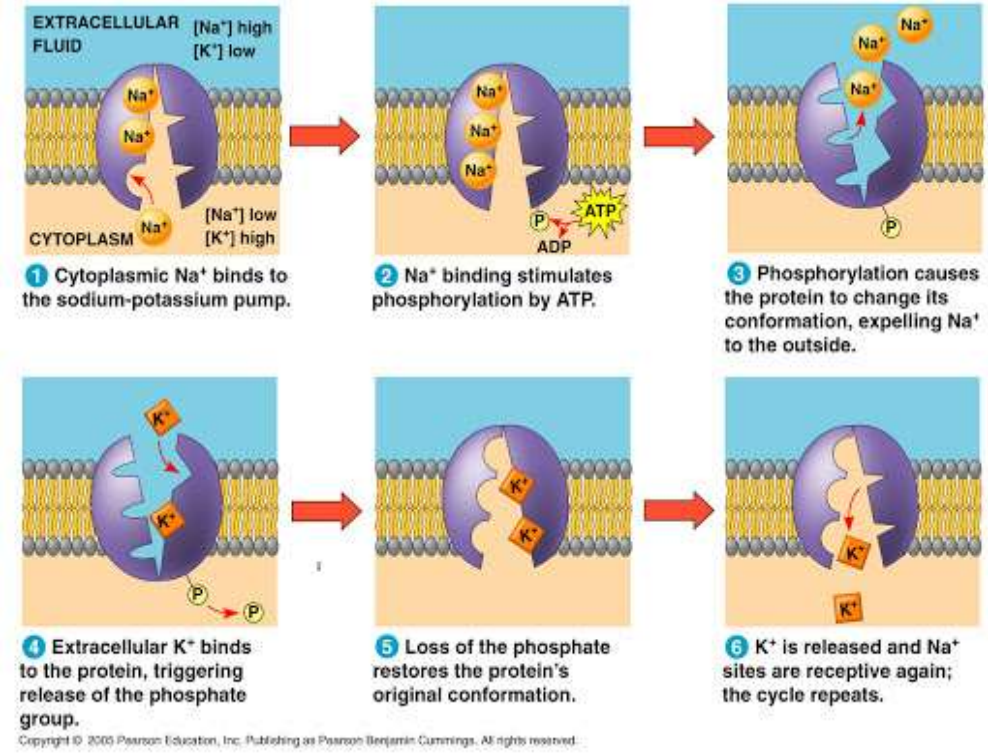
- The sodium-potassium pump moves K+ into the cell while moving Na+ out at the same time, at a ratio of three Na+ for every two K+ ions moved in.
- **The Na+-K+ ATPase exists in two forms**, depending on its orientation to the interior or exterior of the cell and its affinity for either sodium or potassium ions.



The process consists of the following six steps.

1. With the **enzyme oriented towards the interior of the cell,** the **carrier has a high affinity for sodium ions**. Three ions bind to the protein.
2. **ATP is hydrolyzed by the protein carrier** and a low-energy phosphate group attaches to it.
3. As a result, the **carrier changes shape and re-orients** itself towards the exterior of the membrane. The protein's affinity for sodium decreases and the three sodium ions leave the carrier.
4. The **shape change increases the carrier's affinity for potassium ions**, and two such ions attach to the protein. Subsequently, the low-energy phosphate group detaches from the carrier.
5. With the phosphate group removed and potassium ions attached, the carrier protein repositions itself towards the interior of the cell.

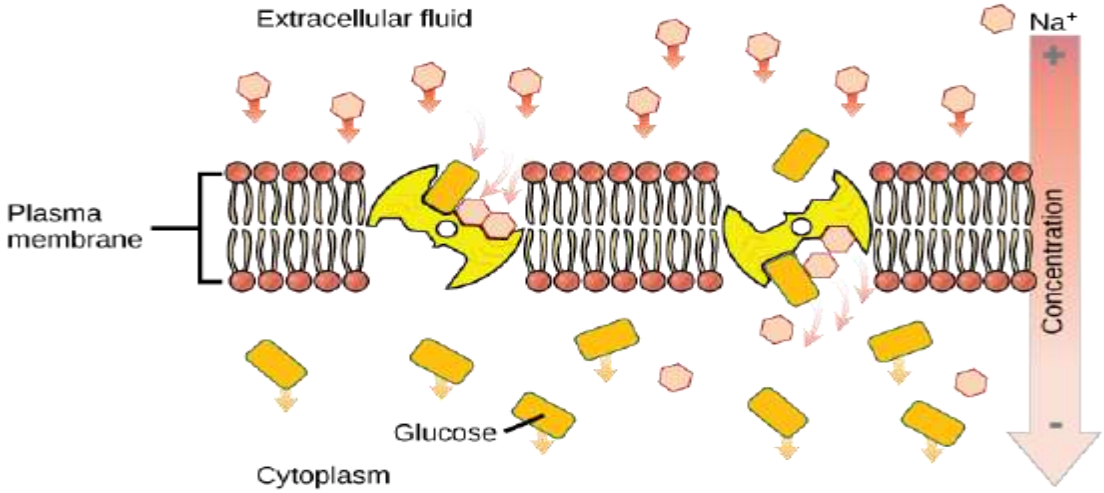
6. The carrier protein, in its new configuration, **has a decreased affinity for potassium,** and the **two ions are released into the cytoplasm.** The protein now has a higher affinity for sodium ions, and the process starts again.

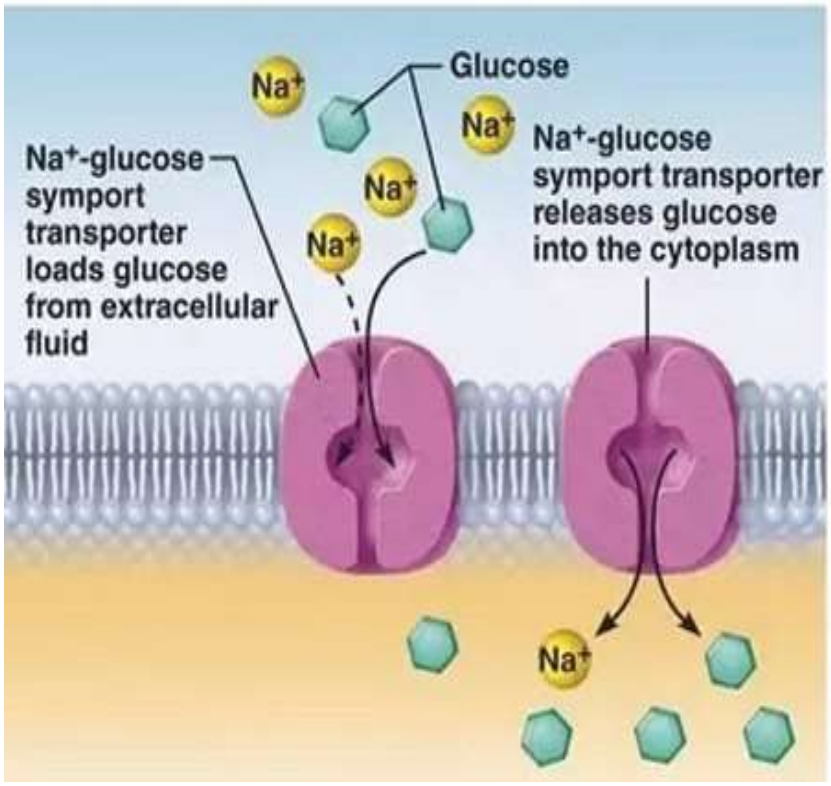


Secondary Active Transport (Co-transport)

- Secondary active transport brings sodium ions, and possibly other compounds, into the cell.
- As sodium ion concentrations build outside of the plasma membrane because of the action of the primary active transport process, an **electrochemical gradient is created**.
- If a channel protein exists and is open, the sodium ions will be pulled through the membrane. This movement is used to transport other substances that can attach themselves to the transport protein through the membrane.
- Many amino acids, as well as glucose, enter a cell this way.
- This secondary process is also used to store high-energy hydrogen ions in the mitochondria of plant and animal cells for the **production of ATP**.

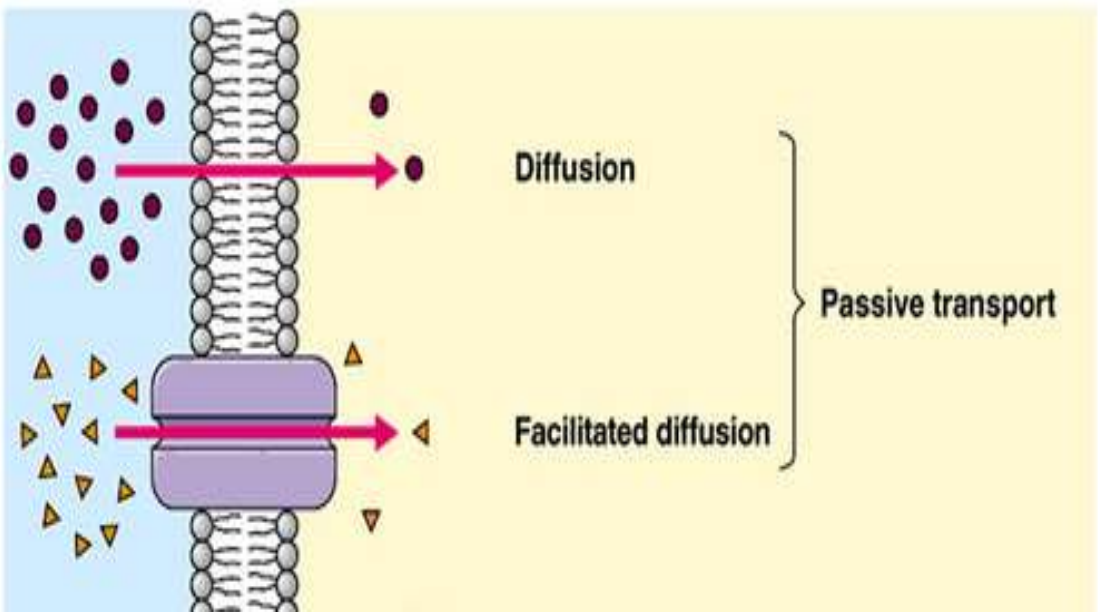
- The potential energy that accumulates in the stored hydrogen ions is translated into kinetic energy as the ions surge through the channel protein ATP synthase, and that energy is used to convert ADP into ATP.





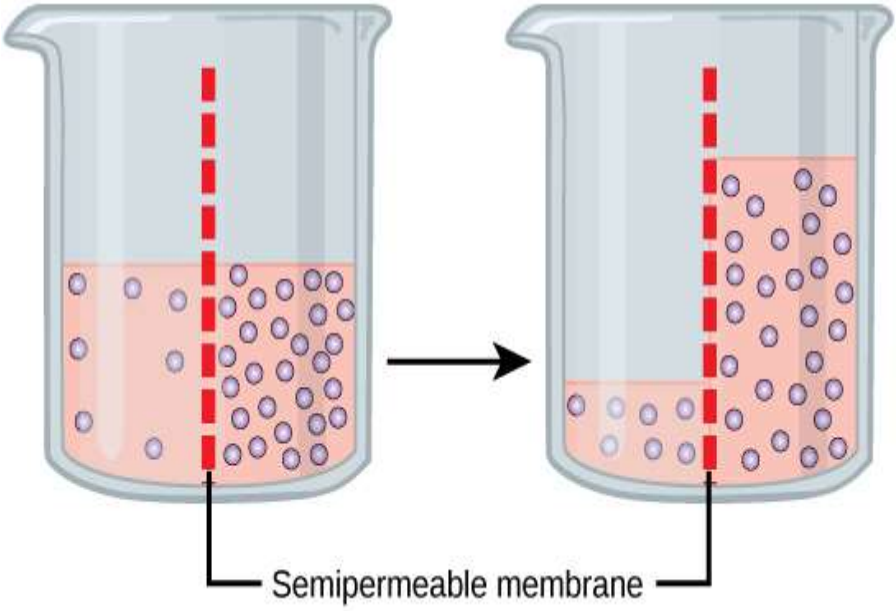
Passive Transport

- In this biological process, energy is not required for transporting the molecules, as the biochemicals move from a region of higher concentration to a region of lower concentration.
- All particles which are easily soluble are transported through passive transport.
- This process is carried out to maintain the balance and the equilibrium level in a cell.
- All the wastes molecules including, water and carbon dioxide is separated and moved out of the cell using passive transport.
- **Osmosis, diffusion and facilitated diffusion** are some of the examples of passive transport.



Osmosis

- Osmosis is a passive process and happens without any expenditure of energy.
- It involves the *movement of molecules from a region of higher concentration to lower concentration* until the concentrations become equal on either side of the membrane.
- *Osmosis is a process by which the molecules of a solvent pass from a solution of low concentration to a solution of high concentration through a semi-permeable membrane."*



Osmotic Solutions

There are three different types of solutions:

1. Isotonic Solution
2. Hypertonic Solution
3. Hypotonic Solution

An isotonic solution is one that has the same concentration of solutes both inside and outside the cell.

A hypertonic solution is one that has a higher solute concentration outside the cell than inside.

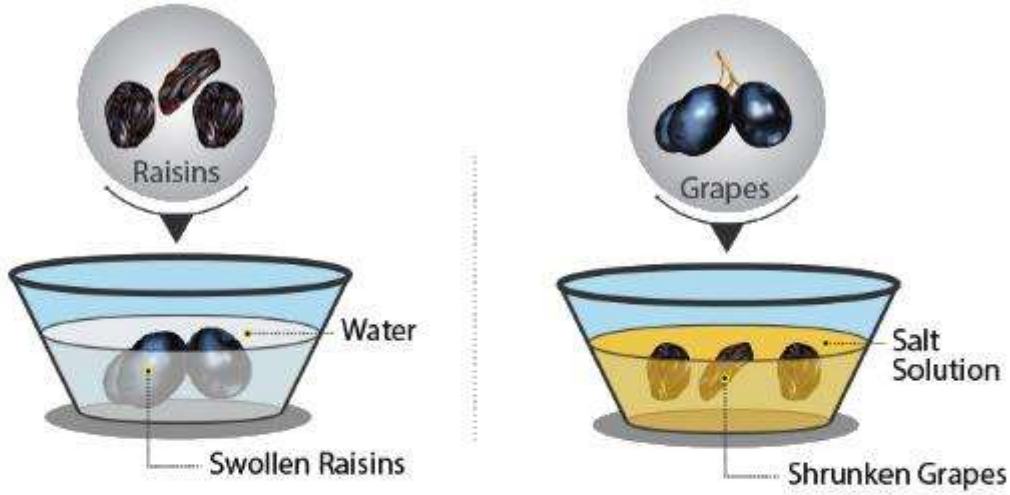
A hypotonic solution is the one that has a higher solute concentration inside the cell than outside.

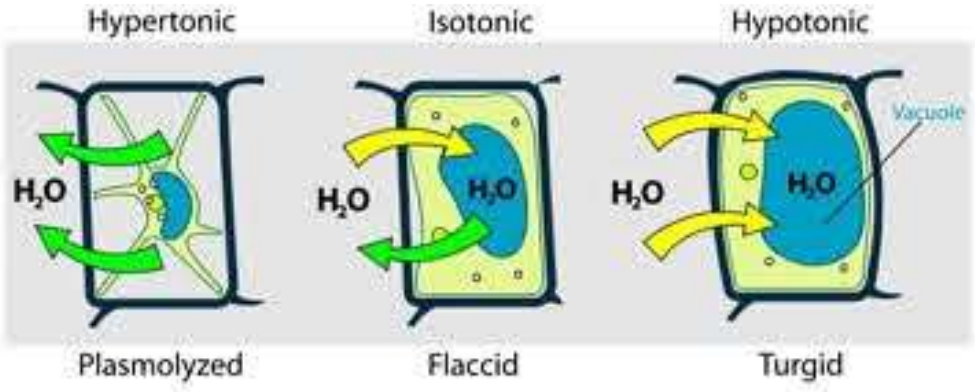
Types of Osmosis

Osmosis is of two types:

Endosmosis– When a substance is placed in a hypotonic solution, the solvent molecules move inside the cell and the cell becomes **turgid** or undergoes deplasmolysis. This is known as endosmosis.

Exosmosis– When a substance is placed in a hypertonic solution, the solvent molecules move outside the cell and the cell becomes flaccid or undergoes plasmolysis. This is known as exosmosis.



- 

Osmosis affects the cells differently.

- An animal cell will lyse when placed in a hypotonic solution compared to a plant cell.
- The plant cell has thick walls and requires more water. The cells will not burst when placed in a hypotonic solution. In fact, a hypotonic solution is ideal for a plant cell.
- An animal cell survives only in an isotonic solution.
- In an isotonic solution, the plant cells are no longer turgid and the leaves of the plant droop.

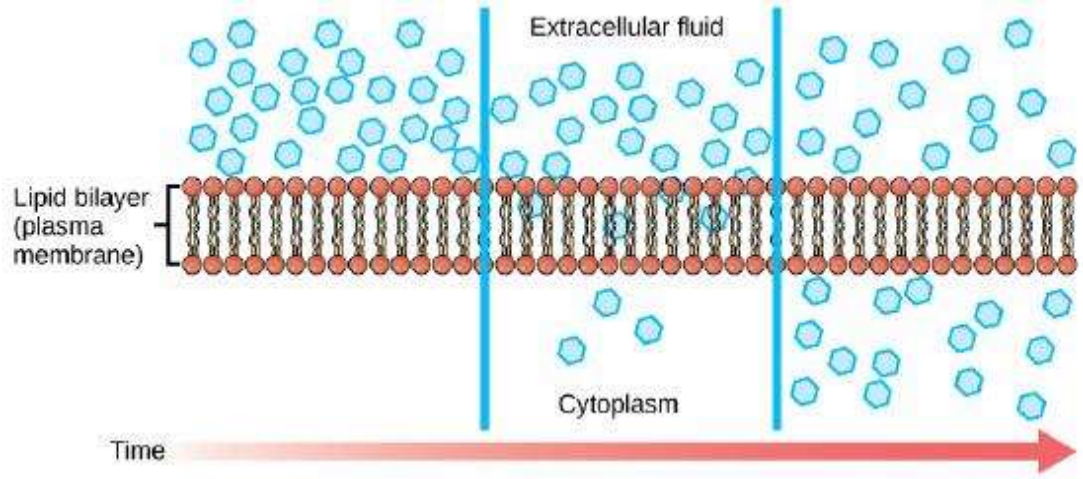
In an animal cell, osmosis helps in absorbing water from the intestines to the blood.

Osmosis has a significant role to play in plants, animals and also in humans.

- The absorption of water from the soil is due to osmosis. The plant roots have a higher concentration than the soil, therefore, the water flows into the roots.
- The guard cells of the plants are also affected by osmosis. When the plant cells are filled with water, the guard cells swell up and the stomata open.
- If a freshwater or saltwater fish is placed in the water with different salt concentrations, the fish dies due to entry or exit of water in the cells of the fish.
- Humans suffering from cholera are also affected by osmosis. The bacteria that overpopulate the intestines reverse the flow of absorption and do not allow water to be absorbed by the intestines, which results in **dehydration.**

Diffusion

- **Diffusion** is a passive process of transport.
- A single substance tends to move from an area of high concentration to an area of low concentration until the concentration is equal across a space.
- Materials move within the cell's cytosol by diffusion, and certain materials move through the plasma membrane by diffusion.



Fick's First Law(Fick's Laws of Diffusion)

The tendency for solutes to move from a region of higher concentration to one of lower concentration was first defined in 1855 by the physiologist Adolf Fick

$$\text{Diffusion rate} = -DA\frac{dc}{dx}$$

D = diffusion coefficient (bigger molecules have lower Ds);

A = cross-sectional area over which diffusion occurs;

dc/dx is the solute concentration gradient (diffusion occurs from a region of higher concentration to one of lower concentration).

Factors influencing diffusion include:

- **Extent of the concentration gradient:** The greater the difference in concentration, the more rapid the diffusion. The closer the distribution of the material gets to equilibrium, the slower the rate of diffusion becomes.
- **Shape, size and mass of the molecules diffusing:** Large and heavier molecules move more slowly; therefore, they diffuse more slowly. The reverse is typically true for smaller, lighter molecules.

- **Temperature:** Higher temperatures increase the energy and therefore the movement of the molecules, increasing the rate of diffusion. Lower temperatures decrease the energy of the molecules, thus decreasing the rate of diffusion.
- **Solvent density:** As the density of a solvent increases, the rate of diffusion decreases. The molecules slow down because they have a more difficult time getting through the denser medium. If the medium is less dense, rates of diffusion increase. Since cells primarily use diffusion to move materials within the cytoplasm, any increase in the cytoplasm's density will decrease the rate at which materials move in the cytoplasm.
- **Solubility:** As discussed earlier, nonpolar or lipid-soluble materials pass through plasma membranes more easily than polar materials, allowing a faster rate of diffusion.
- **Surface area and thickness of the plasma membrane:** Increased surface area increases the rate of diffusion, whereas a thicker membrane reduces it.
- **Distance travelled:** The greater the distance that a substance must travel, the slower the rate of diffusion. This places an upper limitation on cell size. A large, spherical cell will die because nutrients or waste cannot reach or leave the center of the cell, respectively. Therefore, cells must either be small in size, as in the case of many prokaryotes, or be flattened, as with many single-celled eukaryotes.

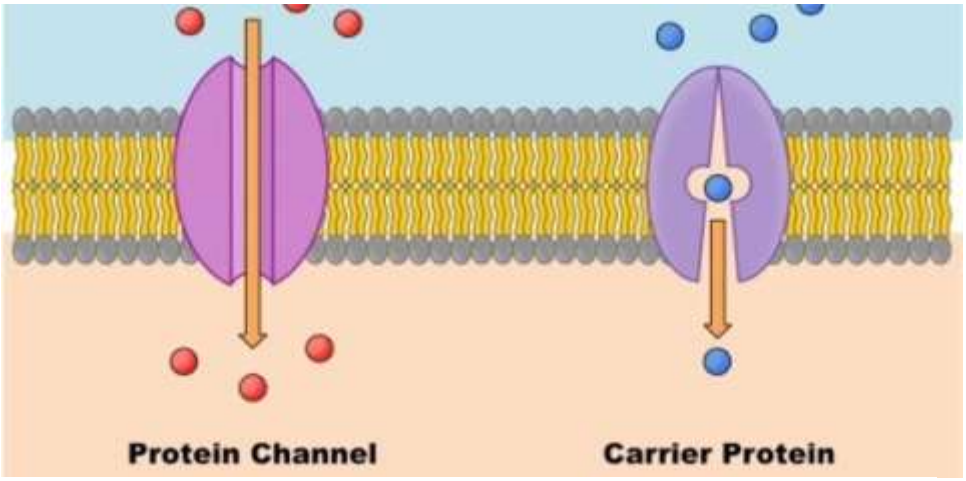
Facilitated transport

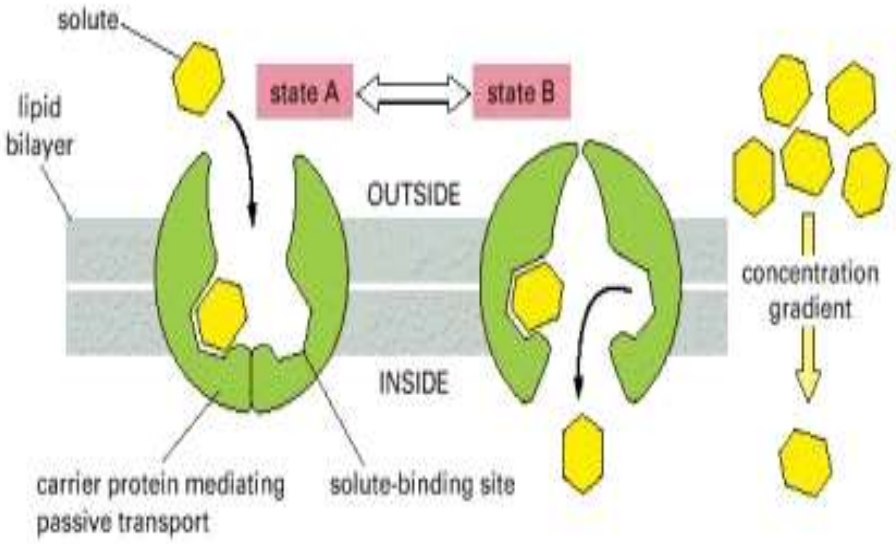
- In **facilitated transport**, also called facilitated diffusion, materials diffuse across the plasma membrane **with the help of membrane proteins**.
- In facilitated transport, materials are moving down a concentration gradient. In other words, they are moving from an area of high concentration to low concentration, as in passive diffusion.
- Presence of the cell membrane prevents passive diffusion from moving the materials easily, because a **protein-free lipid bilayer is highly impermeable to ions.**
- Small **nonpolar molecules like O2 and CO2 are soluble in lipids** and diffuse rapidly across lipid bilayer membranes.
- Uncharged polar molecules like water and urea also diffuse across the bilayer, but at a slower rate. Charged molecules, however, do not readily diffuse across a lipid bilayer membrane and they require additional assistance.
- In facilitated transport, membrane proteins assist the diffusion of materials through the cell membrane.

- The protein binds the molecule being transported on the surface of the membrane, then passes it to interior proteins that typically form a channel or pore in the membrane. These proteins are called **transport proteins.**

Carrier Proteins

- **One type of transport protein is known as a carrier protein**.
- When the target molecule to be transported binds to it, it undergoes a conformational change which moves the molecule from one side of the membrane to the other.
- There is usually only one target protein per carrier protein, and there are a limited number of them on the cell membrane.
- The limitations on these proteins can, at times, limit the availability of material in the cell.

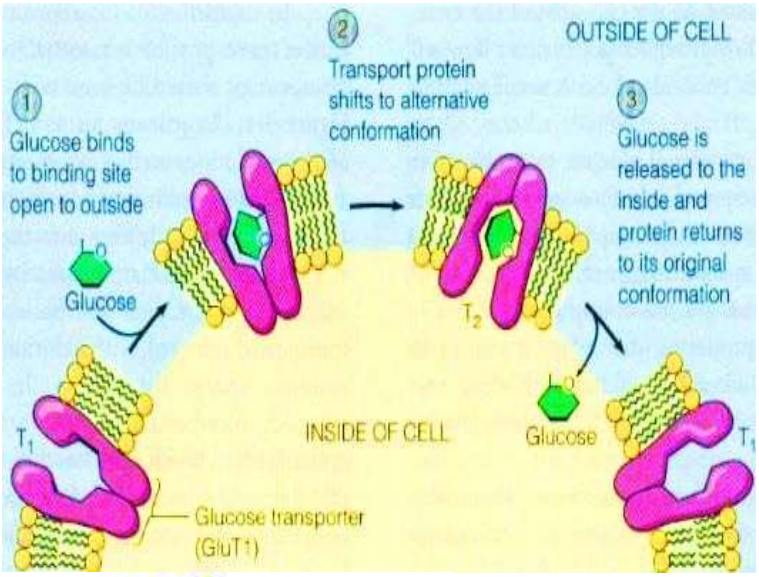
- 

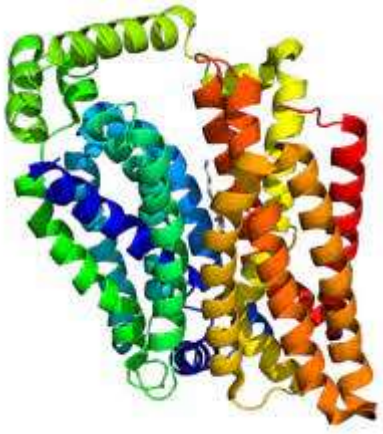


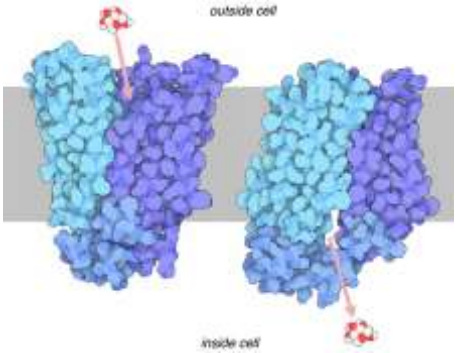
The glucose transporter 1 (GLUT1) protein is an example of a carrier protein for facilitated transport of glucose into cells.

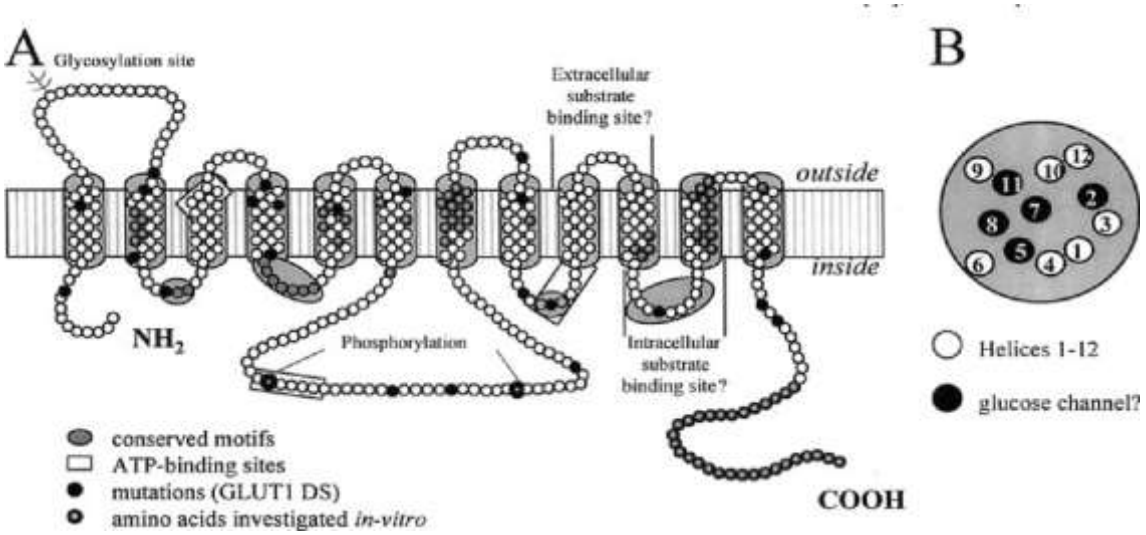
- Glucose is required for production of energy in cells.
- A supply of glucose is provided through the blood plasma.
- GLUT1 has 12 hydrophobic helical segments arranged **around a central channel through which glucose passes.**
- The rate of facilitated diffusion of glucose into the cell is about 50,000 times greater than uncatalyzed diffusion through the membrane.

- GLUT1 permits the necessary low level of glucose uptake to sustain respiration in cells.



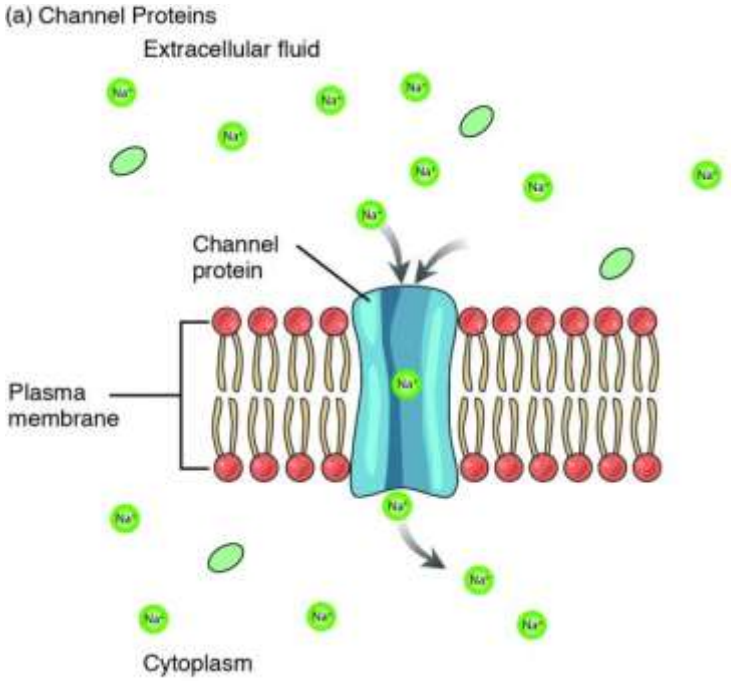




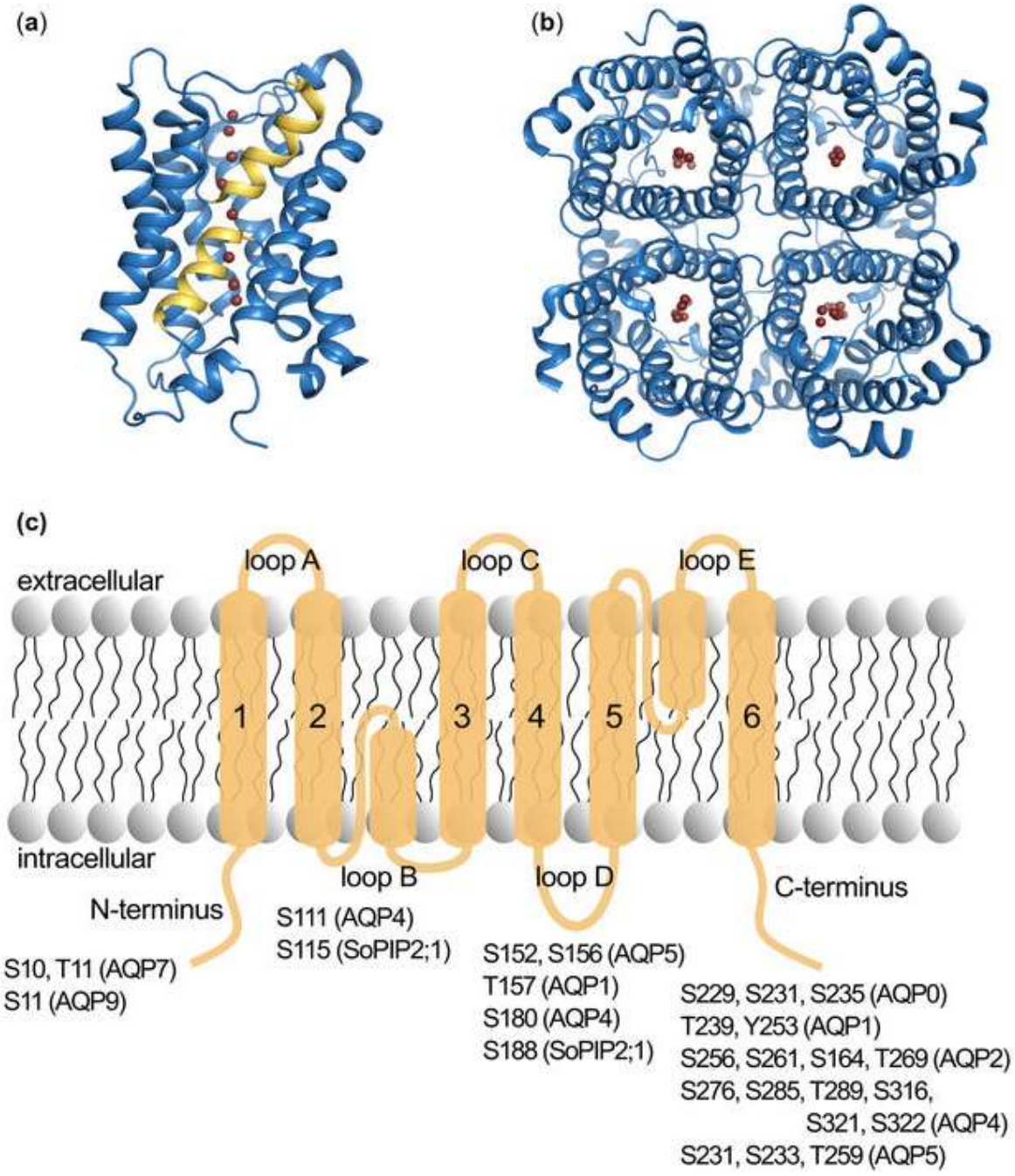


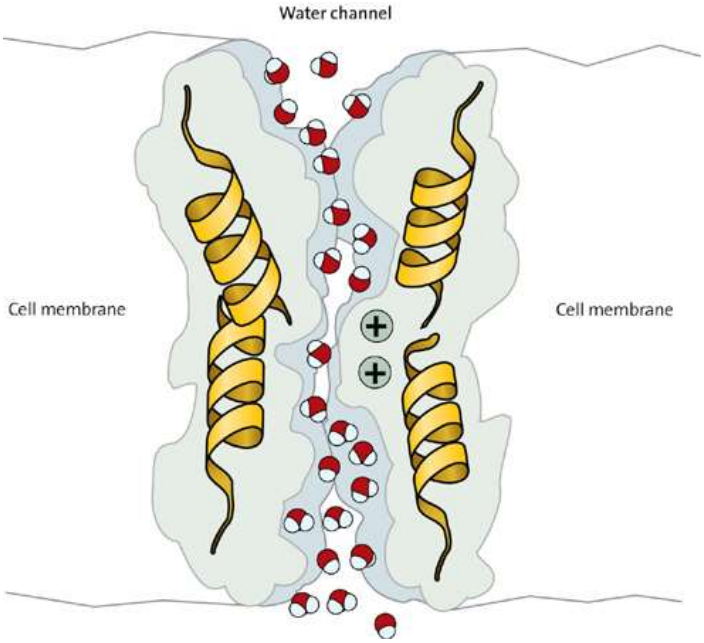
Channels

- The other category of transport protein is the channel.
- A channel protein has a hydrophilic portion on the inside and outside of the membrane, and a hydrophobic potion that penetrates the membrane that forms a channel. The inside of the channel is hydrophilic, so that polar molecules can diffuse through it.



- **Aquaporins are one type of channel protein** that transport water or small solutes.
- They are highly conserved in bacteria, plants, and animals.
- More than 10 isoforms of aquaporin have been identified in mammalian cells.
- These proteins are expressed differently in different types of cells and tissues, indicating that each has a specific role in its organ.


(a)
(b)
(c)
extracellular
loop A
loop C
loop E
1
2
3
4
5
6
intracellular
loop B
loop D
N-terminus
C-terminus
S10, T11 (AQP7)
S11 (AQP9)
S111 (AQP4)
S115 (SoPIP2;1)
S152, S156 (AQP5)
T157 (AQP1)
S180 (AQP4)
S188 (SoPIP2;1)
S229, S231, S235 (AQP0)
T239, Y253 (AQP1)
S256, S261, S164, T269 (AQP2)
S276, S285, T289, S316,
S321, S322 (AQP4)
S231, S233, T259 (AQP5)


Water channel
Cell membrane
Cell membrane

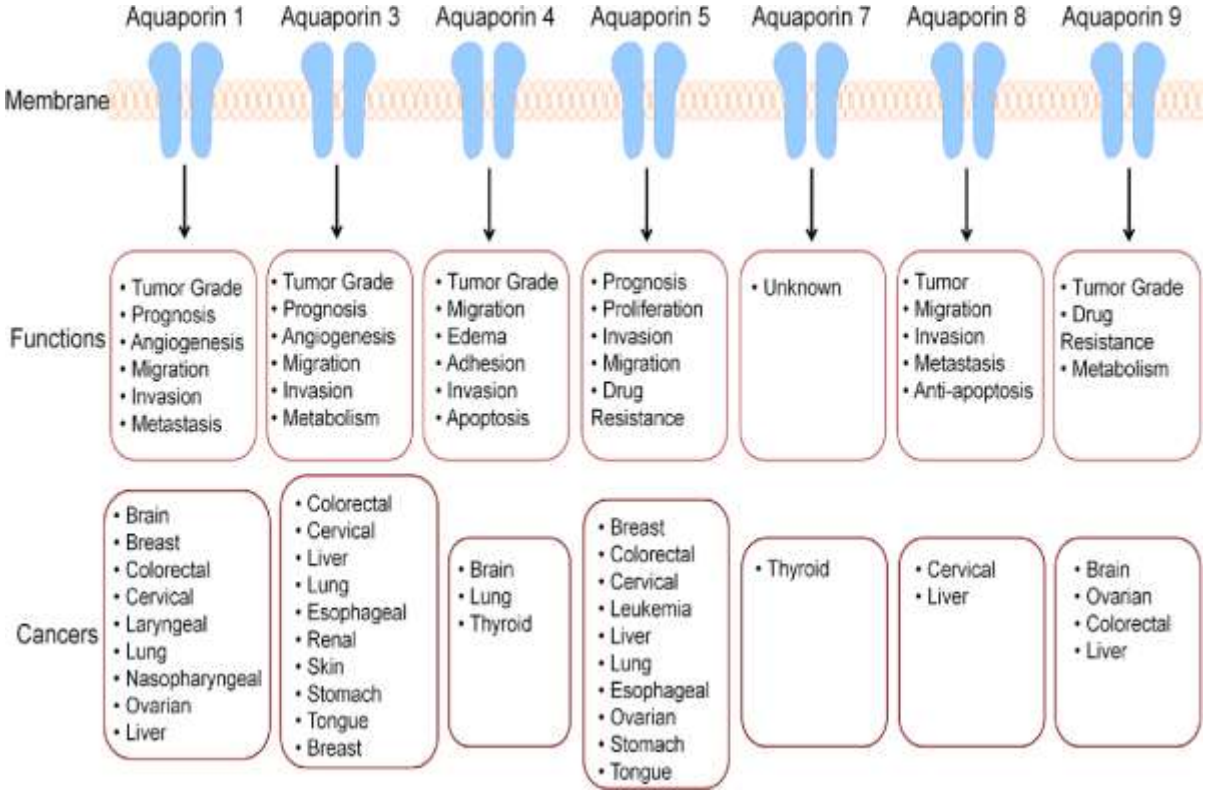
Type	Exocrine/endocrine pancreas	Cellular location	Biological function
AQP0	Not detected (mice, rats and humans)	–	–
AQP1	Exocrine pancreas (rat and humans)	Acinar cells, intercalated ducts and capillaries	Pancreatic fluid secretion
AQP2	Not detected (rats and humans)	–	–
AQP3	Exocrine pancreas (humans)	Acinar and collecting duct cells	Marker of tumor aggressiveness in pancreatic ductal adenocarcinomas
AQP4	Negligible expression (rat and humans)	–	–
AQP5	Exocrine pancreas (humans)	Intercalated and intralobular ductal cells	Pancreatic fluid secretion and marker of tumor differentiation in pancreatic ductal adenocarcinomas
AQP6	Not detected (mice, rats and humans)	–	–
AQP7	Endocrine pancreas (mice and rats)	β- and δ-cells	Control of insulin synthesis and secretion, triacylglycerol accumulation and proliferation of β-cells
AQP8	Exocrine pancreas (rat and humans)	Acinar cells	Pancreatic fluid secretion
AQP9	Not detected (rats and humans)	–	–
AQP10	Not detected (humans)	–	–
AQP11	Negligible expression (humans)	–	–
AQP12	Exocrine and endocrine pancreas (rats)	Acinar cells and β-cells	Maturation and exocytosis of zymogen granules, marker of pancreatic damage in acute pancreatitis and pancreatic steatosis

AQP, aquaporin.

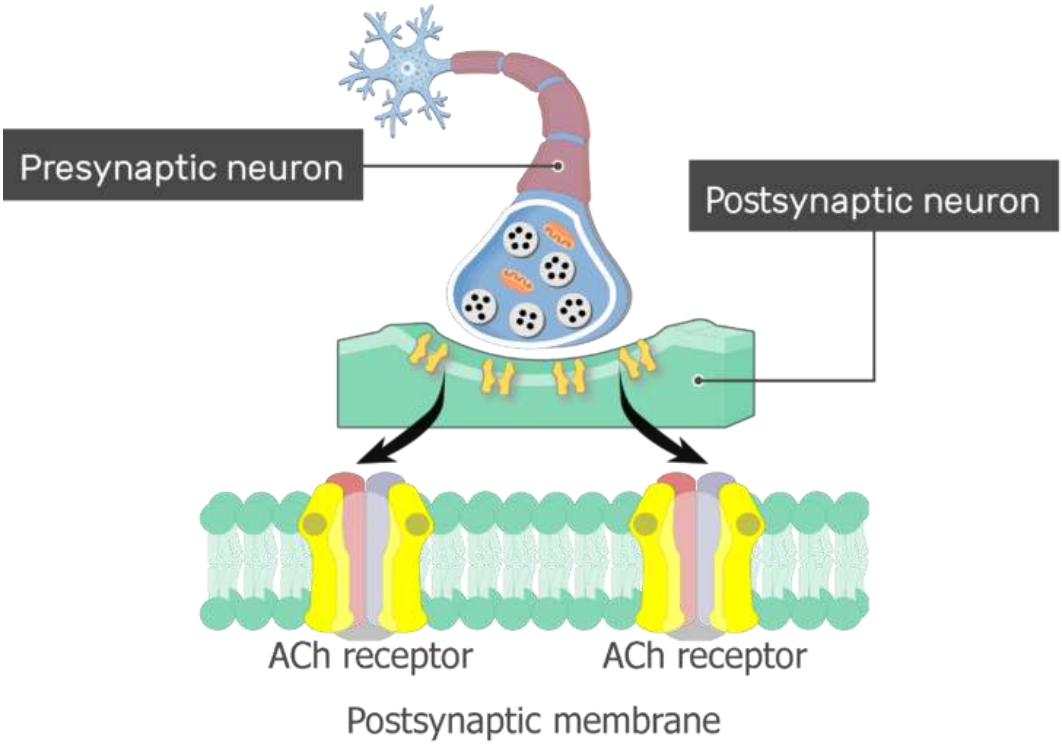
AQPs display altered expression various cancer types and are implicated in numerous processes.

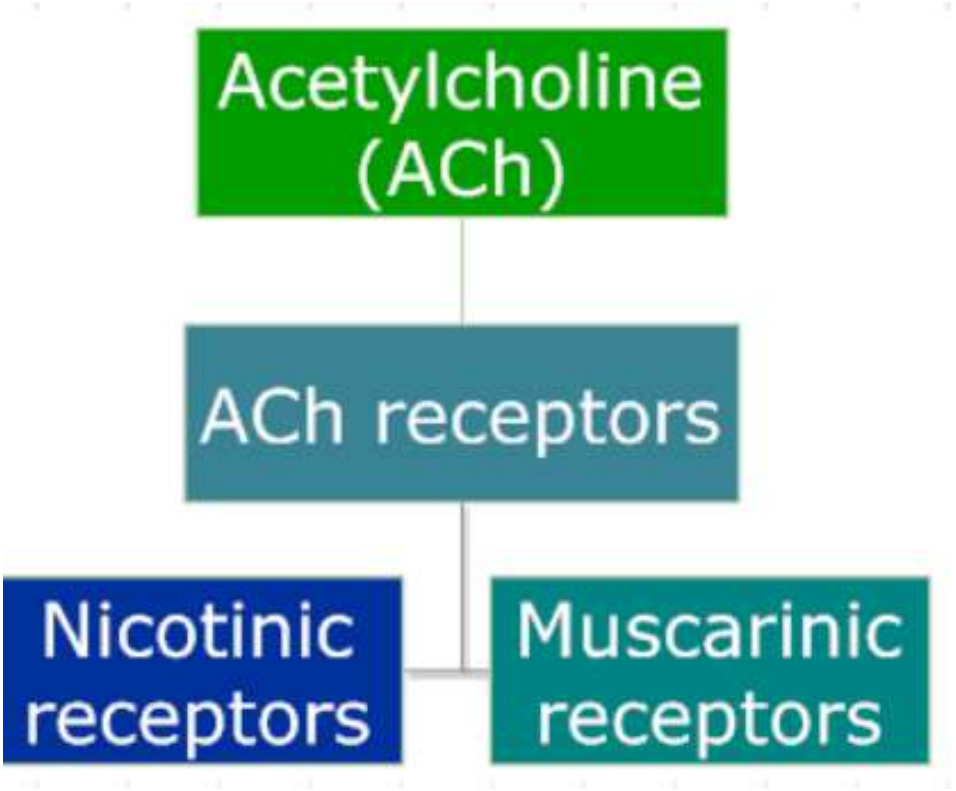
- Since cancer is a disease of failing molecular machinery, it is important to note that these malfunctions can occur in any region where the molecular machinery is normally located.
- There is relationship between various cancer types and AQP channels.
- AQPs are implicated in numerous cancer types and various processes, **abolishing the previous belief that they play a passive role in only water transport.**

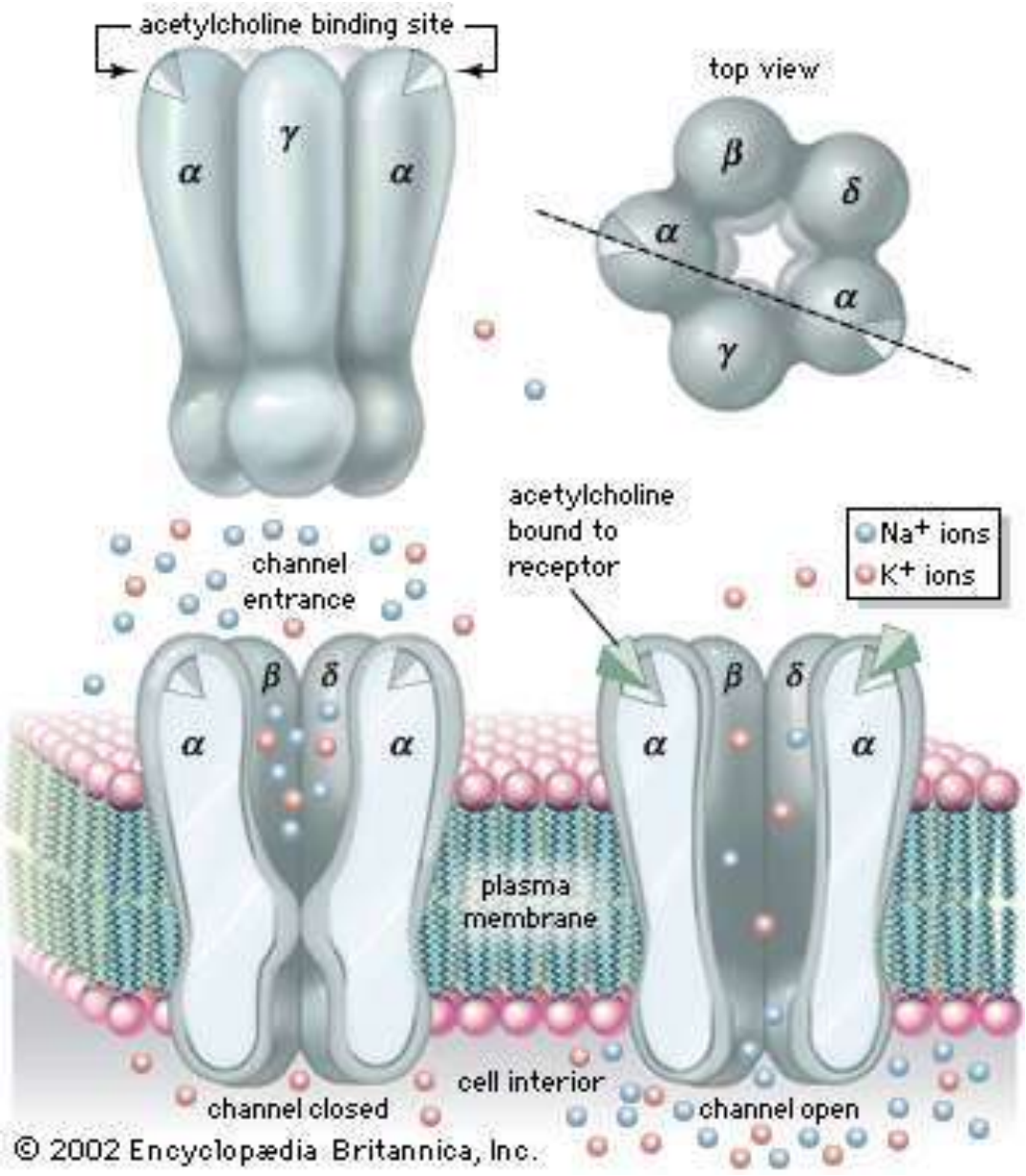
- Alterations in AQP expression indicate AQPs may be used as a biomarker, prognostic factor, and therapeutic target

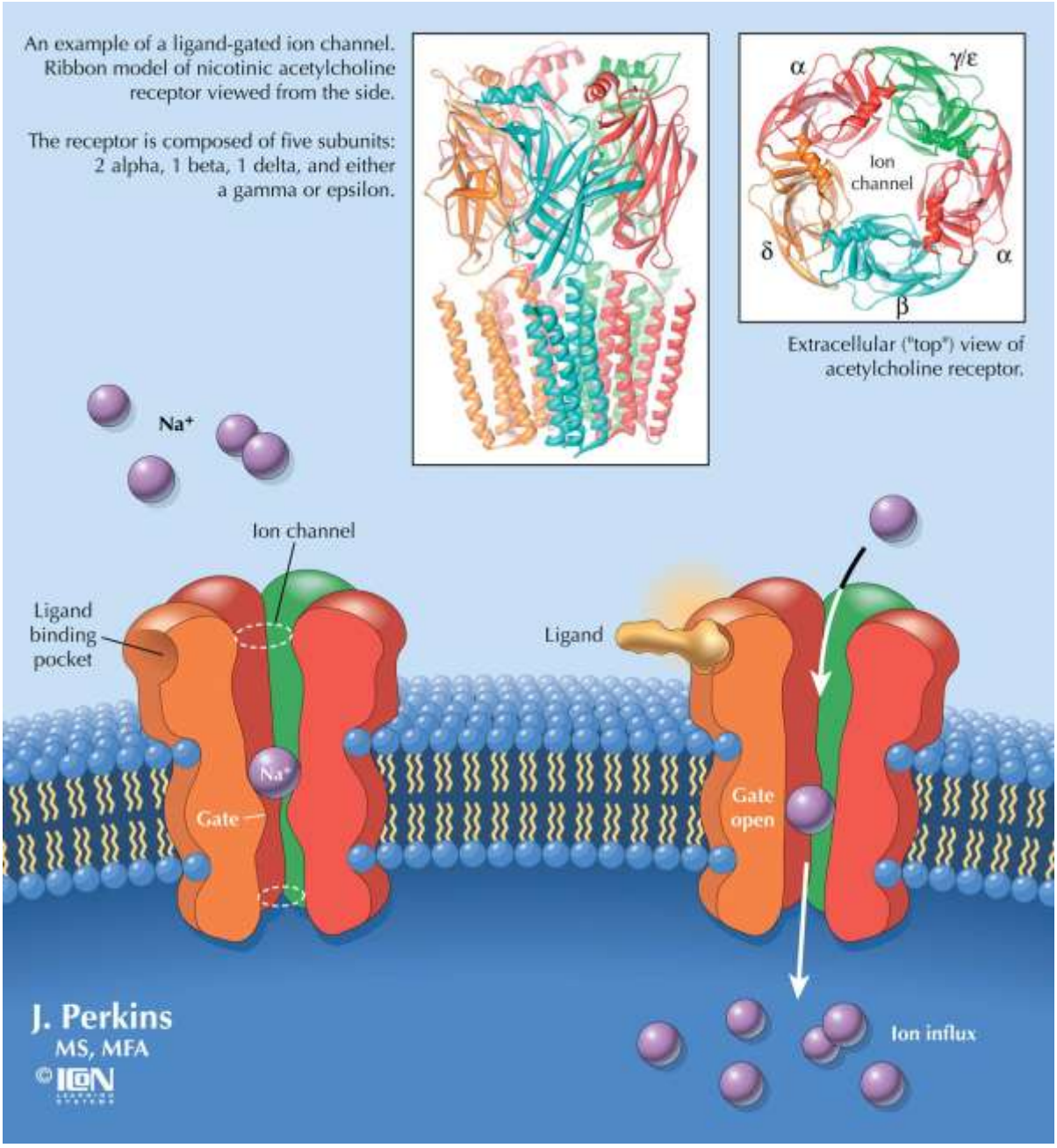


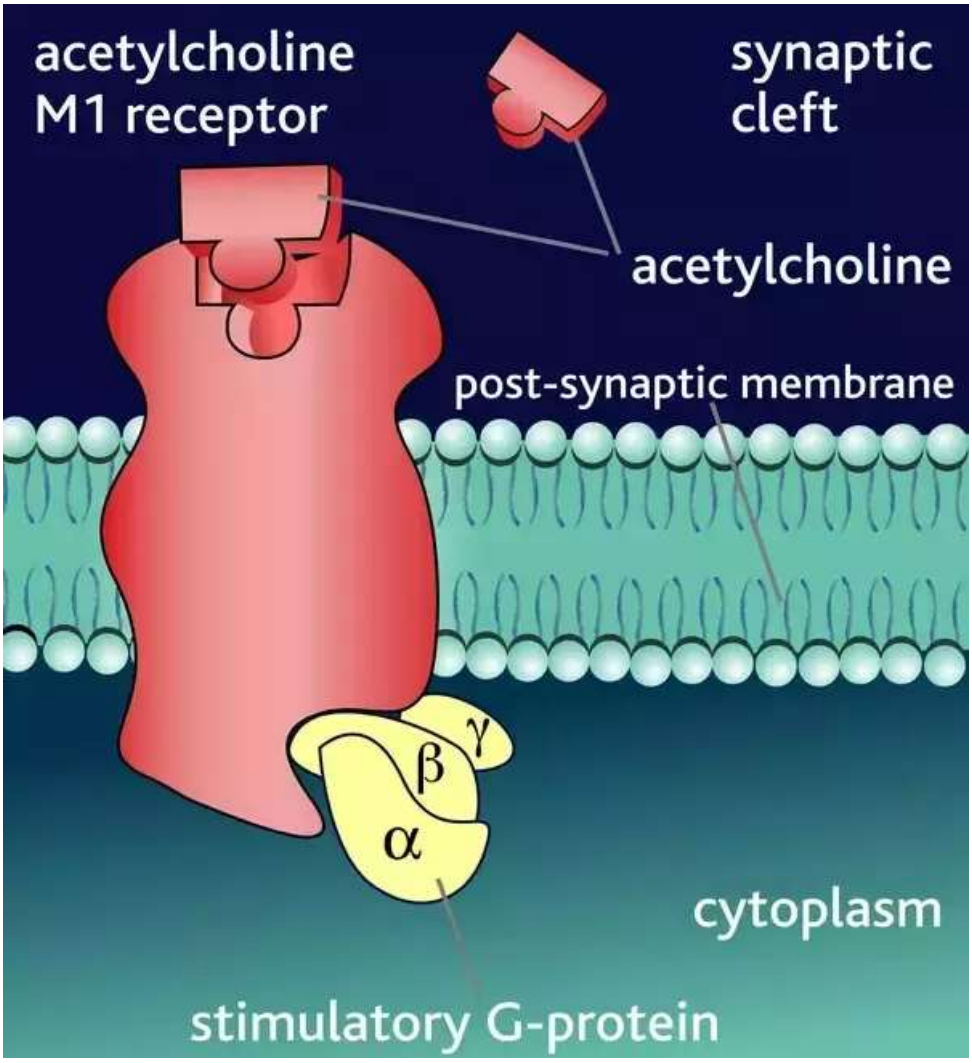
- **The acetylcholine receptor is another type of channel protein**.
- It mediates transmission of nerve signals across synapses, or junctions between neurons.
- The receptor opens in response to the binding of acetylcholine.
- A channel protein that opens upon binding of a ligand is called a ligand-gated channel.


Presynaptic neuron
Postsynaptic neuron
ACh receptor
ACh receptor
Postsynaptic membrane


Acetylcholine (ACh)
ACh receptors
Nicotinic receptors
Muscarinic receptors


acetylcholine binding site
α
γ
α
top view
β
δ
α
α
γ
acetylcholine
bound to
receptor
Na+ ions
K+ ions
channel
entrance
β
δ
α
α
β
δ
α
α
plasma
membrane
cell interior
channel closed
channel open
© 2002 Encyclopædia Britannica, Inc.

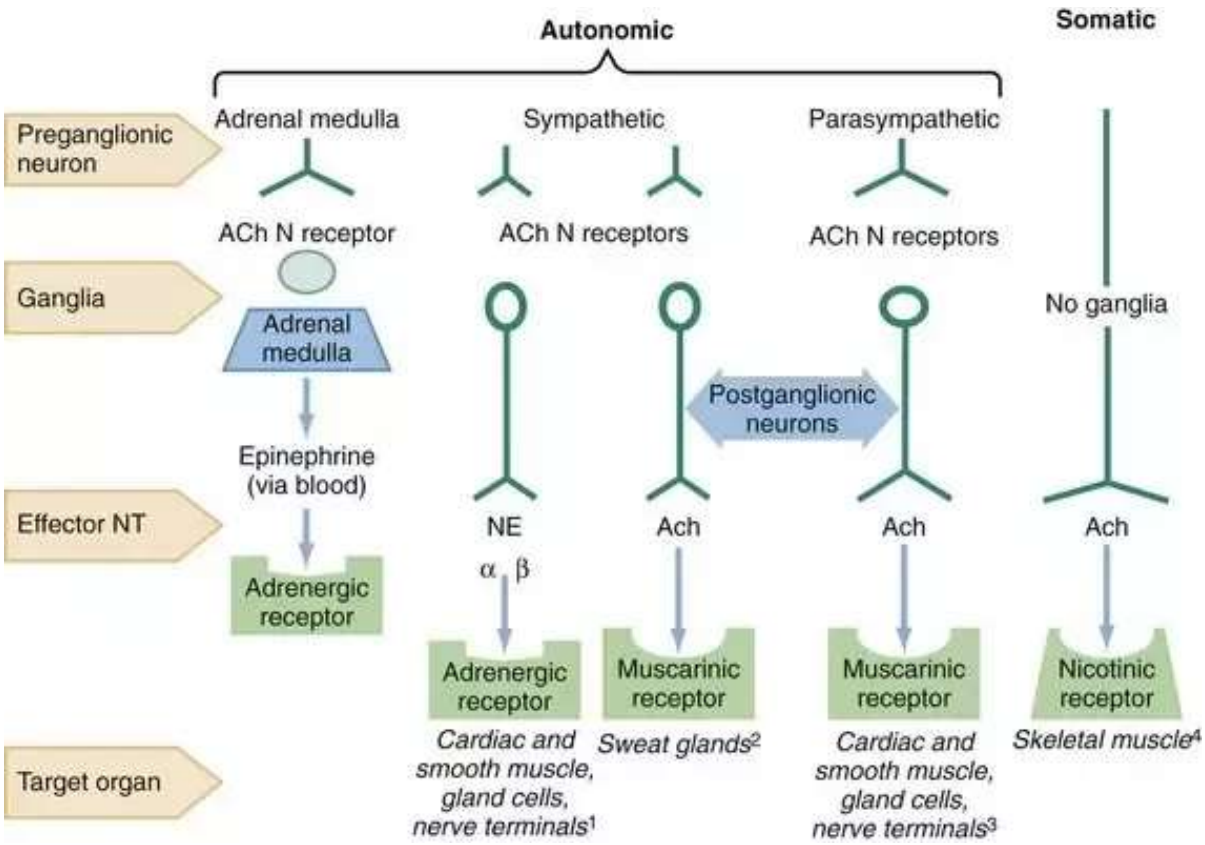

An example of a ligand-gated ion channel. Ribbon model of nicotinic acetylcholine receptor viewed from the side.
The receptor is composed of five subunits: 2 alpha, 1 beta, 1 delta, and either a gamma or epsilon.
α
γ/ε
Ion channel
δ
α
β
Extracellular ("top") view of acetylcholine receptor.
Na+
Ion channel
Ligand binding pocket
Ligand
Na+
Gate
Gate open
Ion influx
J. Perkins
MS, MFA
©ION



Muscarinic receptors have a different mechanism of action. Instead of becoming an ion channel for sodium, they **use a G-protein**.

- When **ACh binds to the receptor, this special protein changes shape,** which then allows **it to phosphorylate various second messengers.**
- There are five different types of muscarinic receptors. M1, M3 & M5 are excitatory receptors because their G-protein stimulates phospholipase C, which then activates IP3 and DAG. The two others, M2 and M4, are inhibitory.
- You can find **muscarinic receptors in the brain, heart and smooth muscle**.

- Like nicotinic receptors, they are found in both the parasympathetic and sympathetic nervous systems.


Autonomic
Somatic
Preganglionic neuron
Adrenal medulla
Sympathetic
Parasympathetic
ACh N receptor
ACh N receptors
ACh N receptors
Ganglia
Adrenal medulla
No ganglia
Postganglionic neurons
Epinephrine (via blood)
Effector NT
NE
Ach
Ach
Ach
α β
Adrenergic receptor
Adrenergic receptor
Muscarinic receptor
Muscarinic receptor
Nicotinic receptor
Target organ
Cardiac and smooth muscle, gland cells, nerve terminals[1]
Sweat glands[2]
Cardiac and smooth muscle, gland cells, nerve terminals[3]
Skeletal muscle[4]

Difference Between Active And Passive Transport

Following are the important difference between active and passive transport:

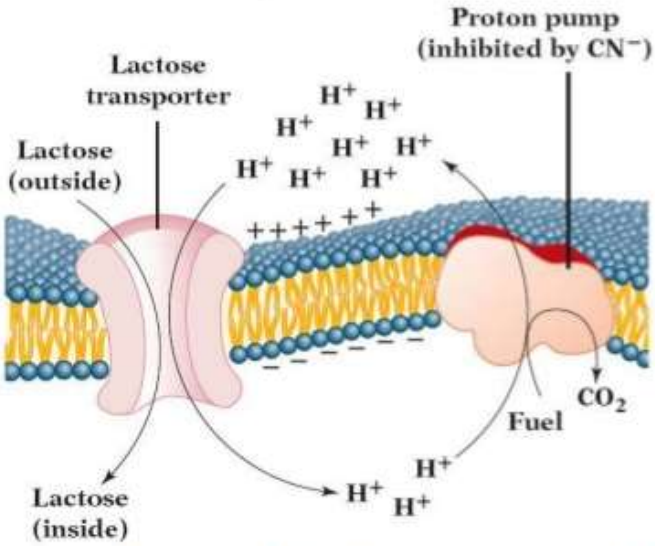
Active Transport	Passive Transport
Requires cellular energy.	Do not require cellular energy.
It circulates from a region of lower concentration to a region of higher concentration	It circulates from a region of higher concentration to a region of lower concentration
Required for the transportation of all the molecules such as proteins, large cells, complex sugars, ions, etc.	Required for the transportation of all soluble molecules, including oxygen, water, carbon dioxide, lipids, sex hormones, etc.
It transports various molecules in the cell.	It is involved in the maintenance of the equilibrium level inside the cell.
Active transport is a dynamic process.	Passive Transport is a physical process.
It is highly selective.	It is partly non-selective
Active transport is a rapid process.	Passive transport is a comparatively slow process.
Transpires in one direction.	Transpires bidirectionally.
Active transportation is influenced by temperature.	Passive transportation is not influenced by temperature.
In active transport, carrier proteins are required	In passive transport, carrier proteins are not required
This process reduces or halts as the oxygen content level is reduced.	This process is not affected by the level of oxygen content.
Metabolic inhibitors can influence and stop the active transport.	Passive transportation is not influenced by metabolic inhibitors.
Different types of Active Transport are – Exocytosis, endocytosis, sodium-potassium pump	Different types of Passive Transport are – Osmosis, diffusion, and facilitated diffusion

Permeases

- The permeases or porter proteins are membrane transport proteins, a class of multipass transmembrane proteins that facilitate the diffusion of a specific molecule in or out of the cell by passive transport.

Transport Proteins: Symporters

- Lactose Permease of *E. Coli*
- Secondary active transport that uses ion gradients

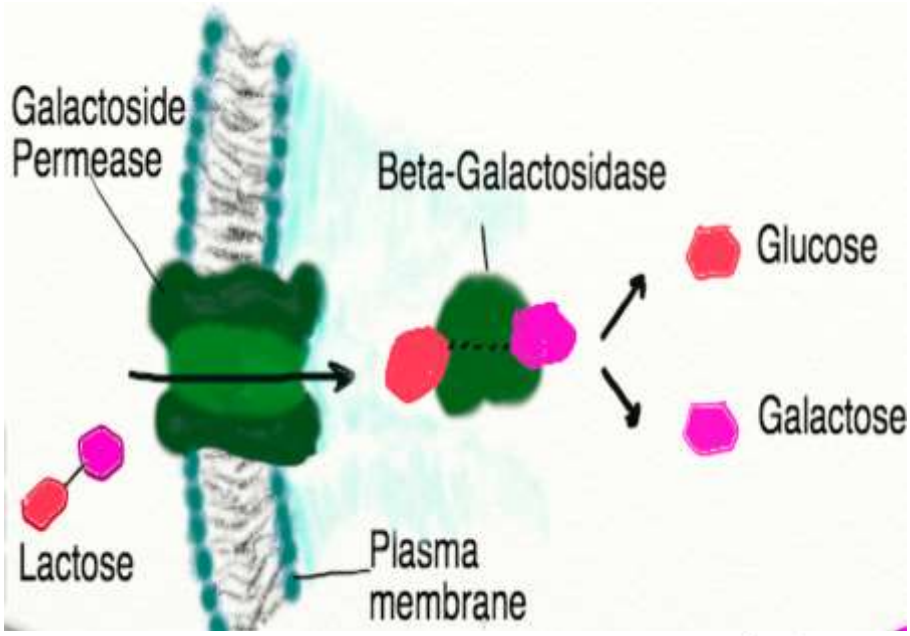


The proton gradient made by the respiratory chain is used to drive the uptake of lactose by lactose permease.

Galactoside permease is a protein coded by the lacY gene of the lac operon, and is found bound to the membrane of a cell for the purpose.

E. coli needs to make **two proteins to utilize lactose, as shown below.**

In addition to β-galactosidase, it must also make a permease that allows lactose to pass through the plasma membrane.



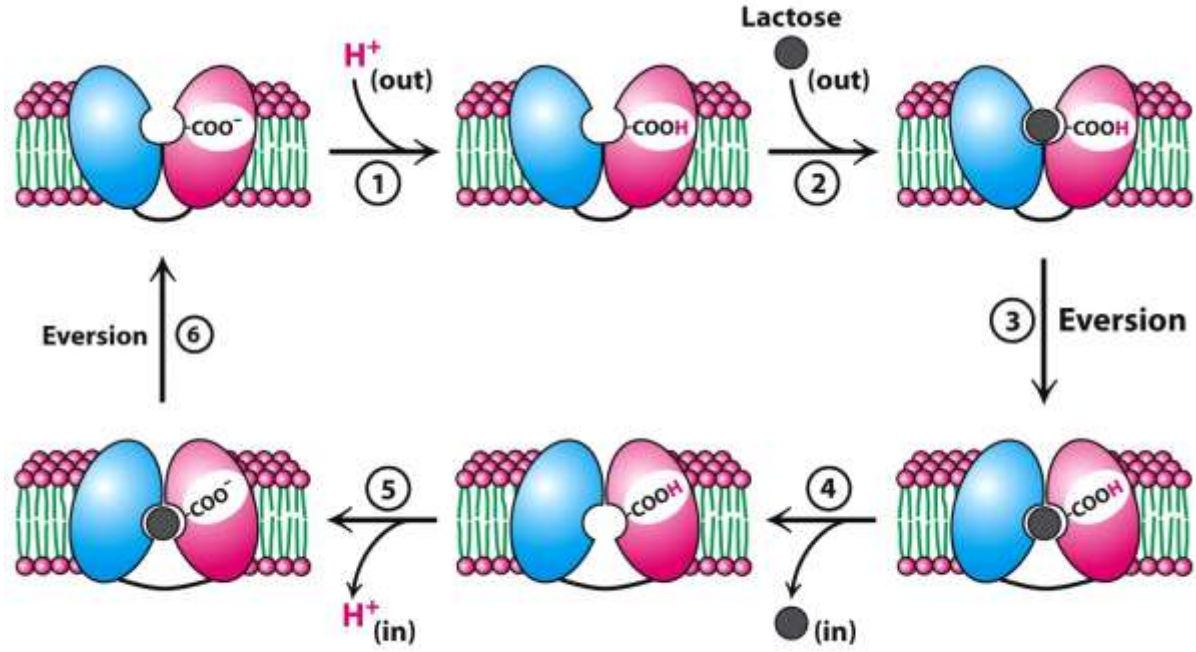
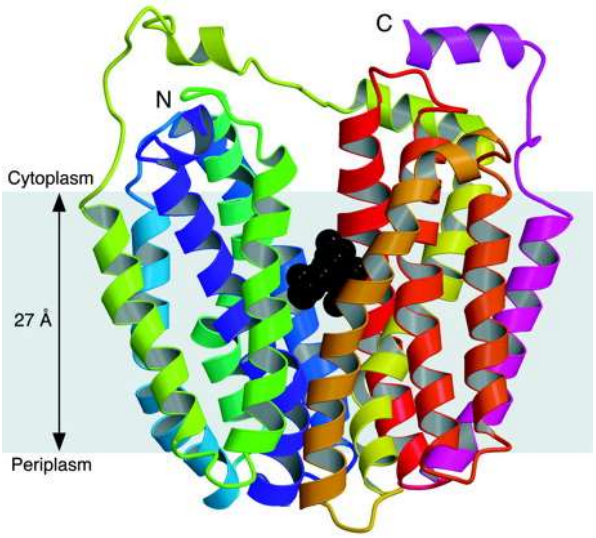
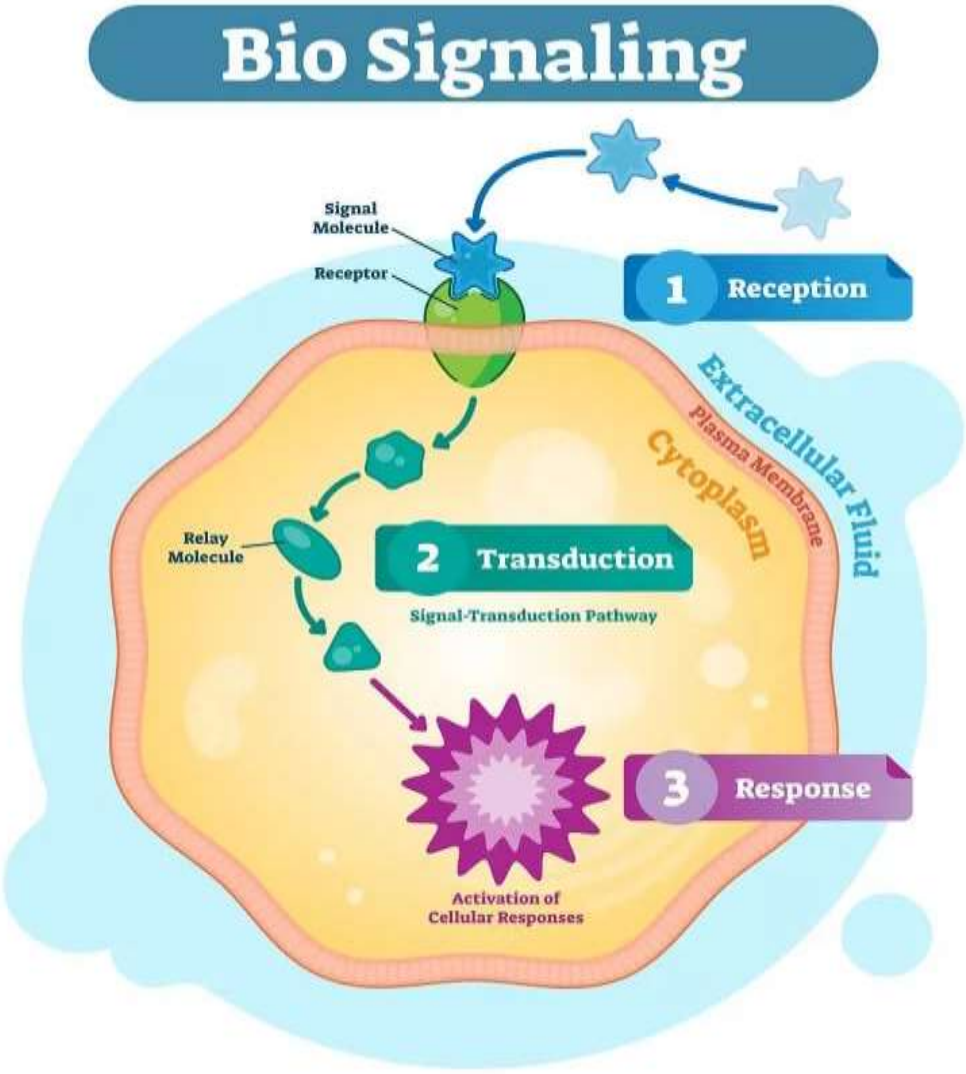
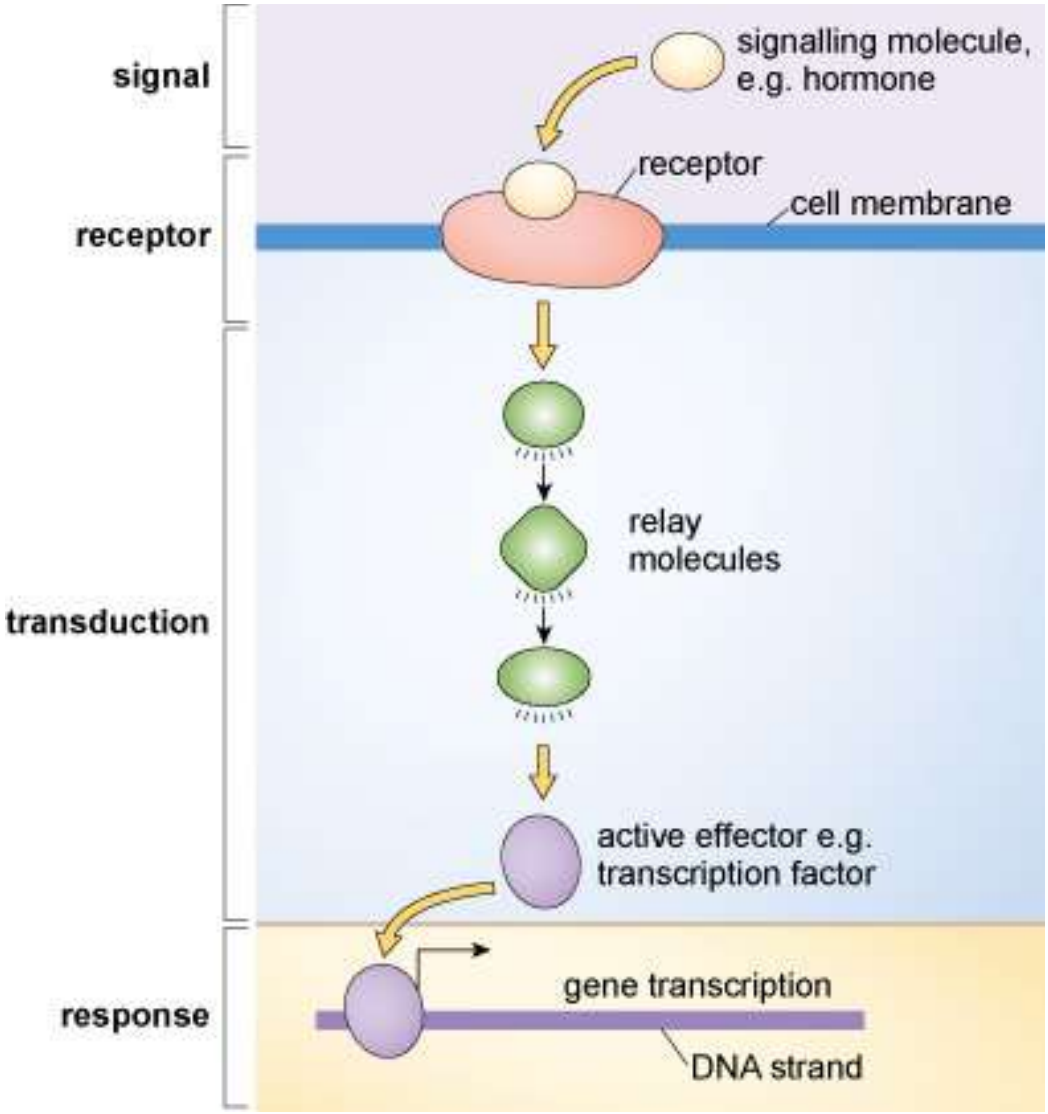


Figure 13.12
Biochemistry, Seventh Edition


C
N
Cytoplasm
27 Å
Periplasm


Bio Signaling
Signal Molecule
Receptor
1 Reception
Extracellular Fluid
Plasma Membrane
Cytoplasm
Relay Molecule
2 Transduction
Signal-Transduction Pathway
3 Response
Activation of Cellular Responses

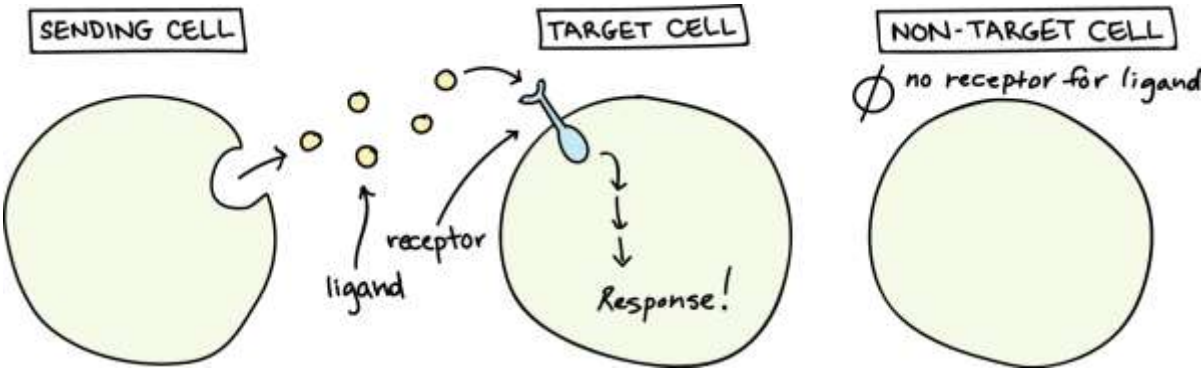


- **Even the simplest organisms can detect and respond to events in their ever-changing environment.**
- **Similarly, within a multicellular organism, cells are surrounded by an extracellular environment from which signals are received and responded to.**
- **Extracellular events are decoded and transmitted to relevant parts of individual cells by way of a series of activation/deactivation steps involving many intracellular molecules.**

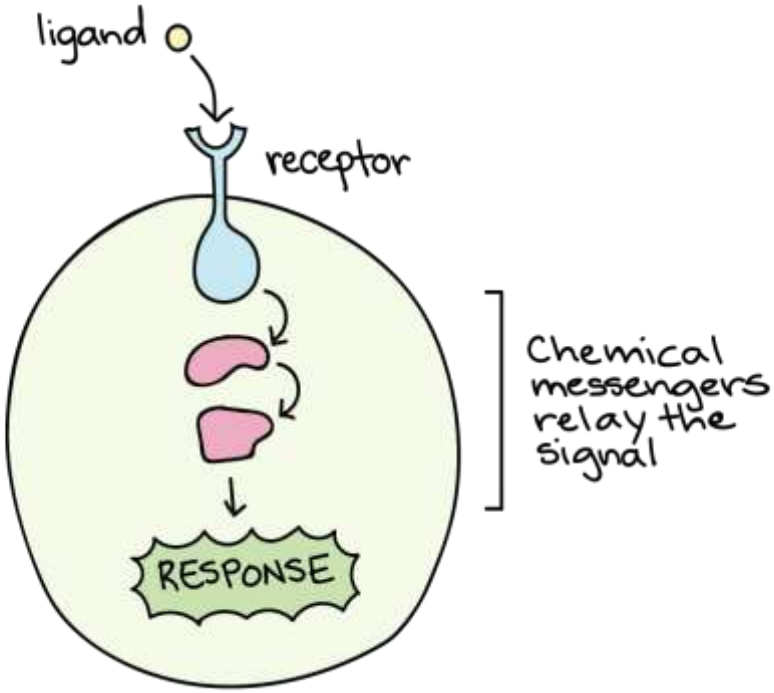
- **This relay of information along molecular pathways is called signal transduction; it is sometimes also simply referred to as 'signalling'.**

Basics of cell signalling- autocrine, paracrine and endocrine signalling

Cells typically communicate using chemical signals. These chemical signals**, which are proteins or other molecules** produced by a **sending cell**, are often **secreted from the cell** and released into the extracellular space. There, they can float – like messages in a bottle – over to neighboring cells.



- Not all cells can "hear" a particular chemical message.
- In order to detect a signal (that is, to be a target cell), a neighbor cell must have the right receptor for that signal.
- When a signaling molecule binds to its receptor, it alters the shape or activity of the receptor, triggering a change inside of the cell.
- **Signaling molecules are often called ligand**s, a **general term for molecules that bind specifically to other molecules (such as receptors).**
- The **message carried by a ligand is often relayed through a chain of chemical messengers inside the cell**.
- Ultimately, it leads to a change in the cell, such as alteration in the activity of a gene or even the induction of a whole process, such as cell division.
- Thus, the original **intercellular** (between-cells) signal is converted into an **intracellular** (within-cell) signal that triggers a response.



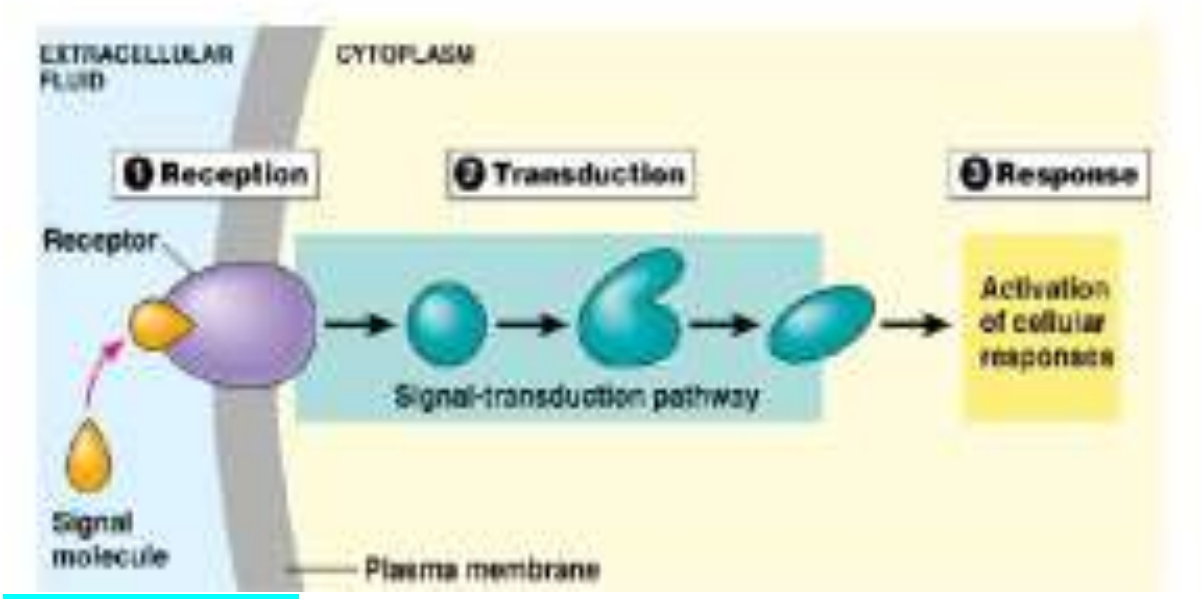
Three Stages of Cell Signaling:

Reception: A cell detects a signaling molecule from the outside of the cell. A signal is detected when the chemical signal (also known as a ligand) binds to a receptor protein on the surface of the cell or inside the cell.

Transduction: When the signaling molecule binds the receptor it changes the receptor protein in some way. This change initiates the process of transduction. Signal transduction is usually a pathway of several steps. Each relay molecule in the signal transduction pathway changes the next molecule in the pathway.

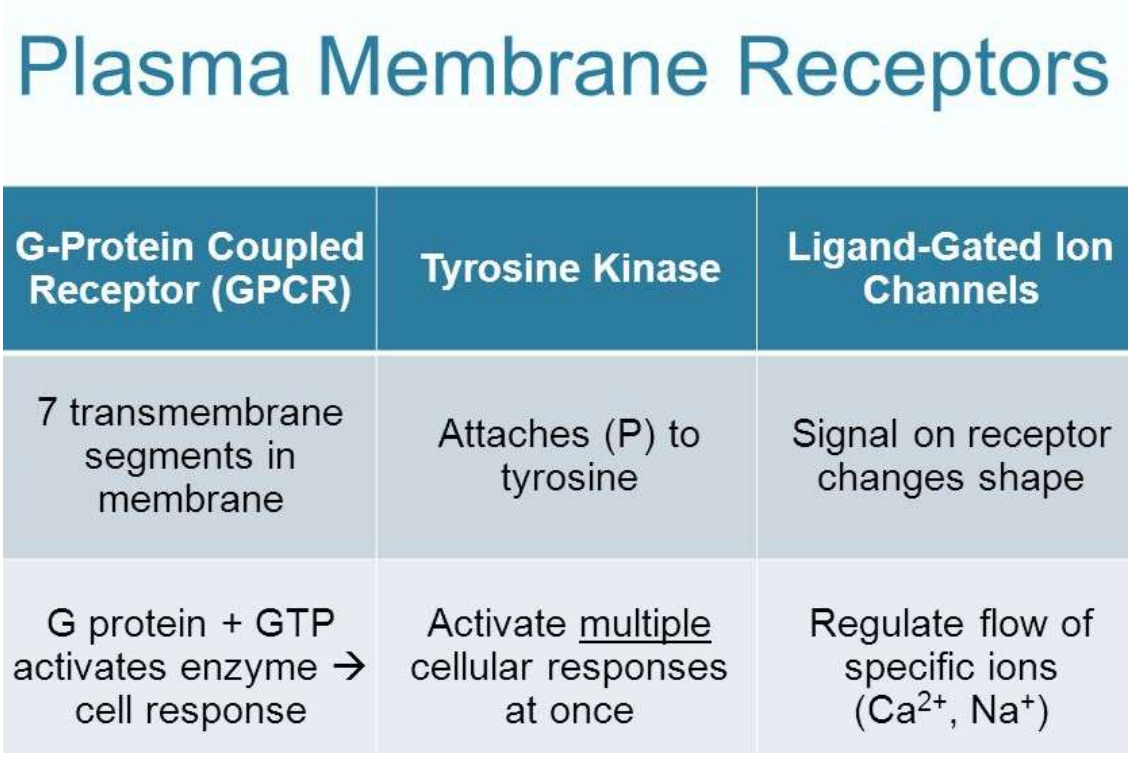
Response: Finally, the signal triggers a specific cellular response.

Three Stages of Signal Transduction



- **Membrane receptors** function by binding the signal molecule (ligand) and **causing the production of a second signal (also known as a second messenger) that then causes a cellular response**.
- These type of receptors **transmit information from the extracellular environment to the inside of the cell by changing shape or by joining** with another protein once a specific ligand binds to it.
- There are three general categories of cell-surface receptors:

1. **Ion channel-linked receptors,**
2. **G-protein-linked receptors,**
3. **Enzyme-linked receptors.**



- Each cell-surface receptor has three main components: an external ligand-binding domain (extracellular domain), a hydrophobic membrane-spanning region, and an intracellular domain inside the cell. The size and extent of each of these domains vary widely, depending on the type of receptor.

G protein-coupled receptors (GPCR)

- 7 transmembrane domain receptors on the cell membrane that sense the external environments
- ligands activate the G protein by causing a conformational change
- this change propagates to a second messenger which detaches from the GPCR to carry the signal to other effector proteins
- 3 types of GPCR second messengers and functions

Gq activates phospholipase which results in the formation of

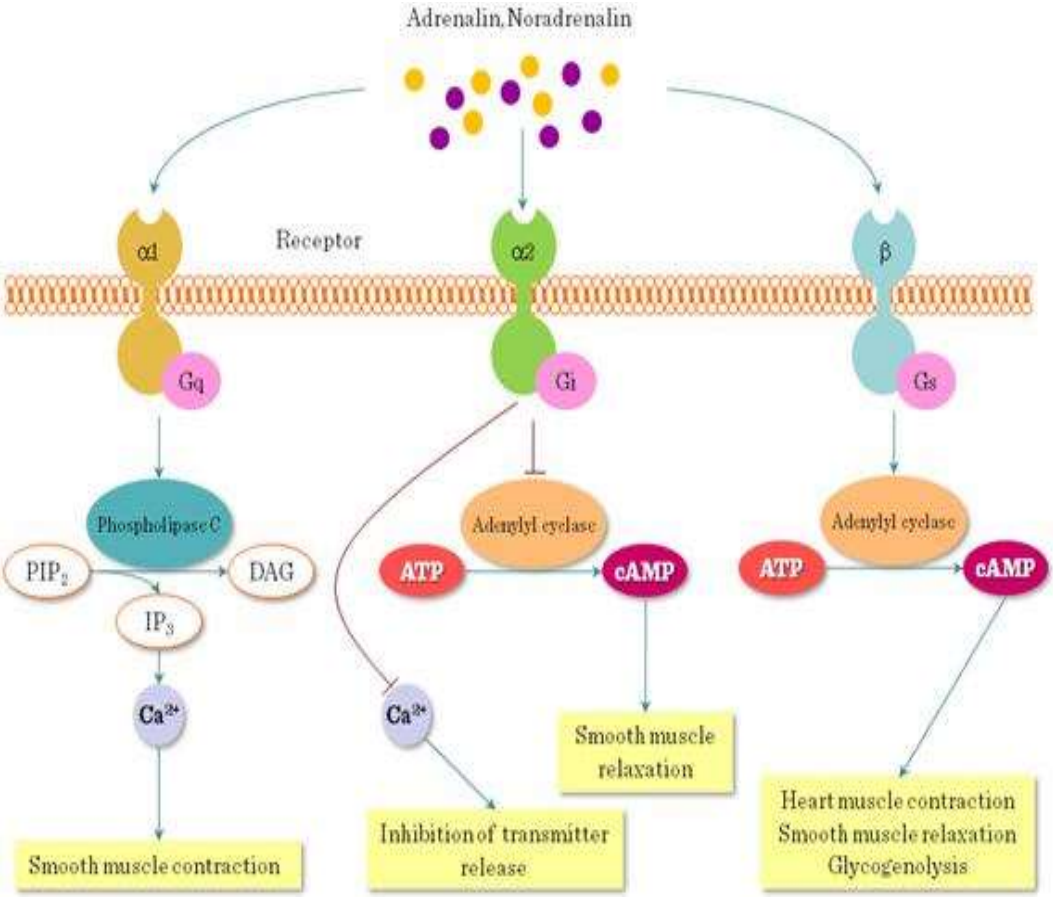
- inositol phosphate (IP3) → ↑ [Ca2+]
- diacylglycerol → activation of protein kinase C (PKC)
- examples of receptor types: α1, H1, V1, M1, M3

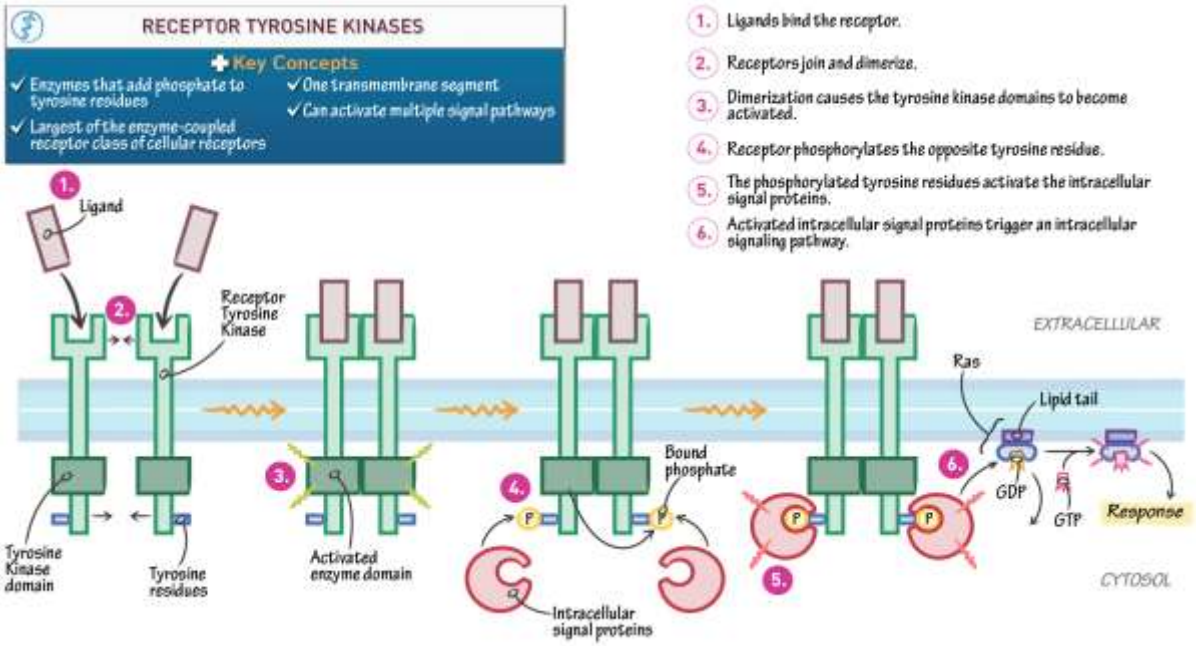
Gs activates adenyl cyclase resulting in

- ↑ cAMP → ↑ activity of protein kinase A (PKA)
- examples of receptor types: β1, β2 , D1, H2, V2

Gi inhibits adenyl cyclase resulting in

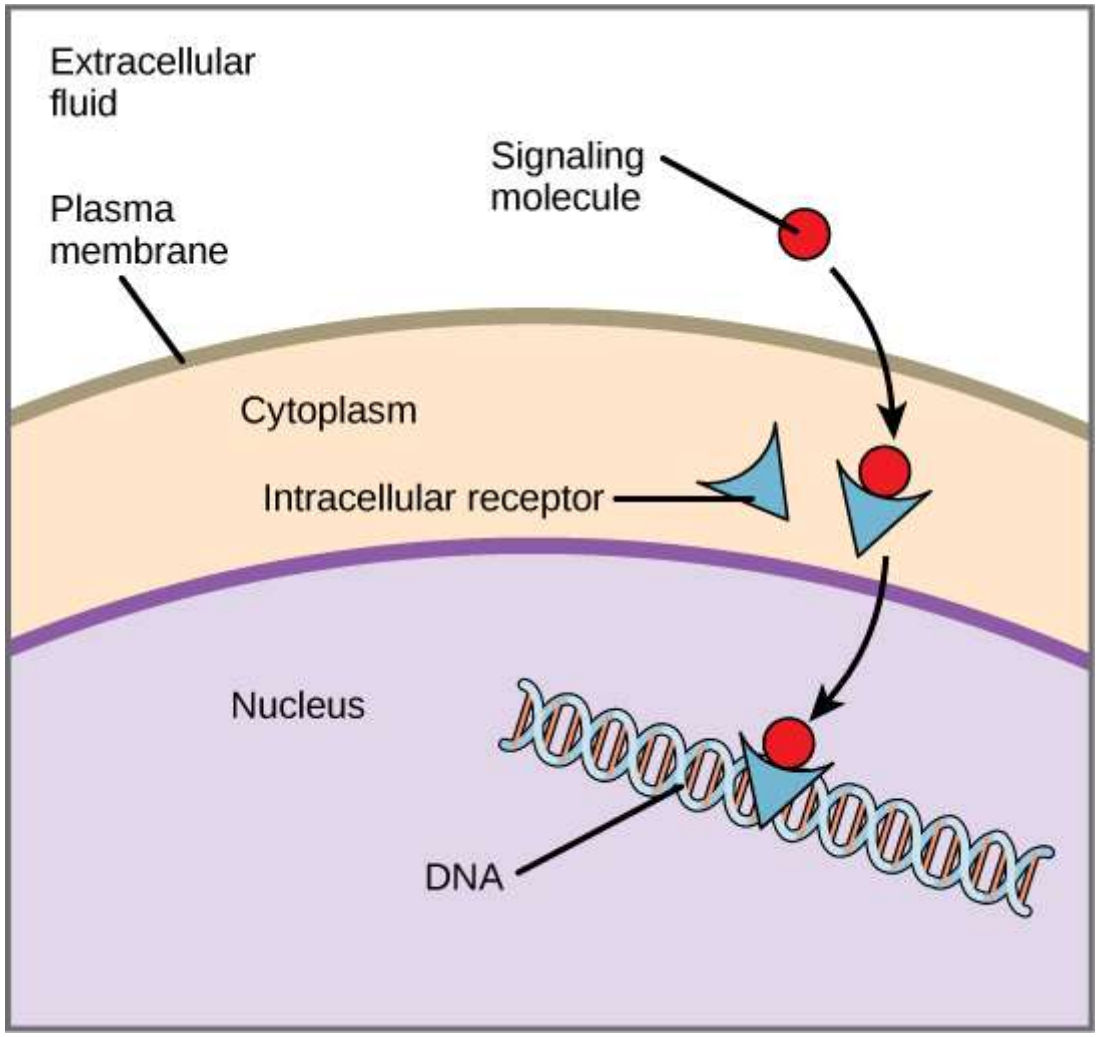
- ↓ cAMP → ↓ activity of protein kinase A (PKA)
- examples of receptor types: α2, D2, M2


Adrenalin, Noradrenalin
α1
Receptor
α2
β
Gq
Gi
Gs
Phospholipase C
PIP2
DAG
IP3
Ca2+
Adenylyl cyclase
ATP
cAMP
Adenylyl cyclase
ATP
cAMP
Ca2+
Smooth muscle contraction
Inhibition of transmitter release
Smooth muscle relaxation
Heart muscle contraction
Smooth muscle relaxation
Glycogenolysis

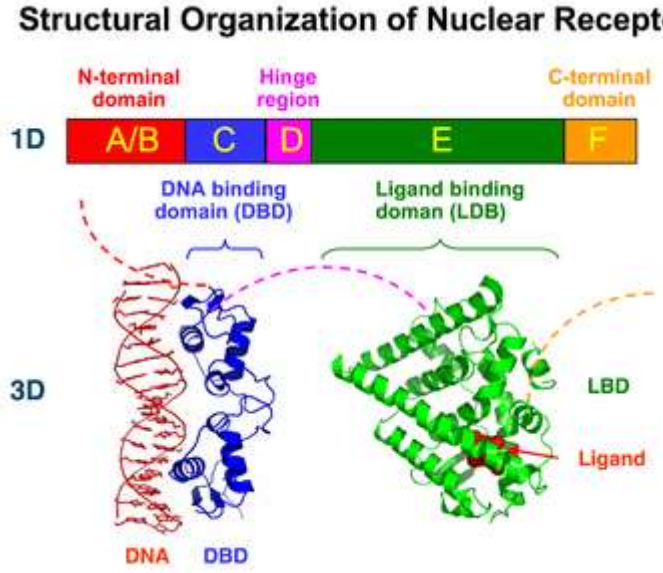


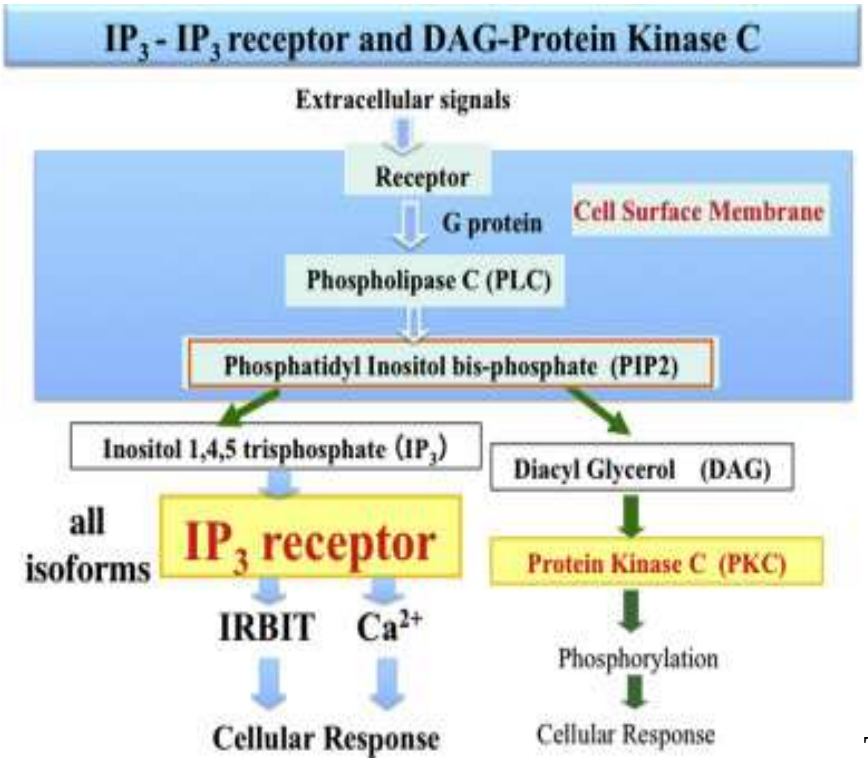
Internal receptors

- Internal receptors, also known as intracellular or cytoplasmic receptors, are found in the cytoplasm of the cell and respond to hydrophobic ligand molecules that are able to travel across the plasma membrane.
- Once inside the cell, many of these molecules bind to proteins that act as regulators of mRNA synthesis to mediate gene expression.
- Gene expression is the cellular process of transforming the information in a cell's DNA into a sequence of amino acids that ultimately forms a protein.
- When the ligand binds to the internal receptor, a conformational change exposes a DNA-binding site on the protein.
- The ligand-receptor complex moves into the nucleus, binds to specific regulatory regions of the chromosomal DNA, and promotes the initiation of transcription.
- Internal receptors can directly influence gene expression without having to pass the signal on to other receptors or messengers.



- Examples are the class of **nuclear receptors located in the cell nucleus and cytoplasm and the IP3 receptor located on the endoplasmic reticulum.**
- The ligands that bind to them are usually intracellular second messengers like inositol trisphosphate (IP3) and extracellular lipophilic hormones like steroid hormones. Some intracrine peptide hormones also have intracellular receptors





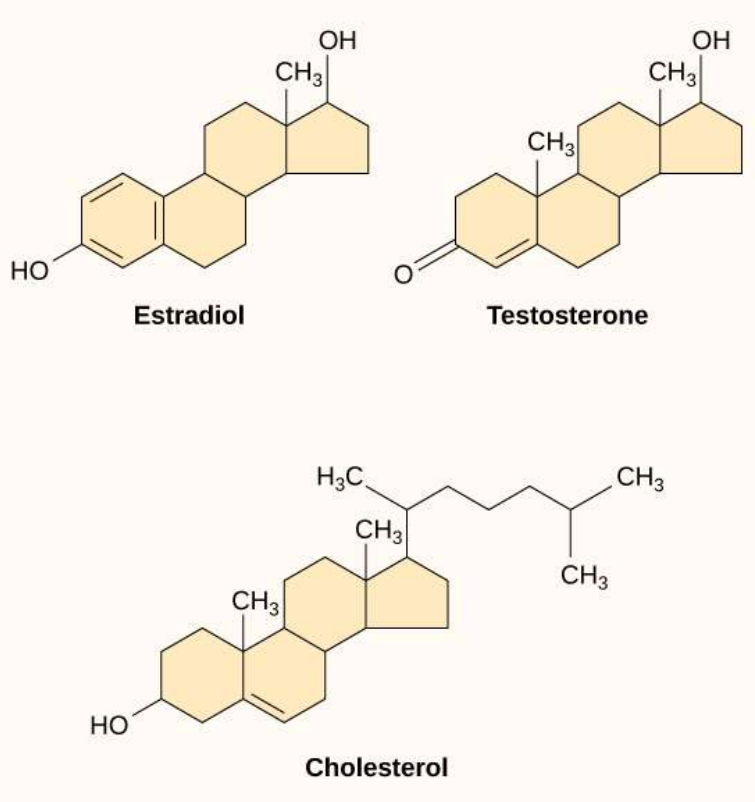
Transduction

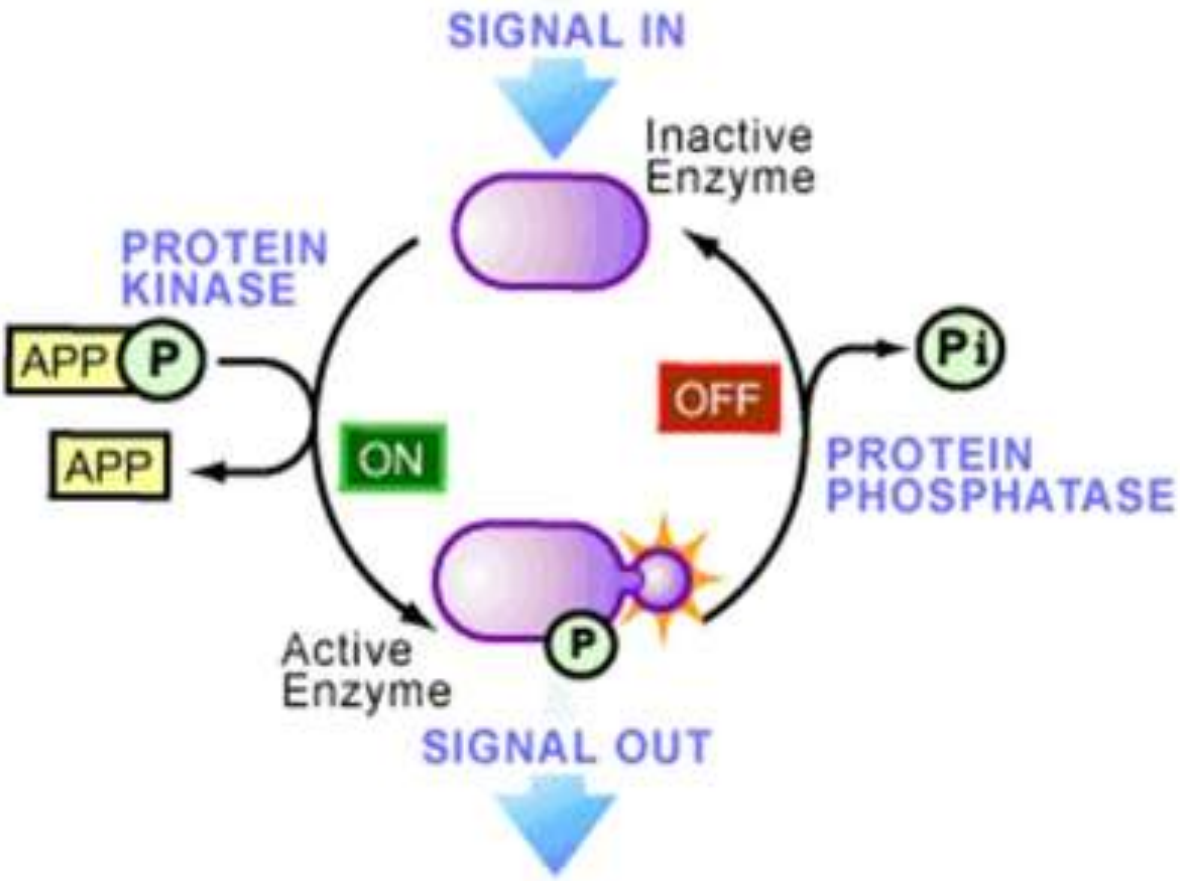
- Since signaling systems need to be responsive to small concentrations of chemical signals and act quickly, cells often use a multi-step pathway that transmits the signal quickly, while amplifying the signal to numerous molecules at each step.
- Steps in the signal transduction pathway **often involve the addition or removal of phosphate groups** which results in the activation of proteins. Enzymes that transfer phosphate groups from ATP to a protein are called **protein kinases**. Many of the relay molecules in a signal transduction pathway are protein kinases and often act on other protein kinases in the pathway. Often this creates a **phosphorylation cascade**, where one enzyme phosphorylates another, which then phosphorylates another protein, causing a chain reaction.
- Also important to the phosphorylation cascade are a group of proteins known as protein phosphatases. **Protein phosphatases** are enzymes that can rapidly remove phosphate groups from proteins (dephosphorylation) and thus inactivate protein kinases. Protein phosphatases are the "off switch" in the signal transduction pathway. Turning the signal transduction pathway off when the signal is no longer present is important to ensure that the cellular response is regulated appropriately. Dephosphorylation also makes protein kinases available for reuse and enables the cell to respond again when another signal is received.
- Kinases are not the only tools used by cells in signal transduction.
- ***Small, nonprotein, water-soluble molecules or ions called second messengers*** (the ligand that binds the receptor is the first messenger) can also relay signals received by receptors on the cell surface to target molecules in the cytoplasm or the nucleus.
- Examples of second messengers **include cyclic AMP (cAMP) and calcium ions.**
- **Signaling Molecules**
- Produced by signaling cells and the subsequent binding to receptors in target cells, **ligands act as chemical signals** that travel to the target cells to coordinate responses. The types of molecules that serve as ligands are incredibly varied and range from ***small proteins to small ions like calcium (Ca2+).***

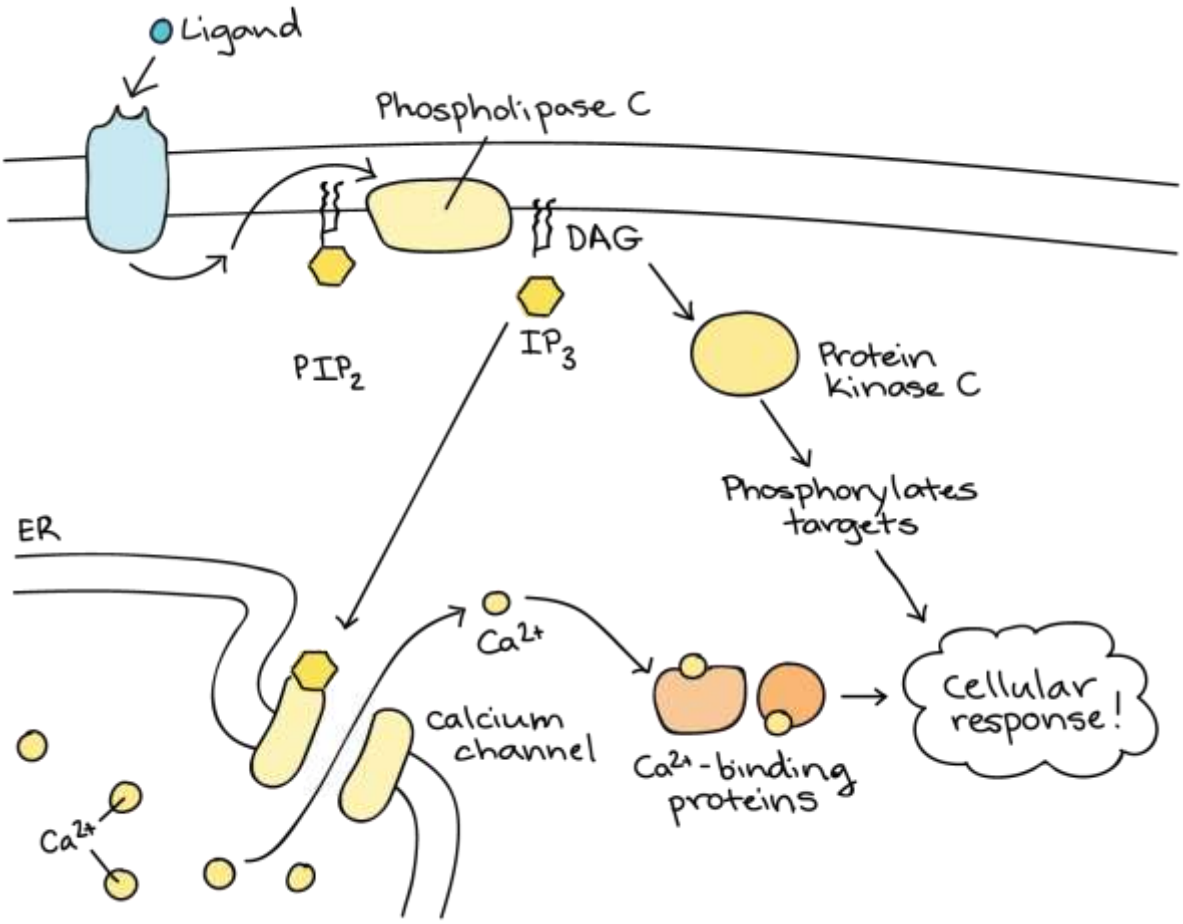
Small Hydrophobic Ligands

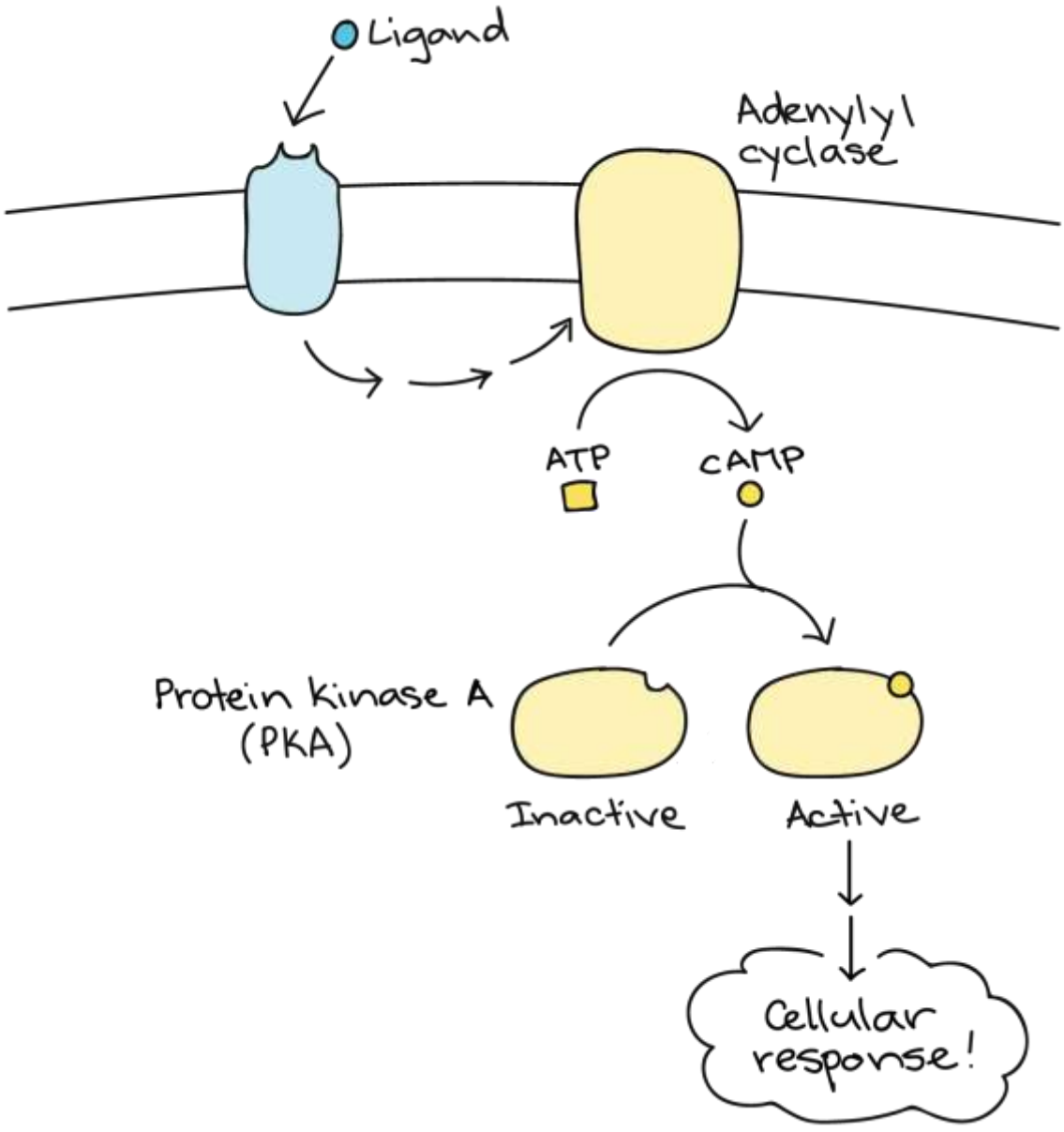
- **Small hydrophobic ligands** can directly diffuse through the plasma membrane and interact with internal receptors.
- Important members of this class of ligands are the **steroid hormones**.
- **Steroids are lipids** that have a **hydrocarbon skeleton with four fused rings;** different steroids have different functional groups attached to the carbon skeleton.

- Steroid hormones include the **female sex hormone, estradiol, which is a type of estrogen; the male sex hormone, testosterone; and cholesterol, which is an important structural component of biological membranes and a precursor of steriod hormones**.




SIGNAL IN
Inactive Enzyme
PROTEIN KINASE
APP
P
APP
ON
OFF
Pi
PROTEIN PHOSPHATASE
P
Active Enzyme
SIGNAL OUT


Ligand
Phospholipase C
DAG
IP_3
PIP_2
Protein kinase C
Phosphorylates targets
ER
Ca^{2+}
calcium channel
Ca^{2+}-binding proteins
cellular response!
Ca^{2+}



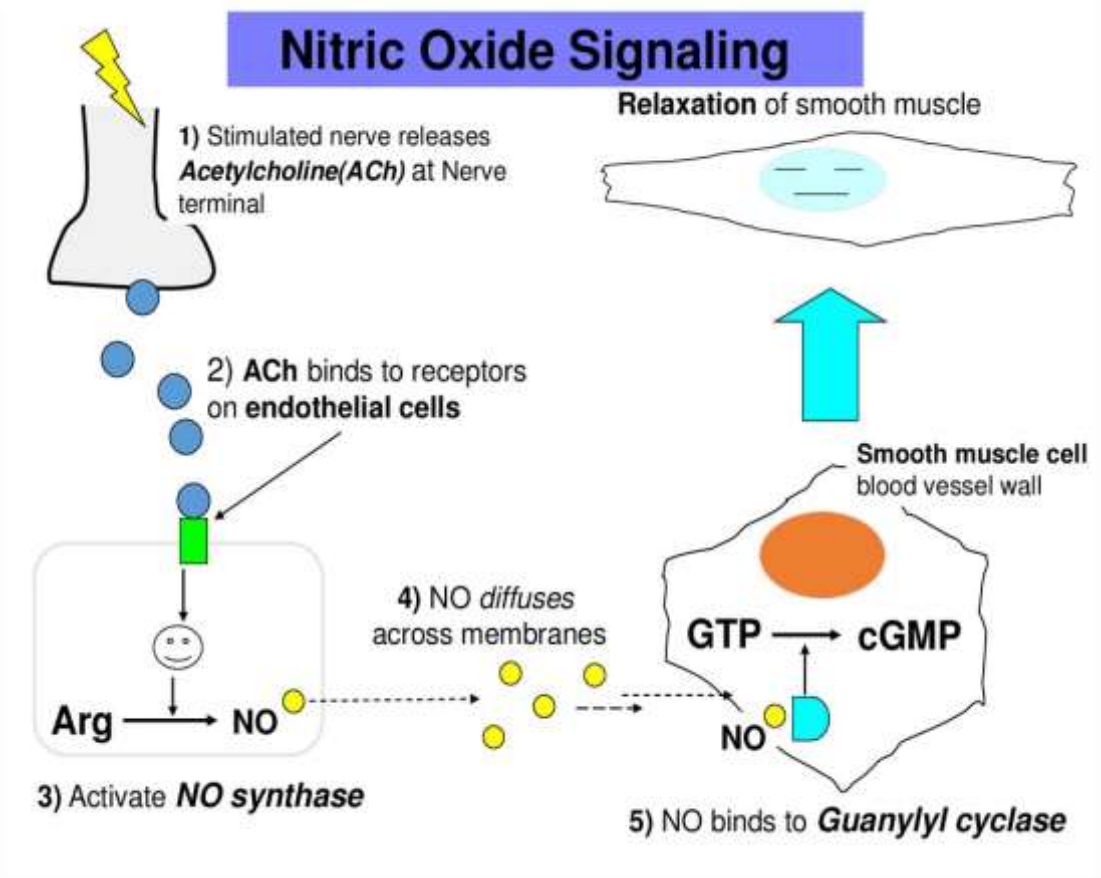
Other hydrophobic hormones include ***thyroid hormones and vitamin D.*** *In order to be* ***soluble in blood, hydrophobic ligands must bind to carrier proteins while they are being transported through the bloodstream****.*

Water-Soluble Ligands

- Water-soluble ligands are polar and, therefore, cannot pass through the plasma membrane unaided; sometimes, they are too large to pass through the membrane at all.
- Instead, most water-soluble ligands bind to the extracellular domain of cell-surface receptors.
- Cell-surface receptors include: **ion-channel, G-protein**, and enzyme-linked protein receptors.
- The binding of these ligands to these receptors results in a series of cellular changes. These water soluble ligands are quite diverse and include small molecules, peptides, and proteins.

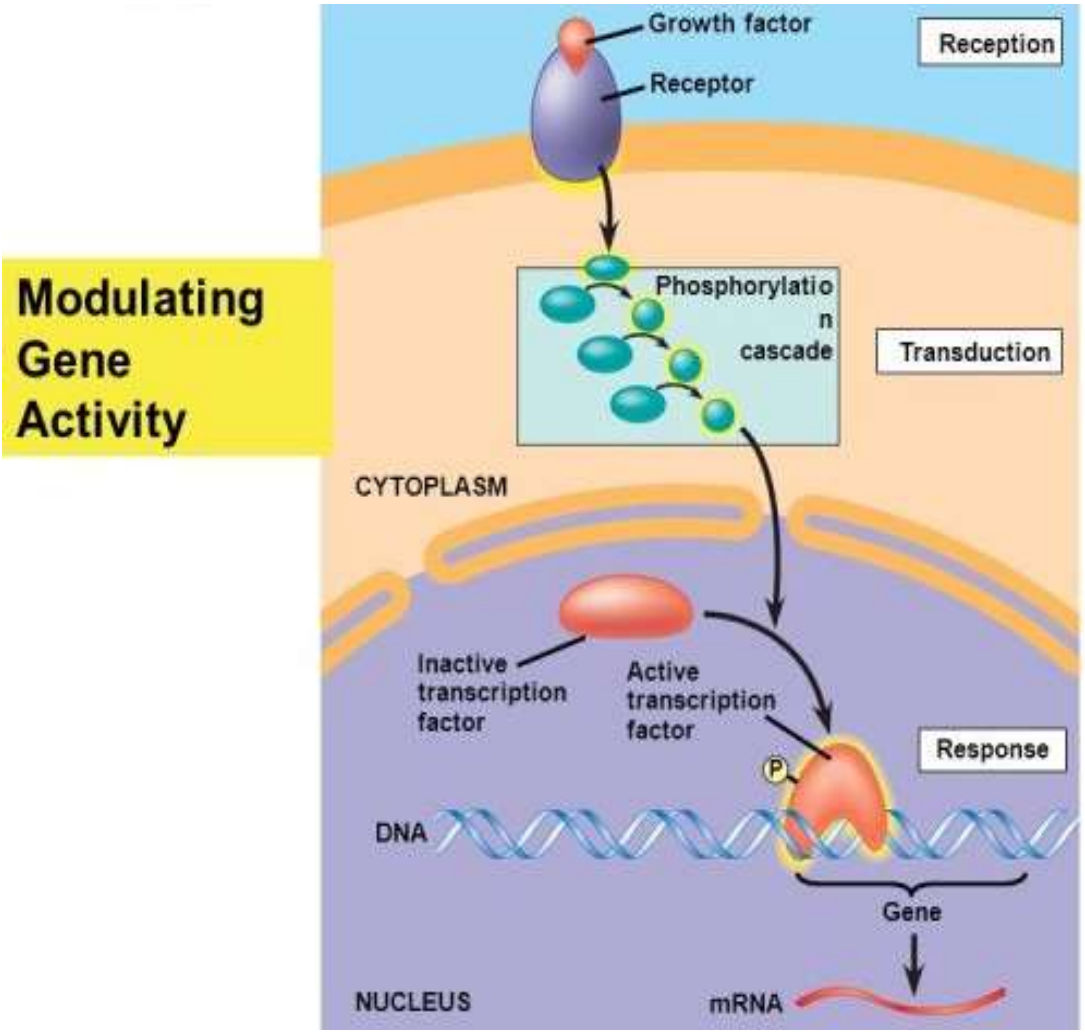
Other Ligands

- **Nitric oxide (NO)** is a gas that also acts as a ligand.
- It is able to diffuse directly across the plasma membrane; one of its roles is to interact with receptors in smooth muscle and induce relaxation of the tissue.
- NO has a **very short half-life**; therefore, it only functions over short distances.
- ***Nitroglycerin, a treatment for heart disease, acts by triggering the release of NO, which causes blood vessels to dilate (expand), thus restoring blood flow to the heart.***



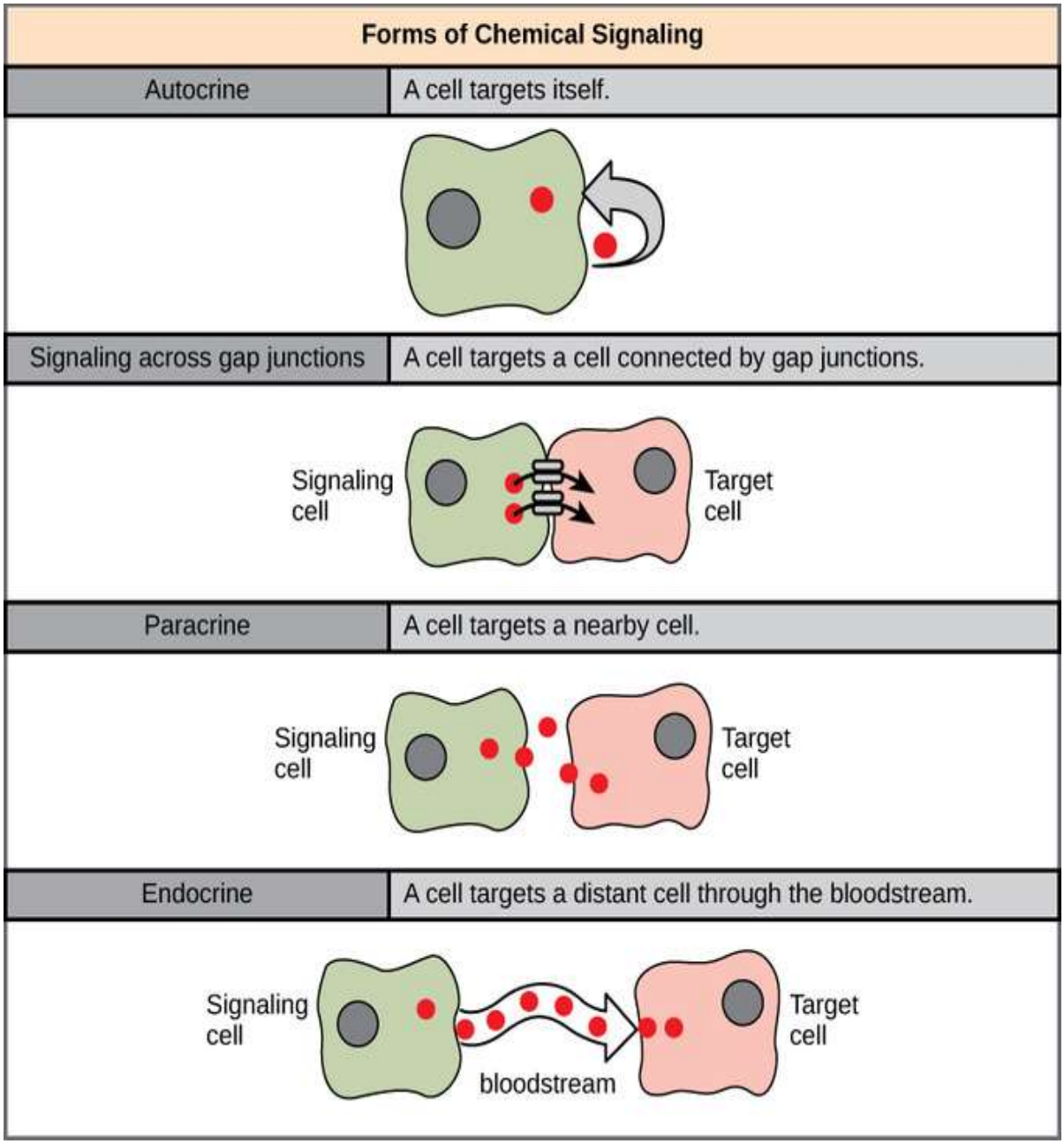
Response

- Cell signaling ultimately leads to the regulation of one or more cellular activities.
- Regulation of gene expression (turning transcription of specific genes on or off) is a common outcome of cell signaling.
- A signaling pathway may also regulate the activity of a protein, for example opening or closing an ion channel in the plasma membrane or promoting a change in cell metabolism such as catalyzing the breakdown of glycogen.
- Signaling pathways can also lead to important cellular events such as cell division or apoptosis (programmed cell death).



The major types of signaling mechanisms that occur in multicellular organisms are paracrine, endocrine, autocrine, and direct signaling.

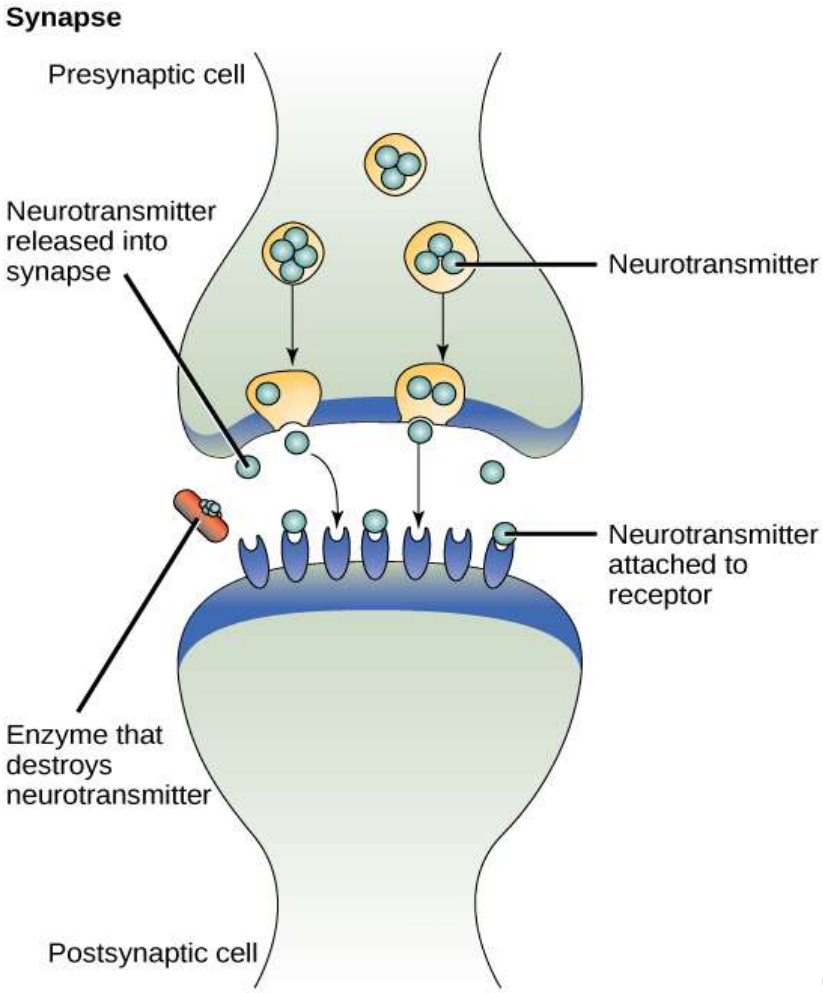
- **Endocrine signaling**: signals from distant cells that originate from endocrine cells, usually producing a slow response, but having a long-lasting effect
- **Autocrine signaling**: produced by signaling cells that can also bind to the ligand that is released: the signaling cell and the target cell can be the same or a similar cell.
- **Paracrine signaling**: a form of cell signaling in which the target cell is near (para = near) the signal-releasing cell



Paracrine Signaling

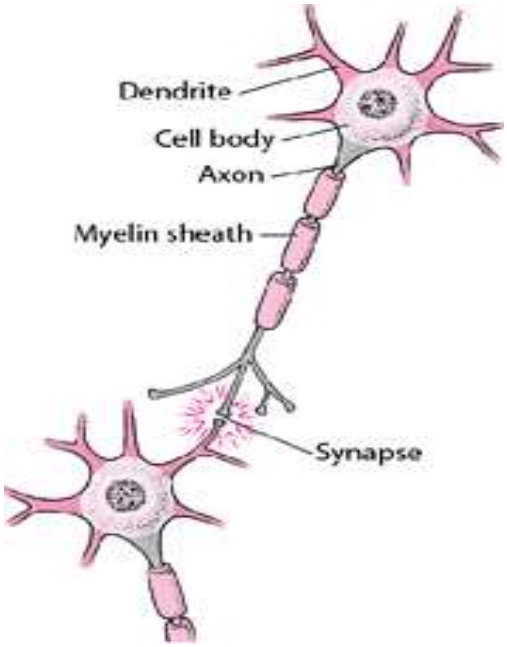
- Signals that act locally between cells that are close together are called paracrine signals. Paracrine signals move by diffusion through the extracellular matrix.

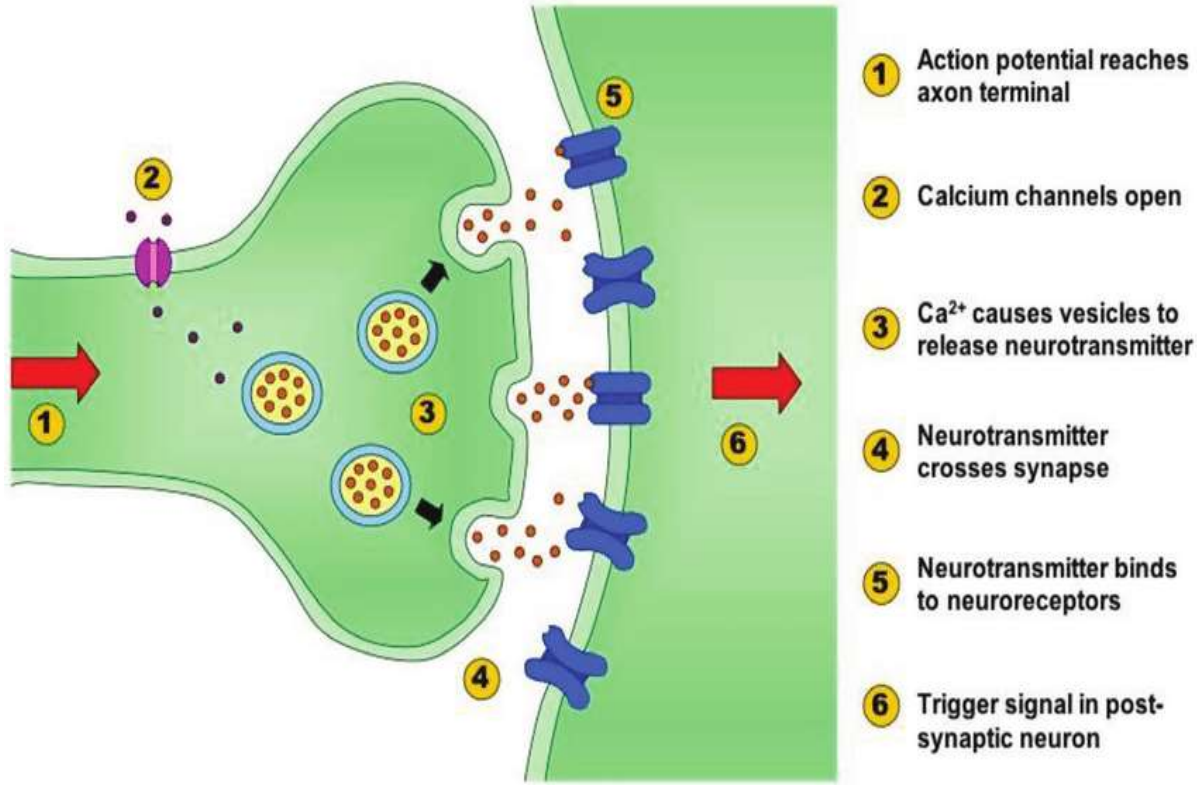
- These types of signals usually elicit quick responses that last only a short amount of time.
- In order to keep the response localized, **paracrine ligand molecules are normally quickly degraded by enzymes or removed by neighboring cells**.
- Removing the signals will **reestablish the concentration gradient for the signal, allowing them to quickly diffuse** through the intracellular space if released again.



- One ***example of paracrine signaling is the transfer of signals across synapses between nerve cells.***
- A nerve cell consists of a cell body, several short, branched extensions called **dendrites that receive stimuli**, and a **long extension called an axon**, which **transmits signals to other nerve cells or muscle cells**. The junction between nerve cells where signal transmission occurs is **called a synapse**.

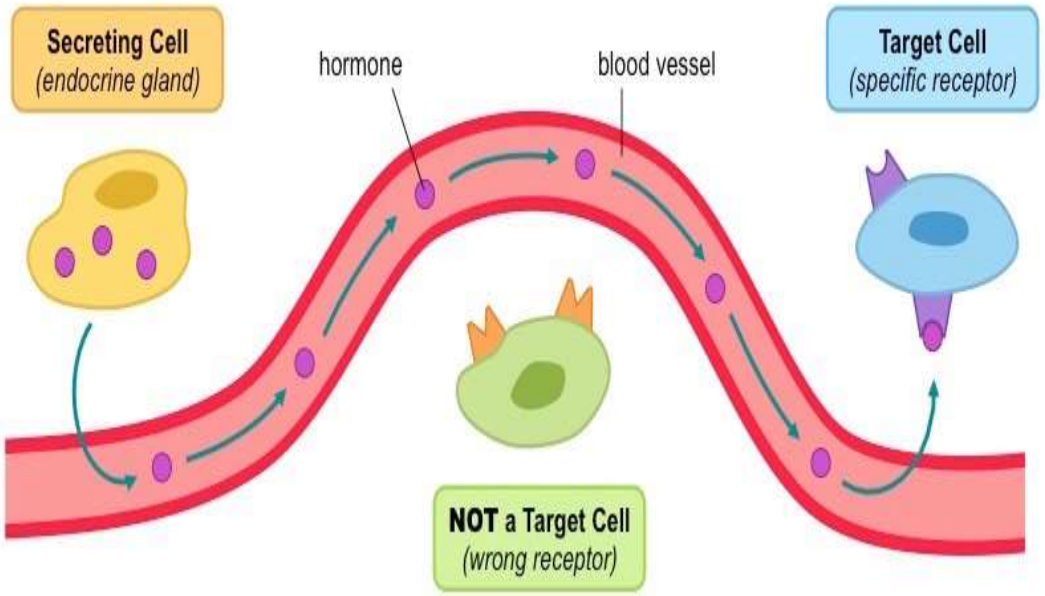
- A synaptic signal is a **chemical signal that travels between nerve cells**.
- Signals **within the nerve cells are propagated by fast-moving electrical impulses**. When these impulses reach the end of the axon, the signal continues on to a dendrite of the next cell by the release of chemical ligands **called neurotransmitters** by the presynaptic cell (the cell emitting the signal).
- The **neurotransmitters are transported across the very small distances between nerve cells, which are called chemical synapses.**
- The small distance between nerve cells allows the signal to travel quickly; **this enables an immediate response.**





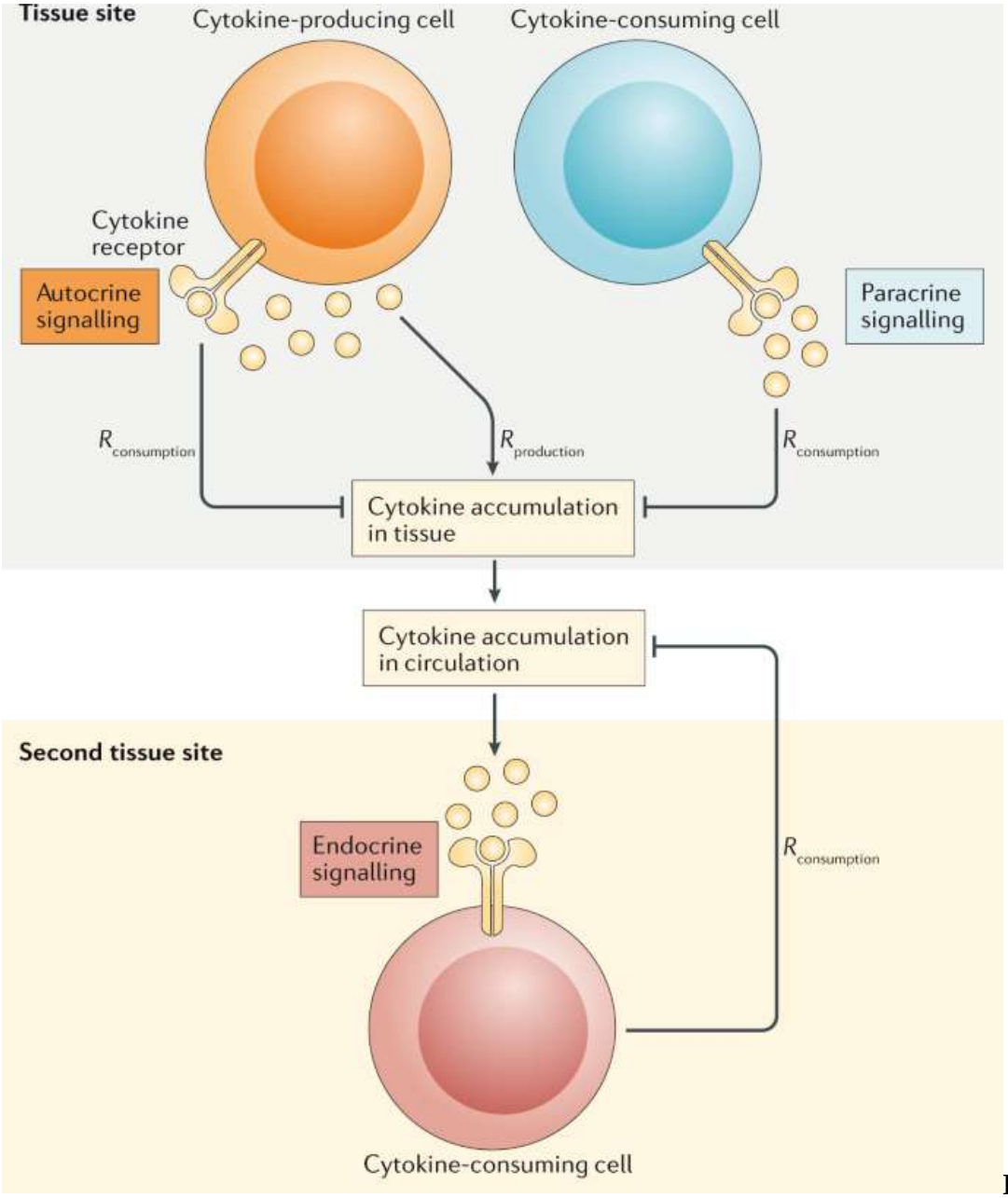
Endocrine Signaling

- Signals from ***distant cells are called endocrine signal***s; they originate from **endocrine cells**.
- In the body, many **endocrine cells are located in endocrine glands, such as the thyroid gland, the hypothalamus, and the pituitary gland**.
- These types of signals usually produce a **slower response, but have a longer-lasting effect**.
- The ligands released in **endocrine signaling are called hormones, signaling molecules that are produced in one part of the body, but affect other body regions some distance away.**
- Hormones **travel the large distances between endocrine cells and their target cells via the bloodstream,** which is a relatively slow way to move throughout the body.
- Because of their form of transport, **hormones get diluted and are present in low concentrations when they act on their target cells**.
- This is different from paracrine signaling in which local concentrations of ligands can be very high.



Autocrine Signaling

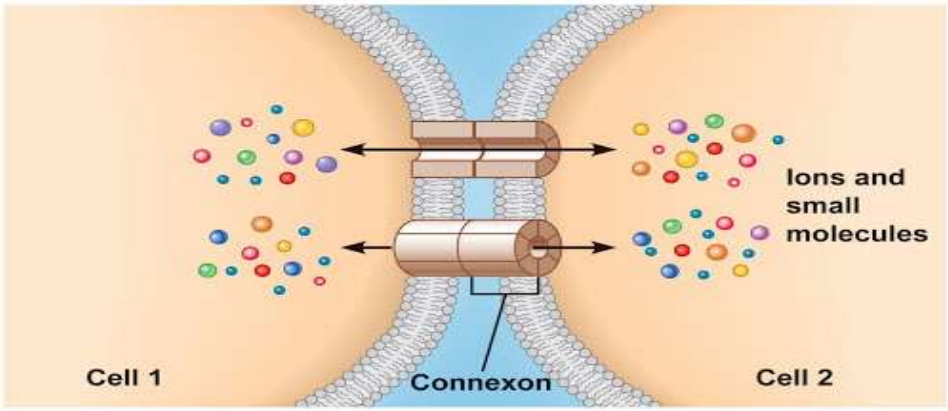
- Autocrine signals **are produced by signaling cells that can also bind to the ligand that is released**. This means the signaling cell and the target cell can be the same or a similar cell (the prefix auto- means self, a reminder that the signaling cell sends a signal to itself).
- This type of **signaling often occurs during the early development of an organism to ensure that cells develop into the correct tissues and take on the proper func**tion.
- Autocrine signaling also regulates pain sensation and inflammatory responses.
- Further**, if a cell is infected with a virus, the cell can signal itself to undergo programmed cell death, killing the virus in the process**.
- In some cases, neighboring cells of the same type are also influenced by the released ligand.
- In embryological development, this process of stimulating a group of neighboring cells may help to direct the differentiation of identical cells into the same cell type, thus ensuring the proper developmental outcome.

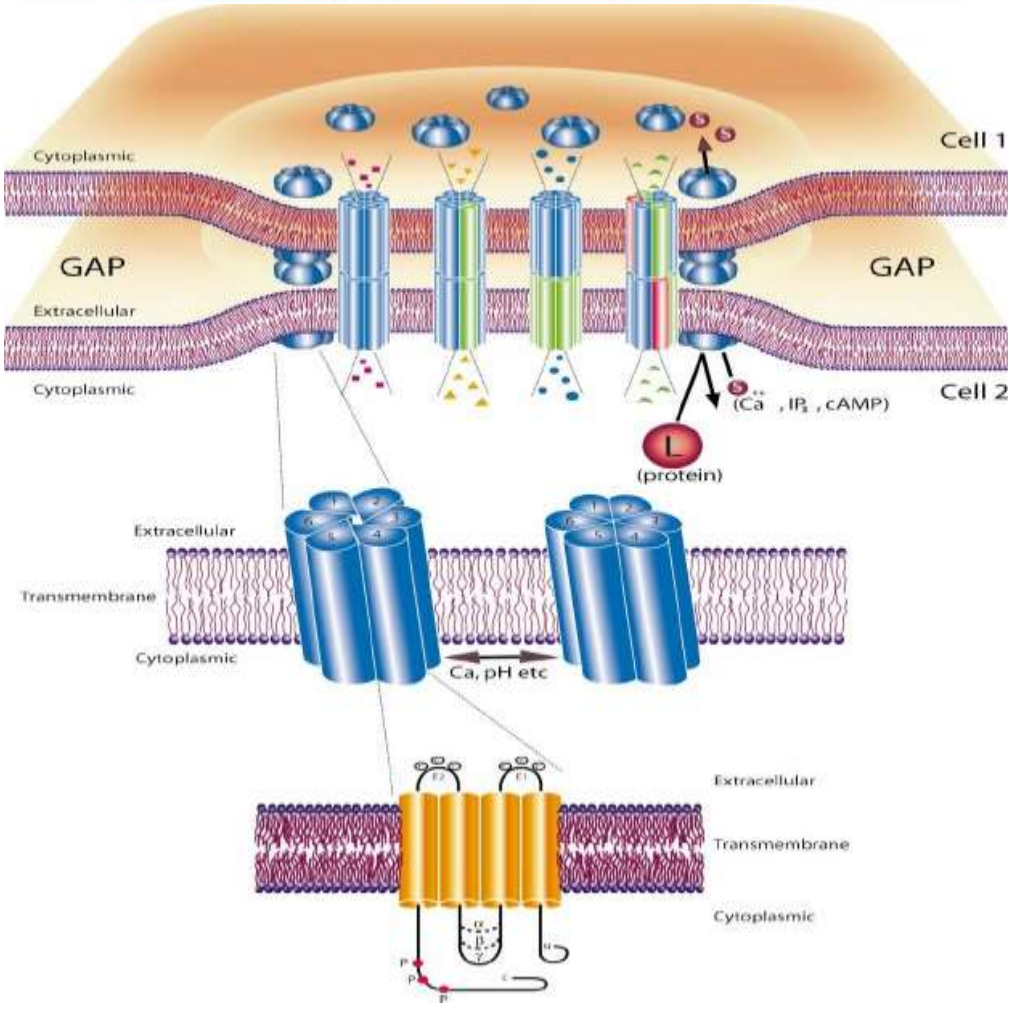


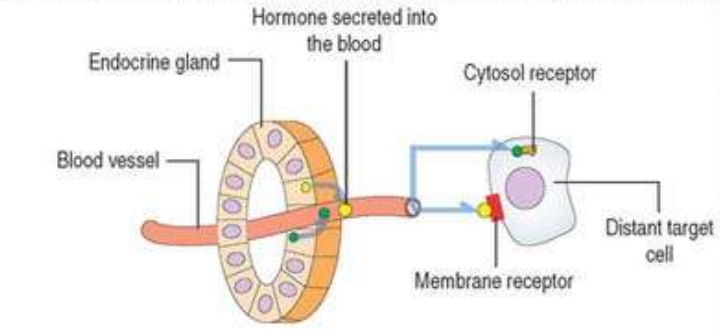
Direct Signaling Across Gap Junctions

- Gap junctions in animals and plasmodesmata in plants are connections between the plasma membranes of neighboring cells.

- These water-filled channels allow small signaling molecules, called **intracellular mediators**, to diffuse between the two cells.
- ***Small molecules, such as calcium ions (Ca2+),*** are able to move between cells, but **large molecules, like proteins and DNA, cannot fit through the channels**.
- The specificity of ***the channels ensures that the cells remain independent, but can quickly and easily transmit signals***.
- The transfer of signaling molecules communicates the current state of the cell that is directly next to the target cell; this allows a group of cells to coordinate their response to a signal that only one of them may have received.
- In plants, plasmodesmata are ubiquitous, making the entire plant into a giant communication network.


Ions and
small
molecules
Cell 1
Connexon
Cell 2

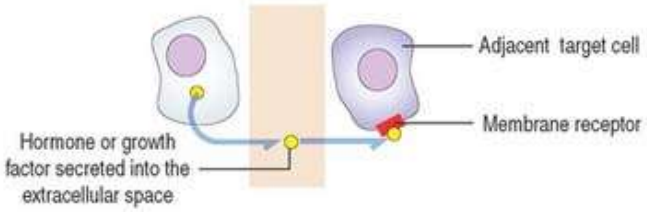

Cytoplasmic
Cell 1
GAP
GAP
Extracellular
Cytoplasmic
Cell 2
(protein)
Extracellular
Transmembrane
Cytoplasmic
Ca, pH etc
Extracellular
Transmembrane
Cytoplasmic



Endocrine signaling

Endocrine cells secrete a **polypeptide** or **steroid hormone** into a blood vessel. The hormone is then carried to a target cell, which may be located at a considerable distance from the secreting cell.

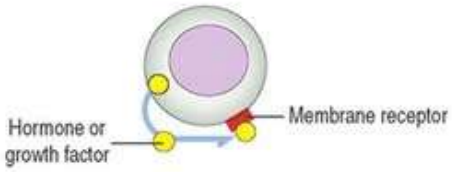
An example of a polypeptide hormone is **thyrotrophic hormone**, secreted by the hypophysis and acting on the thyroid gland. An example of a steroid hormone is **estradiol**, produced by the ovaries and acting on the endometrium.



Paracrine signaling

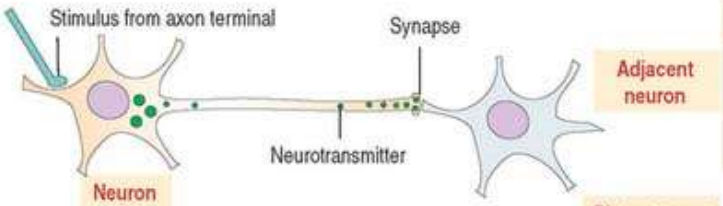
Paracrine cells secrete hormones or growth factors that act on an **adjacent cell.**

Examples are **glucagon** and **somatostatin** acting on adjacent cells of the islets of Langerhans that secrete **insulin.**



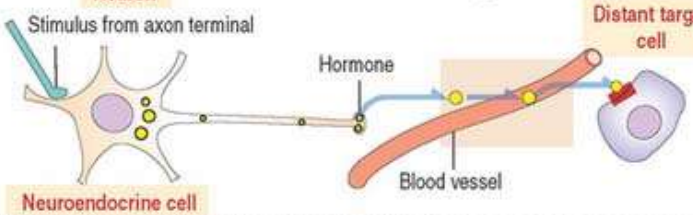
Autocrine signaling

Some hormones or growth factors, such as **prostaglandins** and **interleukins**, can act **on the originating cell** and exert an autocrine control.



Neurotransmitter signaling

In response to a neural signal, neurons secrete **neurotransmitters** from the axon terminals to activate adjacent neurons.



Neuroendocrine signaling

In response to a neural signal, neuroendocrine cells secrete a **hormone** into the blood to travel to a target organ. An example is **norepinephrine** acting on hepatocytes or adipocytes.

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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF BIOINFORMATICS

UNIT – IV – CELL BIOLOGY AND BIOCHEMISTRY – SBIA1102

UNIT-IV

CARBOHYDRATES

Carbohydrates are the most abundant biomolecules on earth. Oxidation of carbohydrates is the central energy-yielding pathway in most non-photosynthetic cells.

Definition: Carbohydrates are polyhydroxy aldehydes or ketones, or substances that yield such compounds on hydrolysis.

Carbohydrates have the empirical formula $(CH_2O)_n$.

There are three major classes of carbohydrates:

1. Monosaccharides

Monosaccharides, or simple sugars, consist of a single polyhydroxy aldehyde or ketone unit. The most abundant monosaccharide in nature is the six-carbon sugar D- glucose, sometimes referred to as dextrose.

2. Oligosaccharides

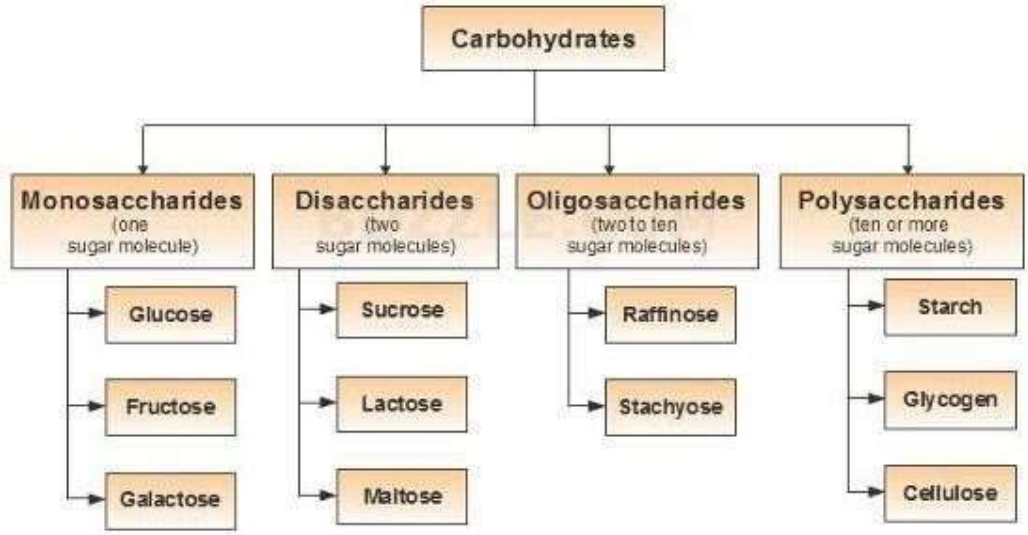
Oligosaccharides consist of short chains of monosaccharide units, or residues, joined by characteristic linkages called glycosidic bonds. The most abundant are the disaccharides, with two monosaccharide units. Example: sucrose (cane sugar).

3. Polysaccharides

The polysaccharides are sugar polymers containing more than 20 or so monosaccharide units, and some have hundreds or thousands of units. Example: starch.

Polysaccharides are of two types based on their function and composition. Based on function, polysaccharides are of two types: storage and structural. A. Storage polysaccharide - starch.

B. Structural polysaccharide - cellulose.



General properties of carbohydrates

- Carbohydrates act as energy reserves, also stores fuels, and metabolic intermediates.
- Ribose and deoxyribose sugars forms the structural frame of the genetic material, RNA and DNA.
- Polysaccharides like cellulose are the structural elements in the cell walls of bacteria and plants.
- Carbohydrates are linked to proteins and lipids that play important roles in cell interactions.
- Carbohydrates are organic compounds, they are aldehydes or ketones with many hydroxyl groups.

Physical Properties of Carbohydrates:

- Stereoisomerism - Compound shaving same structural formula but they differ in spatial configuration. Example: Glucose has two isomers with respect to penultimate carbon atom. They are D-glucose and L-glucose.
- Optical Activity - It is the rotation of plane polarized light forming (+) glucose and (-) glucose.
- Diastereoisomerism - It is the configurational change with respect to C2, C3, or C4 in glucose. Example: Mannose, galactose.

- Anomerism - It is the spatial configuration with respect to the first carbon atom in aldoses and second carbon atom in ketoses.

Biological Importance

- Carbohydrates are chief energy source, in many animals, they are instant source of energy. Glucose is broken down by glycolysis/ Kreb's cycle to yield ATP.
- Glucose is the source of storage of energy. It is stored as glycogen in animals and starch in plants.
- Stored carbohydrates act as energy source instead of proteins.
- Carbohydrates are intermediates in biosynthesis of fats and proteins.
- Carbohydrates aid in regulation of nerve tissue and as the energy source for brain.
- Carbohydrates get associated with lipids and proteins to form surface antigens, receptor molecules, vitamins and antibiotics.
- They form structural and protective components, like in cell wall of plants and microorganisms.
- In animals they are important constituent of connective tissues.
- They participate in biological transport, cell-cell communication and activation of growth factors.
- Carbohydrates rich in fibre content help to prevent constipation.
- Also they help in modulation of immune system.

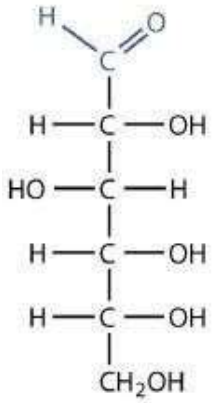
Monosaccharides

- The word "Monosaccharides" derived from the Greek word "Mono" means Single and "saccharide" means sugar
- Monosaccharides are polyhydroxy aldehydes or ketones which cannot be further hydrolysed to simple sugar.
- Monosaccharides are simple sugars. They are sweet in taste. They are soluble in water. They are crystalline in nature.
- They contain 3 to 10 carbon atoms, 2 or more hydroxyl (OH) groups and one aldehyde (CHO) or one ketone (CO) group.

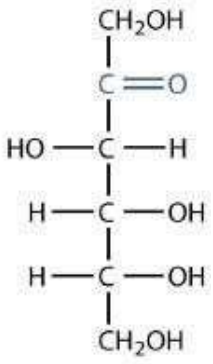
Classification of Monosaccharides

Monosaccharides are classified in two ways. (a) First of all, based on the number of carbon atoms present in them and (b) secondly based on the presence of carbonyl group.

The naturally occurring monosaccharides contain three to seven carbon atoms per molecule. Monosaccharides of specific sizes may be indicated by names composed of a stem denoting the number of carbon atoms and the suffix *-ose*. For example, the terms *triose*, *tetrose*, *pentose*, and *hexose* signify monosaccharides with, respectively, three, four, five, and six carbon atoms. Monosaccharides are also classified as aldoses or ketoses. Those monosaccharides that contain an aldehyde functional group are called aldoses; those containing a ketone functional group on the second carbon atom are ketoses. Combining these classification systems gives general names that indicate both the type of carbonyl group and the number of carbon atoms in a molecule. Thus, monosaccharides are described as aldotetroses, aldopentoses, ketopentoses, ketoheptoses, and so forth. Glucose and fructose are specific examples of an aldohexose and a ketohexose, respectively.



Glucose
(an aldohexose)



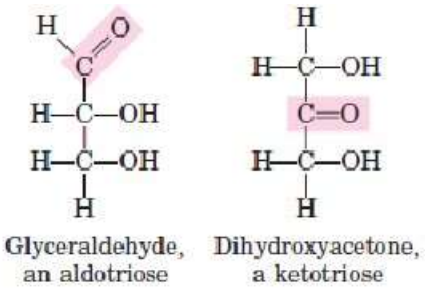
Fructose
(a ketohexose)

Name	Formula	Aldose	Ketose
Triose	$C_3H_6O_3$	Glycerose	Dihydroxy acetone
Tetrose	$C_4H_8O_4$	Erythrose	Erythrulose
Pentose	$C_5H_{10}O_5$	Ribose	Ribulose
Hexose	$C_6H_{12}O_6$	Glucose	Fructose
Heptose	$C_7H_{14}O_7$	Glucoheptose	Sedo heptulose

Trioses

Trioses are "Monosaccharides" containing 3 carbon atoms. The molecular formula of triose is $C_3H_6O_3$ Characteristics:

- Trioses are simple sugars
- They are soluble in water ➢ They are sweet in taste.
- The triose may contain an aldehyde group (aldotriose) or a ketone group (ketotriose). Example: Glyceraldehyde and Dehydroxyacetone

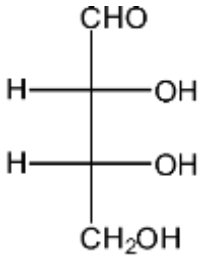


Glyceraldehyde, an aldotriose — Dihydroxyacetone, a ketotriose

Tetroses

Tetroses are "Monosaccharides" containing 4 carbon atoms. The molecular formula of tetrose is $C_4H_8O_4$ Characteristics:

- Tetroses are simple sugars
- Tetroses are soluble in water ➢ They are sweet in taste.
- They are crystalline forms.
- The tetroses may contain an aldehyde group (aldotetrose) or a ketone group (ketotetrose).



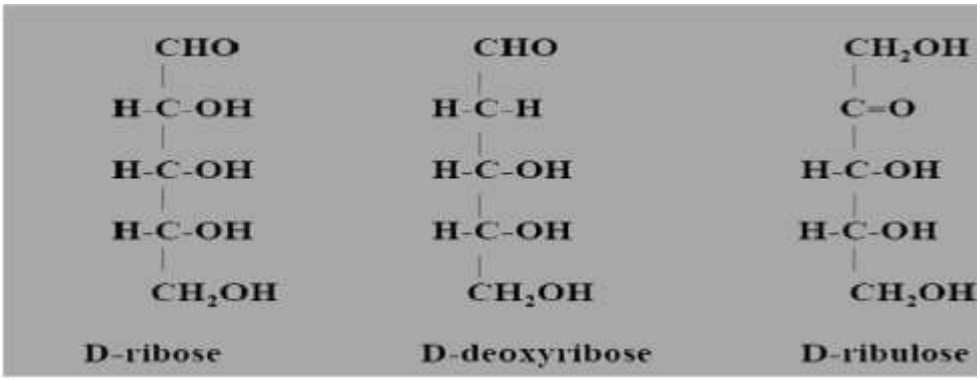
Erythrose

D-Erythrulose

Pentoses

Pentoses are "Monosaccharides" containing 5 carbon atoms. It is an important component of "nucleic acid". The molecular formula of Pentose is C5H10O5 Characteristics:

- Pentoses are simple sugars ➢ Pentoses are soluble in water ➢ They are sweet in taste.
- They are crystalline forms.
- The pentoses may contain aldehyde group (aldopentose) or ketone group (ketopentose).



Hexoses

Hexoses are "Monosaccharides" containing 6 carbon atoms. The molecular formula of Hexose is $C_6H_{12}O_6$

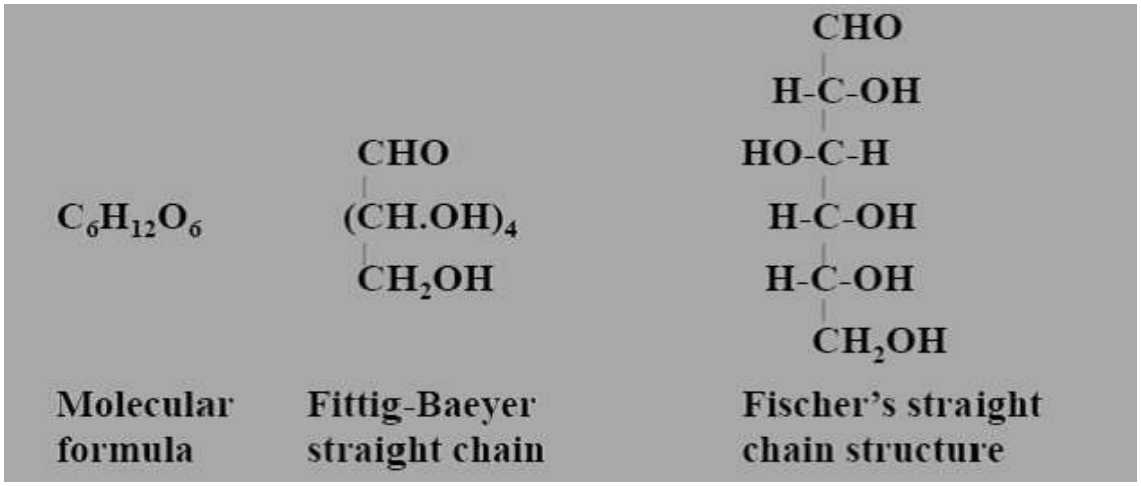
Characteristics:

- Hexoses are simple sugars ➢ Hexoses are soluble in water ➢ They are sweet in taste.
- They are crystalline forms.
- The hexoses may contain an aldehyde group (aldohexose) or a ketone group (ketohexose).

Structure of Monosaccharides

1. **Straight or Open Chain Structure**: Here 6 carbon atoms of glucose are arranged in a straight line. It is also called open chain structure because the two ends remain separate and they are not linked. Open chain structures are of two types:

- (a)Structure proposed by Fittig and Baeyer
- (b)Structure proposed by Fischer known as Fischer's Projection Formula.

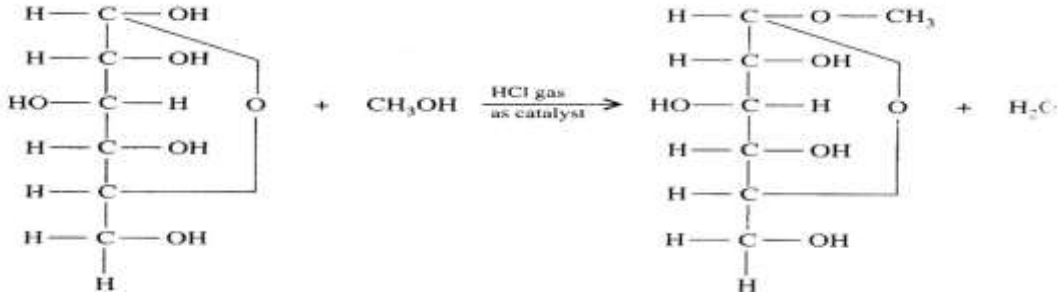


2. **Cyclic or Ring Structure:** Here the atoms are arranged in the form of a ring. Haworth (1929) proposed this formula and hence the name Haworth's Projection Formula. The sugar molecules exist in two type of rings which are as follows – (a)Furanose Ring – 5 membered ring (b)Pyranose Ring- 6 membered ring

Properties of Monosaccharides

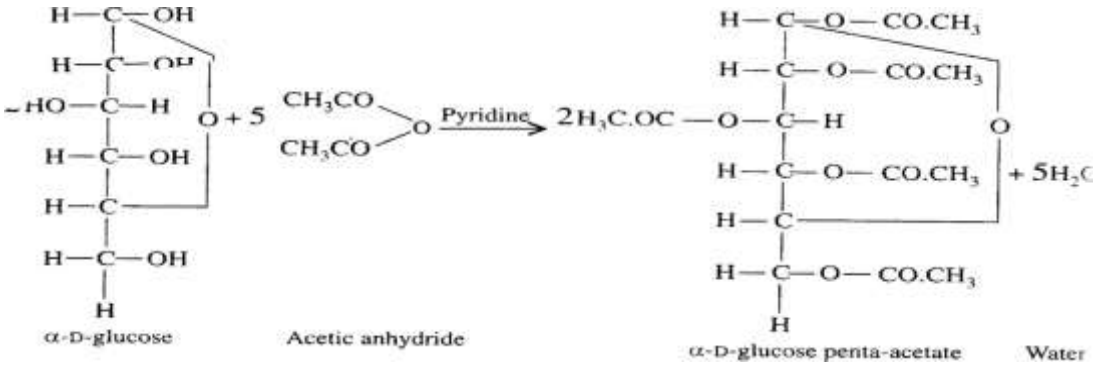
1. Colour - colourless

2. Shape - crystalline
3. Solubility – in Water
4. Taste - sweet
5. Optical activity – Optically active. (a) Dextrorotatory ('d' form) and (b) Levorotatory ('l' form)
6. **Mutarotation** – The change in specific rotation of an optically active compound is called mutarotation. +1120 +52.50 +190 α-D-glucose β -D-glucose
7. **Glucoside formation** -



Glucose + Methyl alcohol = Methyl glucoside

8. Esterification –

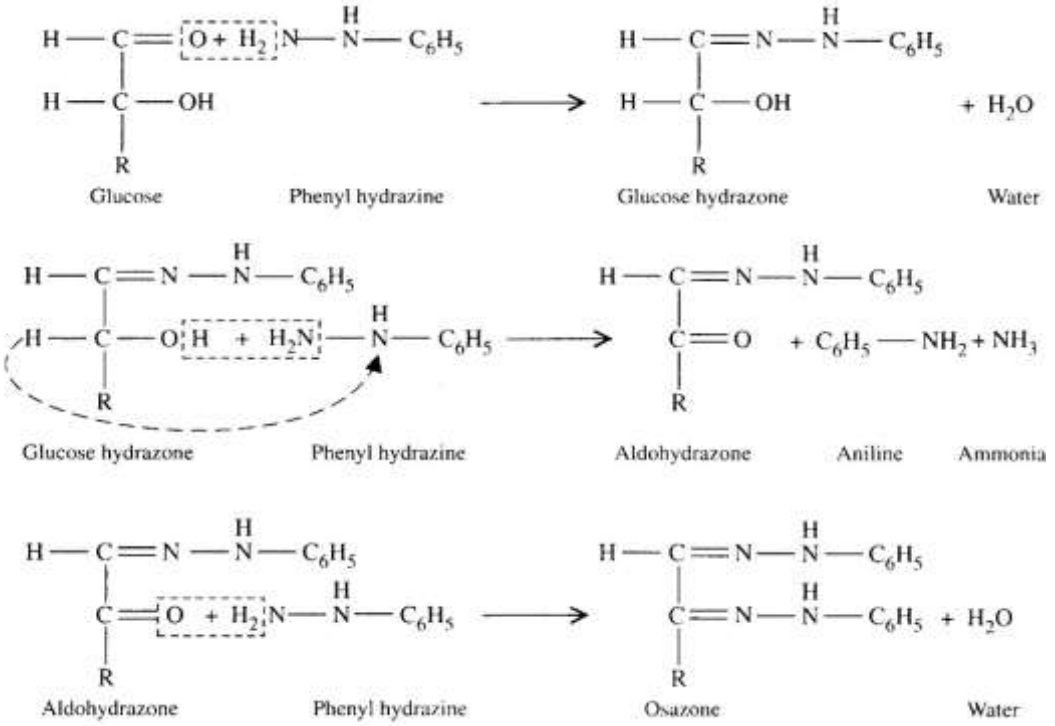


9. Reducing agents –

Monosaccharides reduce oxidizing agent such as hydrogen peroxide. In such reaction, sugar is oxidized at the carbonyl group and oxidizing agent becomes reduced.

$C_6H_{12}O_6 + 2\ Cu(OH)_2 \rightarrow C_6H_{12}O_7 + Cu_2O + 2H_2O$

10. Formation of Osazone –



Disaccharides

Disaccharides consist of two sugars joined by an O-glycosidic bond. The most abundant disaccharides are sucrose, lactose and maltose. Other disaccharides include isomaltose, cellobiose and trehalose.

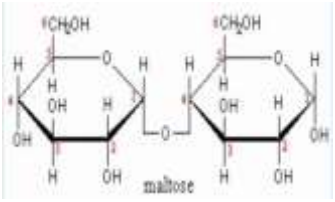
The disaccharides can be classified into:

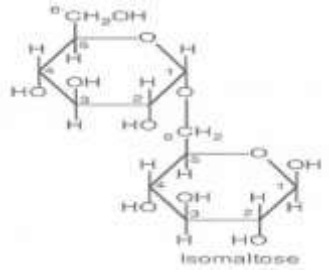
1. Homodisaccharides

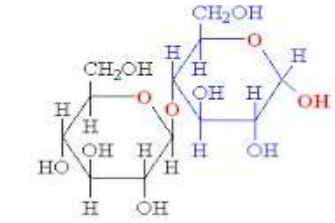
2. Heterodisaccharides.

Homodisaccharides	**Maltose (malt sugar)**	**Isomaltose**	**Cellobiose**
Structure	2α-glucose	2 α-glucose	2β-D-glucose

Type of bond	α-1-4 glucosidicbond	α1-6 glucosidicbond	β1-4 glucosidicbond.
Anomeric Carbon	Free	Free	Free
Reducing Property	Reducing	Reducing	Reducing
Produced by	It is produced from starch by the action of amylase	by the hydrolysis of some polysaccharides such as dextran	by the acid hydrolysis of cellulose







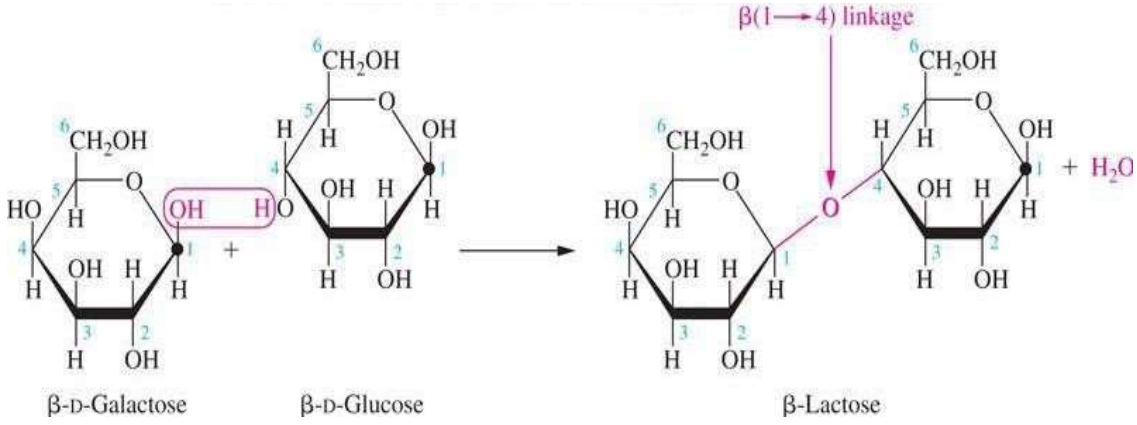
cellobiose

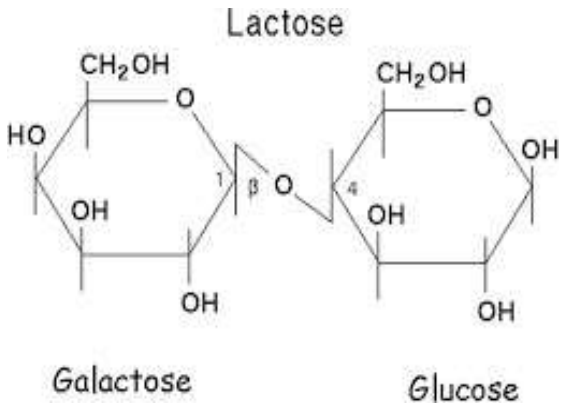
4-(β-D-glucopyanosyl)-D-glucose

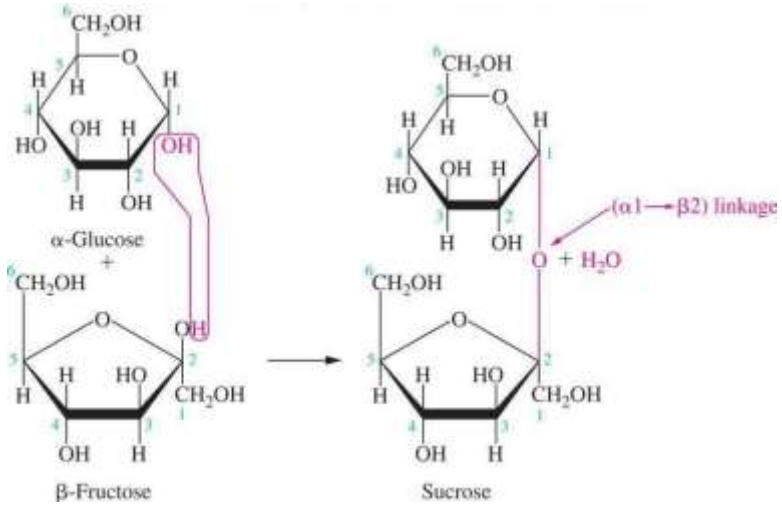
Heterodisaccharides: are formed of 2 different monosaccharide units

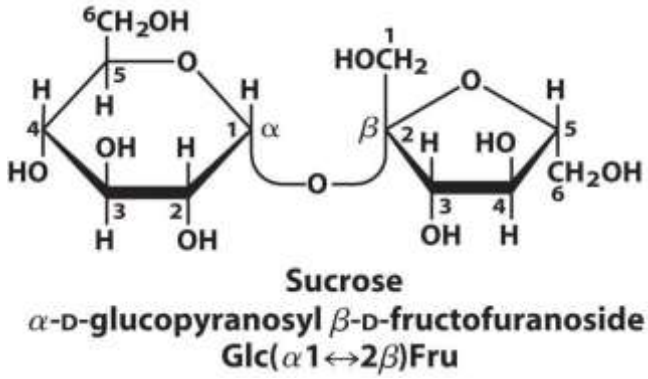
Heterodisaccharides	**Sucrose**	**Lactose**
Composition	α-D-glucose+ β–D-fructose	β-D-galactose and β-D-glucose
Type of bond	α-1-β-2 glucosidic bond OR β 2-α-1 fructosidic bond	a β (1→4) galactosidic bond

Anomeric C	no free aldehyde or ketone group	free
Reducing property	is not a reducing sugar	Reducing
Composition	α-D-glucose+β–D-fructose	β-D-galactose and β-D-glucose
Effect of hydrolysis	The hydrolysis of sucrose to glucose and fructose is catalysed by sucrase (also called invertase)	Hydrolysed by the intestinal lactase enzyme into galactose and glucose
Present in	Table sugar Cane sugar, beet sugar	Milk sugar It may appear in urine in late pregnancy and during lactation









Polysaccharides

Polysaccharides contain hundreds or thousands of carbohydrate units.

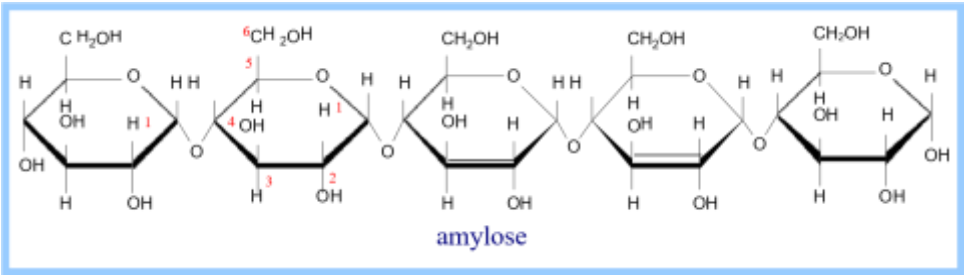
- Polysaccharides are *not* reducing sugars, since the anomeric carbons are connected through glycosidic linkages.
- **Nomenclature:**

  Homopolysaccharide- a polysaccharide is made up of **one type** of monosaccharide unit

  Heteropolysaccharide- a polysaccharide is made up of more than **one type** of monosaccharide unit

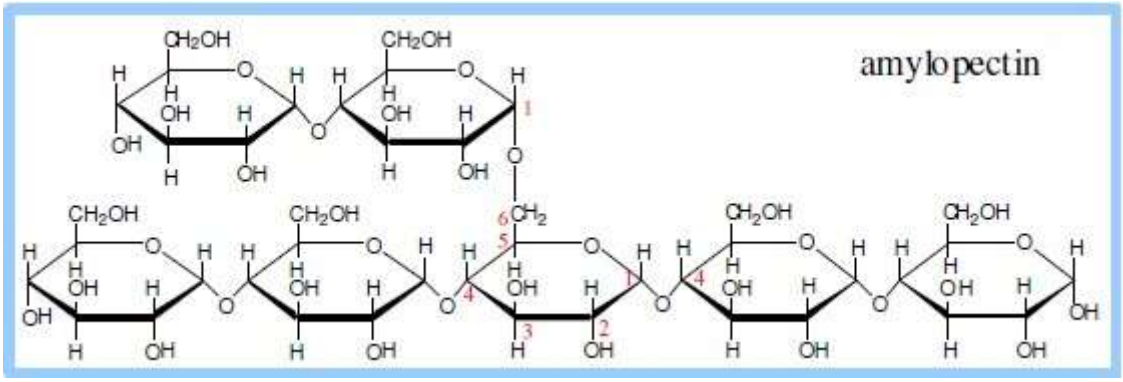
Starch

- Starch is a polymer consisting of D-glucose units.
- Starches (and other glucose polymers) are usually insoluble in water because of the high molecular weight, but they can form thick colloidal suspensions with water.
- Starch is a **storage** compound in plants, and made of glucose units
- It is a homopolysaccharide made up of two components: **amylose** and **amylopectin**.
- Most starch is 10-30% amylose and 70-90% amylopectin.
- **Amylose** – a straight chain structure formed by **1,4 glycosidic bonds** between **α-D-glucose** molecules.



Structure of Amylose Fraction of Starch

- The amylose chain forms a helix.
- This causes the blue colour change on reaction with iodine.
- Amylose is poorly soluble in water, but forms micellar suspensions
- Amylopectin-a glucose polymer with mainly α -(1→4) linkages, but it also has branches formed by α -(1→6) linkages. Branches are generally longer than shown above.

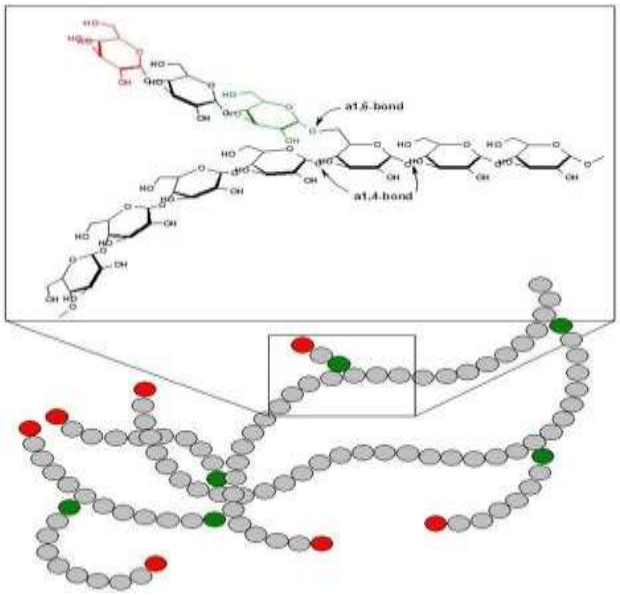


Structure of Amylopectin Fraction of Starch

- Amylopectin causes a red-violet colour change on reaction with iodine.
- This change is usually masked by the much darker reaction of amylose to iodine.

Glycogen

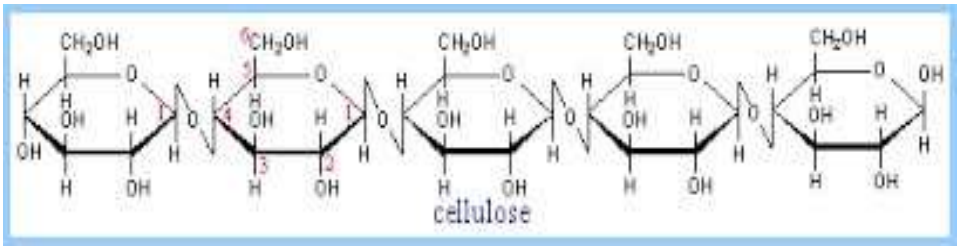
- Storage polysaccharide in animals
- Glycogen constitutes up to 10% of liver mass and 1-2% of muscle mass
- Glycogen is stored energy for the organism
- Similar in structure to amylopectin, only difference from starch: number of branches
- Alpha(1,6) branches every 8-12 residues
- Like amylopectin, glycogen gives a red-violet color with iodine



Cellulose

- The β-glucose molecules are joined by condensation, i.e. the removal of water, forming β-(1,4) glycosidic linkages.
- The glucose units are linked into straight chains each 100-1000 units long.
- Weak hydrogen bonds are formed between parallel chains binding them into cellulose microfibrils.
- Cellulose microfibrils arrange themselves into thicker bundles called microfibrils. (These are usually referred to as fibres.)
- The cellulose fibres are often "glued" together by other compounds such as hemicelluloses and calcium pectate to form complex structures such as plant cell walls.
- Because of the β-linkages, cellulose has a different overall shape from amylose, forming extended straight chains which hydrogen bond to each other, resulting in a very rigid structure.
- Cellulose is an important structural polysaccharide, and is the single most abundant organic compound on earth. It is the material in plant cell walls that provides strength and rigidity; wood is 50% cellulose.
- Most animals lack the enzymes needed to digest cellulose, although it does provide needed roughage (dietary fiber) to stimulate contraction of the intestines and thus help pass food along through the digestive system

- Some animals, such as cows, sheep, and horses, can process cellulose through the use of colonies of bacteria in the digestive system which are capable of breaking cellulose down to glucose; ruminants use a series of stomachs to allow cellulose a longer time to digest. Some other animals such as rabbits reprocess digested food to allow more time for the breakdown of cellulose to occur.
- Cellulose is also important industrially, from its presence in wood, paper, cotton, cellophane, rayon, linen, nitrocellulose (gun cotton), photographic films (cellulose acetate), etc.

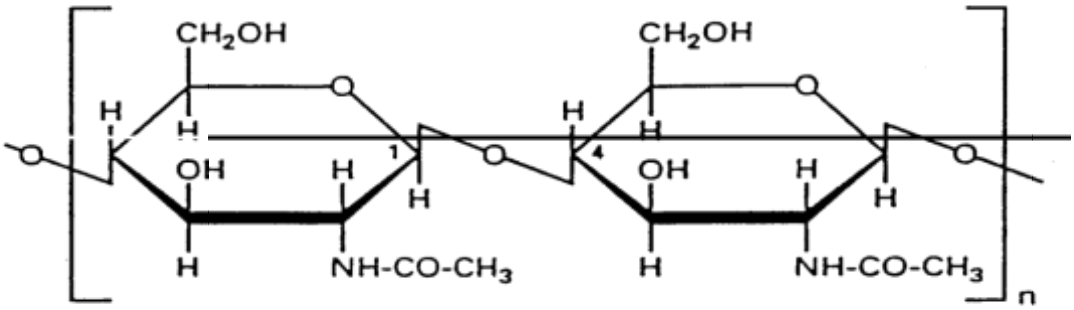


Chitin

- Chitin is a polymer that can be found in anything from the shells of beetles to webs of spiders. It is present all around us, in plant and animal creatures.
- It is sometimes considered to be a spinoff of cellulose, because the two are very molecularly similar.
- Cellulose contains a hydroxy group, and chitin contains acetamide.
- Chitin is unusual because it is a "natural polymer," or a combination of elements that exists naturally on earth.

- Usually, polymers are man-made. Crabs, beetles, worms and mushrooms contain large amount of chitin.
- Chitin is a very firm material, and it helps to protect an insect against harm and pressure.

Chitin

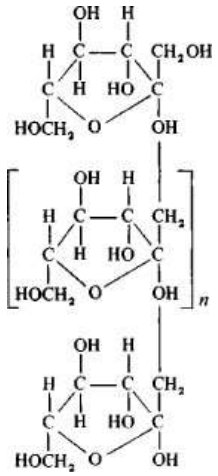


N-Acetylglucosamine N-Acetylglucosamine

Inulin

- Inulin is stored in the tubers of the dahlia and artichoke and in the roots of dandelion. It is also found in onion and garlic.
- Inulin (Fig. 8–4) has a molecular weight of about 5,000 and consists of about 30–35 fructose units per molecule.
- It is formed in the plants by eliminating a molecule of water from the h glycosidic

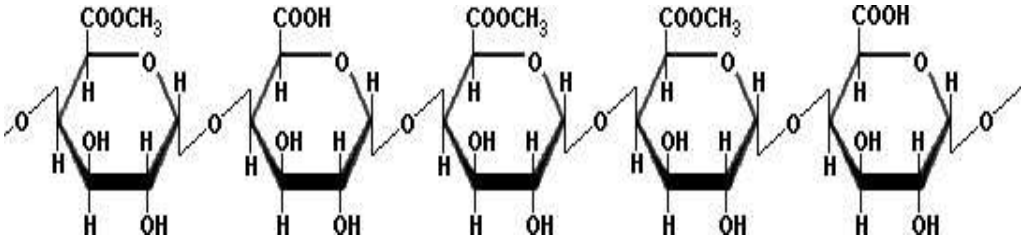
  OH group on carbon atom 2 of one β-D-fructose unit and the alcoholic OH group on carbon atom 1 of the adjacent β-D-fructose unit.



Pectin

- Pectins are found as intercellular substances in the tissues of young plants and are especially abundant in ripe fruits such as guava, apples and pears.
- Pectin is a polysaccharide of α-D-galacturonic acid where some of the free carboxyl groups are, either partly or completely, esterified with methyl alcohol and others are combined with calcium or magnesium ions.

  Chemically, they are called polygalacturonides.



Mucopolysaccharides

Polysaccharides that are composed not only of a mixture of simple sugars but also of derivatives of sugars such as amino sugars and uronic sugars are called mucopolysaccharides.

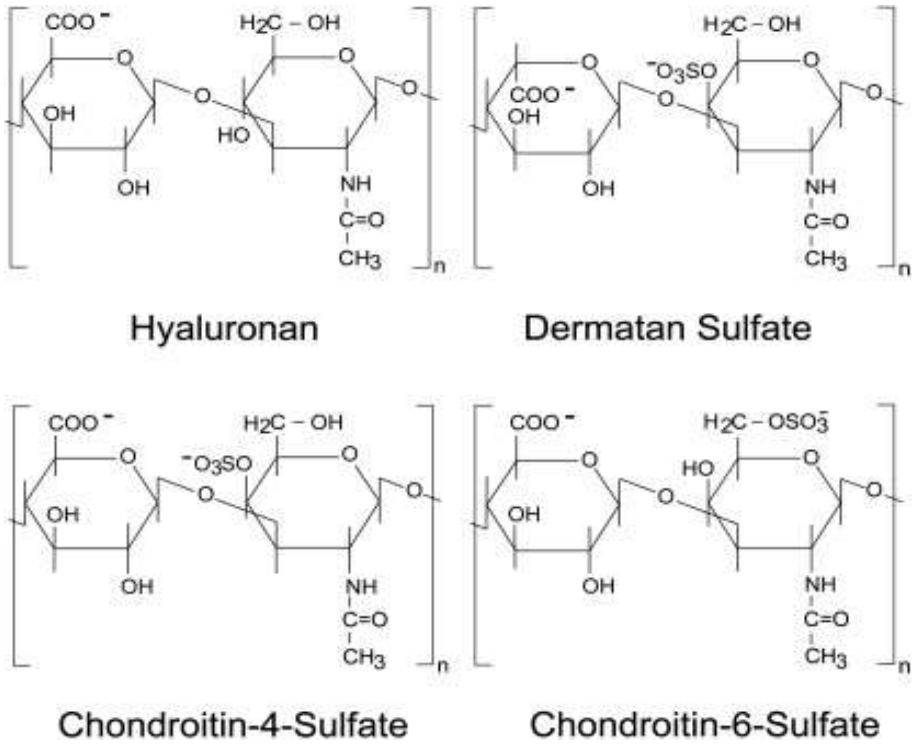
Hyaluronic acid

- It is the most abundant member of mucopolysaccharides and is found in higher animals as a component of various tissues such as the vitreous body of the eye, the umbilical cord and the synovial fluid of joints.
- It is a straight-chain polymer of D-glucuronic acid and N-acetyl-D- glucosamine (NAG) alternating in the chain. Its molecular weight approaches approximately, 5,000,000. Linkages involved are β-1 → 3 and β-1 → 4.

Chondroitin

- Chondroitin is of limited distribution. It is found in cartilage and is also a component of cell coats. It is a parent substance for two more widely distributed mucopolysaccharides, chondroitin sulfate A and chondroitin sulfate B.
- Chondroitin is similar in structure to hyaluronic acid except that it contains galactosamine rather than glucosamine. It is, thus, a polymer of β- D glucuronido- 1, 3-N-acetyl-D-galactosamine joined by β- 1 → 4 linkages.
- The two chondroitin sulfate A and C are widely distributed and form major structural components of cartilage, tendons and bones.

- Chondroitin sulfates may be regarded as derivatives of chondroitin where, in the galactosamine moiety, a sulfate group is esterified either at carbon 4 as in chondroitin sulfate A or at carbon 6 as in chondroitin sulfate C
- The two linkages involved in both types of chondroitin sulfate would, obviously, be the same. These are β-1 → 3 and β-1 → 4.



Dermatan Sulfate

- Dermatan sulfate is a mucopolysaccharide structurally similar to chondroitin sulfate A except that the D-glucuronic acid is replaced by L-iduronic acid
- The two linkages involved are α-1 → 3 and β-1 → 4. Dermatan sulfate is also known by its conventional name, **chondroitin sulfate B**.

Keratosulfate

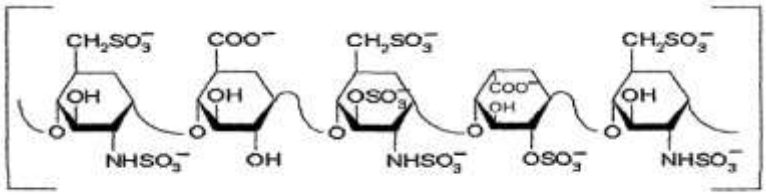
- Keratosulfate differs from other mucopolysaccharides in that the uronic acid component is replaced by D-galactose. Here, the second acetylated amino sugar component (which is N-acetyl-D-glucosamine in this case) is esterified by a sulfate group at carbon 6. Although,

the two alternating linkages involved are β-1 → 4 and β-1 → 3, in this case the linkage between the repeating disaccharide units is β-1 →3 rather than β-1 → 4.

Heparin

- It is composed of D-glucuronic acid units, most of which (about 7 out of every 8) are esterified at C2 and D-glucosamine-N-sulfate (= sulfonylaminoglucose).

- Heparin acts as an anticoagulant. It prevents coagulation of blood by inhibiting the prothrombin thrombin conversion. This eliminates the effect of thrombin on fibrinogen.



Heparin

The following table is the list of biologically important polysaccharides and their functions:

Name of the Polysaccharide	Composition	Occurrence	Functions
Starch	Polymer of glucose containing a straight chain of glucose molecules (amylose) and a branched chain of glucose molecules (amylopectin)	In several plant species as main storage carbohydrate	storage of reserve food
Glycogen	Polymer of glucose	Animals (equivalent of starch)	Storage of reserve food
Cellulose	Polymer of glucose	Different regions of plant, in sieve tubes of phloem	Cell wall matrix
Insulin	Polymer of fructose	In roots and tubers (like Dahlia)	Storage of reserve food

Pectin	Polymer of galactose and its derivatives	Plant cell wall	Cell wall matrix
Hemi cellulose	Polymer of pentoses and sugar acids	Plant cell wall	Cell wall matrix
Lignin	Polymer of glucose	Plant cell wall (dead cells like sclerenchyma)	Cell wall matrix
Chitin	Polymer of glucose	Bodywall of arthropods. In some fungi also	Exoskeleton Impermeable to water
Murein	Polysaccharide cross linked with amino acids	Cell wall of prokaryotic cells	Structural protection
Hyaluronic acid	Polymer of sugar acids	Connective tissue matrix, Outer coat of mammalian eggs	Ground substance, protection
Chrondroitin Sulphate	Polymer of sugar acids	Connective tissue matrix	Ground substance
Heparin	Closely related to chrondroitin	Connective tissue cells	Anticoagulant

Gums and mucilages	Polymers of sugars and sugar acids	Gums - bark or trees. Mucilages flower	Retain water in dry seasons

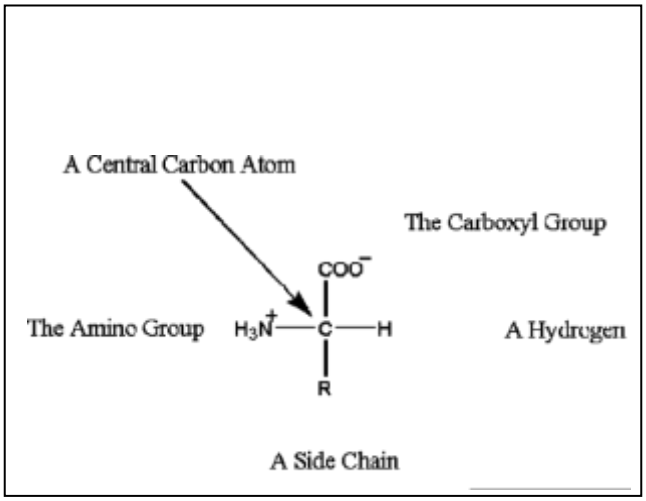
Amino acids

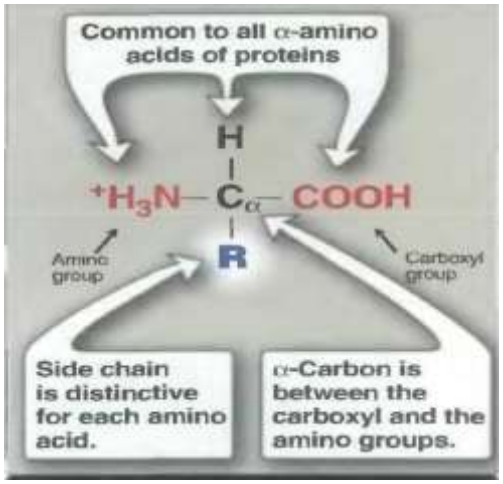
Amino acids are the building blocks of proteins. It has both an amino group ($-NH_2$) and an acid group (-COOH). There are more than 300 amino acids that occur in nature and many more yet to be characterized. Only 20 of the amino acids are found in the protein structure.

The genetic code exists for only the 20 amino acids.

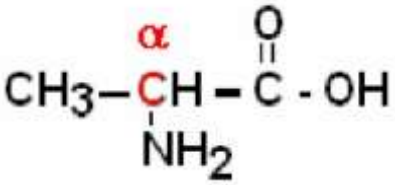
Structure of amino acids

Each amino acid has 4 different groups attached to α-carbon (which is carbon atom next to carboxylic group – COOH).

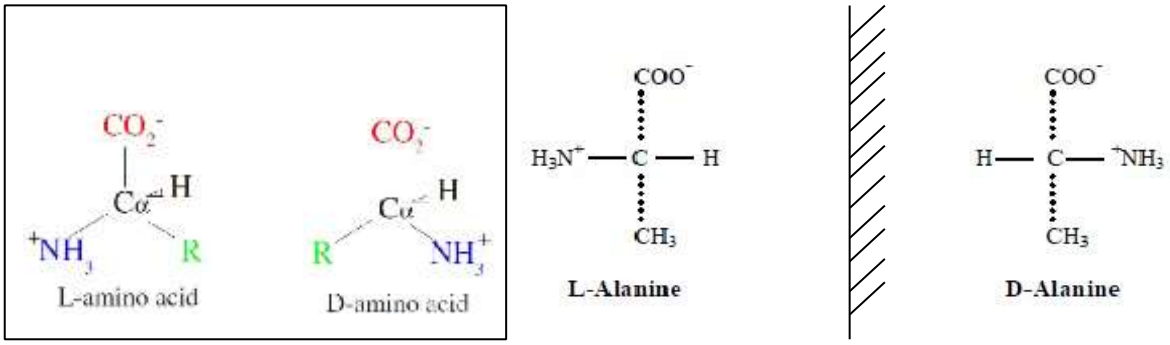




The properties of each amino acid are determined by its specific side chain (R-groups). Rgroups vary in structure, size, electric charge and solubility in water from one amino acid to other. Amino acids found in proteins are α-amino acids. The amino group is always found on the carbon adjacent to the carboxyl group.



Chirality – amino acids (except glycine) have a tetrahedral C_α bonded to four different chemical groups. As a result of this, amino acids are optically active or chiral. Common amino acids are all L stereoisomers. "CO-R-N" mnemonic is used for distinguishing L and D stereoisomers. Looking down the H-C bond, CO-R-N spelled clockwise indicates the L stereoisomer.



There is no definitive answer on why the L isomer is found in proteins. Both D and L isomers have identical energies. Repetitive substructure in proteins (helices, sheets, turns) require all amino acids to have the same configuration. Apparently, living systems evolved from L amino acids based upon an initial random choice.

Amino acid names are often abbreviated as either 3 letters or single letter.

TABLE 5.1 Names and Abbreviations of the Standard Amino Acids

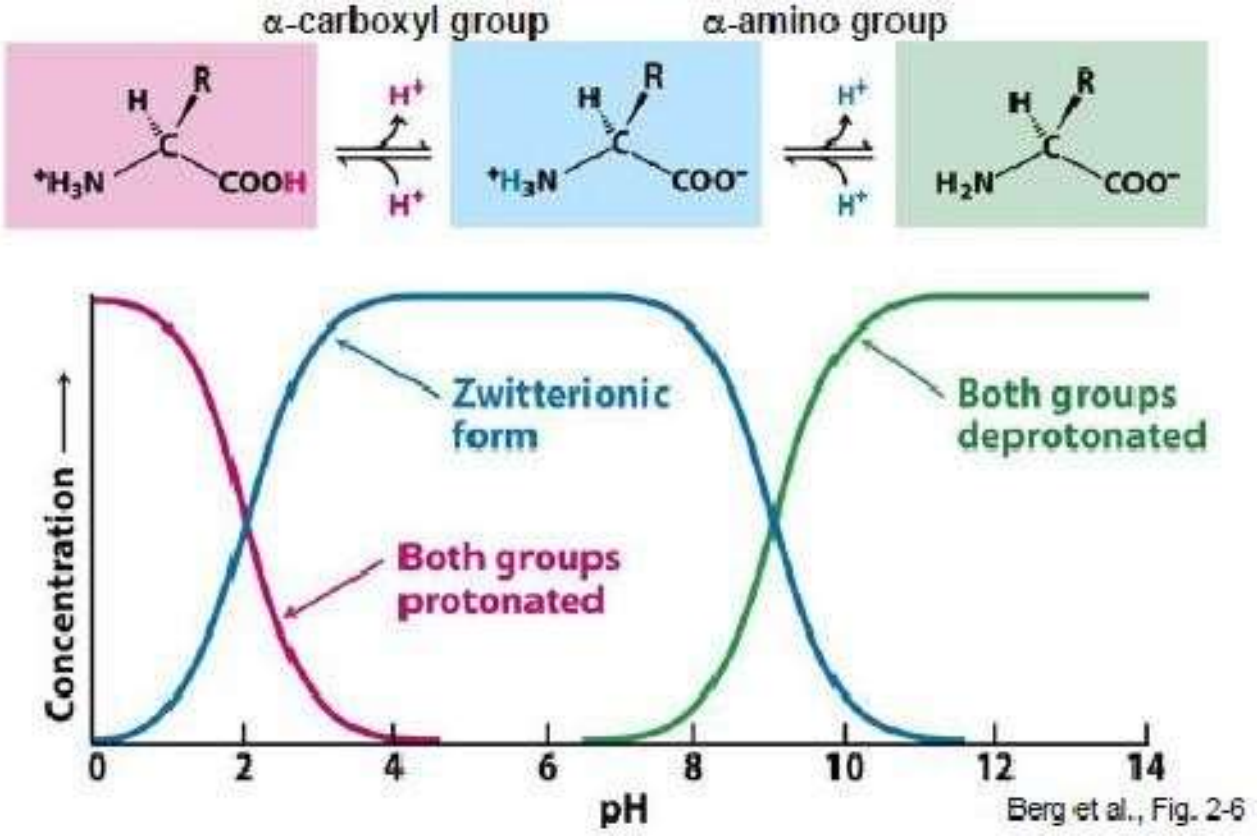
Amino Acid	Three-Letter Abbreviation	One-Letter Abbreviation
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamic acid	Glu	E
Glutamine	Gln	Q
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

Zwitter Ions

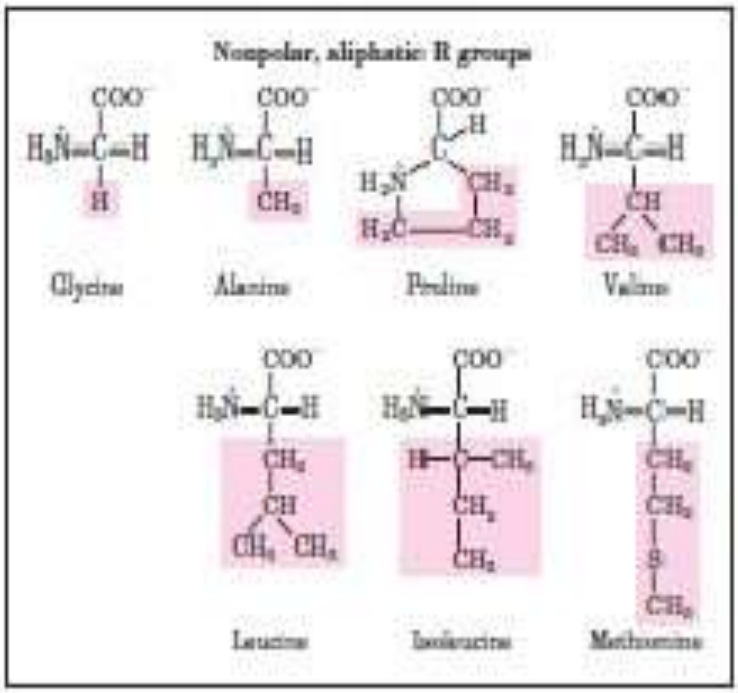
At physiological pH of 7, the carboxyl group of an amino acid is in its conjugate base form (COO^-) and the amino group is in its conjugate acid form ($-NH_3^+$). Thus each amino acid can behave as either an acid or a base. Such molecules which can behave both like an acid and a base are termed amphoteric molecules. Also molecules that bear both positive and negative charges are called zwitter ions.

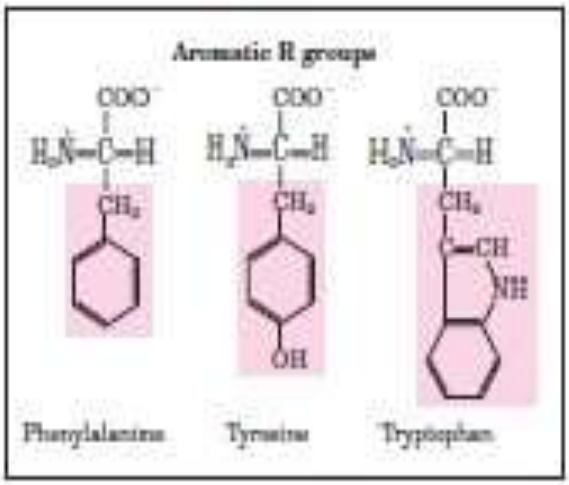
Amino acids contain ionizable groups. The predominant ionic form of these molecules in solution therefore depends on the pH. At acidic pH (pH <7) the carboxyl group (-COOH) is uncharged and the ammonium group ($-NH_3^+$) is protonated. Therefore the net charge on the amino acid is positive (+1). At basic pH (pH >7) the carboxyl group ($-COO^-$) loses its proton and becomes charged and the amino group ($-NH_2$) becomes uncharged

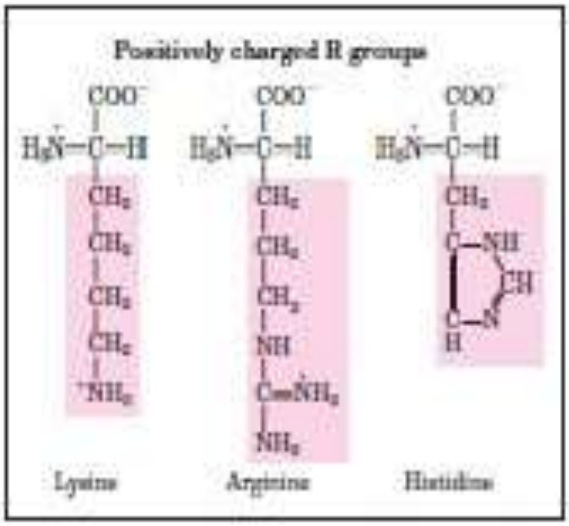
by losing the proton. Therefore the net charge on the amino acid is negative (-1). The pH at which the amino acid has no net charge and is electrically neutral is called as the isoelectric point (pI).

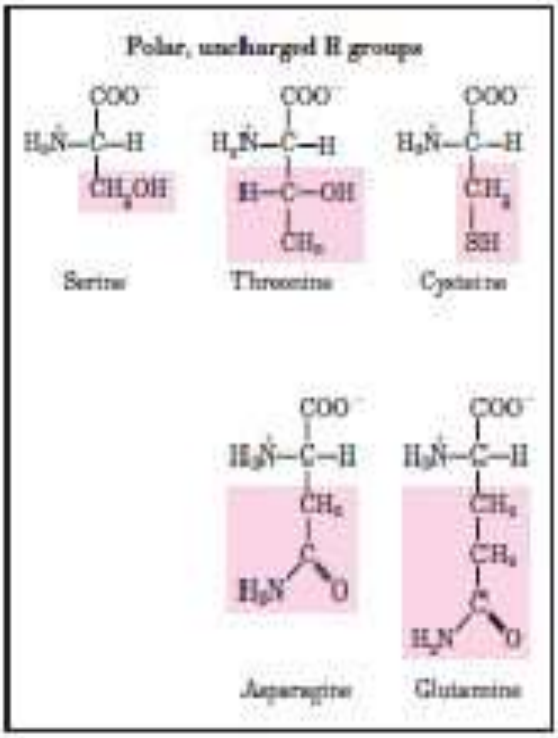


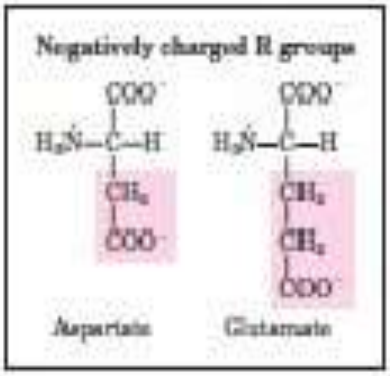
Structure of amino acids











Classification of amino acids

I) **Nutritional classification** – Based on the ability of the body to synthesize amino acids, they can be classified as essential and non-essential amino acids.

1. **Essential amino acids** – These amino acids cannot be formed (synthesized) in the body and so, it is essential to be included in the diet. Their deficiency in the body affects growth, health and protein synthesis. The following amino acids are essential:

1. Valine
2. Isoleucine
3. Lysine
4. Leucine
5. Methionine.
6. Tryptophan
7. Threonine
8. Phenyl alanine

2. **Semi-essential amino acids** – These amino acids are formed in the body but not in sufficient amount for body requirements especially in children. The semi-essential amino acids are:

1. Arginine
2. Histidine

3. **Non-essential amino acids** – The amino acids that can be synthesized in the body by regular metabolism in enough amounts are called as non-essential amino acids. They need not be included in the diet. They are:

1. Glycine
2. Alanine
3. Cysteine
4. Tyrosine
5. Proline
6. Serine
7. Asparagine
8. Glutamine
9. Aspartic acid
10. Glutamic acid.

II) Protein and Non-protein amino acids

1. **Proteinogenic amino acids –** The amino acids that are included in the genetic code are described as "proteinogenic". With a few exceptions only these amino acids can be included in the protein structure by translation. These amino acids are also called as the standard amino acids. They are

- Alanine • Threonine
- Glycine • Cysteine
- Proline • Asparagine
- Valine • Glutamine
- Leucine • Tyrosine
- Isoleucine • Histidine
- Tryptophan • Lysine

- Phenylalanine • Arginine
- Methionine • Aspartic acid
- Serine • Glutamic acid

2. **Non-protein amino acids –** The amino acids that are not found in protein structures are termed non-protein amino acids. More than 700 amino acids have been detected in living systems which belong to this class. They are also called as non-standard amino acids. These amino acids are formed as metabolic intermediates (eg., ornithine and citrulline). Non-standard amino acids arise from post translational modification.

- Hydroxylysine
- Hydroxyproline
- Methylhistidine
- Methylarginine
- Phosphoserine
- Formylmethionine

Some amino acid derivatives also fall under these category (eg.

Histamine, Catecholamine, Gamma amino butyric acid (GABA) and Dopamine).

Proteins – Introduction

Proteins are polypeptides, which are made up of many amino acids linked together as a linear chain. The structure of an amino acid contains a amino group, a carboxyl group, and a R group which is usually carbon based and gives the amino acid it's specific properties. These properties determine the interactions between atoms and molecules, which are: van der Waals force between temporary dipoles, ionic interactions between charged groups, and attractions between polar groups.

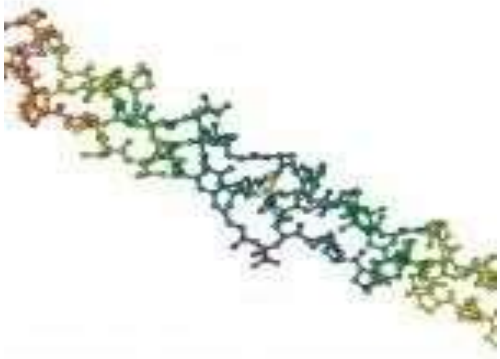
Proteins form the very basis of life. They regulate a variety of activities in all known organisms, from replication of the genetic code to transporting oxygen, and are generally responsible for regulating the cellular machinery and determining the phenotype of an organism. Proteins accomplish their tasks in the body by three-dimensional tertiary and quaternary interactions between various substrates. The functional properties depend upon the proteins three- dimensional structure. The (3D) structures arise because particular sequences of amino acids in a polypeptide chain fold to generate, from linear chains, compact domains with specific structures. The folded domains either serve as modules for larger assemblies or they provide specific catalytic or binding sites.

Protein Types and Functions

Role	Examples	Functions
Digestive enzyme	Amylase, lipase, pepsin	Break down nutrients in food into small pieces that can be readily absorbed
Transport	Hemoglobin	Carry substances throughout the body in blood or lymph
Structure	Actin, tubulin, keratin	Build different structures, like the cytoskeleton
Hormone signaling	Insulin, glucagon	Coordinate the activity of different body systems
Defense	Antibodies	Protect the body from foreign pathogens
Contraction	Myosin	Carry out muscle contraction
Storage	Legume storage proteins, egg white (albumin)	Provide food for the early development of the embryo or the seedling

Protein classification Protein classification based on shape

Collagen



On the basis of their shape, proteins may be divided into two classes: fibrous and globular.

Fibrous proteins

They have primarily mechanical and structural functions, providing support to the cells as well as the whole organism. These proteins are insoluble in water as they contain, both internally and on their surface, many

hydrophobic amino acids. The presence on their surface of hydrophobic amino acids facilitates their packaging into very complex supramolecular structures. In this regard, it should be noted that their polypeptide chains form long filaments or sheets, where in most cases only one type of secondary structure, that repeats itself, is found. In vertebrates, these proteins provide external protection, support and shape; in fact, thanks to their structural properties, they ensure flexibility and/or strength. Some fibrous proteins, such as α-keratins, are only partially hydrolyzed in the intestine.

Here are some examples.

- Fibroin

It is produced by spiders and insects. An example is that produced by the silkworm, *Bombyx mori*.

- Collagen

The term "collagen" indicates not a single protein but a family of structurally related proteins (at least 29 different types), which constitute the main protein component of connective tissue, and more generally, the extracellular scaffolding of multicellular organisms. In vertebrates, they represent about 25-30% of all proteins. They are found in different tissues and organs, such as tendons and the organic matrix of bone, where they are present in very high percentages, but also in cartilage and in the cornea of the eye. In the different tissues, they form different structures, each capable of satisfying a particular need. For example, in the cornea, the molecules are arranged in an almost crystalline array, so that they are virtually transparent, while in the skin they form fibers not very intertwined and directed in all directions, which ensure the tensile strength of the skin itself. Note: the different types of collagen have low nutritional value as deficient in several amino acids (in fact, they contain no tryptophan and low amount of the other essential amino acids). The gelatin used in food preparation is a derivative of collagen.

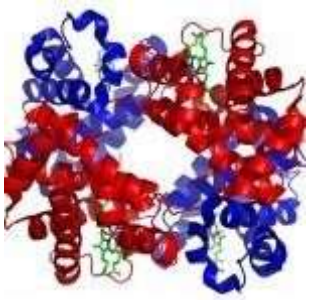
- **α-Keratins**

They constitute almost the entire dry weight of nails, claws, beak, hooves, horns, hair, wool, and a large part of the outer layer of the skin. The different stiffness and flexibility of these structures is a consequence of the number of disulfide bonds that contribute, together with other binding forces, to stabilize the protein structure. And this is the reason why wool keratins, which have a low number of disulfide bonds, are flexible, soft and extensible, unlike claw and beak keratins that are rich in disulfide bonds.

- **Elastin**

This protein provides elasticity to the skin and blood vessels, a consequence of its random coiled structure, that differs it from the structures of the α-keratins and collagens.

Globular proteins



Haemoglobin

Most of the proteins belong to this class. They have a compact and more or less spherical structure, more complex than fibrous proteins. In this regard, motifs, domains, tertiary and quaternary structures are found, in addition to the secondary structures. They are generally soluble in water but can also be found inserted into biological membranes (transmembrane proteins), thus in a hydrophobic environment. Unlike fibrous proteins, that have structural and mechanical functions, they act as:

- enzymes; hormones; membrane transporters and receptors; transporters of triglycerides, fatty acids, and oxygen in the blood; immunoglobulins or antibodies; grain and legume storage proteins.

Examples of globular proteins are myoglobin, haemoglobin, and cytochrome c. At the intestinal level, most of the globular proteins of animal origin are hydrolysed almost entirely to amino acids.

Protein classification based on solubility and chemical composition

Based on their chemical composition, proteins may be divided into two classes: simple and complex.

SIMPLE PROTEINS

Also known as homeoproteins, they are made up of only amino acids. Simple proteins yield only amino acids on hydrolysis. Examples are plasma albumin, collagen, and keratin. These proteins are further classified based on their solubility in different solvents as well as their heat coagulability.

Albumins

- Albumins are readily soluble in water, dilute acids and alkalies, coagulated by heat.

- Seed proteins contain albumin in lesser quantities.
- Albumins may be precipitated out from solution using high salt concentration, a process ‘called **'salting out'**.
- They are deficient in **glycine.**
- Serum albumin and ovalbumin (egg white) are examples.

Globulins

- Globulins are **insoluble or sparingly soluble in water**, but their solubility is greatly increased by the addition of neutral salts such as sodium chloride.
- These proteins are coagulated by heat.
- They are deficient in **methionine**.
- Serum globulin, fibrinogen, myosin of muscle and globulins of pulses are examples.

Prolamins

- Prolamins are insoluble in water but soluble in 70-80% aqueous alcohol.
- Upon hydrolysis they yield much proline and amide nitrogen, hence the name prolamin.
- They are deficient in **lysine**.
- Gliadin of wheat and zein of corn are examples of prolamins.

Glutelins

- Glutelins are insoluble in water and absolute alcohol but soluble in dilute alkalies and acids.
- They are plant proteins e.g., glutenin of wheat.

Histones

- Histones are small and stable basic proteins
- They contain fairly large amounts of basic amino acid, **histidine**.
  - They are soluble in water, but insoluble in ammonium hydroxide.
  - They are not readily coagulated by heat.
  - They occur in **globin of hemoglobin and nucleoproteins**.

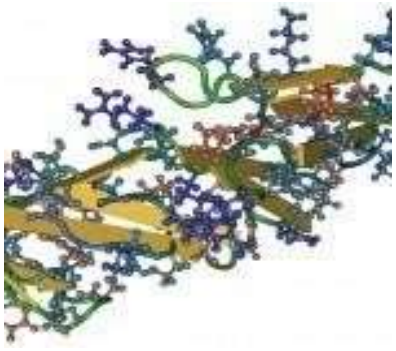
Protamines

- Protamines are the simplest of the proteins.
- They are soluble in water and are not coagulated by heat.
- They are basic in nature due to the presence of large quantities of arginine.
- Protamines are found in association with nucleic acid in the sperm cells of certain fish.
- Tyrosine and tryptophan are usually absent in protamines.

Albuminoids

- These are characterized by great stability and insolubility in water and salt solutions.
- These are called albuminoids because they are essentially similar to albumin and globulins.
- They are highly resistant to proteolytic enzymes.
- They are fibrous in nature and form most of the supporting structures of animals.
- They occur as chief constituent of exoskeleton structure such as hair, horn and nails.

CONJUGATED PROTEINS



Human Fibronectin

Sometimes also called hetero proteins, they contain in their structure a non-protein portion. These non-protein substances are known as prosthetic groups. The examples are glycoproteins, chromoproteins, nucleoproteins, mucoproteins, lipoproteins, metalloproteins and phosphoproteins.

Glycoproteins

They are proteins that covalently bind one or more carbohydrate units to the polypeptide backbone. Typically, the branches consist of not more than 15-20 carbohydrate units, where you can find arabinose, fucose (6-

deoxygalactose), galactose, glucose, mannose, N- acetylglucosamine (GlcNAc, or NAG), and N-acetylneuraminic acid (Neu5Ac or NANA).

Examples of glycoproteins are: glycophorin, the best known among erythrocyte membrane glycoproteins; fibronectin, that anchors cells to the extracellular matrix through interactions on one side with collagen or other fibrous proteins, while on the other side with cell membranes; all blood plasma proteins, except albumin; immunoglobulins or antibodies.

Chromoproteins

They are proteins that contain colored prosthetic groups. Typical examples are: haemoglobin and myoglobin, which bind, respectively, one and four heme groups; chlorophylls, which bind a porphyrin ring with a magnesium atom at its centre; rhodopsins, which bind retinal.

Phosphoproteins

They are proteins that bind phosphoric acid to serine and threonine residues. Generally, they have a structural function, such as tooth dentin, or reserve function, such as milk caseins (alpha, beta, gamma and delta), and egg yolk phosvitin.

Nucleoproteins

- Nucleoproteins are simple basic proteins (protamines or histones) in salt combination with nucleic acids as the prosthetic group.
- They are the important constituents of nuclei and chromatin.

Mucoproteins

- These proteins are composed of simple proteins in combination with carbohydrates like mucopolysaccharides, which include hyaluronic acid and chondroitin sulphates.
- On hydrolysis, mucopolysaccharides yield more than 4% of amino-sugars, hexosamine and uronic acid e.g., ovomucoid from egg white.
- Soluble mucoproteins are neither readily denatured by heat nor easily precipitated by common protein precipitants like trichloroacetic acid or picric acid.
- The term glycoprotein is restricted to the protein that contains small amount of carbohydrate usually less than 4% hexosamine.

Lipoproteins

These are proteins conjugated with lipids such as neutral fat, phospholipids and cholesterol

Metalloproteins

- These are **metal-binding proteins**.
- A globulin, termed **transferrin** is capable of combining with **iron, copper and zinc.**
- This protein constitutes 3% of the total plasma protein.
- Another example is **ceruloplasmin**, which contains **copper.**

Derived proteins

These are proteins derived by partial to complete hydrolysis from the simple or conjugated proteins by the action of acids, alkalies or enzymes. They include two types of derivatives, primary-derived proteins and secondary-derived proteins.

Primary-derived proteins

These protein derivatives are formed by processes causing only slight changes in the protein molecule and its properties. There is little or no hydrolytic cleavage of peptide bonds.

Proteans

Proteans are insoluble products formed by the action of water, dilute acids, and enzymes. These are particularly formed from globulins but are insoluble in dilute salt solutions e.g., myosan from myosin, fibrin from fibrinogen.

Metaproteins

- These are formed by the action of acids and alkalies upon protein.
- They are insoluble in neutral solvents.

Coagulated proteins

Coagulated proteins are insoluble products formed by the action of heat or alcohol on natural proteins e.g., cooked meat and cooked albumin.

Secondary-derived proteins

- These proteins are formed in the progressive hydrolytic cleavage of the peptide bonds of protein molecule.
- They are roughly grouped into **proteoses, peptones and peptides according to average molecular weight.**
- Proteoses are hydrolytic products of proteins, which are soluble in water and are not coagulated by heat.
- Peptones are hydrolytic products, which have simpler structure than proteoses.
- They are soluble in water and are not coagulated by heat.
- Peptides are composed of relatively few amino acids.
- They are water-soluble and not coagulated by heat.
- The complete hydrolytic decomposition of the natural protein molecule into amino acids generally progresses through successive stages as follows: Protein -----> Protean ----- ->Metaprotein

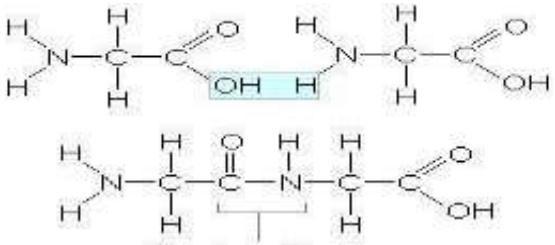
  Proteoses ------>Peptones ------->Peptides ---- ->amino acids

Protein Structures: Primary, Secondary, Tertiary, Quaternary

- Proteins are the largest and most varied class of biological molecules, and they show the greatest variety of structures. Many have intricate three-dimensional folding patterns that result in a compact form, but others do not fold up at all ("natively unstructured proteins") and exist in random conformations. The function of proteins depends on their structure and defining the structure of individual proteins is a large part of modern Biochemistry and Molecular Biology. To understand how proteins fold, we will start with the basics of structure, and progress through to structures of increasing complexity.

Peptide Bonds

- To make a protein, amino acids are connected together by a type of amide bond called a "peptide bond". This bond is formed between the alpha amino group of one amino acid and the carboxyl group of another in a condensation reaction. When two amino acids join, the result is called a dipeptide, three gives a tripeptide, etc. Multiple amino acids result in a polypeptide (often shortened to "peptide"). Because water is lost while creating the peptide bond, individual amino acids are referred to as "amino acid residues" once they are incorporated. Another property of peptides is polarity: the two ends are different. One end has a free amino group (called the "Nterminal") and the other has a free carboxyl group ("C-terminal").

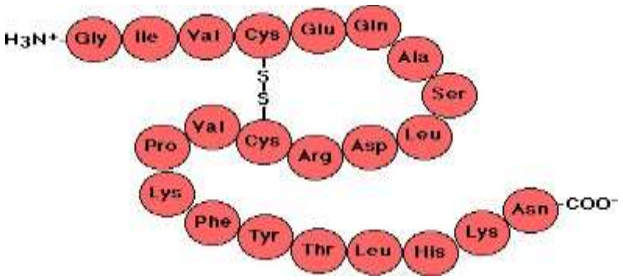


A molecule of water is removed from two glycine amino acids to form a peptide bond.

- In the natural course of making a protein, polypeptides are elongated by the addition of amino acids to the C-terminal end of the growing chain. Conventionally, peptides are written N-terminal first; therefore gly-ser is not the same as ser-gly or GS is not the same as SG. The connection gives rise to a repeating pattern of "NCC-NCC-NCC…" atoms along the length of the molecule. This is referred to as the "backbone" of the peptide. If stretched out, the side chains of the individual residues project outwards from this backbone.
- The peptide bond is written as a single bond, but it actually has some characteristics of a double bond because of the resonance between the C-O and C-N bonds.
- This means that the six atoms involved are coplanar, and that there is not free rotation around the C–N axis. This constrains the flexibility of the chain and prevents some folding patterns.

Primary Structure of Proteins

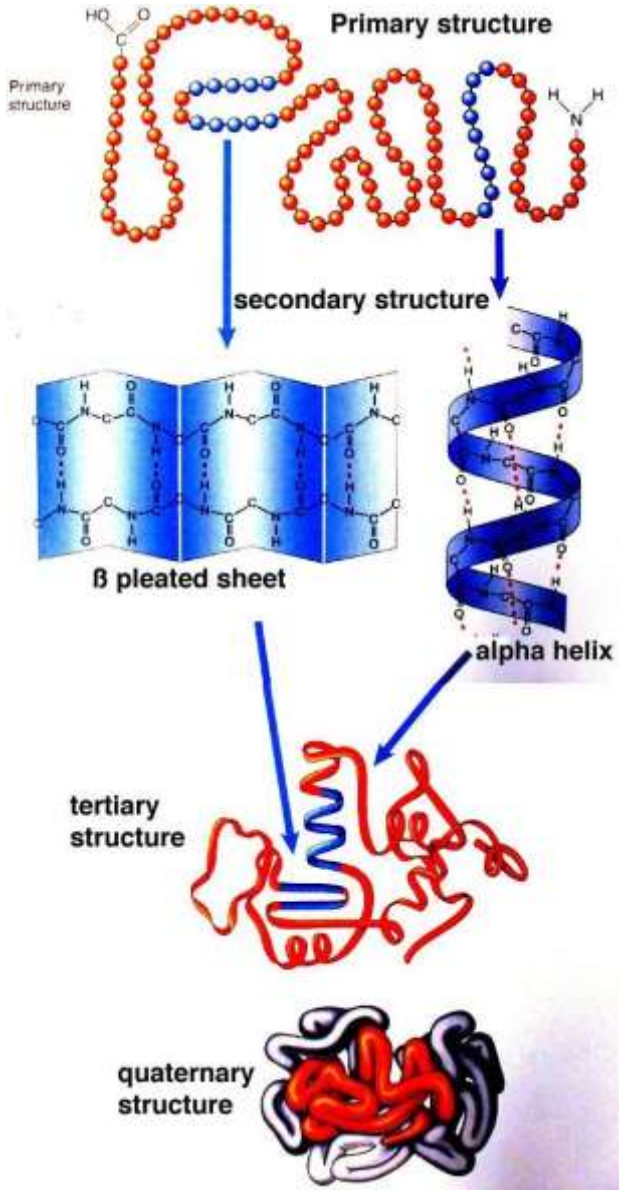
- It is convenient to discuss protein structure in terms of four levels (primary to quaternary) of increasing complexity. Primary structure is simply the sequence of residues making up the protein. Thus primary structure involves only the covalent bonds linking residues together.



- The minimum size of a protein is defined as about 50 residues; smaller chains are referred to simply as peptides. So the primary structure of a small protein would consist of a sequence of 50 or so residues. Even such small proteins contain hundreds of atoms and have molecular weights of over 5000 Daltons (Da). There is no theoretical maximum size, but the largest protein so far discovered has about 30,000 residues. Since the average molecular weight of a residue is about 110 Da, that single chain has a molecular weight of over 3 million Daltons.

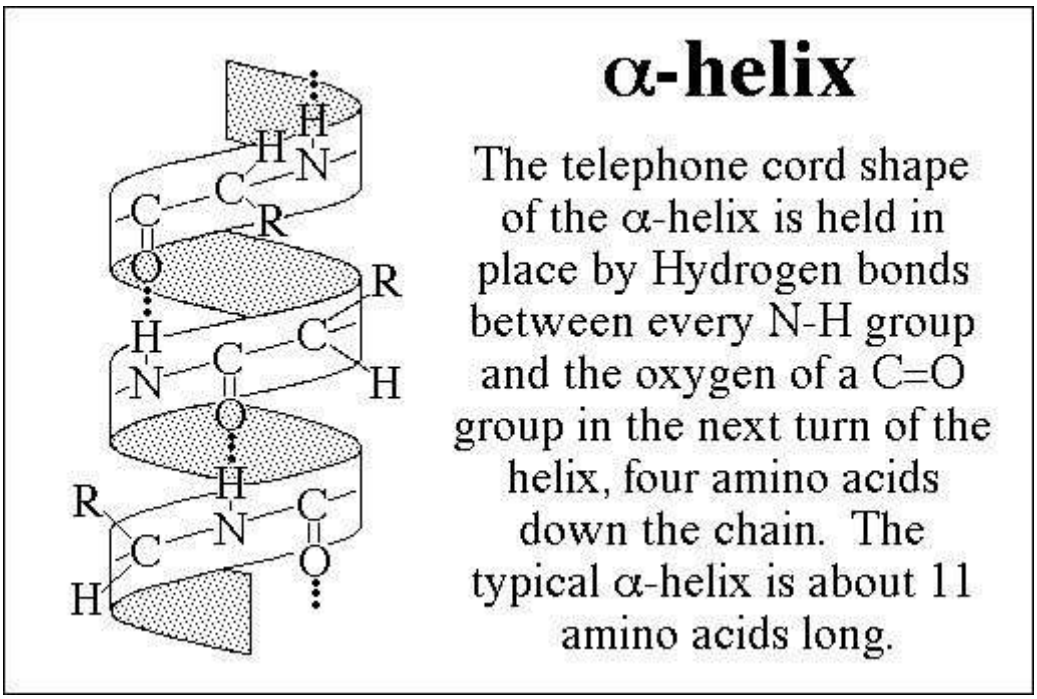
Secondary Structure

- This level of structure describes the local folding pattern of the polypeptide backbone and is stabilized by hydrogen bonds between N-H and C=O groups. Various types of secondary structure have been discovered, but by far the most common are the orderly repeating forms known as the alpha helix and the beta sheet.



- Alpha helix, as the name implies, is a helical arrangement of a single polypeptide chain, like a coiled spring. In this conformation, the carbonyl and N-H groups are oriented parallel to the axis. Each carbonyl is linked by a hydrogen bond to the N-H of a residue located 4 residues further on in the sequence within the same chain. All C=O and N-H groups are involved in hydrogen bonds, making a fairly rigid cylinder. The alpha helix has precise dimensions: 3.6 residues per turn, 0.54 nm per turn. The side chains project outward and contact any solvent, producing a structure something like a bottle brush or a round hair brush. An example of a protein with many helical structures is the keratin that makes up human hair.

- The structure of a beta sheet is very different from the structure of an alpha helix. In a beta sheet, the polypeptide chain folds back on itself so that polypeptide strands like side by side, and are held together by hydrogen bonds, forming a very rigid structure. Again, the polypeptide N-H and C=O groups form hydrogen bonds to stabilize the structure, but unlike the alpha helix, these bonds are formed between neighbouring polypeptide (beta) strands. Generally the primary structure folds back on itself in either a parallel or antiparallel arrangement, producing a parallel or antiparallel beta sheet. In this arrangement, side chains project alternately upward and downward from the sheet. The major constituent of silk (silk fibroin) consists mainly of layers of beta sheet stacked on top of each another.



- Other types of secondary structure. While the alpha helix and beta sheet are by far the most common types of structure, many others are possible. These include various loops, helices and irregular conformations. A single polypeptide chain may have different regions that take on different secondary structures. In fact, many proteins have a mixture of alpha helices, beta sheets, and other types of folding patterns to form various overall shapes.

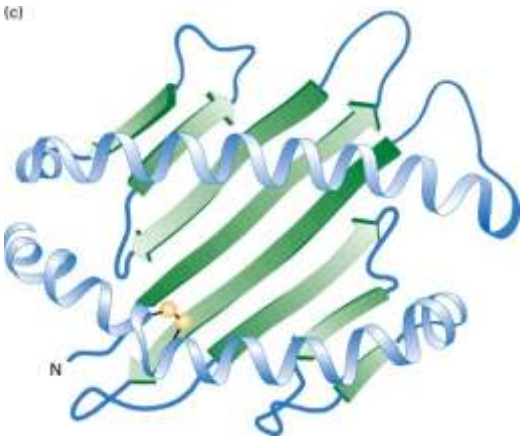
- What determines whether a particular part of a sequence will fold into one or the other of these structures? A major determinant is the interactions between side chains of the residues in the polypeptide. Several

factors come into play: steric hindrance between nearby large side chains, charge repulsion between nearby similarly-charged side chains, and the presence of proline. Proline contains a ring that constrains bond angles so that it will not fit exactly into an alpha helix or beta sheet. Further, there is no H on one peptide bond when proline is present, so a hydrogen bond cannot form. Another major factor is the presence of other chemical groups that interact with each other. This contributes to the next level of protein structure, the tertiary structure.

Tertiary Structure

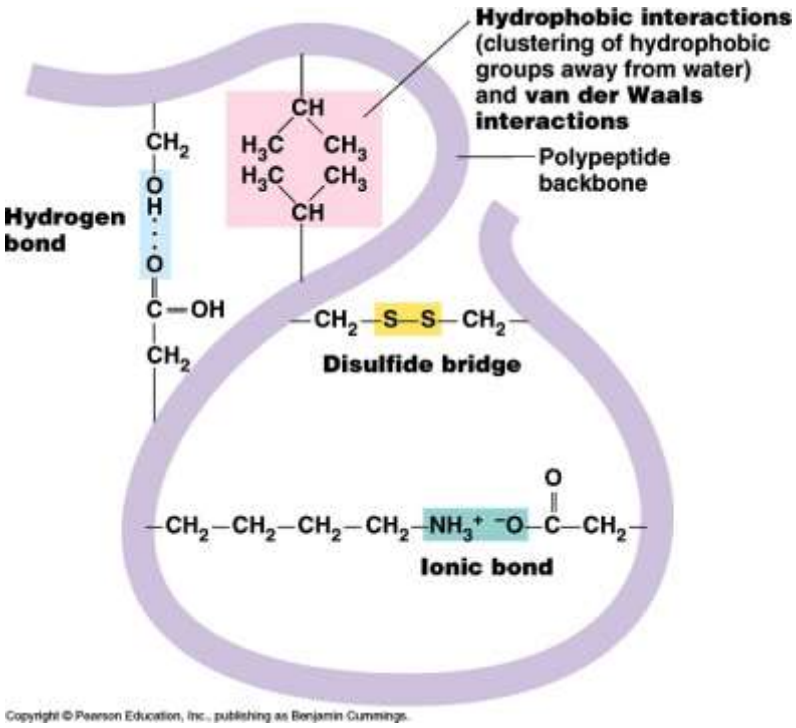
- This level of structure describes how regions of *secondary* structure fold together – that is, the 3D arrangement of a polypeptide chain, including alpha helices, beta sheets, and any other loops and folds. Tertiary structure results from interactions between side chains, or between side chains and the polypeptide backbone, which are often distant in sequence. Every protein has a particular pattern of folding and these can be quite complex.

- Whereas secondary structure is stabilized by H-bonding, all four "weak" forces contribute to tertiary structure. Usually, the most important force is hydrophobic interaction (or hydrophobic bonds). Polypeptide chains generally contain both hydrophobic and hydrophilic residues. Much like detergent micelles, proteins are most stable when their hydrophobic parts are buried, while hydrophilic parts are on



the surface, exposed to water. Thus, more hydrophobic residues such as trp are often surrounded by other parts of the protein, excluding water, while charged residues such as asp are more often on the surface.

- Other forces that contribute to tertiary structure are ionic bonds between side chains, hydrogen bonds, and van der Waals forces. These bonds are far weaker than covalent bonds, and it takes multiple interactions to stabilize a structure.
- There is one covalent bond that is also involved in tertiary structure, and that is the disulfide bond that can form between cysteine residues. This bond is important only in non-cytoplasmic proteins since there are enzyme systems present in the cytoplasm to remove disulfide bonds.
- Visualization of protein structures Because the 3D structures of proteins involve thousands of atoms in complex arrangements, various ways of depicting them so they are understood visually have been developed, each emphasizing a different property of the protein. Software tools have been written to depict proteins in many different ways, and have become essential to understanding protein structure and function.

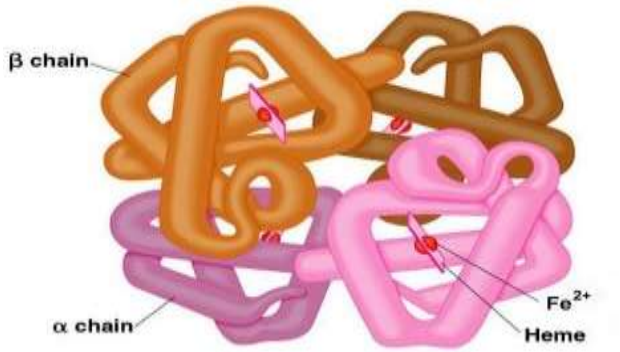


Structural Domains of Proteins

- Protein structure can also be described by a level of organization that is distinct from the ones we have just discussed. This organizational unit is the protein “domain" and the concept of domains is extremely important for understanding tertiary structure. A domain is a distinct region (sequence of amino acids) of a protein, while a structural domain is an independentlyfolded part of a protein that folds into a stable structure. A protein may have many domains, or consist only of a single domain. Larger proteins generally consist of connected structural domains. Domains are often separated by a loosely folded region and may create clefts between them.

Quaternary Structure

- Some proteins are composed of more than one polypeptide chain. In such proteins, quaternary structure refers to the number and arrangement of the individual polypeptide chains. Each polypeptide is referred to as a subunit of the protein. The same forces and bonds that create tertiary structure also hold subunits together in a stable complex to form the complete protein.
- Individual chains may be identical, somewhat similar, or totally different. As examples, CAP protein is a dimer with two identical subunits, whereas hemoglobin is a tetramer containing two pairs of non-identical (but similar) subunits. It has 2 a subunits and 2 b subunits. Secreted proteins often have subunits that are held together by disulfide bonds. Examples include tetrameric antibody molecules that commonly have two larger subunits and two smaller subunits (“heavy chains" and “light chains") connected by disulfide bonds and noncovalent forces.



- In some proteins, intertwined a helices hold subunits together; these are called coiled- coils. This structure is stabilized by a hydrophobic surface on each a helix that is created by a heptameric repeat pattern of hydrophilic/hydrophobic residues. The sequence of the protein can be represented as “abcdefgabcdefgabcdefg…" with positions “a" and “d" filled with hydrophobic residues such as A, V, L etc. Each a helix has a hydrophobic surface that therefore matches the other. When the two helices coil around each other, those surfaces come together, burying the hydrophobic side chains and forming a stable structure. An example of such a protein is myosin, the motor protein found in muscle that allows contraction.

Protein Folding

- How and why do proteins naturally form secondary, tertiary and quaternary structures? This question is a very active area of research and is certainly not completely understood. A folded, biologically-active protein is considered to be in its “native" state, which is generally thought to be the conformation with least free energy.

- Proteins can be unfolded or “denatured" by treatment with solvents that disrupt weak bonds. Thus organic solvents that disrupt hydrophobic interactions, high concentrations of urea or guanidine that interfere with Hbonding, extreme pH or even high temperatures, will all cause proteins to unfold. Denatured proteins have a random, flexible conformation and usually lack biological activity. Because of exposed hydrophobic groups, they often aggregate and precipitate. This is what happens when you fry an egg.

- If the denaturing condition is removed, some proteins will re-fold and regain activity. This process is called “renaturation." Therefore, all the information necessary for folding is present in the primary structure (sequence) of the protein. During renaturation, the polypeptide chain is thought to fold up into a loose globule by hydrophobic effects, after which small regions of secondary structure form into especially favorable sequences. These sequences then interact with each other to stabilize intermediate structures before the final conformation is attained.
- Many proteins have great difficulty renaturing, and proteins that assist other proteins to fold are called “molecular chaperones." They are thought to act by reversibly masking exposed

hydrophobic regions to prevent aggregation during the multi-step folding process. Proteins that must cross membranes (eg. mitochondrial proteins) must stay unfolded until they reach their destination, and molecular chaperones may protect and assist during this process.

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SCHOOL OF BIO AND CHEMICAL ENGINEERING

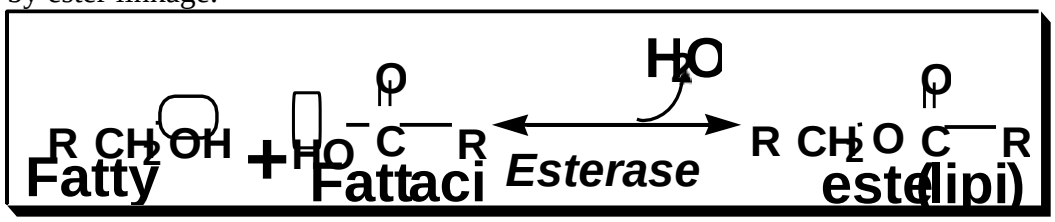
DEPARTMENT OF BIOINFORMATICS

UNIT – V –CELL BIOLOGY AND BIOCHEMISTRY-SBIA1102

UNIT - V

LIPDS Definition

Lipids are organic compounds formed mainly from alcohol and fatty acids combined together by ester linkage.



- Lipids are insoluble in water, but soluble in fat or organic solvents (ether, chloroform, benzene, acetone).
- Lipids include fats, oils, waxes and related compounds.
- They are widely distributed in nature both in plants and in animals.

Biological Importance of Lipids

1. They are more palatable and storable to unlimited amount compared to carbohydrates.
2. They have a high-energy value (25% of body needs) and they provide more energy per gram than carbohydrates and proteins but carbohydrates are the preferable source of energy.
3. Supply the essential fatty acids that cannot be synthesized by the body.
4. Supply the body with fat-soluble vitamins (A, D, E and K).
5. They are important constituents of the nervous system.
6. Tissue fat is an essential constituent of cell membrane and nervous system. It is mainly phospholipids in nature that are not affected by starvation.
7. Stored lipids "depot fat" is stored in all human cells acts as:

- A store of energy.
- A pad for the internal organs to protect them from outside shocks.
- A subcutaneous thermal insulator against loss of body heat.

8. Lipoproteins, which are complex of lipids and proteins, are important cellular constituents that present both in the cellular and subcellular membranes.
9. Cholesterol enters in membrane structure and is used for synthesis of adrenal cortical hormones, vitamin D3 and bile acids.
10. Lipids provide bases for dealing with diseases such as obesity, atherosclerosis, lipidstorage diseases, essential fatty acid deficiency, respiratory distress syndrome,

Classification of Lipids

Bloor (1943) has proposed the following classification of lipids based on their chemical composition.

I. Simple lipids or Homolipids

These are esters of fatty acid with farious alcohols.

1. **Fats and oils** (triglycerides, triacylglycerols): These are esters of fatty acids with a trihydroxy alcohol, glycerol. A fat is solid at ordinary room temperature wheras an oil is liquid.
2. **Waxes:** These are esters of fatty acids with high molecular weight monohydroxy alcohols.

II. Compound lipids or Heterolipids.

These are esters of fatty acids with alcohol and possess additional group(s). e.g., sulfur, phosphorus, amino group, carbohydrate, or proteins beside fatty acid and alcohol.

Compound or conjugated lipids are classified into the following types according to the nature of the additional group 1. Phospholipids

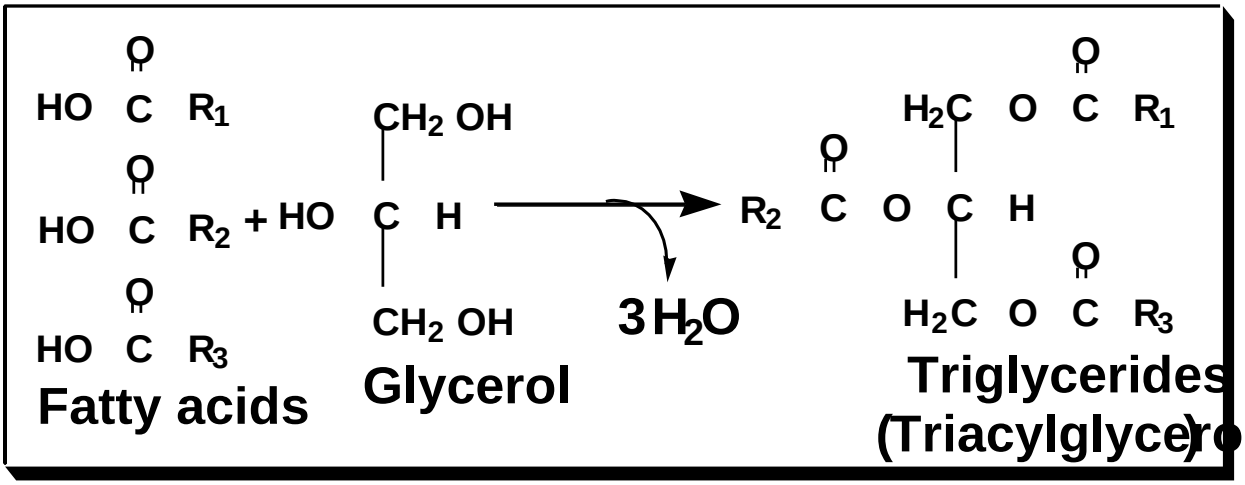
2. Glycolipids.
3. Lipoproteins
4. Sulfolipids and amino lipids.

III. Derived lipids.

These are the substances derived from simple and compound lipids by hydrolysis. These include fatty acids, alcohols, mono- and diglycerides, steroids, terpenes and carotenoids.

Simple Lipids

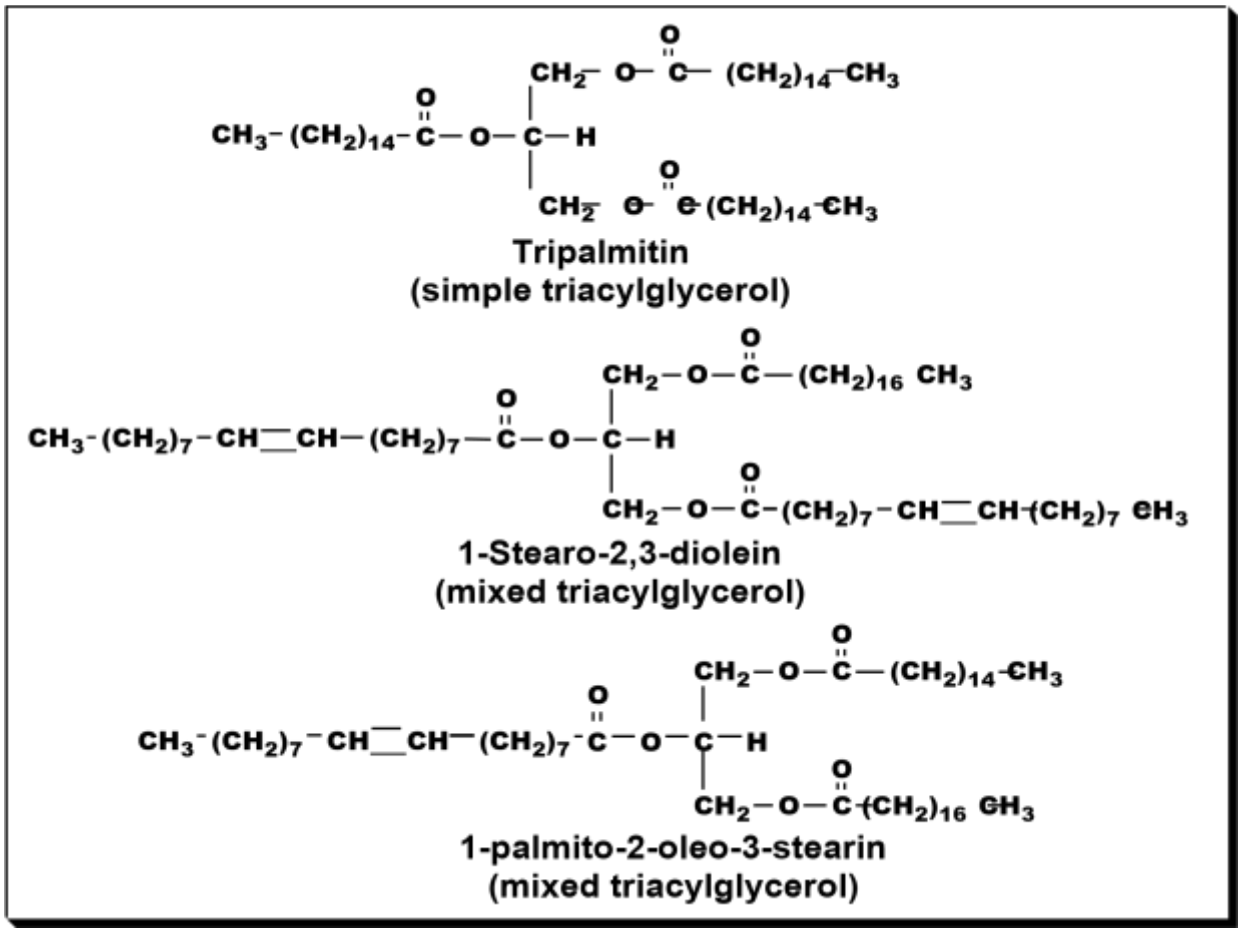
- They are called neutral because they are uncharged due to absence of ionizable groups in it.
- The neutral fats are the most abundant lipids in nature. They constitute about 98% of the lipids of adipose tissue, 30% of plasma or liver lipids, less than 10% of erythrocyte lipids.
- They are esters of glycerol with various fatty acids. Since the 3 hydroxyl groups of glycerol are esterified, the neutral fats are also called “Triglycerides”.
- Esterification of glycerol with one molecule of fatty acid gives monoglyceride, and that with 2 molecules gives diglyceride.



Types of triglycerides

1. Simple triglycerides: If the three fatty acids connected to glycerol are of the same type the triglyceride is called simple triglyceride, e.g., tripalmitin.
2. Mixed triglycerides: if they are of different types, it is called mixed triglycerides, e.g., stearo-diolein and palmito-oleo-stearin.

- Natural fats are mixtures of mixed triglycerides with a small amount of simple triglycerides.



- The common fatty acids in animal fats are palmitic, stearic and oleic acids.
- The main difference between fats and oils is for oils being liquid at room temperature, whereas, fats are solids.
- This is mainly due to presence of larger percentage of unsaturated fatty acids in oils than fats that has mostly saturated fatty acids.

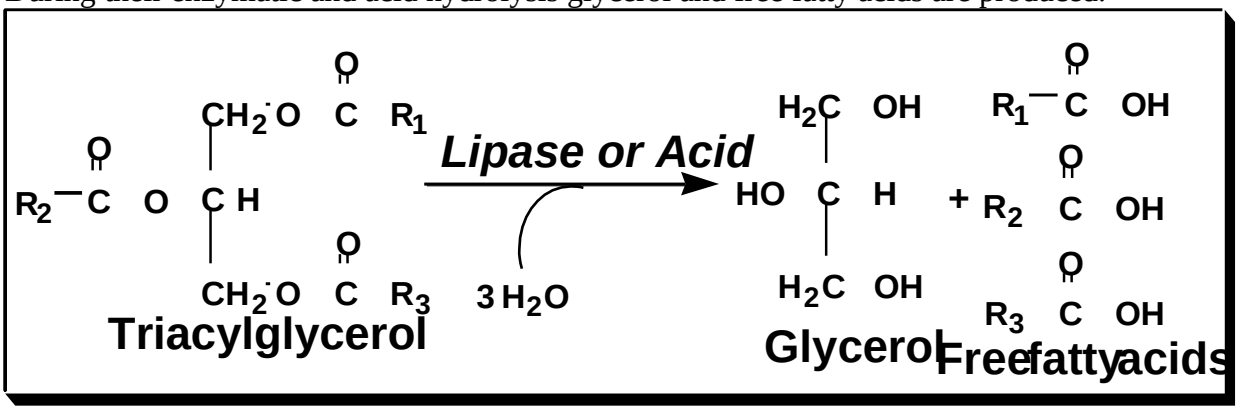
Physical properties of fat and oils

1. Freshly prepared fats and oils are colorless, odorless and tasteless. Any color, or taste is due to association with other foreign substances, e.g., the yellow color of body fat or milk fat is due to carotene pigments(cow milk).
2. Fats have specific gravity less than 1 and, therefore, they float on water.
3. Fats are insoluble in water, but soluble in organic solvents as ether and benzene.
4. Melting points of fats are usually low, but higher than the solidification point.

Chemical Properties of fats and oils

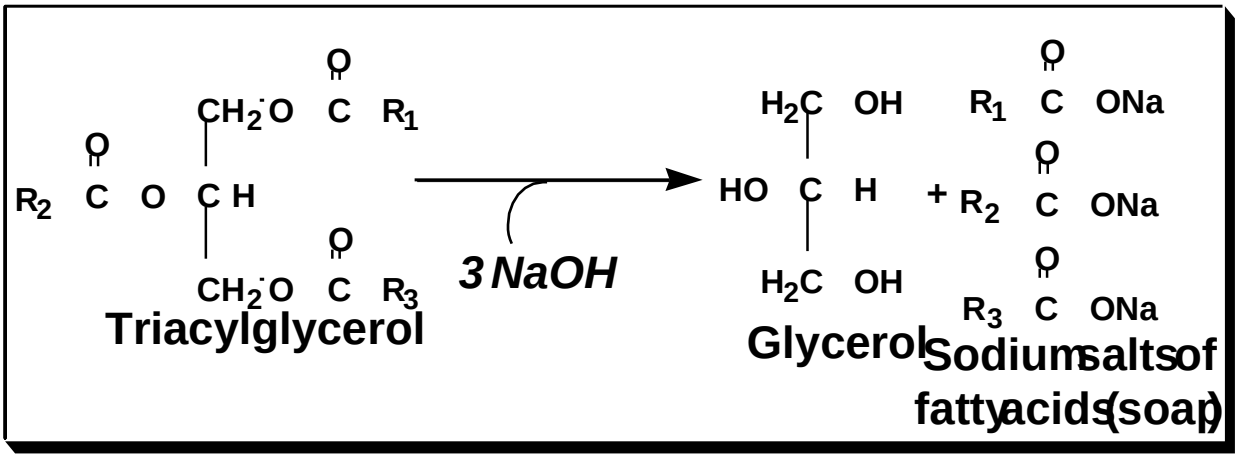
1. Hydrolysis:

- They are hydrolyzed into their constituents (fatty acids and glycerol) by the action of super heated steam, acid, alkali or enzyme (e.g., lipase of pancreas).
- During their enzymatic and acid hydrolysis glycerol and free fatty acids are produced.



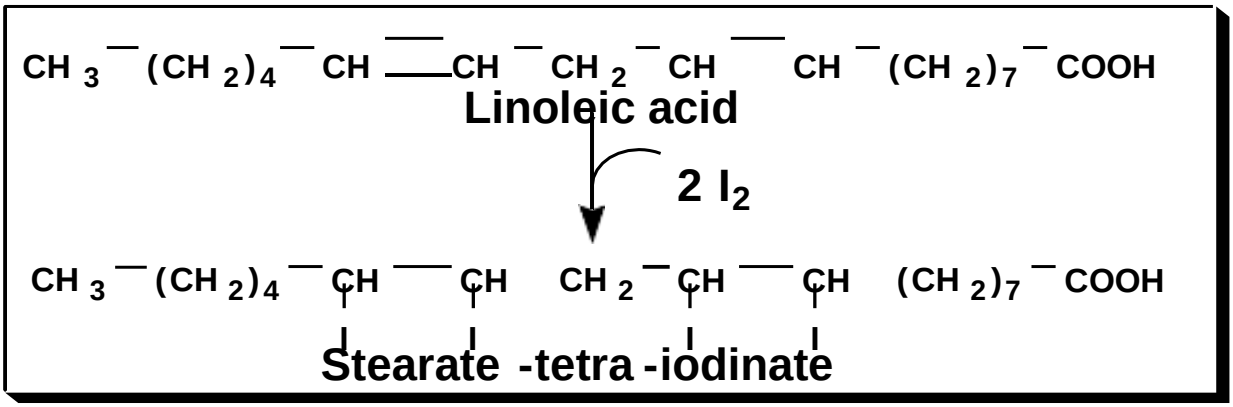
2. **Saponification**.

Alkaline hydrolysis produces glycerol and salts of fatty acids (soaps). Soaps cause emulsification of oily material this help easy washing of the fatty materials



3. Halogenation

- Neutral fats containing unsaturated fatty acids have the ability of adding halogens (e.g., iodine or iodination) at the double bonds.
- It is a very important property to determine the degree of unsaturation of the fat or oil that determines its biological value



4. **Hydrogenation or hardening of oils**:

- It is a type of addition reactions accepting hydrogen at the double bonds of unsaturated fatty acids.
- The hydrogenation is done under high pressure of hydrogen and is catalyzed by finely divided nickel or copper and heat.
- It is the base of hardening of oils (margarine manufacturing), e.g., change of oleic acid of fats (liquid) into stearic acid (solid).

5. Oxidation (Rancidty)

- This toxic reaction of triglycerides leads to unpleasant odour or taste of oils and fats developing after oxidation by oxygen of air, bacteria, or moisture.
- Also this is the base of the drying oils after exposure to atmospheric oxygen. Example is linseed oil, which is used in paints and varnishes manufacturing

Rancidity

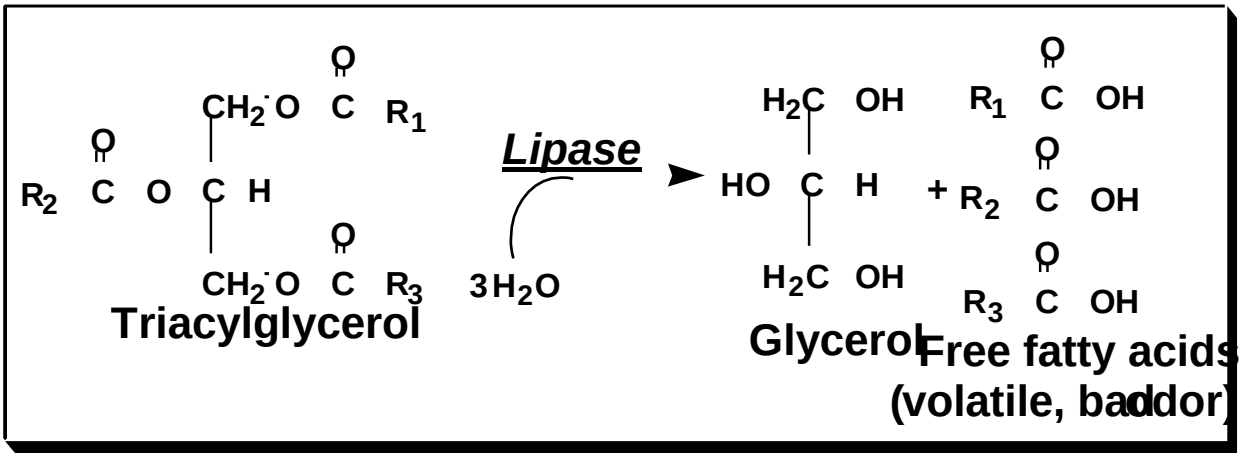
- It is a physico-chemical change in the natural properties of the fat leading to the development of unpleasant odor or taste or abnormal color particularly on aging after exposure to atmospheric oxygen, light, moisture, bacterial or fungal contamination and/or heat.
- Saturated fats resist rancidity more than unsaturated fats that have unsaturated double bonds.

Types of Rancidity:

1. Hydrolytic rancidity
2. Oxidative rancidity
3. Ketonic rancidity

1. Hydrolytic rancidity:

- It results from slight hydrolysis of the fat by lipase from bacterial contamination leading to the liberation of free fatty acids and glycerol at high temperature and moisture.
- Volatile short-chain fatty acids have unpleasant odor.



2. Oxidative Rancidity:

- It is oxidation of fat or oil catalyzed by exposure to oxygen, light and/or heat producing peroxide derivatives which on decomposition give substances, e.g., peroxides, aldehydes, ketones and dicarboxylic acids that are toxic and have bad odor.
- This occurs due to oxidative addition of oxygen at the unsaturated double bond of unsaturated fatty acid of oils.

3. Ketonic Rancidity:

- It is due to the contamination with certain fungi such as *Asperigillus niger* on fats such as coconut oil.
- Ketones, fatty aldehydes, short chain fatty acids and fatty alcohols are formed.

- Moisture accelerates ketonic rancidity.

1. Iodine number (or value):

- Definition: It is the number of grams of iodine absorbed by 100 grams of fat or oil.
- Uses:It is a measure for the degree of unsaturation of the fat, as a natural property for it.

2. Saponification number (or value):

- Definition: It is the number of milligrams of KOH required to completely saponify one gram of fat.
- Uses: Since each carboxyl group of a fatty acid reacts with one mole of KOH during saponification, therefore, the amount of alkali needed to saponify certain weight of fat depends upon the number of fatty acids present per weight.
- Thus, fats containing short-chain acids will have more carboxyl groups per gram than long chain fatty acids and consume more alkali, i.e., will have higher saponification number

3. Acids Number (or value):

- Definition: It is the number of milligrams of KOH required to neutralize the free fatty acids present in one gram of fat.
- Uses: It is used for detection of hydrolytic rancidity because it measures the amount of free fatty acids present.

4. Reichert- Meissl Number (or value):

- Definition: It is the number of milliliters of 0.1 N KOH required to neutralize the water-soluble fatty acids distilled from 5 grams of fat. Short-chain fatty acid (less than 10 carbons) is distillated by steam.
- Uses: This studies the natural composition of the fat and is used for detection of fat adulteration.
    - Butter that has high percentage of short-chain fatty acids has highest Reichert- Meissl number compared to margarine.

5. Acetyl Number (or value):

- Definition: It is number of milligrams of KOH needed to neutralize the acetic acid liberated from hydrolysis of 1 gram of acetylated fat (hydroxy fat reacted with acetic anhydride).

- Uses: The natural or rancid fat that contains fatty acids with free hydroxyl groups are converted into acetylated fat by reaction with acetic anhydride.
  - Thus, acetyl number is a measure of number of hydroxyl groups present. It is used for studying the natural properties of the fat and to detect adulteration and rancidity.

Waxes

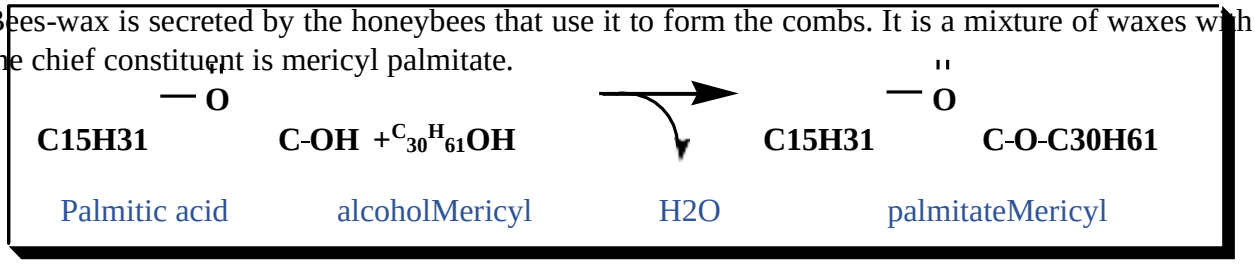
Waxes are solid simple lipids containing a monohydric alcohol (with a higher molecular weight than glycerol) esterified to long-chain fatty acids. Examples of these alcohols are palmitoyl alcohol, cholesterol, vitamin A or D. **Properties of waxes**

- Waxes are insoluble in water, but soluble in fat solvents and are negative for acrolein test. (**Acrolein test** is used to detect the presence of glycerol or fat. When fat is treated strongly in the presence of a dehydrating agent like potassium bisulphate ($KHSO_4$), the glycerol portion of the molecule is dehydrated to form an unsaturated aldehyde, **acrolein** that has a pungent irritating odour.)
- Waxes are not easily hydrolyzed as the fats and are indigestible by lipases and are very resistant to rancidity.
- Thus they are of no nutritional value. **Type of Waxes**

Waxes are widely distributed in nature such as the secretion of certain insects as bees- wax, protective coatings of the skins and furs of animals and leaves and fruits of plants. They are classified into true-waxes and wax-like compounds as follows:

1. True waxes

Bees-wax is secreted by the honeybees that use it to form the combs. It is a mixture of waxes with the chief constituent is mericyl palmitate.



2. Wax-like compounds

- Cholesterol esters: Lanolin (or wool fat) is prepared from the wool-associated skin glands and is secreted by sebaceous glands of the skin.
  - It is very complex mixture, contains both free and esterified cholesterol, e.g., cholesterol-palmitate and other sterols.

Compound Lipids

They are lipids that contain additional substances, e.g., sulfur, phosphorus, amino group, carbohydrate, or proteins beside fatty acid and alcohol.

Compound or conjugated lipids are classified into the following types according to the nature of the additional group:

1. Phospholipids
2. Glycolipids.
3. Lipoproteins
4. Sulfolipids and amino lipids.

1. Phospholipids

Phospholipids or phosphatides are compound lipids, which contain phosphoric acid group in their structure.

Importance:

1. They are present in large amounts in the liver and brain as well as blood. Every animal and plant cell contains phospholipids.
2. The membranes bounding cells and subcellular organelles are composed mainly of phospholipids. Thus, the transfer of substances through these membranes is controlled by properties of phospholipids.
3. They are important components of the lipoprotein coat essential for secretion and transport of plasma lipoprotein complexes. Thus, they are lipotropic agents that prevent fatty liver.
4. Myelin sheath of nerves is rich with phospholipids.
5. Important in digestion and absorption of neutral lipids and excretion of cholesterol in the bile.
6. Important function in blood clotting and platelet aggregation.
7. They provide lung alveoli with surfactants that prevent its irreversible collapse.
8. Important role in signal transduction across the cell membrane.
9. Phospholipase A2 in snake venom hydrolyses membrane phospholipids into hemolytic lysolecithin or lysocephalin.
10. They are source of polyunsaturated fatty acids for synthesis of eicosanoids.

Sources: They are found in all cells (plant and animal), milk and egg-yolk in the form of lecithins.

Structure: phospholipids are composed of:

1. Fatty acids (a saturated and an unsaturated fatty acid).
2. Nitrogenous base (choline, serine, threonine, or ethanolamine).
3. Phosphoric acid.

4. Fatty alcohols (glycerol, inositol or sphingosine).

Classification of Phospholipids

They are classified into 2 groups according to the type of the alcohol present into two types: **A-Glycerophospholipids:** They are regarded as derivatives of phosphatidic acids that are the simplest type of phospholipids and include:

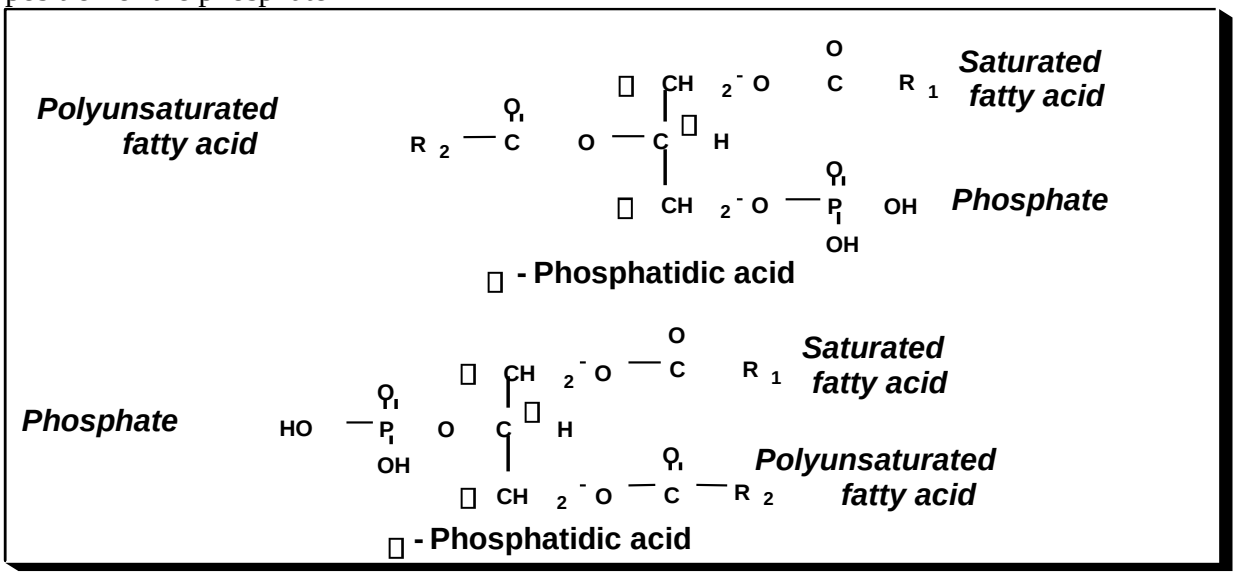
1. Phosphatidic acids.
2. Lecithins
3. Cephalins.
4. Plasmalogens.
5. Inositides.
6. Cardiolipin.

B-Sphingophospholipids: They contain sphingosine as an alcohol and are named Sphingomyelins.

A. Glycerophospholipids

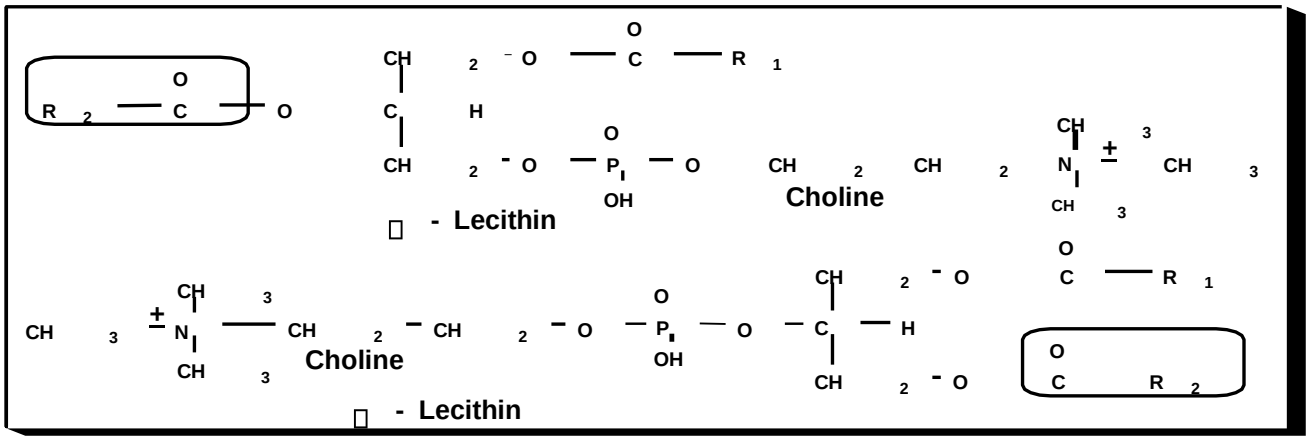
1. Phosphatidic acids:

They are metabolic intermediates in synthesis of triglycerides and glycerophospholipids in the body and may have function as a second messenger. They exist in two forms according to the position of the phosphate



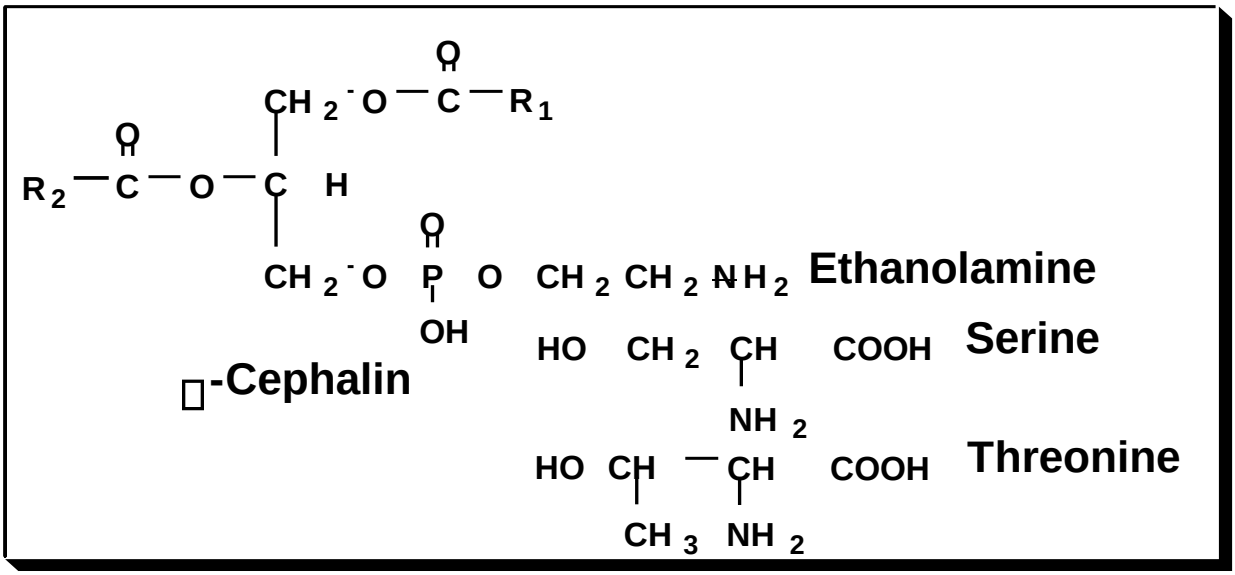
2. Lecithins:

- Lecithins are glycerophospholipids that contain choline as a base beside phosphatidic acid. They exist in 2 forms. Lecithins are a common cell constituent obtained from brain, egg yolk, or liver. Lecithins are important in the metabolism of fat by the liver.
- Structure: Glycerol is connected at C2 or C3 with a polyunsaturated fatty acid, at C1 with a saturated fatty acid, at C3 or C2 by phosphate to which the choline base is connected. The common fatty acids in lecithins are stearic, palmitic, oleic, linoleic, linolenic, clupandonic or arachidonic acids.



3. Cephalins (or Kephalins):

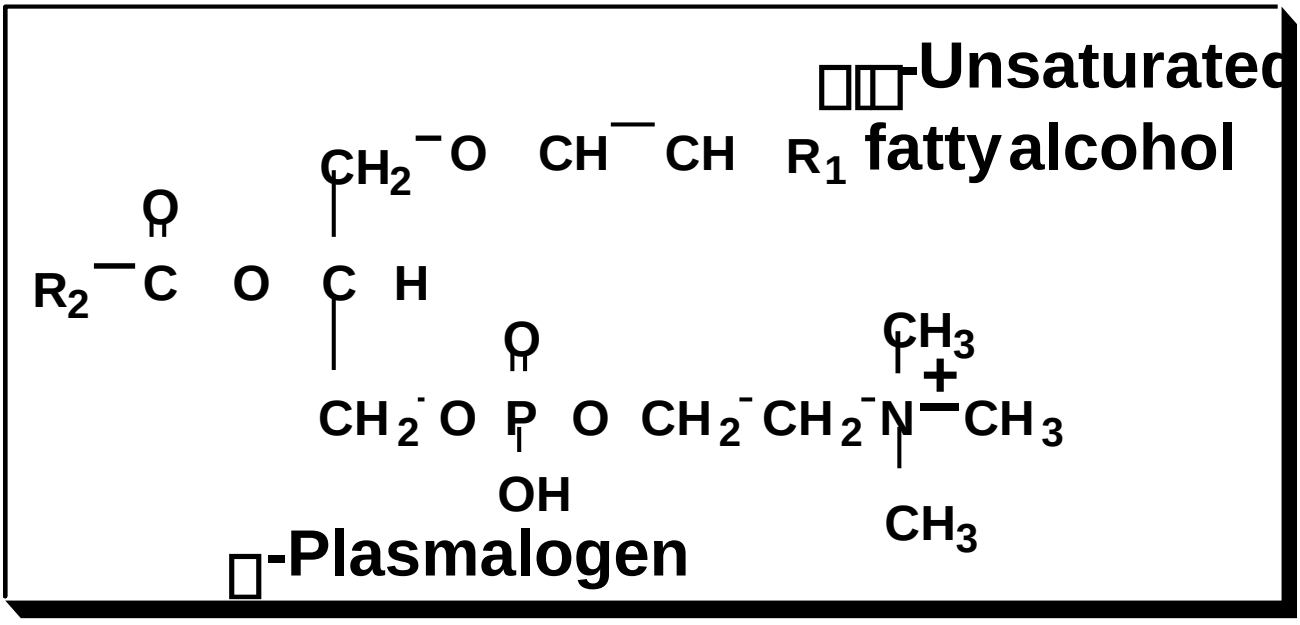
- They are phosphatidyl-ethanolamine or serine. Cephalins occur in association with lecithins in tissues and are isolated from the brain (Kephale = head).



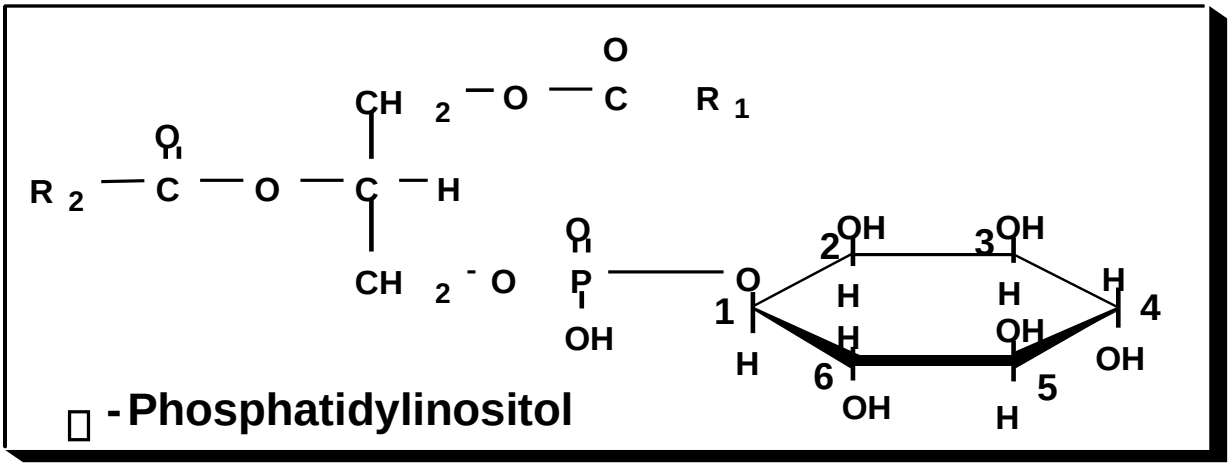
- Structure: Cephalins resemble lecithins in structure except that choline is replaced by ethanolamine, serine or threonine amino acids.

4. Plasmalogens:

- Plasmalogens are found in the cell membrane phospholipids fraction of brain and muscle (10% of it is plasmalogens), liver, semen and eggs.
- Structure: Plasmalogens resemble lecithins and cephalins in structure but differ in the presence of unsaturated fatty alcohol rather than a fatty acid at C1 of the glycerol connected by ether bond.
- At C2 there is an unsaturated long-chain fatty acid, however, it may be a very shortchain fatty acid



5. Inositides:
   They are similar to lecithins or cephalins but they have the cyclic sugar alcohol, inositol as the base. They are formed of glycerol, one saturated fatty acid, one unsaturated fatty acid, phosphoric acid and inositol



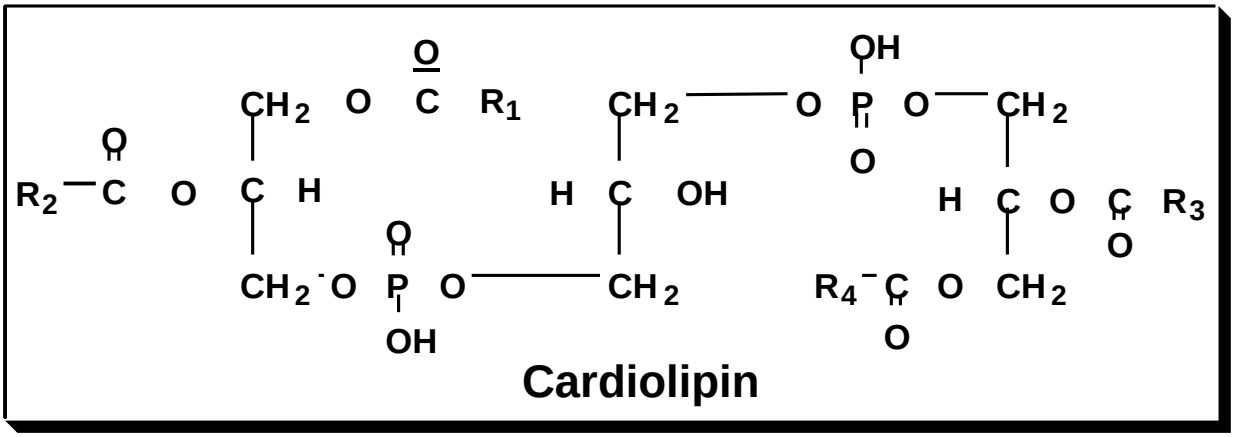
- Source: Brain, tissues. etc.,

Function:

- Phosphatidyl inositol is a major component of cell membrane phospholipids particularly at the inner leaflet of it.
- They play a major role as second messengers during signal transduction for certain hormone..
- On hydrolysis by phospholipase C, phosphatidyl-inositol-4,5-diphosphate produces diacyl-glycerol and inositol-triphosphate both act to liberate calcium from its intracellular stores to mediate the hormone effects.

6. Cardiolipins:

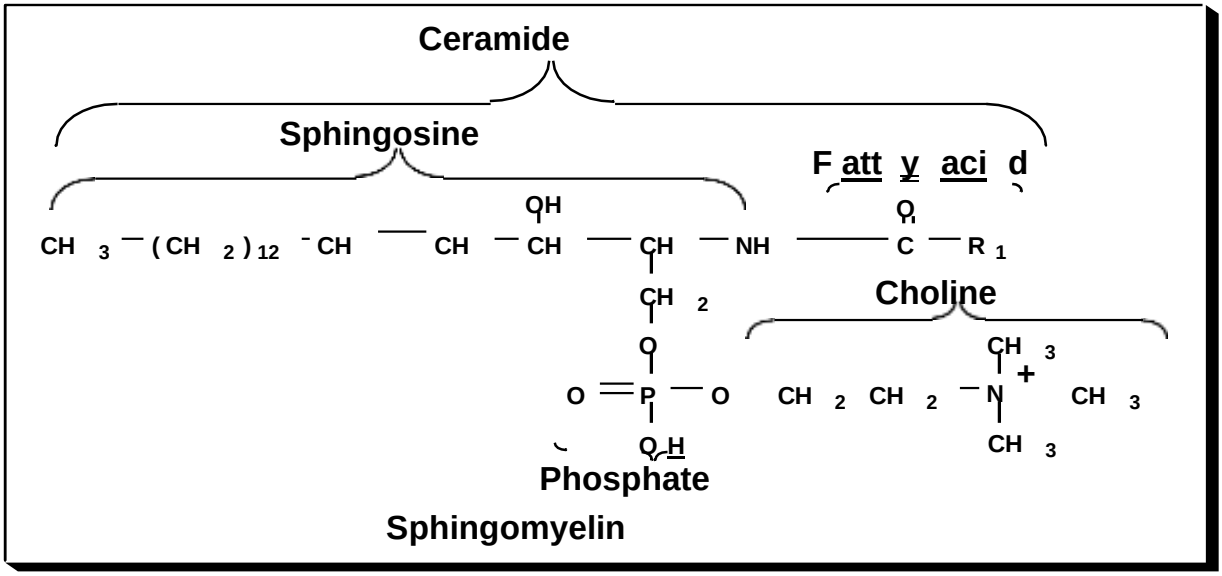
- They are diphosphatidyl-glycerol. They are found in the inner membrane of mitochondria initially isolated from heart muscle (cardio). It is formed of 3 molecules of glycerol, 4 fatty acids and 2 phosphate groups.
- Function: Used in serological diagnosis of autoimmunity diseases.



B. Sphingophospholipids

1. Sphingomyelins

- Sphingomyelins are found in large amounts in brain and nerves and in smaller amounts in lung, spleen, kidney, liver and blood.
- Structure: Sphingomyelins differ from lecithins and cephalins in that they contain sphingosine as the alcohol instead of glycerol, they contain two nitrogenous bases: sphingosine itself and choline.
- Thus, sphingomyelins contain sphingosine base, one long-chain fatty acid, choline and phosphoric acid.
- To the amino group of sphingosine the fatty acid is attached by an amide linkage.
- Ceramide This part of sphingomyelin in which the amino group of sphingosine is attached to the fatty acid by an amide linkage.
- Ceramides have been found in the free state in the spleen, liver and red cells.



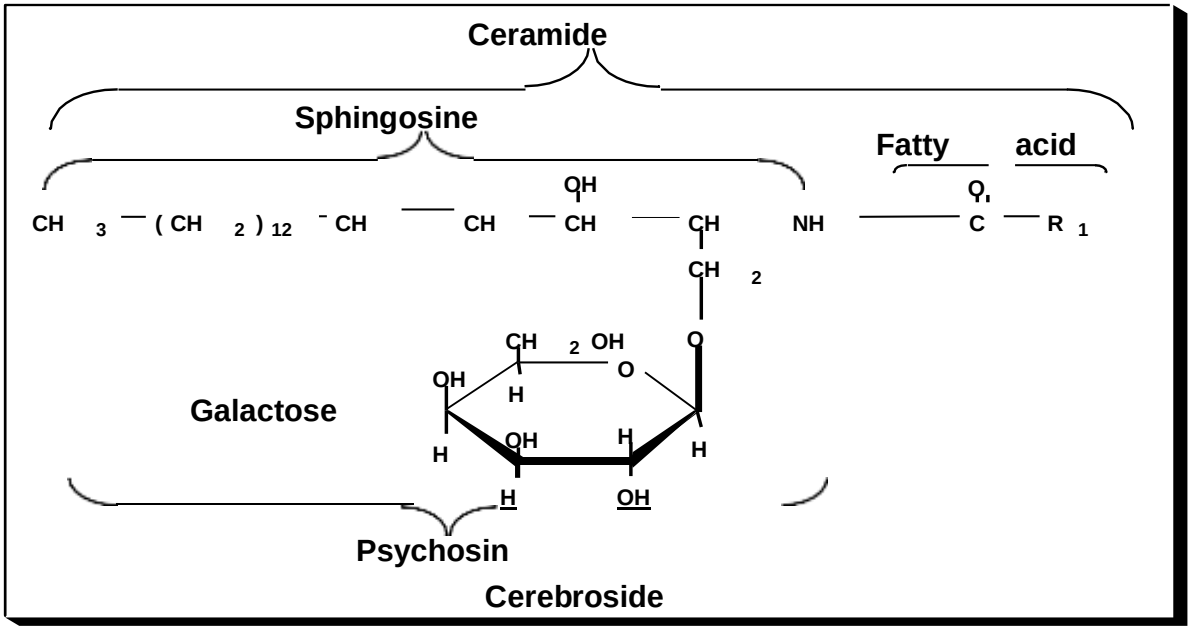
2. Glycolipids

- They are lipids that contain carbohydrate residues with sphingosine as the alcohol and a very long-chain fatty acid (24 carbon series).
- They are present in cerebral tissue, therefore are called cerebrosides
- Classification: According to the number and nature of the carbohydrate residue(s) present in the glycolipids the following are

1. Cerebrosides. They have one galactose molecule (galactosides).
2. Sulfatides. They are cerebrosides with sulfate on the sugar (sulfated cerebrosides).
3. Gangliosides. They have several sugar and sugaramine residues.

1. Cerebrosides:

- Occurrence: They occur in myelin sheath of nerves and white matter of the brain tissues and cellular membranes. They are important for nerve conductance.
- Structure: They contain sugar, usually -galactose and may be glucose or lactose, sphingosine and fatty acid, but no phosphoric acid**.**

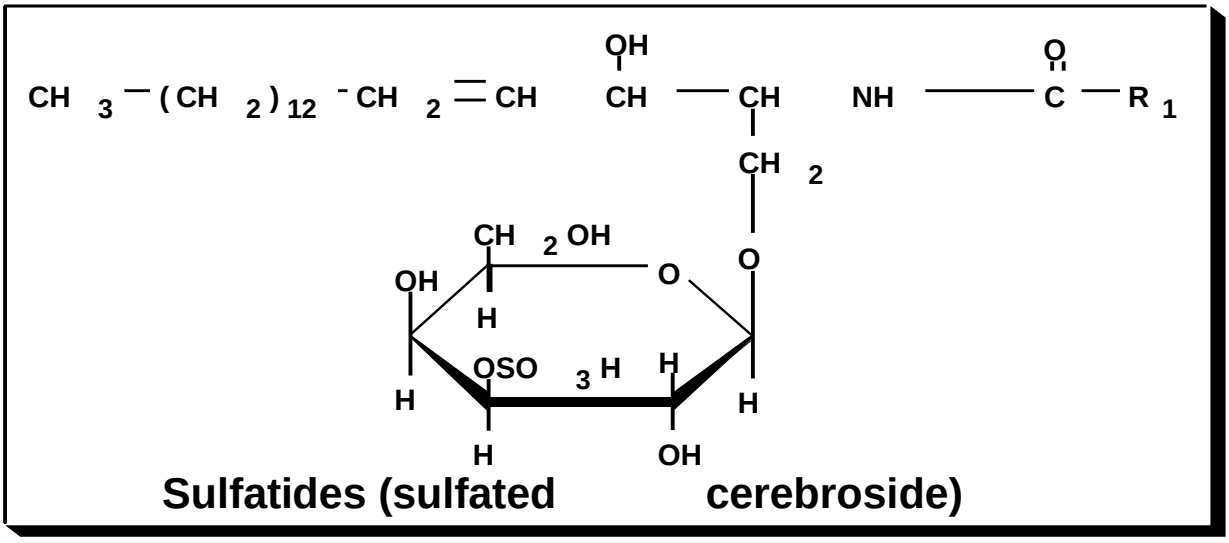


- Types: According to the type of fatty acid and carbohydrate present, there are 4 different types of cerebrosides isolated from the white matter of cerebrum and in myelin sheaths of nerves. Rabbit cerebrosides contain stearic acid.

1. Kerasin contains lignoceric acid (24 carbons) and galactose.
2. Cerebron (Phrenosin) contains cerebronic acid (2-hydroxylignoceric acid) and galactose.
3. Nervon contains nervonic acid (unsaturated lignoceric acid at C15) and galactose.
4. Oxynervon contains oxynervonic acid (2-hydroxynervonic acid) and galactose.

2. Sulfatides:

- They are sulfate esters of kerasin or phrenosin in which the sulfate group is usually attached to the –OH group of C3 or C6 of galactose. Sulfatides are usually present in the brain, liver, muscles and testes.



Sulfatides (sulfated cerebroside)

3. Gangliosides

- They are more complex glycolipids that occur in the gray matter of the brain, ganglion cells, and RBCs. They transfer biogenic amines across the cell membrane and act as a cell membrane receptor.
- Gangliosides contain sialic acid (N-acetylneuraminic acid), ceramide (sphingosine + fatty acid of 18-24 carbon atom length), 3 molecules of hexoses (1 glucose + 2 galactose) and hexosamine. The most simple type of it the monosialoganglioside,. It works as a receptor for cholera toxin in the human intestine.

Ceramide-Glucose-Galactose-N-acetylgalactosamine-Galactose
Sialic acid
Monosialoganglioside

3. Lipoproteins

Lipoproteins are lipids combined with proteins in the tissues. The lipid component is phospholipid, cholesterol or triglycerides. The holding bonds are secondary bonds.

1. Structural lipoproteins: These are widely distributed in tissues being present in cellular and subcellular membranes. In lung tissues acting as a surfactant in a complex of a protein and lecithin. In the eye, rhodopsin of rods is a lipoprotein complex.
2. Transport lipoproteins: These are the forms present in blood plasma. They are composed of a protein called apolipoprotein and different types of lipids. (Cholesterol, cholesterol esters,

phospholipids and triglycerides). As the lipid content increases, the density of plasma lipoproteins decreases

Plasma lipoproteins

a) Chylomicrons:

They have the largest diameter and the least density. They contain 1-2% protein only and 98-99% fat. The main lipid fraction is triglycerides absorbed from the intestine and they contain small amounts of the absorbed cholesterol and phospholipids.

b) Very low-density lipoproteins (VLDL):
Their diameter is smaller than chylomicrons. They contain about 7-10% protein and 90-93% lipid. The lipid content is mainly triglycerides formed in the liver. They contain phospholipid and cholesterol more than chylomicrons.

c) Low-density lipoproteins (LDL):
They contain 10-20% proteins in the form of apolipoprotein B. Their lipid content varies from 80-90%. They contain about 60% of total blood cholesterol and 40% of total blood phospholipids. As their percentage increases, the liability to atherosclerosis increases.

d) High-density lipoproteins (HDL):
They contain 35-55% proteins in the form of apolipoprotein A. They contain 45- 65% lipids formed of cholesterol (40% of total blood content) and phospholipids (60% of total blood content). They act as cholesterol scavengers, as their percentage increases, the liability to atherosclerosis decreases. They are higher in females than in males.
Due to their high protein content they possess the highest density.

Derived lipids

These are the substances derived from simple and compound lipids by hydrolysis. These include fatty acids, alcohols, mono- and diglycerides, steroids, terpenes and carotenoids.

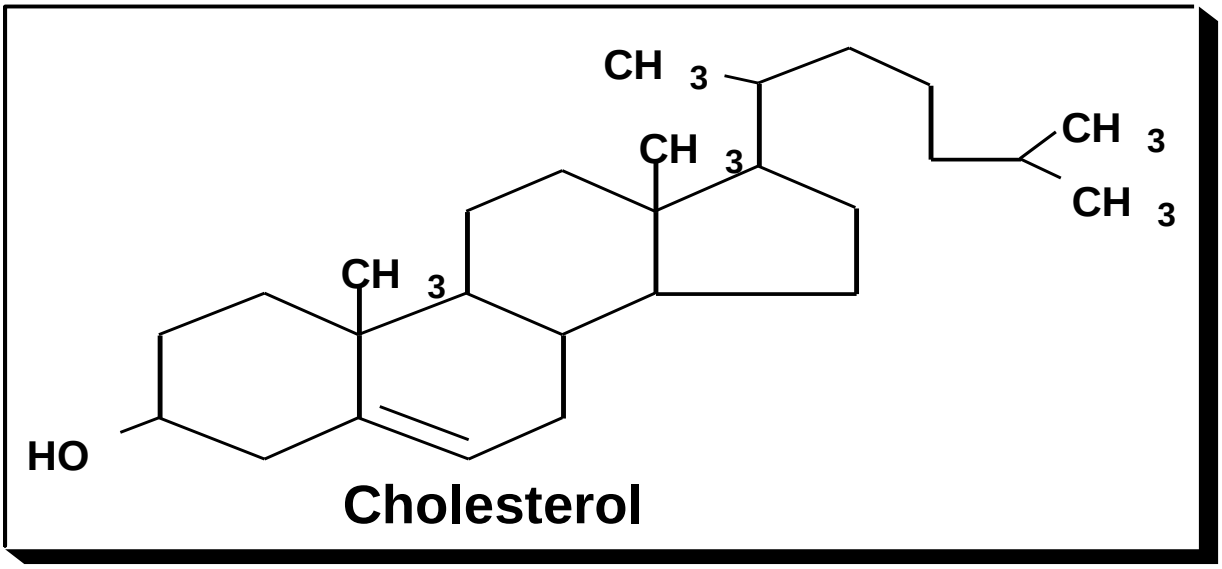
Cholesterol

- Importance: It is the most important sterol in animal tissues as free alcohol or in an esterified form (with linoleic, oleic, palmitic acids or other fatty acids).
- Steroid hormones, bile salts and vitamin D are derivatives from it.
- Tissues contain different amounts of it that serve a structural and metabolic role, e.g., adrenal cortex content is 10%, whereas, brain is 2%, others 0.2-0.3%.
- Source: It is synthesized in the body from acetyl-CoA (1gm/day, cholesterol does not exist in plants) and is also taken in the diet (0.3 gm/day as in, butter, milk, egg yolk, brain, meat and animal fat).

Physical properties

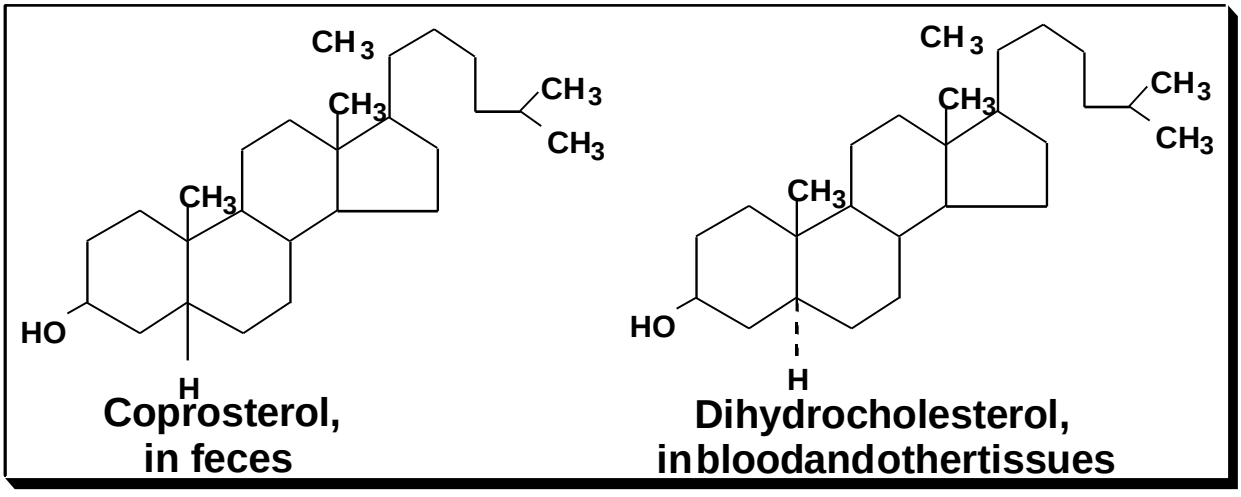
- It has a hydroxyl group on C3, a double bond between C5 and C6, 8 asymmetric carbon atoms and a side chain of 8 carbon atoms.

- It is found in all animal cells, corpus luteum and adrenal cortex, human brain (17% of the solids).
- In the blood (the total cholesterol amounts about 200 mg/dL of which 2/3 is esterified, chiefly to unsaturated fatty acids while the remainder occurs as the free cholesterol.

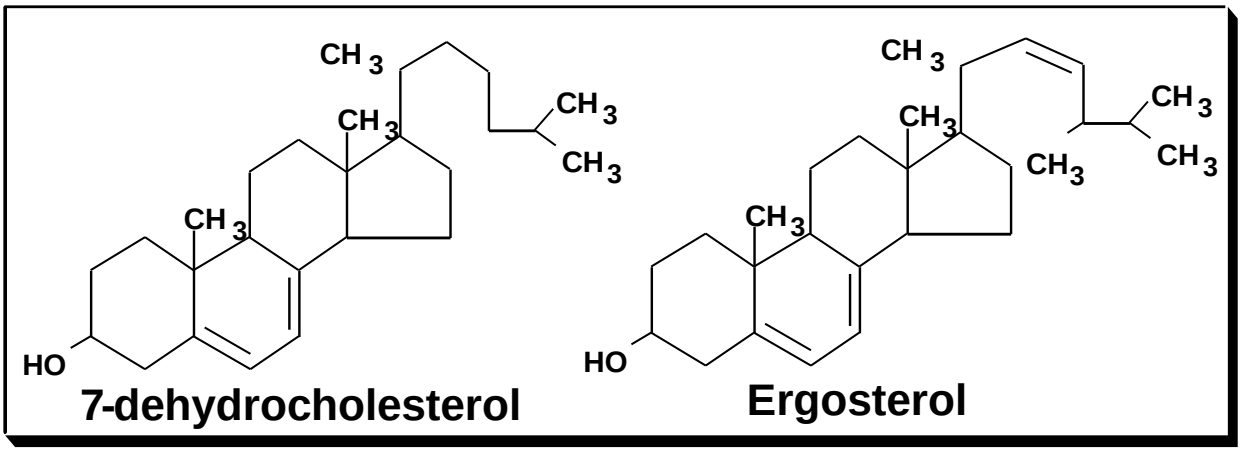


Chemical properties

- Intestinal bacteria reduce cholesterol into coprosterol and dihydrocholesterol.
- It is also oxidized into 7-Dehydrocholesterol and further unsaturated cholesterol with a second double bond between C7 and C8. When the skin is irradiated with ultraviolet light 7-dehydrocholesterol is converted to vitamin D3. This explains the value of sun light in preventing rickets.



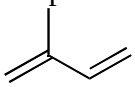
- Ergosterol differs from 7-dehydrocholesterol in the side chain.
- Ergosterol is converted to vitamin D2 by irradiation with UV Ergosterol and 7- dehydrocholesterol are called Pro-vitamins D or precursors of vitamin D.
- It was first isolated from ergot, a fungus then from yeast. Ergosterol is less stable than cholesterol (because of having 3 double bonds).



TERPENES

Terpenes are a large and diverse class of organic compounds, produced by a variety of plants, particularly conifers, though also by some insects such as termites or swallowtail butterflies, which emit **terpenes** from their osmeteria (defensive organ). Terpenes and terpenoids are the most important constituents in essential oils

These hydrocarbons and their oxygenated derivatives have lesser than 40 carbon atoms.
The simplest terpenes are called monoterpenes with formula $C_{10}H_{16}$ those with the formula $C_{15}H_{24}$ are called as sesquiterpenes, with C20H32 as diterpenes and with $C_{30}H_{48}$ as triterpenes.
Terpenes with 40 carbon atoms (or tetraterpenes) include compounds called carotenoids
Terpenes are built from C_5 isoprene units



isoprene (2-methyl-1,3-butadiene)

Terpenes are the building blocks for a number of molecules such as Phytol tail on chlorophyll, Ubiquinone tail, Gibberellins, Cytokinin and Steroids

Membrane Lipids

- Phospholipids are made up of a glycerol backbone with a hydrophilic head region containing a phosphate group and a hydrophobic tail region containing a saturated fatty acid and an unsaturated fatty acid.
- The fact that it has both types of fatty acids ensures the cell membrane is fluid.
- Cholesterol is interspersed throughout the cell membrane to add rigidity to it.
- It also allows the cell membrane to stay fluid over a wider range of temperatures.

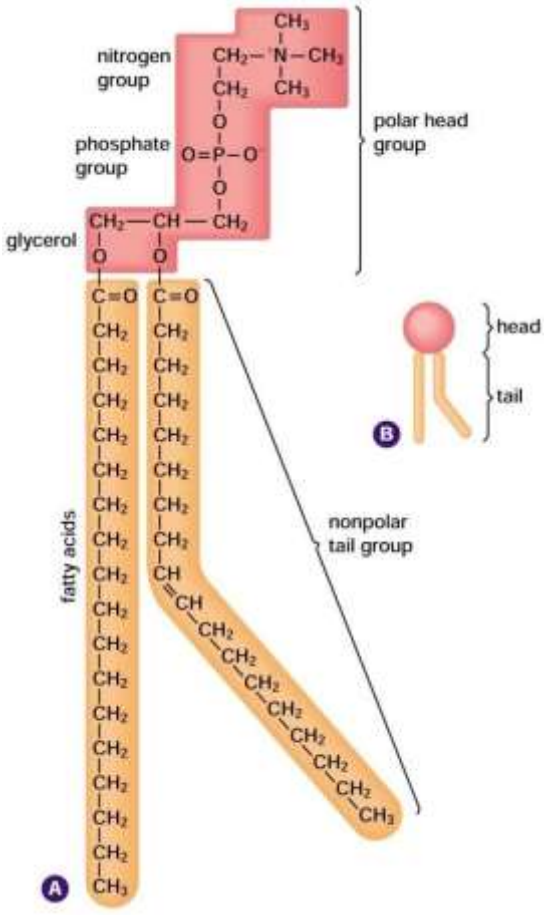


Fig. Head and tail region of phospholipid

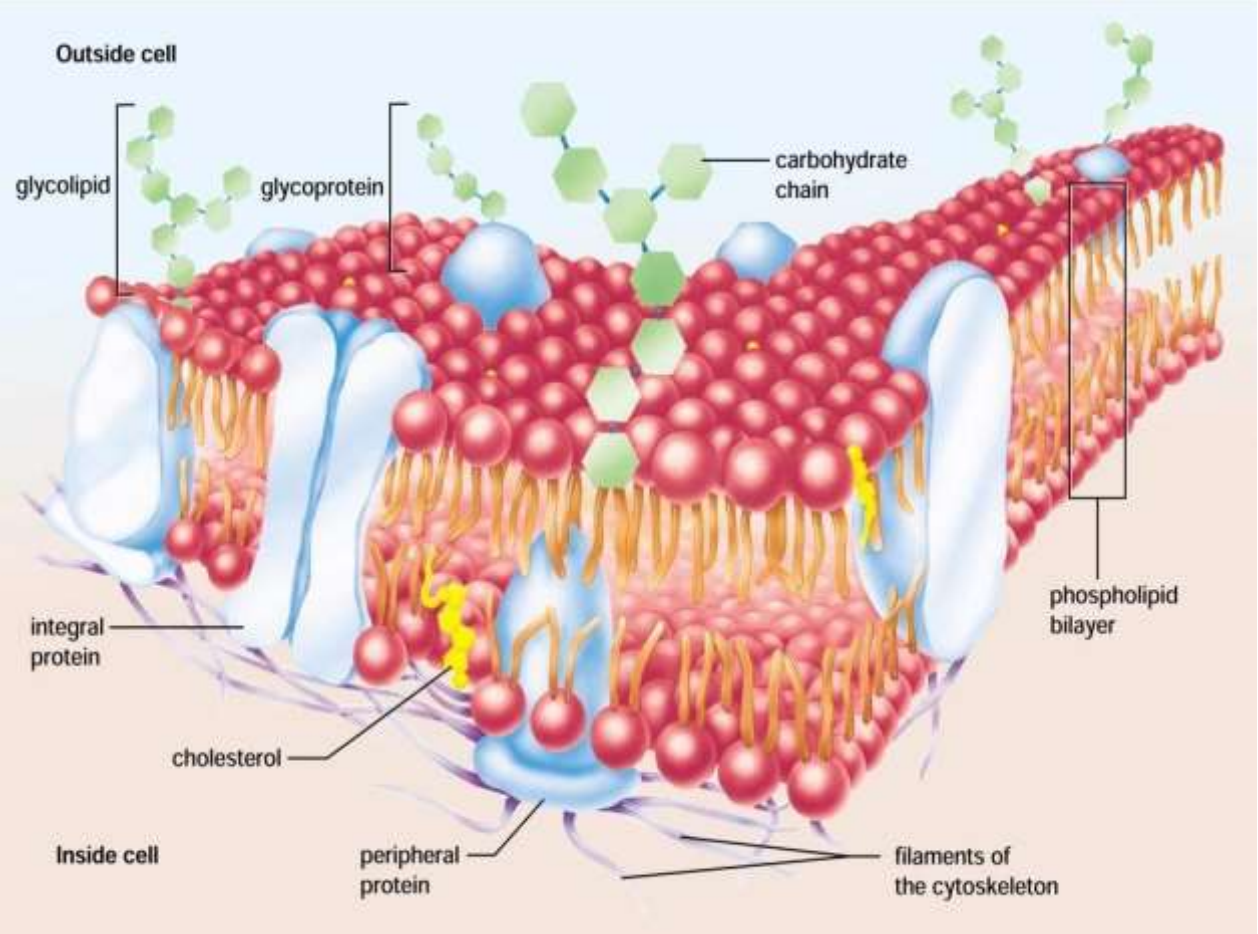


Fig. Lipid bilayer

Lipid membrane has four main functions:

1. Allow the transport of raw materials into the cell
2. Allow the transport of manufactured products and wastes out of the cell
3. Prevent the entry of unwanted material into the cell

Steroid Hormones

Steroid hormones are derived from cholesterol and differ only in the ring structure and side chains attached to it.

Types of steroid hormones

- Glucocorticoids - cortisol is the major representative in most mammals
- Mineralocorticoids - aldosterone being most prominent
- Androgens such as testosterone

- Estrogens including estradiol and estrone
- Progestogens (also known a progestins) such as progesterone

Functions of Steroid Hormones

Steroid hormones play important roles in:

1. carbohydrate regulation (glucocorticoids)
2. mineral balance (mineralocorticoids)
3. reproductive functions (gonadal steroids)

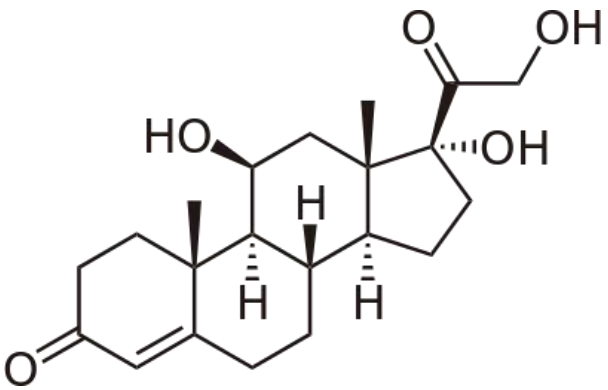
Steroids also play roles in inflammatory responses, stress responses, bone metabolism, cardiovascular fitness, behavior etc.,

Steroid hormone synthesis

All steroid hormones are derived from cholesterol. A series of enzymatic steps in the mitochondria and endoplasmic reticulum of steroidogenic tissues convert cholesterol into all of the other steroid hormones and intermediates.

Glucocorticoids

The name glucocorticoid is composed from its role in regulation of glucose metabolism The primary glucocorticoid in humans is cortisol and produced in adrenal cortex. Functions - promote gluconeogenesis; favor breakdown of fat and protein (fuel mobilization); anti-inflammatory

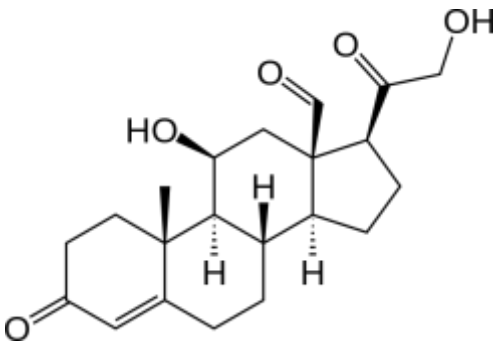


cortisol

Mineralocorticoids

Steroid hormones that affect electrolyte balance. The primary human mineralocorticoid, aldosterone is produced in adrenal cortex.

Functions - maintains blood volume and blood pressure by increasing sodium reabsorption by kidney



Aldosterone

Gonadal steroids

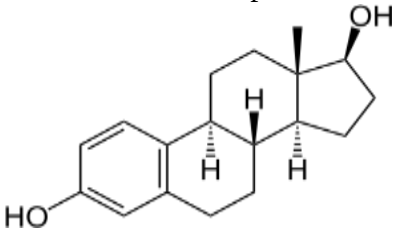
Androgens

Produced in testes primarily but weak androgens in adrenal cortex.

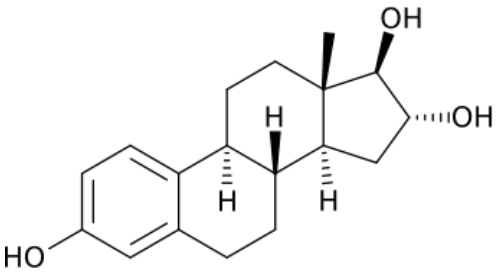
Functions - Development of male secondary sex characteristics and prevents bone resorption Estrogen

Produced in ovaries primarily but also in adipose cells of males and females

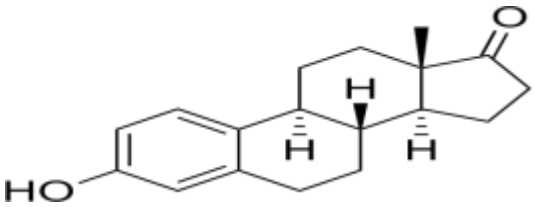
Functions - Development of female secondary sex characteristics; prevents bone resorption



Estradiol (E2)



Estriol (E3)



Estrone (E1)

Vitamins - Introduction

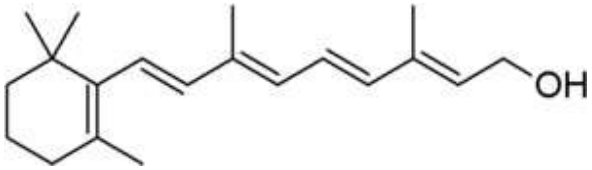
Vitamins are essential nutrients that are required by the body. Since they were discovered and their positive effects became known for us, they became one of the most common products of the pharmaceutical industry. They all have a unique role in maintaining normal cell function, growth and development. Vitamins are classified into two categories:

- Fat soluble vitamins (A, D, E and K),
- Water soluble vitamins (B and C).

Fat-soluble vitamins, once ingested, the body uses what it needs at the time and stores the rest in fat tissue. The vitamins can be stored and remain here until they are needed for future use. If too much is ingested this can cause hypervitaminosis, a potentially dangerous condition. Deficiencies can also occur when fat intake is low or if fat absorption is compromised in certain conditions (e.g. taking certain drugs, cystic fibrosis).

In contrast water-soluble vitamins are not stored in the body. The body uses the amount needed and any excess is excreted in urine. As they are not stored, the body requires a constant supply in order to stay healthy.

Fat Soluble vitamins Vitamin A



Vitamin A structure

Role

- Good vision: It is a component of retinal pigments, which helps especially in low lighting.
- Reproduction, cell division and gene expression.
- Participates in bone and tooth development.
- Maintains mucous membranes of the mouth , nose, throat and lungs, by keeping them moist.
- Maintains healthy skin.
- Antioxidant, which may protect against cancer. Beta-carotene is an antioxidant. • Supports immune function

Source

Vitamin A primarily comes from animal sources: eggs, meat, fortified milk, cheese, cream, liver, kidney, cod, and halibut fish oil. Beta-carotene comes from colourful fruits and vegetables, such as carrots, pumpkin, winter squash, dark green leafy vegetables and apricots. Usually the more intense the colour of the fruit or vegetable, the more beta-carotene it contains.

Excess

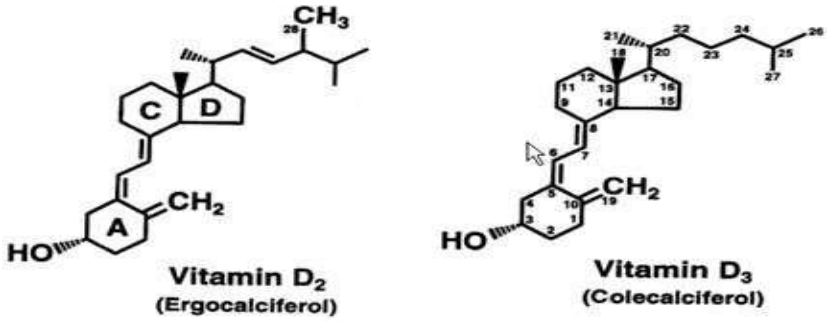
This can either be acute or chronic and can present with a number of symptoms. Acute toxicity causes dry, itchy skin, headache, nausea, loss of appetite and blurred vision. Severe toxicity can result in growth retardation, enlargement of the liver and spleen, loss of hair, bone pain, increased pressure in the skull and skin changes. Increased amounts of beta-carotene can turn the skin yellow or orange.

Deficiency

This is usually associated with strict diet restriction or excessive alcohol intake.

- **Mild:** night blindness, diarrhea, reduced resistance to infection, impaired vision.
- **Severe:** inflammation of the eyes, keratinisation of the skin and eyes and blindness in children.

Vitamin D



Role

Participates in metabolism of calcium and phosphate and maintains adequate serum concentrations of both. It also promotes calcium absorption in the gut. Vitamin D is especially important in growing children, as it is needed for strong bones and teeth. Research shows that it also provides protection against osteoporosis, hypertension, cancer, and some autoimmune diseases.

Source

Primary source is milk and other dairy products. It is also found in oily fish and cod liver oil. It is not only found in foods, it can be synthesized in the skin and is triggered by the exposure to UV rays from sunlight (it is recommended to get 10 to 15 minutes of sunshine three times weekly is enough to produce the body's requirement of vitamin D).

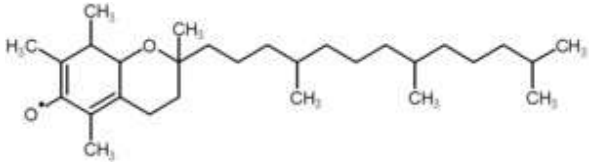
Excess

Toxicity causes elevated plasma concentration of calcium which can have some side effects: Blood vessel contract, high blood pressure and Calcium deposits in soft tissues such as the heart and lungs, Kidney stones, Nausea, vomiting, constipation, poor appetite, weakness, and weight loss.

Deficiency

The main diseases associated with vitamin D deficiency are Osteomalacia and rickets (in children). The symptoms that arise are nausea, weight loss and irritability for mild cases, and mental and physical growth retardation, kidney damage and movement of calcium from bones into soft tissues for the severe cases.

Vitamin E



Vitamin E structure

Role

It is an antioxidant that protects Vitamin A and C, red blood cells and essential fatty acids from becoming destroyed. It also prevents cell membranes from being damaged.

Source

It can be found in natural or synthetic forms. It is found in vegetable oils, cereals, meat, poultry, eggs, fruits, vegetables, legumes, wheat germ oil and whole grain and is also available as a supplement.

Excess

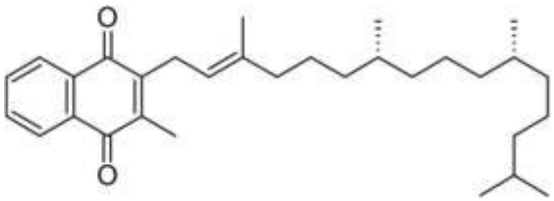
There is an increased risk of bleeding especially in patients taking blood-thinning agents such as heparin, warfarin or aspirin, and in patients with vitamin K deficiency. It can also cause nausea and digestive tract disorders.

Deficiency

This is very rare and impossible to produce without starvation. It generally occurs in infants and people unable to absorb fats.

Vitamin K

Vitamin K is group of compounds derivated from 2-methyl-1,4-naftochinon (IUPAC: 2-methylnaphthalene-1,4-dione)



Vitamin K_1 structure

Role

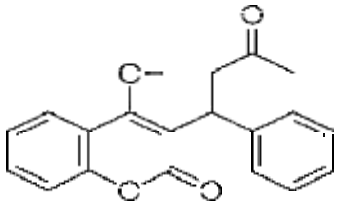
It has an important role in normal blood clotting (**factors II, VII, IX and X** are vitamin K dependent, because it works as cofactor in carboxylation of glutamic acid to γ- carboxyglutamic acid which is essential for calcium binding on these factors), for synthesis of protein C and S and it is also needed to help build strong bones.

Role in coagulation therapy

The role of vitamin K is often exploited in anticoagulation treatments in patients with increased risk of thrombosis. These compounds used are referred to as vitamin K antagonists, many of these are

coumarin based, the best know of which is warfarin. Coumarin based compounds function by preventing the conversion of the inactive epoxide form of vitamin K into its activated form by inhibiting the enzyme responsible for its reduction (vitamin K epoxide reductase).

Alternative anticoagulation treatments include heparin (via the inactivation of thrombin) in vivo and EDTA, oxalate and citrate (which remove Ca^{2+}) but can only be used in vitro due to the biological importance of Ca^{2+}.



Warfarin

Source

It is found in green leafy vegetables, such as broccoli and spinach, pulses, vegetable oils, cereals, milk, milk products, meat, eggs and fruit. Bacteria in the intestines can also synthesis Vitamin K and contribute to the available pool.

- Requirement: 1 µ/kg/day (except newborns)

Excess

This can cause the breakdown of red blood cells and also liver damage. Therefore if a person is taking blood-thinning agents, they may need to limit the amount of Vitamin K intake.

Note: Vitamin K is an antidote for warfarin.

Deficiency

It is very rare in adults, but can occur in individuals that cannot absorb it properly, due to lack of intestinal bacteria, as well as those being treated long term with antibiotics. It can cause excessive bleeding and increased tendency to bruise. It may also be the cause of haemorrhagic disease of newborn, because placental transfer of vitamin K is very low, its level in breast milk is low as well. (prevention: 1 mg of vit K intramuscularly 2–6 hours after birth and then 1 mg of vit K every week till age one month, and for exclusively breast fed children till age 6 months).

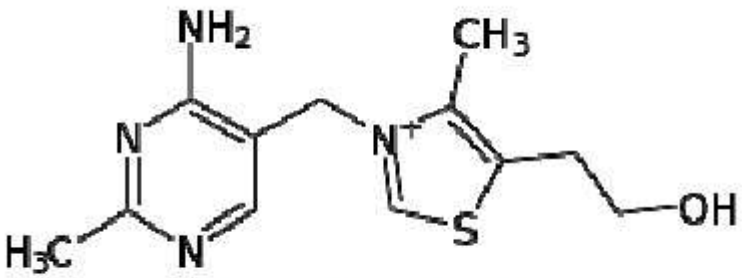
Water Soluble vitamins

Water-soluble vitamins consist of the B-group vitamins and vitamin C. Their deficiency is treated by administration of the deficient vitamin.

B Group Vitamins Features

- A common feature of group B vitamins is their occurrence in yeast (except vitamin B_{12}). However, if the yeast is included in the diet only as a means of rising bread, then yeast is not considered the major source of group B vitamins in humans; a small quantity of yeast does not contain nutritionally significant amount of B vitamins.
- Their metabolic effects are inter-linked.
- Deficiency of only a single vitamin occurs rarely.
- They are produced by the intestinal micro flora but the amount produced is generally only a fraction of the daily recommended intake.
- Some are more frequently called by their name, others by number. Some vitamins may not have a number because it has been found that some substances, originally considered as vitamins, are NOT essential for humans, therefore they are not vitamins or are a mixture of substances.

Vitamin B_1 (thiamine)



Vitamin B1 - structure

Thiamine (vitamin B_1) is a coenzyme decarboxylase important for the metabolism of glucose and energy supply to nerve and muscle cells.

Source

Meat, fish, cereals, yeast, legumes.

Daily recommended intake for adults: 1-1.4 mg

Deficiency

The disease beri-beri from a lack of dietary vitamin B_1 is found today in very poor population groups (e.g. refugees) in countries where people live mostly on polished/white rice. It may also develop in people who live mostly on refined wheat flour products and among alcoholics and food faddists.

A typical image consists of nervous disorders, especially peripheral nerves (dry beri beri), edema and heart disease (beri beri wet). Impaired absorption of vitamin B_1 occurs in alcoholics and is manifested by Wernicke encephalopathy.

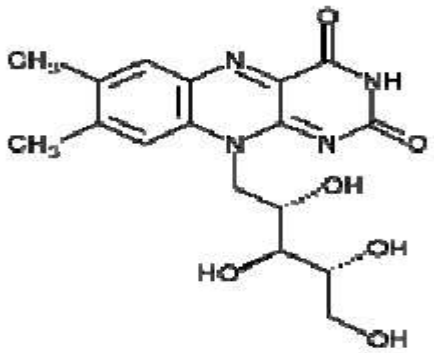
Suboptimal thiamine status based on biochemical criteria in Europe was detected only in 46% of the population. Risk group are alcoholics.

Laboratory evaluation: thiamine excretion in the urine. In the absence of erythrocytes is reduced transketolase concentration in the blood and the sea is high concentrations of glycoxalate.

Excess

Signs of excess are not encountered.

Vitamin B_2 (riboflavin)



Vitamin B2 structure

Riboflavin or vitamin B_2 is part of coenzymes flavinadenine mononucleotide (FAD) and flavin mononucleotide (FMN), plays a key role in oxidative metabolism.

Source

A small amount is found in many foods. Main sources are meat, milk and milk products; good sources are also fish, offal (inner organs), eggs, and whole grain cereals. Milling of cereals removes most of vitamin B_2 - some countries (e.g. USA) fortify cereal products with riboflavin.

Recommended daily intake for adults: 1.2 to 1.5 mg

Deficiency

According to several population studies, the deficiency is widespread in developing countries, where diet is poor in animal foods, vegetables and fruits, and where cereals are milled (white flour). Frequently the deficiency is secondary due to malabsorption, enterocolitis, coeliac disease, chronic hepatitis; in children often after the use of broad- spectrum antibiotics. It may develop in cancer, cardiac disease, diabetes

Clinical picture: The description of the signs of riboflavin deficiency is somewhat inconsistent in various scientific publications. Riboflavin deficiency occurs almost always together with deficiencies of other group B vitamins, which may cause some of the signs. The signs most frequently described are: angular stomatitis, peeling lips (cheilosis), glossitis, and normocytic normochromic anemia.

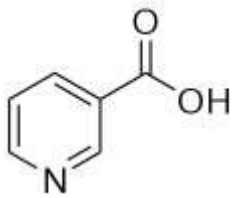
Laboratory evaluation: decreases secretion of vitamin B_2 in urine (normal values are 106– 638 nmol/l), decreased concentrations of glutathione and glutathione reductase in erythrocytes.

Excess

Signs of excess are not known.

Vitamin B_3 (niacin)

Niacin (vitamin B_3) is the name for nicotinamide and nicotinic acid. It is part of enzymes, oxido-reduction systems (nicotinamide adenine dinucleotide -NAD, nicotinamide adenine diphosphate - NADP). May form in the liver from tryptophan and its biosynthesis is very slow and it is needed vitamin B_6.



Structure of Niacin

Source

The source of most foods - meat, fish, cereals. The recommended daily dose for adults is by age and sex of 13-17 mg.

Deficiency

Disease pellagra is caused by the current lack of niacin and its precursor tryptophan. Today it has rarely occurs in a very poor population groups or for refugees in developing countries. Occurs in

people who eat mostly corn/maize. The symptoms are as a mnemonic device used sometimes called "disease of three D" - dermatitis, diarrhea, dementia.

Surplus

Signs of excess food are not known. High doses of dietary supplements induce vasodilatation, warmth, gastritis, damage to liver cells. Income should not exceed 35 mg/ kg / day.

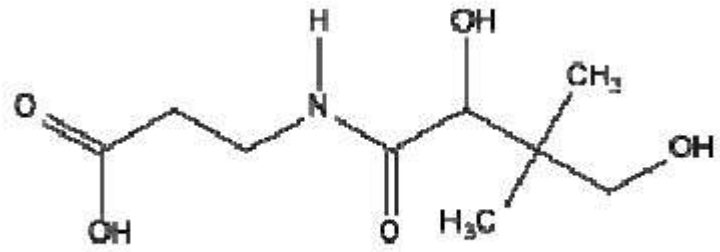
Pharmacological use

Nicotinic acid (niacin) and its derivatives are used to treat hyperlipidemia by inhibiting the secretion of VLDL from the liver and increasing the activity of peripheral lipoprotein lipase.
This leads to a reduction in circulating VLDL (ie, TAG) and, consequently, LDL (cholesterol).

In contrast adipose tissueblocking the intracellular lipase, thus releasing the MK inventory, further reducing supply to the liver TAG and reduces VLDL synthesis.

- Adverse effects: harmless vasodilation (mediated release of prostaglandins) in the skin associated with subjective stream feeling hot - it can handle submitting aspirin; at 1 / 5 of patients treated with hyperuricemia; skin rash.

Vitamin B_5 (pantothenic acid)



Vitamin B5 structure

Pantothenic acid (vitamin B_5) is part of coenzyme A.

Source

Small amounts are in almost all foods contain a large amount of yeast, liver, meat, milk, whole grains and legumes. The daily recommended dose for adults: 6 mg

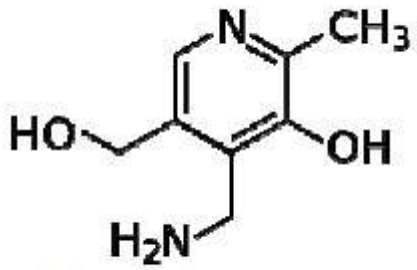
Deficit

Lack is not present - described only when administered pantothenic acid antagonists and extremely malnourished people with symptoms of deficiency of other nutrients, is manifested hair follicle atrophy, loss of pigmentation, dermatitis.

Surplus

Signs of excess are not known.

Vitamin B_6 (Pyridoxine)



Vitamin B6 structure

Pyridoxine the name vitamin B_6 comprises a group of compounds (pyridoxine, pyridoxamine, pyridoxal and phosphate). It is coenzyme for more than 50 enzymatic reactions - decarboxylase and transaminases, synthesis of acid nicotine and arachidonic acid, affects the function of the nervous system, immune reactions and synthesis of haemoglobin.

Source

It is abundant in food. The daily recommended dose for adults: 13-17 mg

Deficit

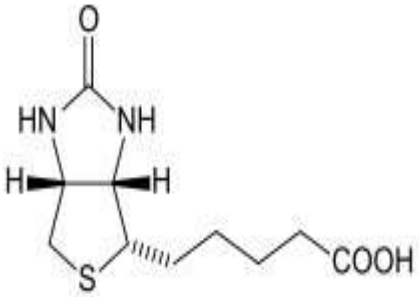
Deficiency with normal eating habits does not occur; manifested skin and mucosal changes, rhagades corners, peripheral neuropathy.

Surplus

Excess of food does not occur. After a prolonged intake of 50-500 mg - sensory neuropathy

Vitamin B_7 (Biotin)

Biotin Vitamin B_7, vitamin H, factor R - Several scholars have described it, only later discovered that it is the same substance) is important for the metabolism of amino acids and fatty acids, is a cofactor for carboxylases.



Biotin Structure

Source

At low concentrations in many foods. Rich sources are yeast, liver, egg yolk, nuts, lentils. The daily requirement (RDA cannot be estimated): 30-60 mg

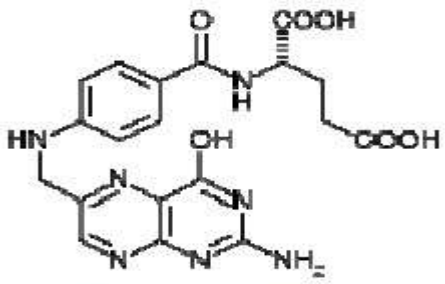
Deficit

Deficiency of food does not occur. Scientists described the people who long consumed a large amount of raw eggs (irreversibly binds to biotin with avidin contained in raw egg white) and improper parenteral nutrition. Symptoms: seborrheic dermatitis, fatigue, anorexia, nausea, hypercholesterolemia, vascular disorders.

Surplus

Signs of excess are not known.

Vitamin B_9 (Folic acid)



Vitamin B9 structure

Folic acid also is known as vitamin B_9, folate or folacin. Includes a group of compounds: Folic Acid (contains pterin, p-aminobenzoic acid and glutamic) and folic acid. Along with vitamin B_{12} is essential for the formation of nucleic acids and thus for synthesis of DNA, participate in the transfer radicals and in all processes of cell division, it is important for cell division and tissue with high

mitotic activity.Absorbed in the proximal parts of the small intestine and when excess it is excreted in the urine.

Source

Liver, yeast, green leafy vegetables, as well as whole grain cereals, meat, milk, eggs and legumes. The recommended daily adult dose: 400mg. In pregnancy, 600mg for prevention of congenital malformations (mainly cleft neural tube).

Deficit

Deficiency of vitamin B_9 occurs in low supply, absorption or increased need during pregnancy. There is a megaloblastic anaemia, which is characterized by the presence of abnormal precursors of red blood cells in the bone marrow. Compared with normal cells are cells arising from these abnormal precursors of different shape, larger size, reduced viability and reduced ability to transport oxygen. Along with the lack of iron is its lack of a significant cause of anaemia in developing countries. Deficiency during pregnancy causes spina neural tube in the fetus.

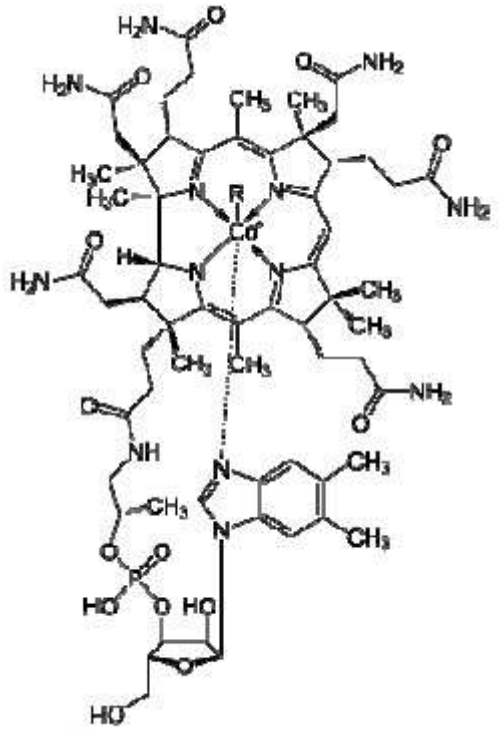
- Laboratory evaluation: serum levels of folate, total homocysteine (increases in the absence, also in the absence of vitamin B_{12})

Surplus

High intake of folic acid can mask vitamin B_{12}, so the upper limit of the daily recommended intake of up to 1000 mg / day.

Vitamin B_{12} (cobalamin)

Vitamin B_{12}(cobalamin) is the collective name for several compounds that are in the center of porphyrin skeletal cobalt . Vitamin B_{12} has a number of biological functions - plays an important role in hematopoiesis, is essential for the development of the central nervous system in children, contributes to the formation of nucleic acids, transmethylation and has anabolic effect. Deficiency of vitamin B_{12} in adults causes macrocytic anemia, impaired rear and lateral spinal cords, peripheral nerves and dementia or depression. Lack of vitamin B_{12} also affects secondary folate cycle resulting in impaired synthesis of purines and pyrimidines necessary for the formation of DNA and RNA.



Vitamin B12 structure

Source

In nutritionally significant quantities occurs only in animal foods. Rich sources are liver, kidney, meat warm-blooded animals (1-2 ig/100 g), fish, egg yolk and dairy products (milk ìg/100, 0.3 ml cheese ìg/100 0.2 to 0.6g). Plant foods contain trace amounts of vitamin B_{12} only if it has been processed by bacterial fermentation (e.g beer). Absorbed in the small intestine only if the stomach creates a complex with an internal factor. Therefore it is necessary to properly functioning stomach and large amounts of vitamin B_{12} are formed by the intestinal flora in humans unusable. Cobalamine with an internal factor in the distal ileum bind to specific receptor cubilin and this complex then enters by endocytosis into enterocytes.

Inside the enterocyte cobalamin binds to other carriers and excreted into the plasma. 75-80% is bound to haptocorrin and goes to hepatocytes. The cells of other organs enter only vitamin B_{12} bound to transcobalamin II (the holotranscobalamin) after binding to specific receptors through endocytosis. The cell cobalamin is converted to active metabolites and adenosylcobalamine methylcobalamin, which serve as cofactors of enzymes. The daily recommended dose for adults: 3 mg. Minimal in infants: approximately 0.1 to 0.3 mg.

Function

Haemopoiesis; development of the central nervous system in childhood; cofactor of two metabolic reactions: conversion of homocysteine to methionine by methionine synthase (failure of this reaction leads to the accumulation of homocysteine); conversion methylmalonyl-CoA to succinyl-CoA

action methylmalonyl-CoA mutase (failure of this reaction leads to an accumulation of methylmalonic acid and its increased urinary excretion).

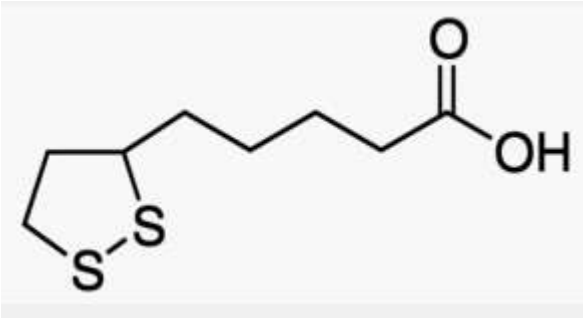
Deficit

Its deficiency is clinically manifested failure to thrive, macrocytic anemia and neurological symptoms. An adult is a stock (2-5 mg) of vitamin B_{12} in the liver, which cover the need for a period of 5-10 years. Stocks, which creates the infant in utero (approximately 25 micrograms), will be exhausted as early as 3-5 months. Among laboratory manifestations include mostly macrocytic anemia, elevated aminotransferases, hyperhomocysteinemia and increased acid secretion methylmalonic acid plasma concentrations of homocysteine and methylmalonic acid excretion increased in the urine. Metabolic changes precede clinical manifestations. Pernicious anemia is an autoimmune disease that leads to atrophy of the gastric mucosa and by the lack of intrinsic factor.

Surplus

Signs of excess were reported even after a high intake (5 mg) of the supplement.

Lipoic acid



Lipoic acid Structure

Alpha-lipoic acid is an antioxidant that's in many foods, and it's made naturally in our bodies. Yeast, liver, kidney, spinach, broccoli, and potatoes are good sources of alpha-lipoic acid.

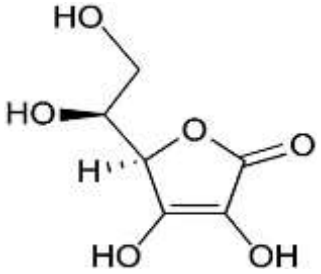
Alpha-lipoic acid is used for diabetes and nerve-related symptoms of diabetes including burning, pain, and numbness in the legs and arms.

Some people use alpha-lipoic acid for memory loss, chronic fatigue syndrome (CFS), HIV/AIDS, cancer, liver disease, diseases of the heart and blood vessels (including a disorder called cardiac autonomic neuropathy) and Lyme disease.

Alpha-lipoic acid is also used to treat eye-related disorders, such as damage to the retina, cataracts, glaucoma, and an eye disease called Wilson's disease.

600 milligrams daily for three weeks can be taken on symptoms of diabetic neuropathy

Vitamin C



Vitamin C structure

L-ascorbic acid, also known as vitamin C is water soluble strongly reducing effects. Man (as well as other primates and guinea pigs) cannot synthesize it, since it lacks L- gulonolactonexidase activity, therefore it must receive in food. L-ascorbate is involved in the hydroxylation of collagen, the synthesis of carnitine, the metabolism of tyrosine, acts as an antioxidant, supports immune system, iron absorption, has an effect on beta- oxidation of fatty acids, increases the activity of microsomal enzymes, accelerates the detoxification of xenobiotics. Reducing the effects of ascorbic acid is due to its easy oxidation to dehydroascorbate:

Source

Fruits, vegetables (including potatoes), liver. Average losses in cook foods are 30%. The daily recommended dose for adults: 100 mg. When the determination is considered, in addition to prevention of deficiency symptoms, as well as strengthening the immune system and prevention of degenerative diseases. Increased need for considerable physical exertion, psychological stress, alcohol abuse and drugs, some diseases (eg diabetes, renal insufficiency, infection). Intake of 150 mg / day is recommended for smokers.

Deficit

Ascorbic acid deficiency - scurvy (scurvy) - now appears only in extreme conditions. With a slight lack of preclinical manifestations we see in our country (fatigue, prolonged convalescence, impaired wound healing and decreased resistance to infection).

• Laboratory evaluation of the situation: the level of vitamin C in plasma. Clinical symptoms appear with values ≤ 10 µmol/L, an indicator of low intake of vitamin C are considered to values below 37 µmol/L. In terms of prevention of atherosclerosis and the tumors are regarded as desirable values ≥ 50 µmol / L.

Surplus

Signs of excess food are not. Approximately 1% of the unused vitamin C is converted to oxalate, the risk of urinary calculi, but low in healthy subjects. The daily intake should not exceed 1000 mg.

Very high doses (5 g) can cause diarrhea. At high ascorbate intake (about grams per day), most of the substance is excreted in the urine.