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EXTRAIT DE P.V DU CONSEIL SCIENTIFIQUE

Du 27 AVRIL 2026

Objet : Retour Expertise polycopié de cours

Suite à l'expertise du polycopié de cours du Dr **KARIM Abdelkadir** intitulé **« Cellular Biology»** réalisée par les experts cités dans le tableau ci-dessous. Le Conseil Scientifique de la Faculté tenu le 27/04/2026 a émis **un avis favorable.**

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كواش بن موسى

People's Democratic Republic of Algeria
Ministry of Higher Education and Scientific Research
Djilali Bounaama University Khemis Miliana
Faculty of Natural and Life Sciences and Earth Sciences
Department of Common Core SNV

Course Handout

Cell Biology

U.E.F

According to the official pedagogical program for
First Year Undergraduate, Common Core SNV

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Chapter 1 : General Concepts

1 Introduction:

The cell is the fundamental structure of living matter, containing a set of units necessary for growth and reproduction using simple nutrients. Defining a cell has been challenging, with various biologists defining it differently. A.G. Loewy and P. Siekevitz (1963) defined it as a biological activity unit delimited by a semipermeable membrane, capable of self-reproduction in a medium free of other living systems. Wilson and Morrison (1966) defined it as an integrated and continuously changing system, while John Paul (1970) defined it as the simplest integrated organization in living systems capable of independent survival.

Understanding the structure and function of cells is fundamental to all areas of biological science. Gaining insights into the similarities and differences between various cell types is especially crucial for cell biology. These similarities and differences form a core concept in biology, enabling researchers to apply knowledge gained from studying one type of cell to others. For instance, studying the functioning of single-celled organisms or bacteria can provide valuable insights into how human cells operate. Additionally, research in cell biology is deeply interconnected with fields like genetics, biochemistry, molecular biology, and developmental biology.

2 Historical Background:

The study of cells has a long history that has evolved alongside advancements in technology. The concept of the cell as the basic unit of life emerged after the development of early microscopes.

In 1665, Hooke observed a honeycomb-like structure under a microscope and described it as perforated and porous. He published his book Micrographia, which described the cells as irregular, like to honeycombs. These pores, or cells, were the first microscopical pores he had ever seen, and no other writer or person had mentioned them previously. Figure 1.1 shows Hooke's illustration (Alberts et al., 2018).

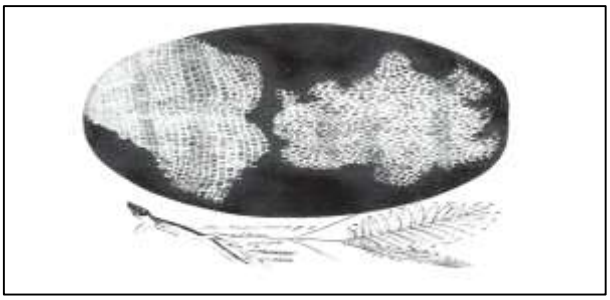


Figure 1 Drawing of the structure of cork from as it appeared under the microscope to Robert Hooke. (Alberts et al., 2018)

As early as 1674, LEEUWENHOEK, after the development of the optical quality of the microscope, described a multitude of living microorganisms: Protists and even Bacteria

In 1838, the Germans Mathias Schleiden and Theodor Schwann, following the observation of multiple animal and plant organisms, succeeded in formulating the cell theory through two principles:

- Principle 1: All organisms are composed of one or more cells.
- Principle 2: The cell is the structural unit of life.

With the invention of more powerful microscopes in the 19th and 20th centuries, the field of cell biology expanded. Researchers discovered the existence of organelles within cells, such as the nucleus, mitochondria, and the endoplasmic reticulum, leading to a greater understanding of cellular functions. The discovery of DNA's structure in the mid-20th century further linked cell biology with genetics and molecular biology. Today, research on cells continues to advance with technologies such as electron microscopy and molecular imaging, allowing us to explore cells in more detail than ever before (Verma and Agarwal, 2004).

3 Classification and Relative Importance of Kingdoms

The living universe comprises well over 10 million different types of organism, which are sorted into **groups** based on **common features**. This is called **classification** (or **taxonomy**). Those organisms that share many similar features are placed in the same group. Those that share few features are placed in separate groups. The number of shared features between different groups gives an indication of how closely related the groups may be.

The largest groups are called kingdoms, of which there are five:

- Prokaryote (Bacteria)
- Protoctist
- Fungus
- Plant
- Animal.

Each kingdom is divided into sub-groups and each subgroup is divided into smaller groups. The last two groups in this succession are the genus and finally, the species. (The plural of genus is genera.)

A species is defined as a group of organisms that can interbreed (reproduce) and produce fertile offspring. A species is therefore said to be 'reproductively isolated'(Verma and Agarwal, 2004).

- Organisms within a species are not identical and the differences between them are called variations.

Example: classification of the human being

- Kingdom: Animal
- Phylum: Chordata
- Class: Mammals
- Order: primates.
- Family: Hominidae.
- Genre: Homo.
- Species: Homo sapiens (homme moderne)

4 The Cell Theory

Later, biologists discovered cells everywhere. Biologists suggested in the early nineteenth century that all living things were made of cells, but the role of cells as the primary building block of life was not discovered until 1839, when two German scientists, Theodor Schwann, a zoologist, and Matthias Jakob Schleiden, a botanist, proposed that cells were the fundamental unit of all living things. Later, in 1858, the German scientist Rudolf Virchow discovered that cells divide to create new cells. He proposed that all cells originate solely from other cells. The cell theory is based on the cumulative observations of all three experts. Modern cell theory suggests that:

- Every creature is composed of one or more cells.
- Cells are responsible for all of an organism's life processes.
- All cells originate from preexisting cells.

The cell hypothesis, like any other theory, is based on data that have long supported the core results of Schwann's paper from 1839. However, one of Schwann's original conclusions was that cells developed similarly to crystals. This remark, which pertains to the spontaneous genesis of life, was dismissed when Virchow argued that all cells come exclusively from other cells. The cell theory has withstood severe study of cells using modern sophisticated microscopes and other equipment. Scientists apply new tools and equipment to peer into cells and discover more answers for how they work (Urry et al., 2017).

5 Size and structure of cell

An individual is composed of numerous cells, each performing a variety of functions throughout its life. The main types of cells include prokaryotic cells and eukaryotic cells, such as plant and animal cells. The size and shape of cells can range from millimeters to micrometers, typically reflecting their specialized functions. Cells display a wide array of forms, including spherical, rod-shaped, flat, concave, curved, rectangular, oval, and more. This diversity in morphology allows cells to efficiently carry out their specific roles. Most cells are only visible under a microscope due to their small size (Alberts et al., 2018).

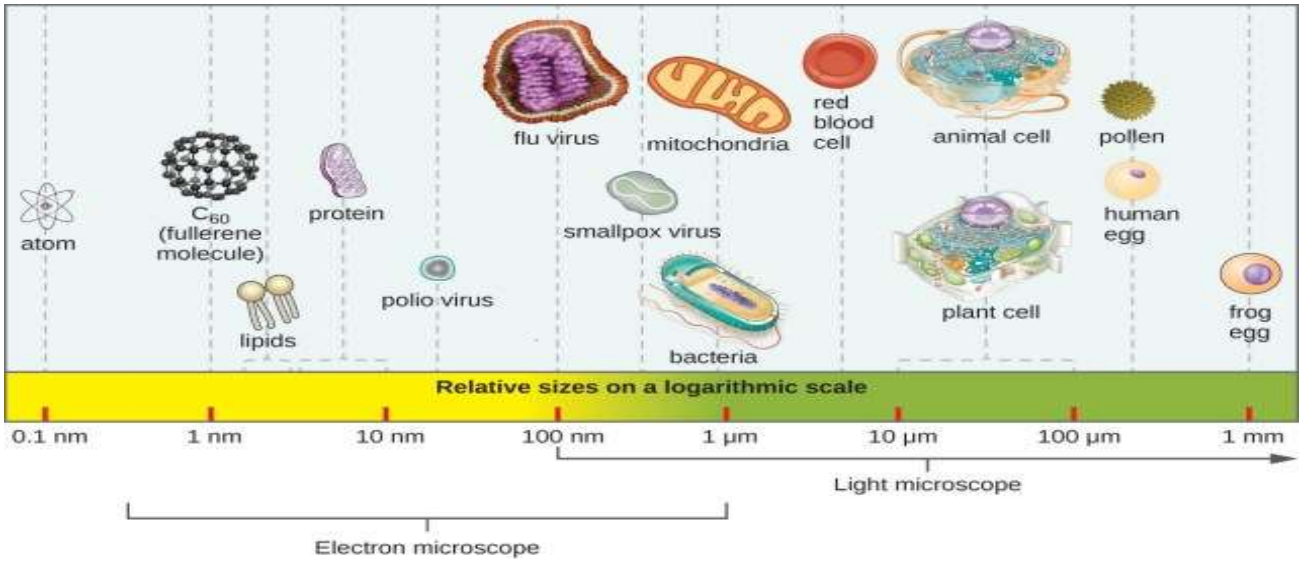


Figure 2: Different types of cells (Alberts et al., 2018*)*

5.1. Cell Shape:

The fundamental morphology of a eukaryotic cell is **spherical**; however, its particular function dictates its shape. ***Amoebae***, **white blood cells**, **leucocytes**, and nearly **all protists**, **plants**, and **animals** exhibit **variable** or **irregular shapes**. The plasma membrane and exoskeleton provide structural integrity to unicellular organisms. Surface tension, protoplasm viscosity, the cytoskeleton's microtubules, microfilaments, and intermediate filaments, the mechanical interactions among adjacent cells, and the plasma membrane's rigidity all influence the shape of multicellular organisms (Alberts et al., 2015).

The morphology of cells can differ across various species and organs, including variations within the same organ. Cells exhibit a variety of shapes, including polyhedral, flattened, cuboidal, columnar, discoidal, spherical, spindle-shaped, elongated, and branched forms. The specialised shapes of glandular hairs on leaves, guard cells of stomata, and root hair cells exemplify how cell function influences cell shape in plants (Verma and Agarwal, 2004).

5.2. Cell Size:

The volume of a specific cell type remains relatively constant, regardless of the organism's size, adhering to the Law of Constant Volume. For instance, kidney and liver cells maintain similar dimensions whether they are in a bull, horse, or mouse. The total mass of an organ is determined by the number of cells it contains, rather than their individual volumes. For cellular efficiency, the volume-to-surface area ratio must stay within a certain limit. As cell volume increases, there is a comparatively smaller increase in the cell's surface area. Consequently, larger cells possess a disproportionately smaller surface area relative to their volume compared to smaller cells (Verma and Agarwal, 2004).

5.3. Cell Number:

The total cell count in an organism ranges from a single cell in unicellular species to numerous cells in multicellular species. Typically, the number of cells in a multicellular organism is proportional to its overall size, meaning smaller organisms have fewer cells compared to larger ones. While many multicellular organisms exhibit a variable cell count, some have a predetermined number of cells. For example, in rotifers, the number of nuclei within various organs remains consistent across individuals of the same species, a phenomenon known as Eutely. Notably, in a specific rotifer species studied by Martini in 1912, there were always 183 nuclei in the brain, 39 in the stomach, and so forth (Verma and Agarwal, 2004).

6 The cell types:

All living organisms, with the exception of viruses, have cellular organisation and may consist of either simply one cell or multiple cells. Unicellular organisms consist of one cell, whereas multicellular organisms are composed of multiple cells. Cell types in cellular organisation can be classified as prokaryotic or eukaryotic, as proposed by Hans Ris in the 1960s (Alberts et al., 2018).

6.1 Eukaryotic Cells:

"The eukaryotic cells (Gr., eu=true, karyotic=nucleated) are larger and more complex than prokaryotic cells, feature a double envelope system encompassing the nucleus and other organelles. Characterized by extensive internal membranes like the endoplasmic reticulum, these cells are true cells found in both plants and animals, ranging from algae and angiosperms to protozoa and mammals. Despite varying in shape, size, and physiology, all eukaryotic cells are composed of a plasma membrane, cytoplasm with organelles such as mitochondria, ribosomes, Golgi apparatus, and a true nucleus **“figure 3 and figure 4”.** Within the nucleus, the DNA, RNA, nucleoproteins, and nucleolus are separated from the cytoplasm by thin, perforated nuclear

membranes. It's beneficial to understand the general features of eukaryotic cells before delving into specific cellular components (Alberts et al., 2018).

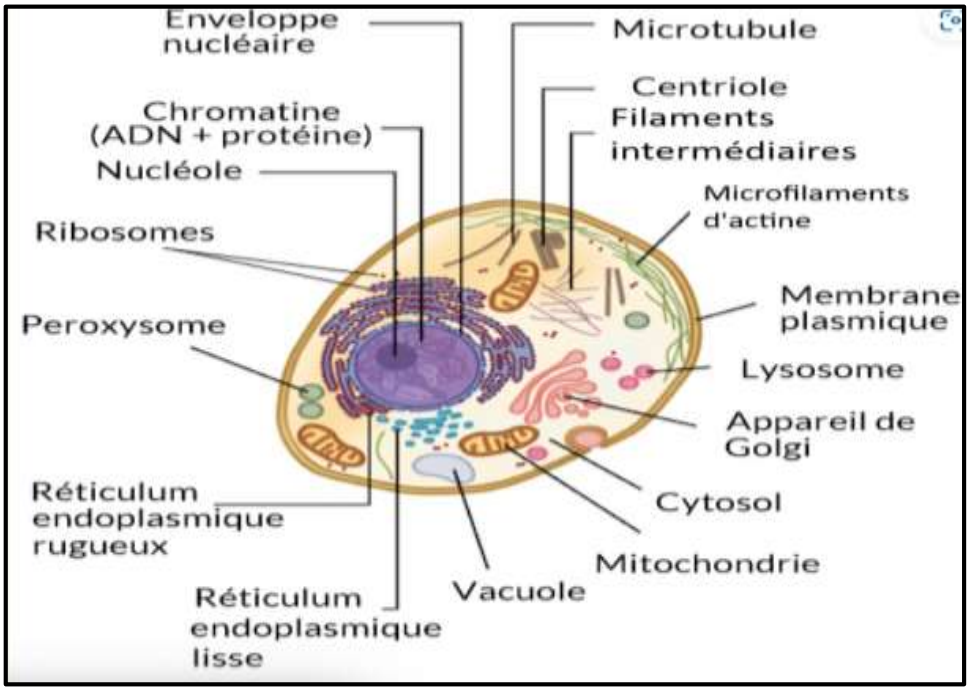


Figure 3: Structure of a typical animal cell

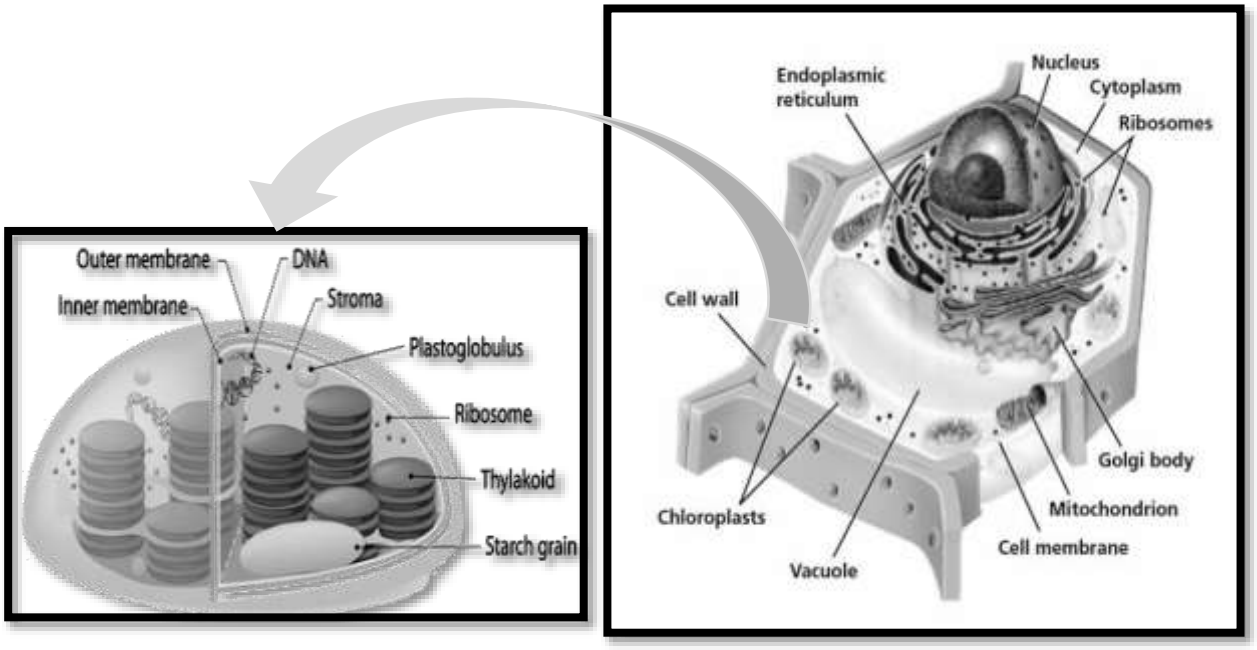


Figure 4: Structure of a Chloroplast and a typical plant cell

Tableau 1: The difference between an animal and plant cell

Animal cells	Plant cells
Cell wall absent	Cell wall present
Small vacuoles are sometimes present	Large central vacuole is present in mature cells
No chloroplasts	Chloroplasts are often present
Cholesterol present in plasma membrane	No cholesterol in plasma membrane
Centrioles present	Centrioles absent
Stores glycogen	Stores starch

6.2 Prokaryotic Cell:

Prokaryotic cells, derived from Greek words '**pro**' meaning **primitive** or before and '**karyon**' meaning **nucleus**, are among the smallest and simplest forms of life. These cells, which likely first appeared around 3.5 billion years ago, are considered the most ancient. Typical examples include bacteria such as Mycoplasma and Cyanobacteria. A prokaryotic cell features a single-envelope structure, consisting of central nuclear material embedded within cytoplasmic matrix, all enclosed by a plasma membrane (Verma and Agarwal, 2004).

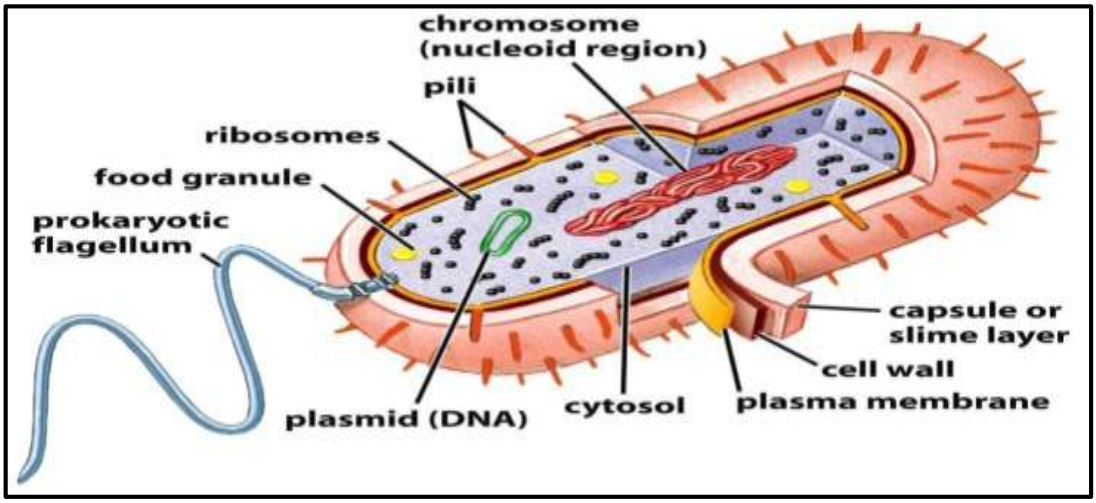


Figure 5 : Structure of a prokaryotic cell

6.2.1. Bacteria:

Bacteria are primitive, unicellular microorganisms that constitute some of the smallest life forms visible exclusively through a microscope. These microorganisms are ubiquitous found in a wide range of environments, including air, water, and soil. Bacteria can sustain themselves through various metabolic strategies. They may be autotrophic, deriving energy from inorganic sources such as sunlight or inorganic chemicals, or heterotrophic, obtaining energy through the consumption of organic compounds.

6.2.2. Bacterial size, shape and arrangement:

The average diameter of spherical bacteria is **0.5-2.0 µm**. For rod-shaped or filamentous is **1-10 µm** and diameter is **0.25-1.0 µm**.

Bacteria are prokaryotic, unicellular microorganisms, which lack chlorophyll pigments. The cell structure is simpler than that of other organisms as there is **no nucleus** or **membrane bound organelles.** Due to the presence of a rigid cell wall, bacteria maintain a definite shape, though they vary as shape, size and structure.

When viewed under light microscope, most bacteria appear in variations of **three major shapes:** the rod (**bacillus**), the sphere (**coccus**) and the spiral type (**vibrio**). In fact, structure of bacteria has two aspects, arrangement and shape. So far as the arrangement is concerned, it may Paired (diplo),

Grape-like clusters (staphylo) or Chains (strepto). In shape, they may principally be Rods (bacilli), Spheres (cocci), and Spirals (spirillum).

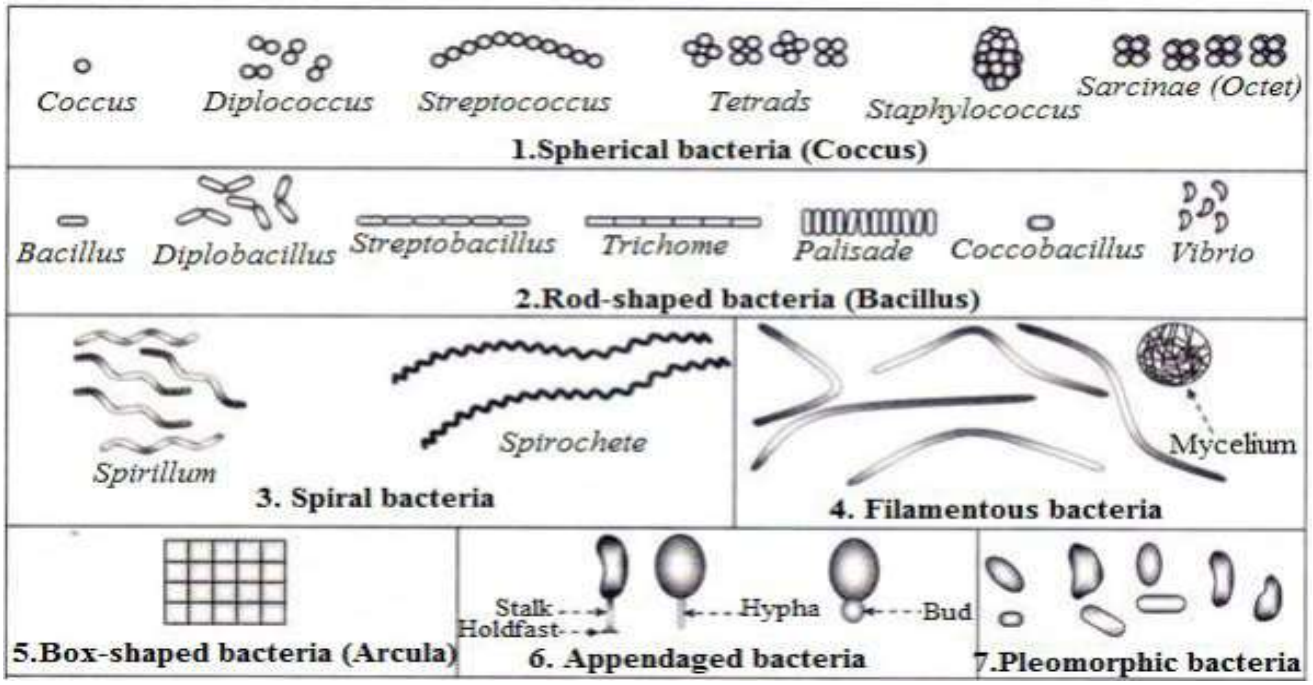


Figure 6: Different shapes of bacteria

6.2.3. Nutritional way:

Bacteria exhibit a range of nutritional types; some are chemosynthetic or photosynthetic, though the majority are heterotrophic. Among heterotrophs, many operate saprophytically or parasitically, with parasitic bacteria depending on host organisms for nutrients. A significant number of bacteria are also pathogenic.

6.2.4. Respiratory Mechanisms:

Bacterial respiration can be either aerobic, occurring in the presence of oxygen (e.g., Lactobacillus), or anaerobic, occurring without oxygen (e.g., Pseudomonas).

6.2.5. Reproductive Strategies:

Bacterial reproduction predominantly occurs asexually via binary fission and endospore formation. Sexual reproduction, though less common, involves conjugation where there is genetic exchange and recombination facilitated by sex pili. This process, a type of horizontal gene transfer, involves the transfer of DNA between two cells but does not replicate the cells themselves.

Tableau 2: The difference bitween a prokaryotic and eukaryotic cell

Cell Component/ Feature	Prokaryotic Cells	Eukaryotic Cells	
		Plant Cells	Animal Cells
Size	Average Diameter: 0.5-5µm	Up to 40µm diameter	
DNA	Naked DNA Circular DNA	DNA associated with histones in chromosomes	
Nucleus	Absent (DNA in cytoplasm, naked DNA)	Present (DNA within a membrane-bound nucleus)	
Organelles	Absent	Present	
Ribosomes	70S (Small)	80S (Large)	
Mitochondria	Absent	Present	
Endoplasmic Reticulum (ER)	Absent	Present	
Golgi apparatus	Absent	Present	
Lysosomes	Absent	Present	
Pili	Present	Absent	
Plasmid	Present (Sometimes)	Absent	
Flagella	Solid	Flexible/Membrane-bound	
Cell Wall	Present (Made of peptidoglycan)	Present (Made of Cellulose)	Absent
Cell Surface Membrane	Present	Present	

6.3 Viruses (Acellular Entities)

Are infectious particles containing **one type** of **nucleic acid** and surrounded by **protein coat**. The viral particle has ability to replicate **only in living host cell**, and cause disease.

Virus infect **all cellular life form**: eukaryotes (vertebrate animals, invertebrate animals, plant, fungi) and prokaryotes (bacteria and archaea).

As a science, virology evolved later than bacteriology because comparatively large size of bacteria made them visible even with simple microscope. The physical nature of viruses was not fully revealed until the invention of the electron microscope (EM), the infections they caused have been known and feared since the dawn of history.

In the latter part of nineteenth century, Iwanowski in Russia and Beijerinck in Holland both showed that a plant infection, Tobacco mosaic, could be transmitted by extracts that had been passed through a chamber and filter, and hence could not contain bacteria. Soon, afterwards, Foot-and-mouth disease of cattle was also transmitted by bacteria-free filtrates, and it came to be realized that living agents, smaller than any known bacteria but capable of multiplying, could cause a wide range of diseases in plants and animals. (Verma and Agarwal, 2004).

6.3.1 General properties of viruses

- ✓ Virus particles are very small in size; they are between 20-500 nm (nanometer) in diameter.
- ✓ Viruses are obligatory intra cellular microorganisms.
- ✓ Multiply inside the cells by replicating their genomes which either DNA or RNA, but not both.
- ✓ The virus does not contain any organelles (ribosomes, t RNA, metabolic enzymes, etc), but they depend on infected cells to provide all their needed organelles.
- ✓ Virus does not affect with antibiotics.
- ✓ Most viruses sensitive to interferon.
- ✓ Viruses can not grow on artificial media, but only in living cells (specific host, Lab. Animals, chicken embryonated eggs & tissue culture).
- ✓ Some viruses cause latent infection.
- ✓ Viruses can not be seen by simple microscope, but only by Electron microscope (EM).

6.3.2 Virus components

6.3.2.1 Genome

- ✓ The genomes of viruses can be composed of either DNA or RNA, and some use both as their genomic material at different stages in their life cycle.
- ✓ However, only one type of nucleic acid is found in the virion of any particular type of virus.
- ✓ This can be single-stranded (ss), double-stranded (ds), or in the hepadnaviruses, partially double-stranded.
- ✓ Coding capacity: ranging from few proteins to >200 proteins (Meyers, 1995).

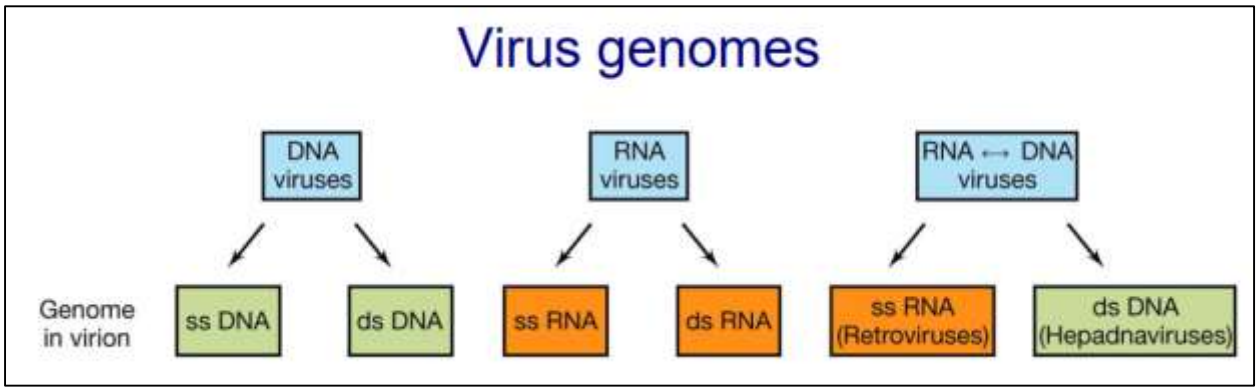


Figure 7 : Virus genomes: a schematic representation

6.3.2.2 Capsid (outer protein coat):

- ✓ Many **protein subunits** are assembled to form a **tight "shell"** (capsid made up of subunits called "**Capsomers**") inside which the nucleic acid genome lodges for protection.
- ✓ The arrangement of capsomers give the virus structure its **genomic symmetry**
- ✓ The capsid together with its enclosed nucleic acid is called the **nucleocapsid.**

❖ **Capsid serves four functions:**

- ✓ Protects the viral genome.
- ✓ Is the site of receptors necessary for naked viruses to initiate infection
- ✓ Stimulates antibody production.
- ✓ Is the site of antigenic determinants important in some serologic tests.

6.3.2.3 Viral envelop (not found on all viruses)

- ✓ Some viruses acquire an outer lipoprotein coat by "budding" through the host cell membranes and are thus called Enveloped viruses.
- ✓ The envelop is important for interaction with cellular components during the process of infection and replication.
- ✓ Enveloped viruses are more sensitive to heat, drying, detergent and lipid solvents such as alcohol and ether than non enveloped virus

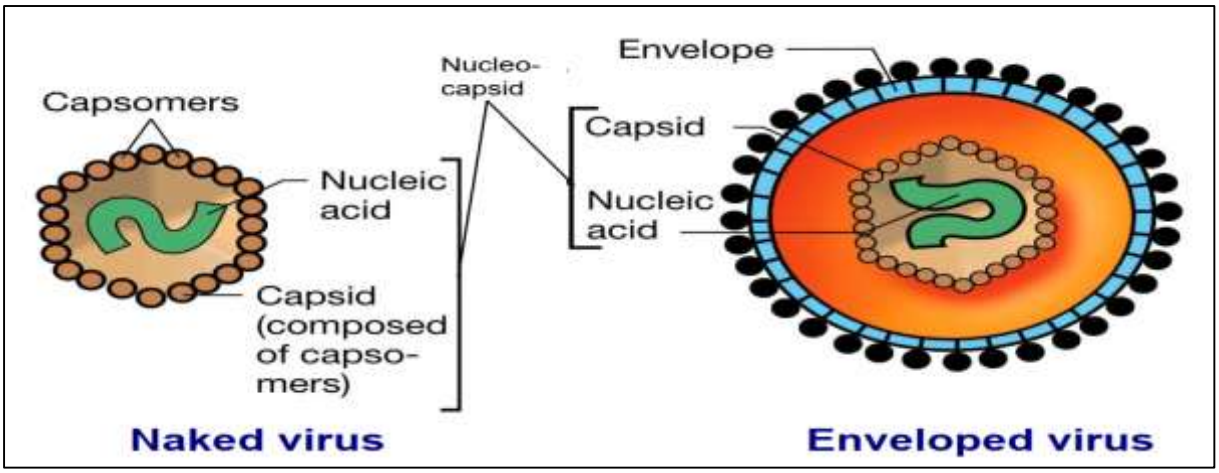


Figure 8: Virus structure: a schematic representation

6.3.3 Classification of viruses

- ✓ A major branch of virology is **virus classification.**
- ✓ Virus classification is the process of naming viruses and placing them into a taxonomic system similar to the classification systems used for cellular organisms. Therefore, classification identifies and groups viruses according to their similarities in order to describe the diversity of viruses.
- ✓ Viruses are classified based on several key characteristics, which help researchers and scientists understand their diversity and evolutionary relationships.
- ✓ The main characteristics used to classify viruses include
    1. **Genetic material (Nucleic acid)**
    2. **Capsid structure**
    3. **Envelope presence**
    4. **Host range**

6.3.3.1 Classification of viruses based on genetic material

Genetic material (Nucleic acid): This is one of the fundamental criteria for classification:

1. **DNA Viruses:** These viruses have a DNA genome. DNA viruses can be further classified based on the nature of their genome (single-stranded or double-stranded) and linear or circular configuration.
2. **RNA Viruses:** These viruses have an RNA genome. Like DNA viruses, RNA viruses can be classified based on similar criteria

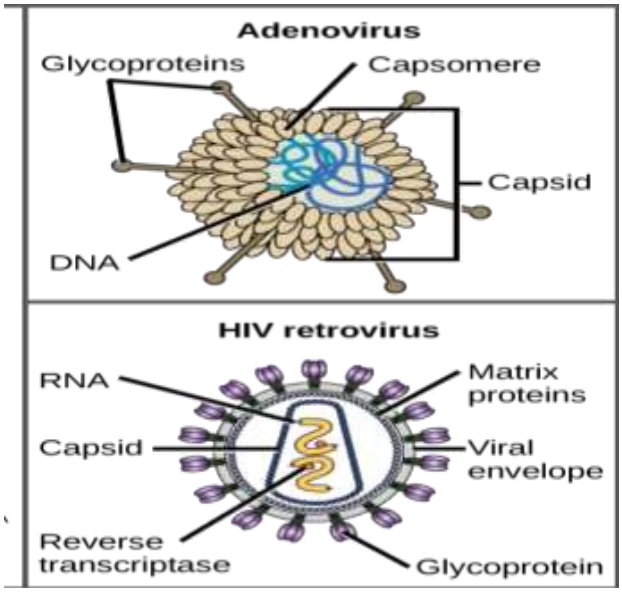


Figure 9: Classification of viruses based on genetic material

6.3.3.2 Classification of viruses based on capsid structure

Capsid Structure: The capsid is the protein coat that surrounds the viral genetic material. Capsid structure is an important classification criterion:

1. **Helical:** Shaped like hollow tubes with protein walls
2. **Icosahedral:** An icosahedron is a regular polyhedron with 20 equilateral faces
3. **Complex:**
    - ✓ Viruses with a combination of icosahedral and helical features
    - ✓ Some viruses do not fit into the caegory of having helical or icsahedral capsids. For example: Poxviruses (largest animal virus).
    - ✓ Bacteriophages have binal symmetry, head resembles icosahedral, and tail is helical**.**

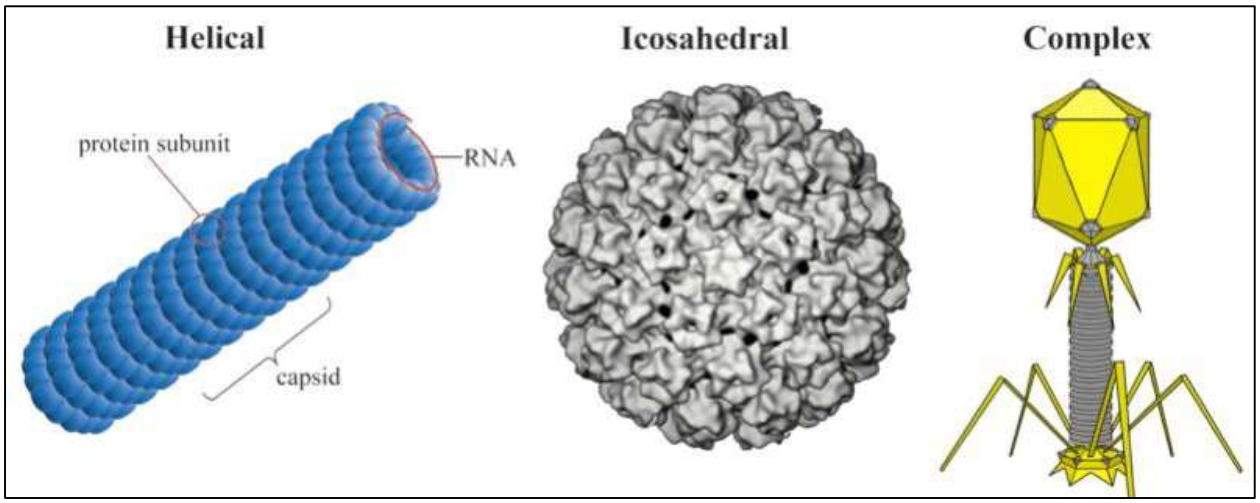


Figure 10: Classification of viruses based on capsid structure

6.3.4 Viral replication:

The life cycle of viruses differs greatly between species but there are six basic stages

1. **Attachment**: is aspecific binding between viral capsid protein and specific receptors on the host cellular receptors.
2. **Penetration**: viruses enter the host cell through receptor- mediated endocytosis or membrane fusion
3. **Uncoating**: the viral capsid is degraded by viral enzyme or host enzymes thus releasing the viral genomic nucleic acid
4. **Replecation**: involves synthesis of viral messenger RNA (mRNA) for viruses except positive sense RNA viruses
5. **Assemble**: viral protein synthesis and assemble of viral protein and viral genome
6. **Release**: viruses are released from the host cell by lyses. Enveloped viruses (e,g, HIV) typically are released from the host cell by budding.

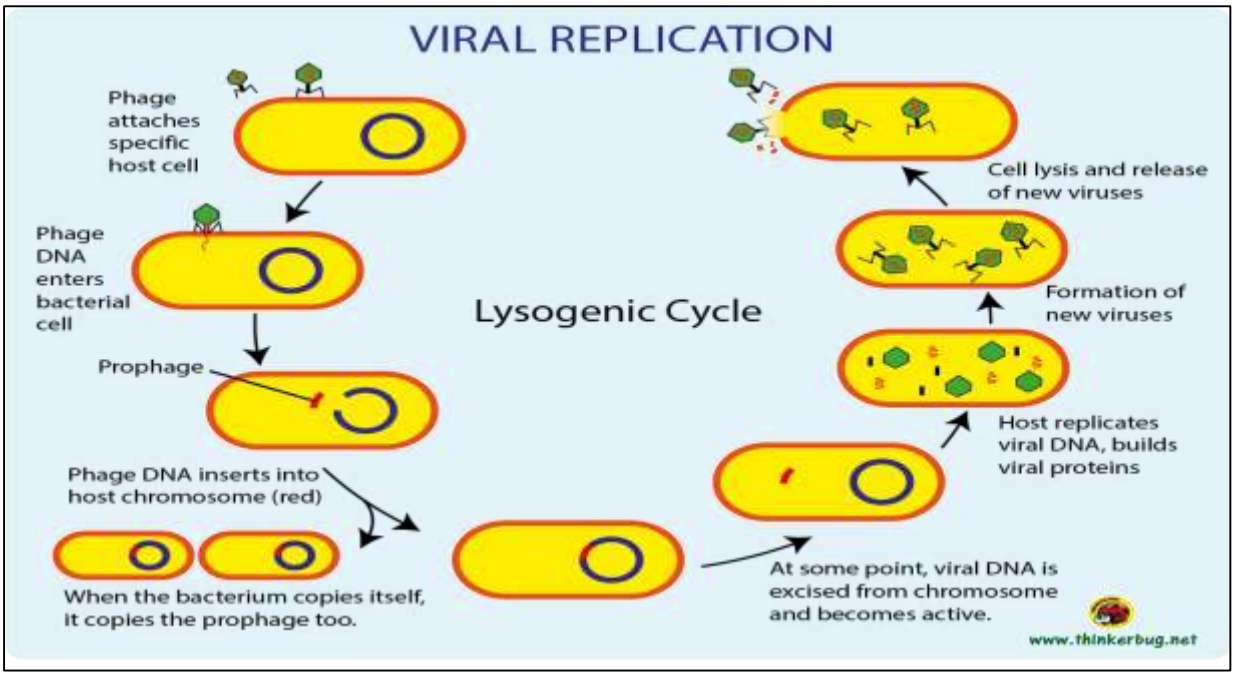


Figure 11: Viral replication.

Chapter 2: Plasma membrane, structure and function.

1 Introduction:

The cell membrane, also called the plasma membrane, is an essential component of both prokaryotic and eukaryotic cells, serving primarily to protect and enclose cellular contents. Its biochemical makeup and structural design allow it to perform critical functions such as cellular signalling, maintaining a state of non-equilibrium with the external environment, and acting as a platform for a variety of functional molecules such as enzymes, transport channels, carriers, receptors, and cell adhesion and recognition elements. The biomembrane's selective permeability and great flexibility stem from its unique structure and composition, which enables it to perform a wide range of specialised activities. Most organisms' membranes follow a fluid mosaic model, with phospholipids providing structural support and proteins contributing to the cell's distinct functional capabilities.

2 The structure of the plasma membrane:

2.1 Observations using the optical microscope:

We observe the plasma membrane as a compact region that distinguishes the intracellular environment from the extracellular environment.

2.2 Employing the transmission electron microscope (TEM):

In transmission electron microscopy, plasma membrane sections are observed as trilaminar (or tri lamellar), consisting of three distinct layers:

- An outer dense layer (osmiophilic) measuring 20 to 25 Å in thickness;
- An intermediate clear layer (osmiophobic) with a thickness of 30 to 40 Å;
- An inner dense layer (osmiophilic) also measuring 20 to 25 Å in thickness. The thickness of the plasma membrane ranges from 70 to 100 Å.

2.3 Using the scanning electron microscope (SEM)

By employing the technique of cryo-scraping, a replica can be obtained with a fracture plane that traverses the area between the two leaflets. Consequently, the plasma membrane is divided into two hemimembranes:

- ✓ Hemi-membrane E: ("E" for exoplasmic) serves as the outer layer.
- ✓ Hemi-membrane P: ("P" for protoplasmic) functions as the inner layer.

3 Composition of plasma membrane:

Lipids, proteins, and carbohydrates make up the membrane's primary composition. Robertson (1959) suggested that cell membrane is three-layered structure where proteins form the outer and inner layers of membrane that encloses lipids to form a unit membrane. The membrane is made of a lipid bilayer. It has made Mostly of phospholipid molecules, which are amphipathic –part hydrophobic and part hydrophilic.

3.1 Membrane Lipids

Membranes made up of a wide diversity of lipids, all of them are amphipathic; That is, they include both hydrophilic and hydrophobic areas. There are three main types of membrane lipids: phosphoglycerides, sphingolipids, and cholesterol.

3.1.1 Phospholipids Molecules

- Phospholipids are one of the most common forms of lipid found in membranes. These have a polar head group and two hydrocarbon tails. The example of a phospholipid is shown in Figure (down). The polar group is the top area that begins with NH3. Glycerol connects two fatty acid tails. One of the tails has a straight chain fatty acid (saturated). The other has a tail kink caused by an unsaturated cis double bond. This kink effects packing and mobility in the membrane's lateral plane. Figure on the left is adapted from
- They contain, from top to bottom:
    - ✓ A polar head group. This can be charged: serine (-), inositol (-), or it can be neutral, with both positively and negatively charged groups: choline, ethanolamine.
    - ✓ A glycerol linker.
    - ✓ A phosphate group.
    - ✓ Two fatty acid chains

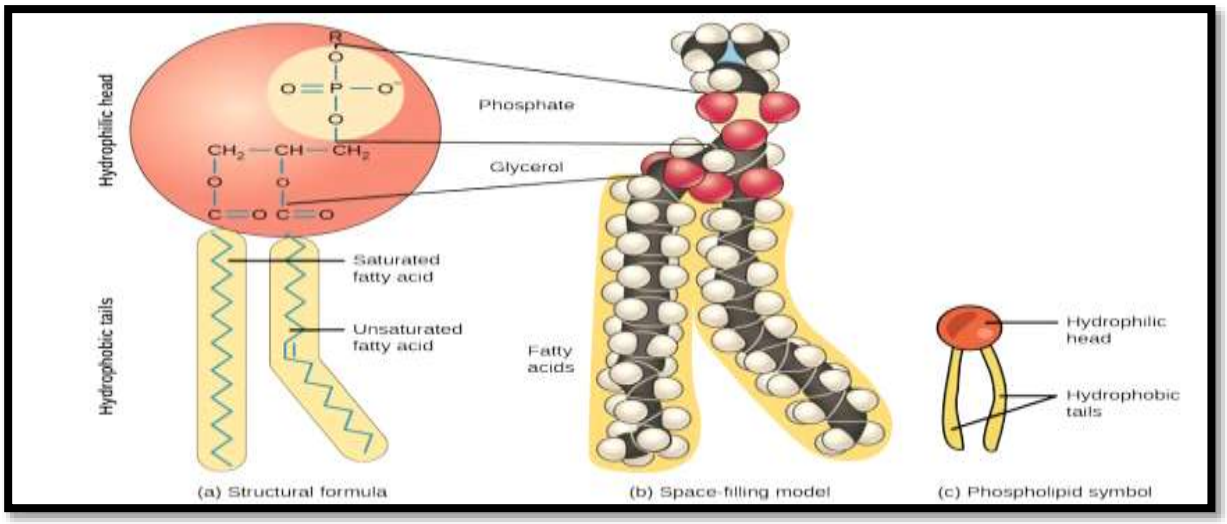


Figure 12: A hydrophilic head and two hydrophobic tails comprise this phospholipid molecule.

- **The hydrophilic** or "water-loving" portions of these molecules (which appear as a cluster of balls in an artist's representation of the model) (Figure 5.2) come into touch with the aqueous fluid inside as well as outside the cell.
- **Hydrophobic** compounds tend to be non-polar. They link with other non-polar molecules during chemical processes but often do not interact with polar molecules. Hydrophobic molecules, when immersed in water, often aggregate into a spherical formation or cluster.

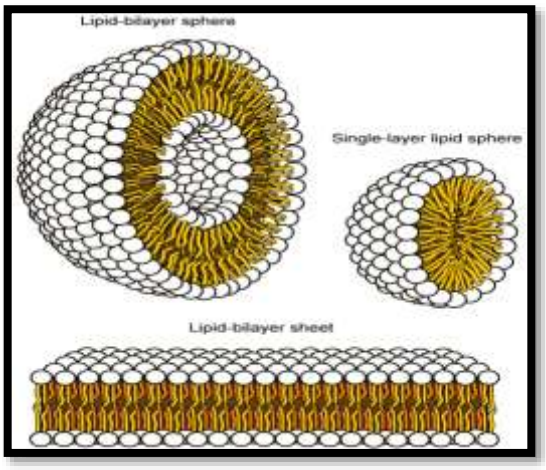


Figure 13 : In an aqueous solution, phospholipids usually arrange themselves with their polar heads facing outwardand their hydrophobic tails facing inward (Alberts et al., 2018).

3.1.2 Cholesterol

Besides phospholipids, the membranes of animal cells include cholesterol as a crucial component. Cholesterol affects the fluidity of the membrane in both directions; it reduces fluidity at elevated temperatures and enhances it at lower temperatures.

Like phospholipids, cholesterol in the bilayer orients with its polar head group facing the aqueous environment and its nonpolar region facing the membrane interior. One of cholesterol's functions is to reduce the fluidity of the membrane.

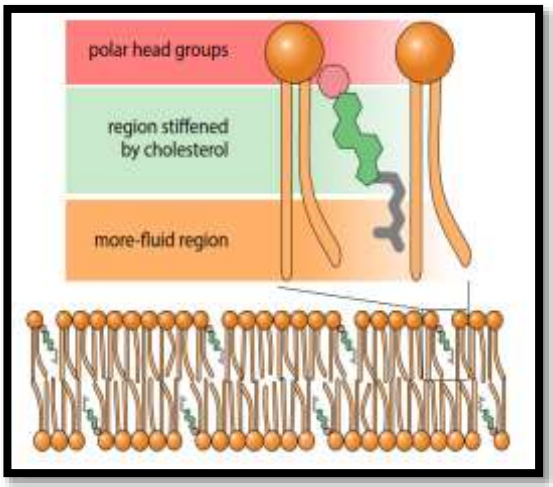


Figure 14: Cholesterol influences membrane fluidity by forming strong interactions with phospholipids

3.2 Proteins (20-70%):

3.2.1 Integral membrane proteins:

Are, as their name means, encased within the membrane: they possess at least one hydrophobic region that secures them to the hydrophobic core of the phospholipid bilayer. Some extend only partially into the membrane, while others span from one side to the other and are visible on both sides. Proteins that span the entire membrane are referred to as **transmembrane proteins**.

The segments of an integral membrane protein located within the membrane are hydrophobic, whereas those that are exposed to the cytoplasm or extracellular fluid are generally hydrophilic.

3.2.2 Peripheral membrane proteins

Are located on both the outer and inner surfaces of membranes, where they are attached to either integral proteins or phospholipids. In contrast to integral membrane proteins, peripheral membrane proteins do not penetrate the hydrophobic core of the membrane and are generally more loosely associated (Alberts et al., 2018).

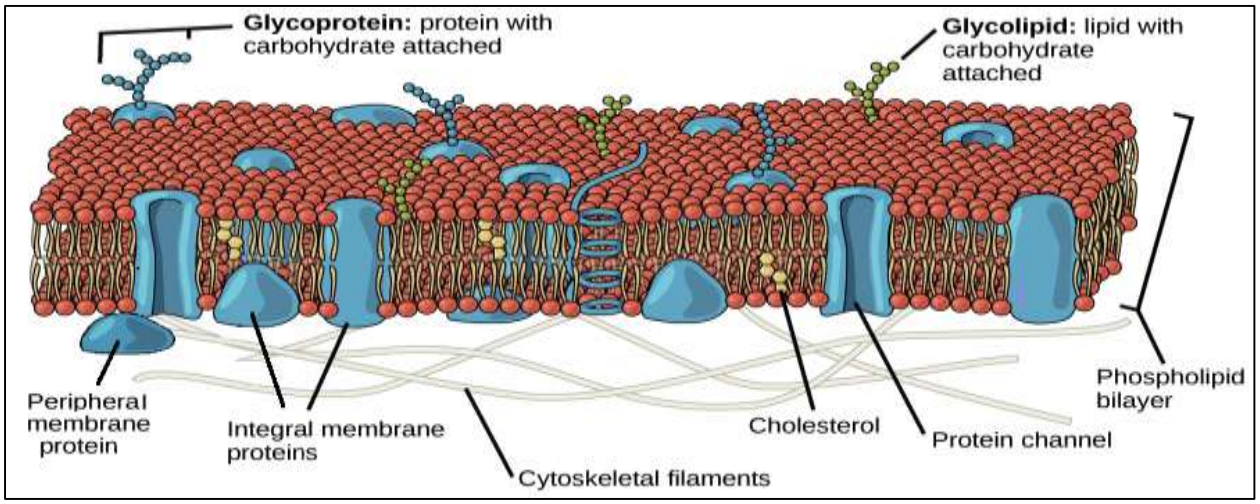


Figure 15: The plasma membrane's exterior surface is not identical to its interior surface (Alberts et al., 2015)

3.3 Carbohydrates

Carbohydrates are the third major plasma membrane component. They are always on the cells' exterior surface and are bound either to proteins (forming glycoproteins) or to lipids (forming glycolipids). These carbohydrate chains may consist of 2–60 monosaccharide units and can be either straight or branched. Along with peripheral proteins, carbohydrates form specialized sites on the cell surface that allow cells to recognize each other. These sites have unique patterns that allow for cell recognition, much the way that the facial features unique to each person allow individuals to recognize him or her (Alberts et al., 2015).

We collectively refer to these carbohydrates on the cell's exterior surface “the carbohydrate components of both glycoproteins and glycolipids” as the glycocalyx (meaning “sugar coating”).

3.3.1 The functions of Cell Coat:

- ✓ Participation in maintaining membrane asymmetry
- ✓ Protection of the plasma membrane against mucolytic or proteolytic enzymes
- ✓ Surface cell charge that can intervene in the movement of charged substances across membranes
- ✓ Cell recognition phenomenon: what is self and what is non-self
- ✓ Enzymatic activities of the cell coat
- ✓ Intercellular adhesiveness and between cells and the extracellular matrix

Tableau 3 : Plasma Membrane Components and Functions

Component	Location
Phospholipid	The membrane's main structural fabric.
Cholesterol	They are bound to phospholipids and interspersed between phospholipid bilayers.
Integral proteins (for example, integrins)	Inside the phospholipid layer or layers, may or may not be able to cross both
Peripheral proteins	On the phospholipid bilayer's inner or outer surface; not embedded within the phospholipids
Carbohydrates (components of glycoproteins and glycolipids)	Generally attached to proteins on the outside membrane layer

4 Functions of Plasma Membrane

4.1 Control of exchanges between the extracellular medium and the intracellular medium

4.1.1 Exchanges without deformation of the plasma membrane

The main function of the plasma membrane is to regulate the flow of materials in and out of the cell called transport. This transport of material is regulated by the size of pores present in the plasma membrane. They are of two types, passive transportation and active transportation.

4.1.1.1 Passive transport

The molecules are transported in the direction of their concentration gradient, without consumption of ATP; they are of two types:

- **Simple diffusion** (without permeases), through the lipid bilayer (hydrophobic and uncharged molecules: H2O, CO2, O2, N2, benzene, ethanol ...).
- **Diffusion facilitated** via protein channels such as specific ion channels (Na+, K+, Cl-) or water channels (aquaporin's), by either specific carrier proteins or permease for the transport of glucose, amino acids, etc.)

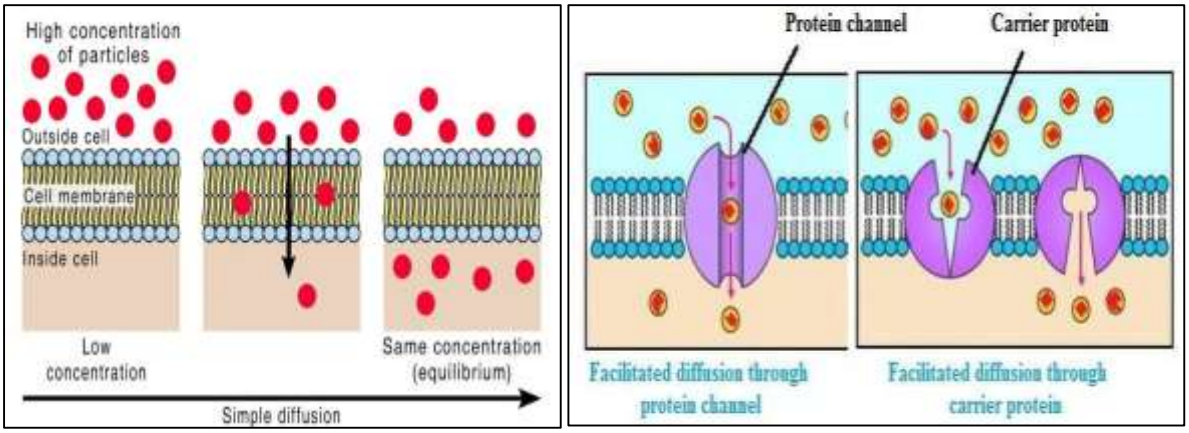


Figure 16: Simple diffusion and facilitated

4.1.1.2 Active Transport

The movement of molecules and ions from the region of lower concentration to the region of higher concentration, against the concentration gradient is called active transport. The transport takes place from region of low concentration to high concentration using an input of energy. This energy is provided by the mitochondria.

In this case, substances do not move by themselves, but they are carried by some carriers present in membrane. These carriers are mainly proteins. This form of transport requires energy and carriers.

- In primary active transport, the energy obtained by ATP hydrolysis used directly for transport. E.g., Na+-K+ pump
- In secondary active transport, indirect energy source is required. E.g., transport of glucose and amino acids is coupled to active transport of Na+.

4.1.2 Exchanges with plasma membrane deformations

It is the transport of large molecules or particles with intervention of the cytoskeleton, case of endocytosis and exocytosis

4.1.2.1 Endocytosis

It is the bulk transport of materials into the cells by vesicles. Vesicle formation takes place by infolding of the cell membrane. It does not occur in plant cells due to rigid cell wall.

It is the engulfing of food or foreign particles through the plasma membrane. There are two types of endocytosis:

- Phagocytosis
- Pinocytosis and

4.1.2.1.1 Phagocytosis: (Cell eating)

(Greek- Phagein= to eat; kytos= cell) The cell ingests or swallows foreign bodies, bacteria, harmful matter and other inert substances and the process is called phagocytosis.

It is the engulfing of solid particles through the plasma membrane. It is observed in number of protozoans and leucocytes. The cells exhibiting phagocytosis are called phagocytes.

4.1.2.1.2 Pinocytosis: (Cell drinking)

(Greek- Pinetin= to drink; kytos= cell) It is the process of engulfing fluid particles through the plasma membrane.

Intake of fluid material into the cell by the formation of pinocytic vesicles or pinosomes is called pinocytosis.

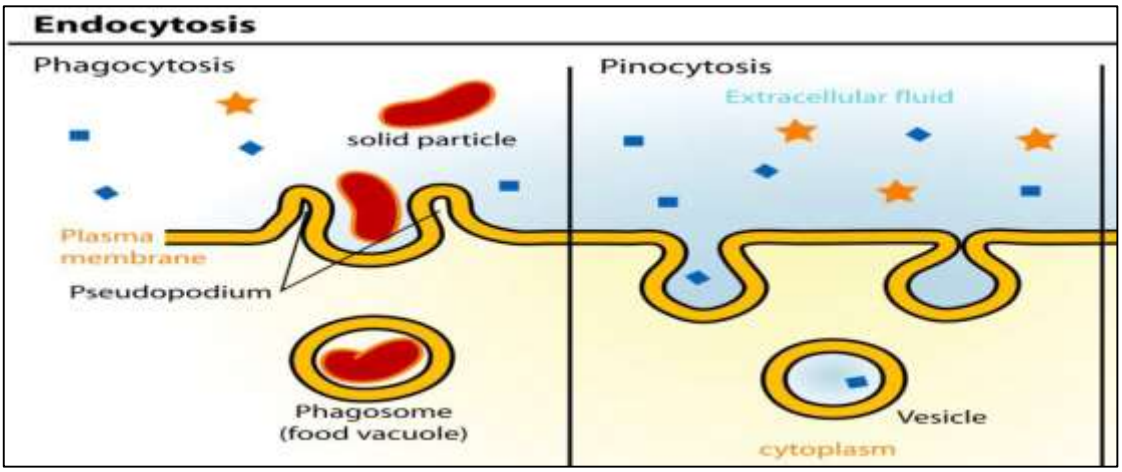


Figure 17: The endocytosis

4.1.2.2 Exocytosis: (Cell vomiting)

The process of exudating the secretory products from the secretory cells to the outsid e of the cell is called **exocytosis.** It is also called as **reverse endocytosis.**

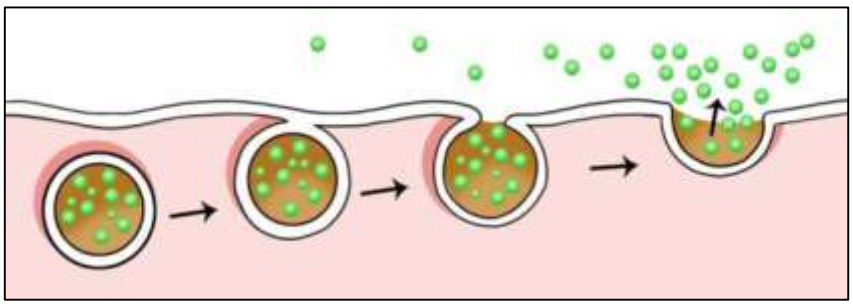


Figure 18: The exocytosis.

4.1.3 Other functions of cell membrane in brief:

- ✓ **Protection:** The primary function of the plasma membrane is to protect the cell from its surroundings. The plasma membrane is composed of a phospholipid bilayer with embedded proteins, selectively permeable to ions and organic molecules and regulates the movement of substances in and out of cells. Plasma membranes must be very flexible in order to allow certain cells, such as red blood cells and white blood cells, to change shape as they pass through narrow capillaries.
- ✓ **Cell Recognition:** Cell-cell recognition occurs when two molecules restricted to the plasma membranes of different cells bind to each other, triggering a response for communication, cooperation, transport, defence, and/or growth. This type of binding requires the cells with the signalling molecules to be in close proximity with each other.
- ✓ **Cell Signalling:** Among the most important functions of the plasma membrane is its ability to transmit signals via complex proteins. These proteins can be receptors, which work as receivers of extracellular inputs and as activators of intracellular processes, or markers, which allow cells to recognize each other.

5 Specializations of the plasma membrane:

The plasma membrane of some cells exhibits adjustments for performing several activities that preserve cellular integrity, including all surfaces: upper, lower, and laterally.

5.1 Upper surface specialization:

The plasma membrane of the apical surface invaginates to create densely packed, homogeneous projections known as microvilli, which increase the surface area for absorption. Located in the epithelial cells of the gut, renal tubules, gallbladder, and hepatic cells.

The microvilli's core comprises microtubules and microfilaments (actin) inside their cytoplasm, providing structural support and stiffness to preserve their morphology and parallel extension.

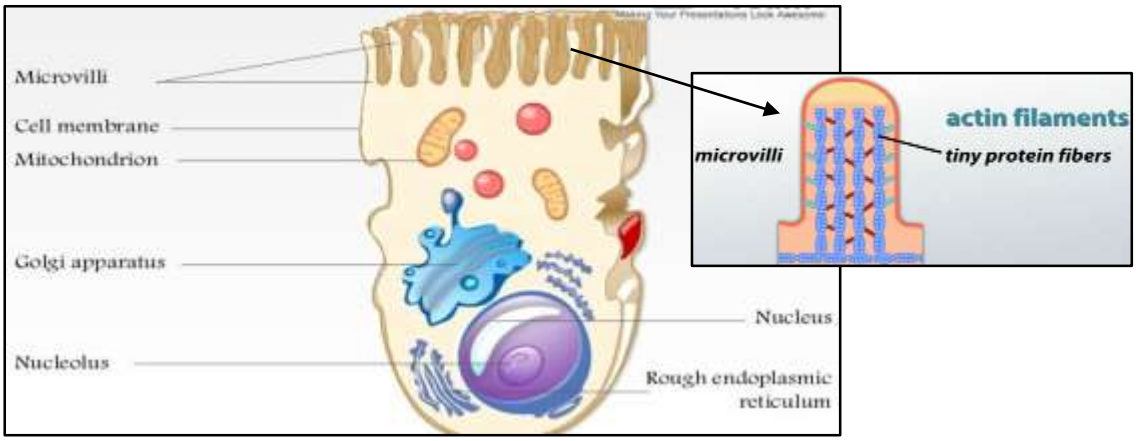


Figure 19: Representative schema of upper surface specialization

5.2 Lateral surface specializations (membrane junctions):

- Cell adhesion is a function of the cell membrane, adapted to facilitate attachment and exc hange activities among epithelial cells.
- This membrane junction connects neighboring cells to their lateral surfaces, creating a continuous, coherent layer of cells.
- Thelateral surface alterations consist of five types: interdigitations, tight junctions, desmo somes, plasmodesmata, and gap junctions.

5.2.1 Inter digitations:

- The plasma membrane of neighbour cells extends into the cytoplasm as digitiform extensions.
- Located in lymph nodes and lymphoid tissues.
- Function: to augment the surface area for the exchange of substances between cells.

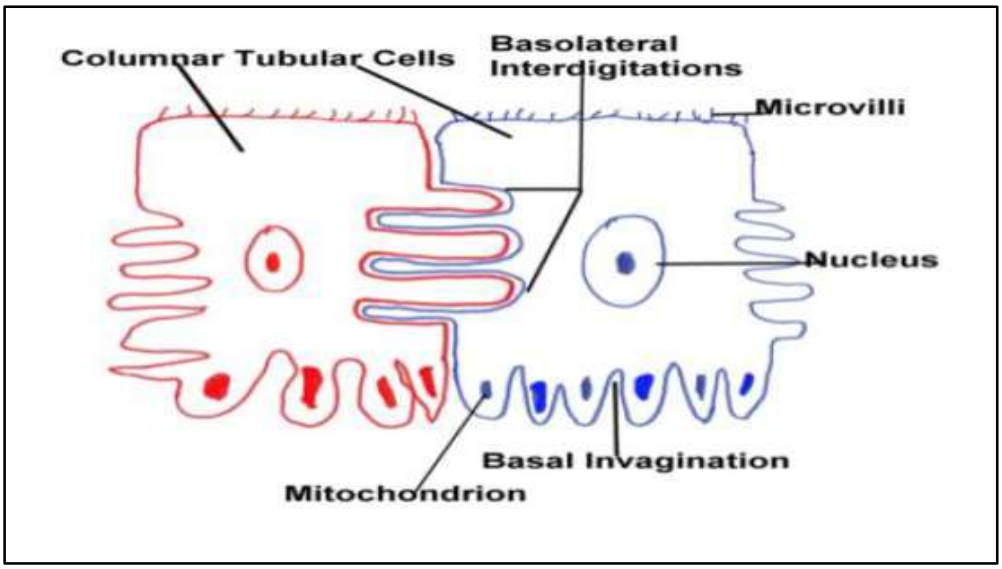


Figure 20 : Representative schema of Inter digitations specialization

5.2.2 Tight junction:

- The plasma membranes of neighbouring cells merge by extrinsic proteins.
- Present in neural cells, gallbladder, and intestinal cells.
- Function: adhesion, with no exchange of substances.

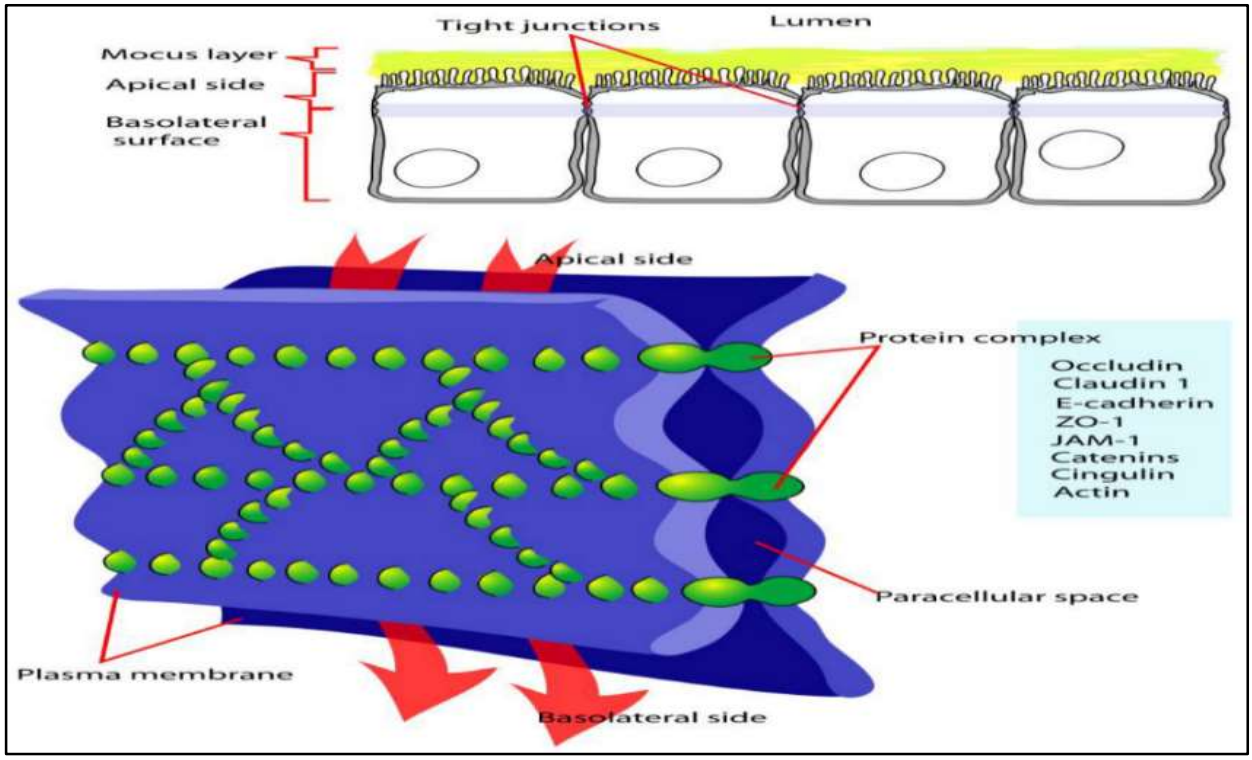


Figure 21 : Representative schema of tight junction specialization

5.2.3 Gap junction:

- Gap junctions are channels that traverse the membranes of two neighbouring cells, facilitating communication across the intercellular gap.
- Found in heart muscle tissue
- Function: facilitate the conduction of electrical impulses and the transport of ions, sugars, vitamins, and metabolites.

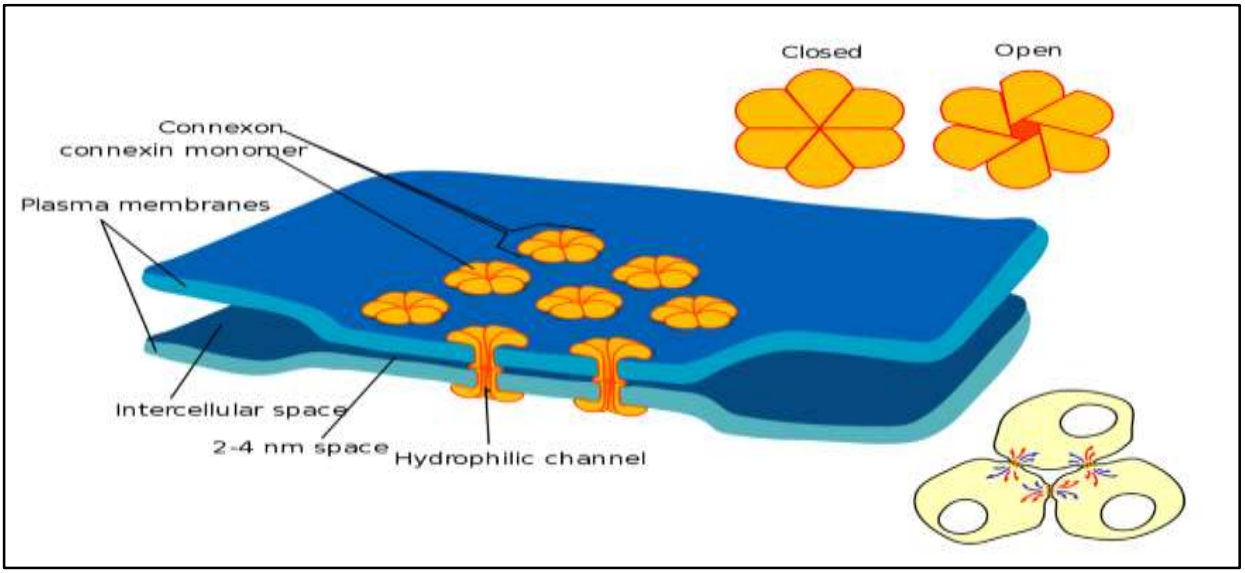


Figure 22 : Representative schema of Gap junction specialization

5.2.4 Desmosomes

- Desmosomes are reinforced regions of the plasma membrane of two neighbouring cells.
- Located in heart muscle and dermal cells.
- Function: assist in adhering the cells together

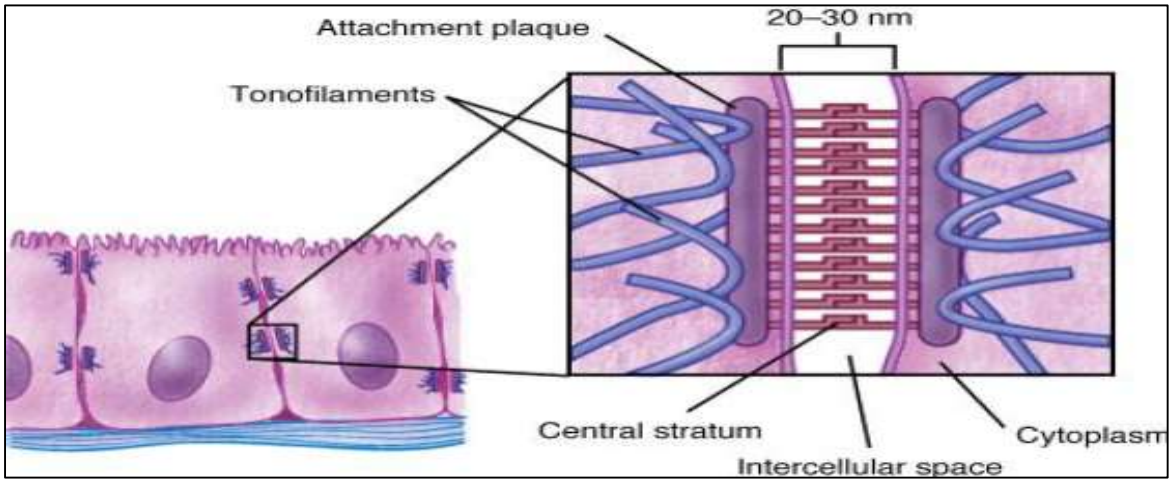


Figure 23: Representative schema of upper surface specialization

5.2.5 Plasmodesmata:

- The cytoplasm of neighbouring cells is inter-connected by cytoplasmic strands.
- Present in plant cells.
- Function: substance exchange between two cells

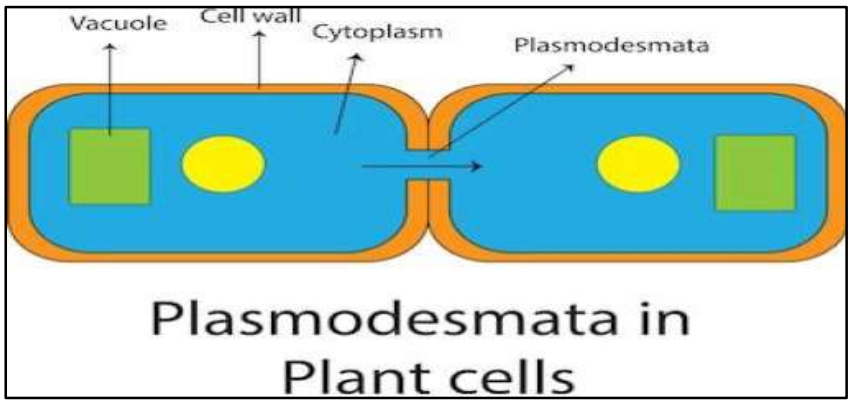


Figure 24 : Representative schema of plasmodesmata specialization

5.3 Basal surface specializations

The basal surface specialisations of a plasma occur near the base of an epithelial cell to perform certain functions, and there are two types. Hemidesmosomes and basal infoldings

5.3.1 Hemidesmosomes

- Attach the cell to its basal membrane.

- This is accomplished via intermediate filaments known as tonofilaments, which attach the cell to the underlying reticular connective tissue of the basement membrane, therefore resisting external abrasion, similar to the function of skin cells.

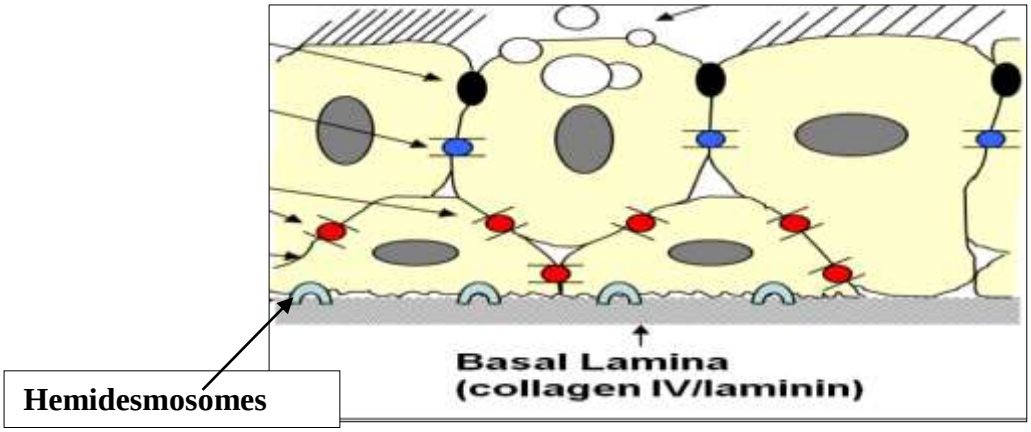


Figure 25 : Representative schema of hemidesmosomes specialization

5.3.2 Basal infolding

Infolding of the basal surface of the plasma membrane to augment the cell's surface area. Located in the cuboidal epithelium of the kidney (Alberts et al., 2015).

Chapter 3: Cytoskeleton and Cell Motility

1 Introduction:

Similar to living things having a skeleton for framework and form, cells contain a cytoskeleton. The cytoskeleton makes up **microtubules**, **microfilaments**, and **intermediate filaments** that together constitute a cohesive network. When a cell is exposed to a nonionic detergent, soluble cytosolic proteins are removed, resulting in the retention of membrane-bound organelles and cytoskeletal components. The three types of cytoskeletal elements may be differentiated based on their diameter, monomeric units, and configurations.

In 1928, Koltzoff suggested the possibility of an organised fibre array or cytoskeleton inside the protoplasmic framework. He envisioned a cytoskeleton that dictates the cell's morphology and its morphological alterations (Alberts et al., 2018).

The principal proteins found in the cytoskeleton include **tubulin** (in **microtubules**), **actin**, **myosin**, **tropomyosin**, and others (in **microfilaments**), as well as **vimentin**, **keratins, lamin, desmin**, and others (in **intermediate filaments**). Tubulin and actin are **globular proteins**, while the components of intermediate filaments consist of **fibrous proteins**. Significant advancements have been achieved in the separation of these cytoskeletal proteins. Furthermore, the generation of specific antibodies against these proteins has facilitated the examination of the arrangement of microtubules and microfilaments using light and electron microscopy.

- **Microtubules:** are inflexible, hollow, tubular formations with an outside diameter of 25 nm and a wall thickness of 4 nm. They are made of globular protein tubulin. A microtubule is a heterodimer composed of 55 kDa protein α- and β-tubulin organised in longitudinal bands to produce protofilaments.
- **Microfilaments:** Are commonly referred to as actin filaments, have a diameter of 7 nm and are formed of the globular protein actin, which is present in two forms: the monomeric form known as globular or G actin, and the polymeric form known as filamentous or F actin.
- **Intermediate filaments**: (IFs) possess a rope-like structure with a diameter of 10 nm and are believed to include about 70 proteins (Alberts et al., 2015).

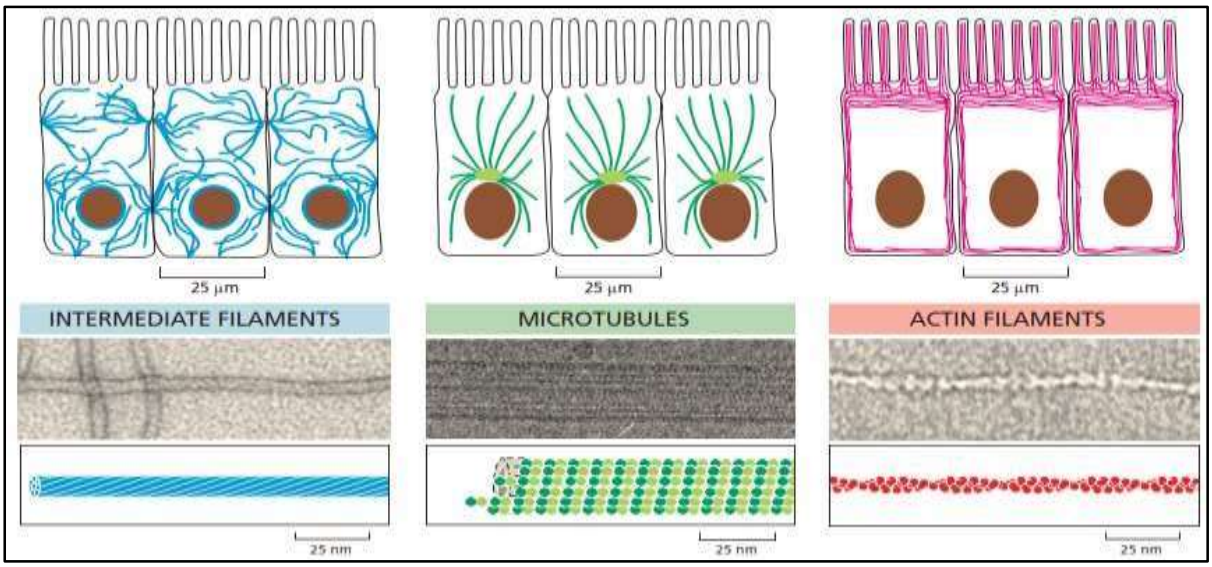


Figure 26 : The three types of protein filaments that form the cytoskeleton inside the cell (Alberts et al., 2018).

2 Organisation of the cytoskeleton

The cytoskeletal components inside a cell are arranged into either **bundles** or **networks**. The configuration of cytoskeletal components in these two organizational categories is distinct. The cytoskeleton organises its filaments into tightly packed parallel arrays in bundles, whereas networks interconnect these components. The network creates a web-like configuration and contributes to the gel- like characteristics of the cytosol.

2.1 Microtubules:

In 1953, Robertis and Franchi first identified microtubules in the axoplasm of myelinated nerve fibers. They referred to them as neurotubules. When Sabatini, Bensch, and Barnett (1963) used glutaraldehyde fixative in electron microscopy, they clarified the precise characteristics of microtubules. Ledbetter and Porter (1963) first detailed the microtubules of plant cells.

2.1.1 Occurrence

All eukaryotic cells, with a few exceptions such as **human erythrocytes**, contain microtubules, either **freely in the cytoplasm** or **as components of centrioles, cilia, and flagella**. Vertebrate brain tissue serves as the primary source of microtubules for biochemical research, containing large concentrations of microtubules in the axons and dendrites of neurones. Microtubules are present in the cytoplasm of animal and plant cells at the following **seven locations**:

- ✓ The cilia and flagella;
- ✓ The centrioles and basal bodies;
- ✓ The nerve processes;
- ✓ The mitotic apparatus;
- ✓ The cortex of meristematic plant cells;

- ✓ Cells that elongate, such as during seed development or the initiation of spermatogenesis in insects.

Chosen structures in Protozoa include the axostyle of parasitic flagellates; the axoneme of Echinosphaerium; the fiber networks of Stentour; and the cytopharyngeal basket of Nassula.

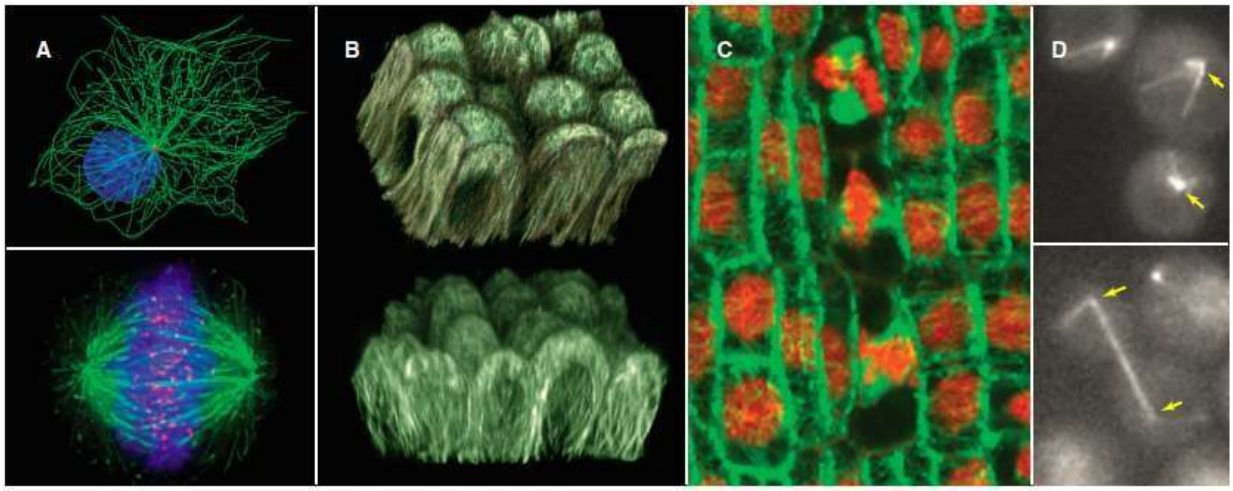


Figure 27 : Arrangement of microtubules in various cells. A, Vertebrate tissue culture cells. B, Columnar epithelial cells in tissue culture. C, Plant cells. D, Live budding yeast (Alberts et al., 2018).

2.1.2 Chemical Composition

A protein called **tubulin**, which is an **acidic protein** with a molecular weight of 55,000 and a sedimentation constant of 6S, forms microtubules, a type of cellular structure. It is found in two forms, **α-tubulin** and **β-tubulin**, each containing about 450 amino acids. These proteins have similar amino acid sequences and are thought to have evolved from a single ancestral protein. They show little divergence from the lowest to the highest eukaryotes, suggesting that most mutations disrupt the functions of microtubules and are lethal.

Tubulin in the form of **dimers** polymerizes into microtubules, forming **linear protofilaments** with the β- tubulin of one dimer in contact with the α- tubulin of the next. Microtubules are polar structures with a **plus (+)** or **fast-growing end** and a **minus (-)** or **slow-growing end**. The minus ends of cytoplasmic microtubules are bound tightly to microtubule organizing centers (MTOCs), which protect them from disassembly (Lodish, 2008).

2.1.3 Structure

Microtubules are made up of subunits of tubulin, each consisting of a dimer of α-tubulin and β-tubulin proteins. These dimers are bound together by noncovalent interactions to form the hollow cylindrical microtubule wall. The structure is made up of 13 parallel protofilaments. Each one is a straight line of tubulin dimers, with α- and β-tubulin switching places along its length. Each protofilament has a structural polarity, with α-tubulin exposed at one end and β-tubulin at the other. This polarity, known as the directional arrow embodied in the structure, gives structural polarity to the microtubule as a whole. The β-tubulin end is called its plus end, while the α-tubulin end is called its minus end. The polarity of the microtubule is crucial for its assembly and role once formed, as it allows microtubules to guide intracellular transport (Lodish, 2008).

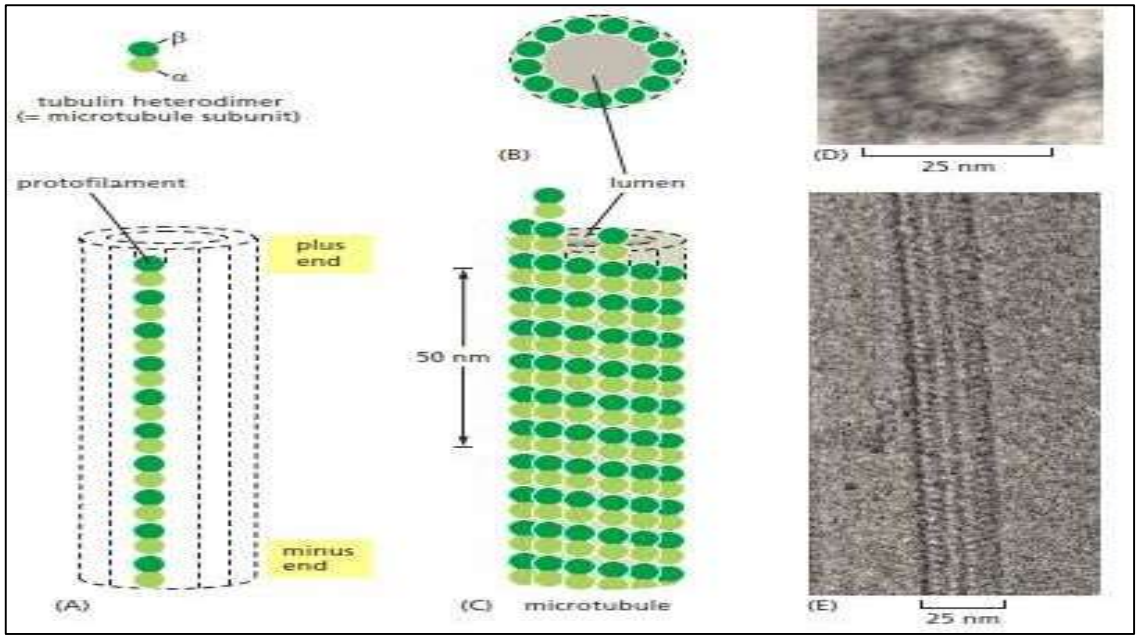


Figure 28 : Microtubules are hollow tubes made of globular tubulin subunits (Lodish, 2008)

2.1.4 Associated Proteins

All proteins associated with microtubules are referred to as MAPs. The so-called motor MAPs belong to the kinesin family or the dynein family. They are responsible for the directed movements of molecules, vesicles, or organelles along microtubules.

- Kinesins transport towards the (+) distal end of microtubules (anterograde transport).
- Dyneins transport towards the (–) distal end of microtubules (retrograde transport).

These proteins are heteropolymers (2 heavy chains + several light chains) organized into three domains:

✓ Two identical heads that attach to the microtubules and possess ATPase activity;

- ✓ A stalk at the end of which the material to be transported attaches (presence of an adapter). The hydrolysis of ATP is necessary for the movement of motor MAPs along MTs (Lodish, 2008).

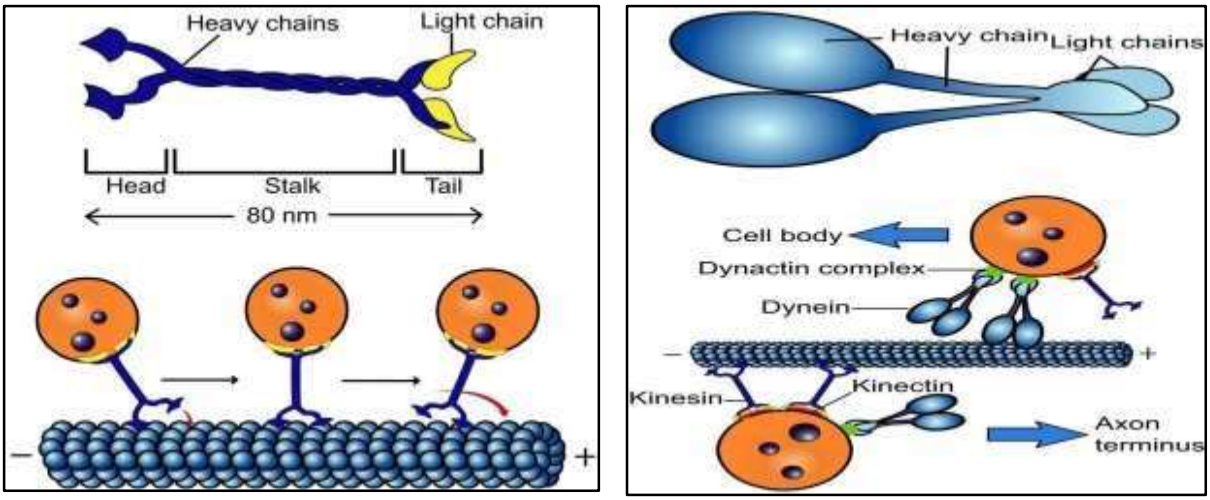


Figure 29 : Both kinesins and dyneins move along microtubules using their globular heads (Lodish, 2008).

2.1.5 Microtubule Organizing Centers (MTOCs):

Microtubules are organised in specific patterns to carry out specific functions within cells. Spontaneous nucleation is not likely to occur in vivo, but instead, assembly is initiated at **microtubule organising centres (MTOCs)**, which serve as templates for tubulin polymerization. MTOCs can be found in **basal bodies, centrioles**, **mitotic spindles**, **chromosomes**, and **membranes**. Most cytoplasmic microtubules originate from densely staining pericentriolar material surrounding the centriole. The turning on and off of these organising centres for microtubule assembly is likely regulated by changes in nucleation centres, changes in Ca2+ concentration, and the involvement of MAPs.

2.1.6 Assembly and Disassembly of Microtubules

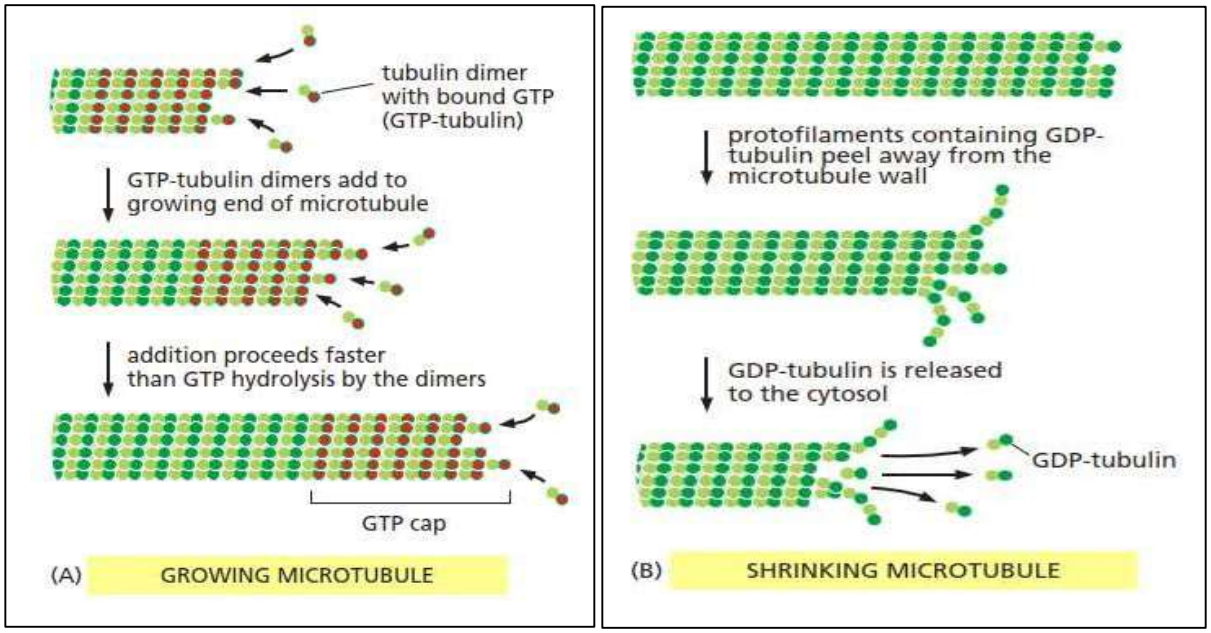
Microtubules in the cytoplasm are **dynamic structures** that continuously emerge and disappear in response to cell activity. They proliferate by hydrolysing nucleotides, changing their structure, and adding subunits reversibly. Self-assembly seems to be a component of the microtubule polymerisation (assembly) and depolymerisation (disassembly) processes. Tubulin dimer-based microtubule assembly is a precisely targeted and regulated activity, with large amounts during interphase and metaphase and low amounts during prophase and anaphase.

The phosphorylation of tubulin monomers by a cyclic AMP-dependent kinase promotes polymerisation inside the cell, where microtubules and free tubulin are in balance. There is a

correlation between cAMP and the quantity and orientation of microtubules as well as cell shape. It is a polarised phenomenon that tubulin assembles and disassembles (Alberts et al., 2015).

Although little is known about the process behind microtubule self-assembly in vivo, in vitro research has provided some intriguing insights. Weingarten et al. (1975) showed in a famous work that tubulin alone was insufficient for in vitro assembly into microtubules using tubulin extracted from bovine brain. However, low calcium concentrations, MAPs, GTP, and a level of free tubulin monomers over a threshold concentration can all contribute to in vitro assembly (Alberts et al., 2015).

The two stages of in vitro polymerisation are initiation and elongation. α- and β-tubulins unite to create heterodimers during initiation, and these heterodimers then associate to form intermediate structures, multimeric rings, and spirals. Protofilaments are assembled side by side to form sheet-like structures that coil into tubes. The direct insertion of additional heterodimers causes elongation at the end.



2.1.7 Functions of Cytoplasmic Microtubules

Microtubules play a crucial role in eukaryotic cells, influencing their **shape**, **orientation**, and **distribution**. They are involved in **cell differentiation**, **determining the shape** of developing cells, such as in spermiogenesis and lens placode in the eye. They also determine **cell polarity and motility**, with directional gliding of cultured cells dependent on microtubules. They also play a role in **contraction, movement of chromosomes and centrioles, and ciliary and flagellar motion.** Additionally, microtubules are involved in **circulation and transport**, transporting macromolecules, granules, and vesicles within the cell. Their mechanical function is crucial for

cell shape and processes, such as axons and dendrites of neurons. Overall, microtubules play a vital role in eukaryotic cell function (Lodish, 2008).

2.2 Intermediate Filaments:

The cytoplasm of the majority of higher eukaryotic cells contains robust, long-lasting protein fibres called **intermediate filaments (IFs).** They are located between thin and thick filaments in muscle cells, microfilaments, and microtubules, and they are usually 8–10 nm in diameter. IFs are sensitive to proteolysis and resistant to cytochalasin B and colchicine. In animal cells, they surround the nucleus like a "basket" and spread out in softly curved arrays to the cell's perimeter. In cells that are under mechanical stress, such epithelia, IFs are most noticeable. They are connected throughout the cytoplasm of smooth muscle cells, at desmosomal junctions, and along the length of axons. IFs are referred to by several names depending on the kind of cell, including glial filaments in neuroglial cells, neurofilaments in nerve cells, and tonofilaments in epidermal cells. In cross-section, they resemble tubules and are made up of polypeptides ranging in size from 40,000 to 130,000 daltons (Lodish, 2008).

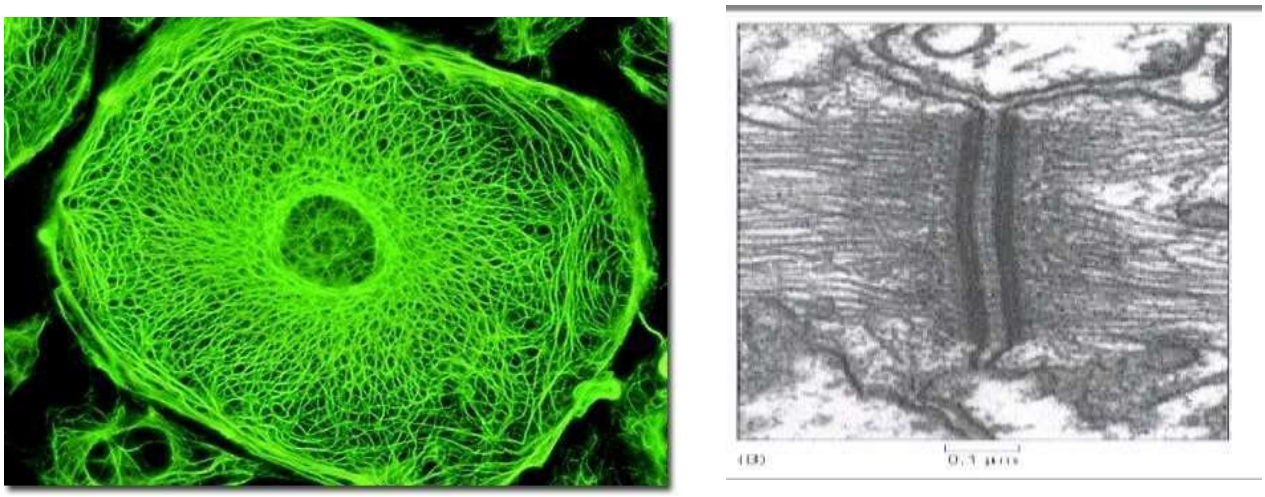


Figure 30: distribution of Intermediates filaments within cel l(Lodish, 2008).

2.2.1 Types of intermediate filaments.

From the perspective of their biochemical characteristics, the intermediate filaments are quite diverse; nonetheless, based on their form and location, they may be divided into the following four primary categories (Alberts et al., 2015).

2.2.1.1 Type I IF proteins.

Acidic keratin and neutral or basic keratin are the two subfamilies of keratin, also referred to as celled tono, perakeratin, or cytokeratin, which are predominantly found in epithelial cells. Each of these two keratin subfamilies has an equal number of subunits, forming keratin filaments, which are invariably heteropolymers. With at least 19 different forms seen in human epithelia and eight

more in the keratins of hair and nails, keratins are the most complicated class of IF proteins. Fibrous proteins called mammalian cytokeratin, produced in the cells of the epidermis' live layers, make up the majority of the dead stratum corneum layers (Verma and Agarwal, 2004).

2.2.1.2 Type II IF proteins.

They consist of four different kinds of polypeptides: **glial fibrillary acidic protein** (also known as glial filaments), **desmin, synemin, and vimentin**. Desmin is present in both striated (skeletal and cardiac) and smooth muscle cells, whereas vitreolin is extensively dispersed in cells of mesenchymal origin, such as fibroblasts, blood vessel endothelial cells, and white blood cells. In the nervous system, glial filaments may be seen in some glial cell types, including astrocytes and certain Schwann cells. Along with desmin and vimentin, the 230,000-dalton protein synemin is also found in muscle's intermediate filaments. The chicken erythrocytes include IFs that contain vitexin and synemin (Verma and Agarwal, 2004).

2.2.1.3 Type III IF proteins.

These IF proteins are referred to as neurofilament proteins because they form neurofilaments, a significant cytoskeletal component of nerve axons and dendrites. The so-called neurofilament triplet is made up of three different polypeptides that make up Type III IFs in vertebrates. Type IVIF proteins.

2.2.1.4 Type IVIF proteins.

These nuclear lamins create very well-organised two-dimensional filament sheets. At a certain point of mitosis, these filaments quickly breakdown and reassemble.

2.2.2 Assembly of IFs

The following stages are included in a current model of intermediate filament assembly:

- A dimer is formed by the pairing of two identical monomers, with the conserved helical core sections orientated in parallel and twisted into a coiled coil.
- Two dimers then align themselves side by side to create a protofilament with four polypeptide chains that measures 48 nm by 3 nm.
- These protofilaments then create progressively bigger structures by staggeredly combining.
- It is believed that the long rope-like filaments, which have a final diameter of 10 nm, are made up of 8-protofilaments, or 32 polypeptide chains, connected end on end to neighbours by staggered overlap. Whether IFs are non-polar (like the DNA double helix) or polar (like actin and tubulin) structures is currently unknown (Verma and Agarwal, 2004).

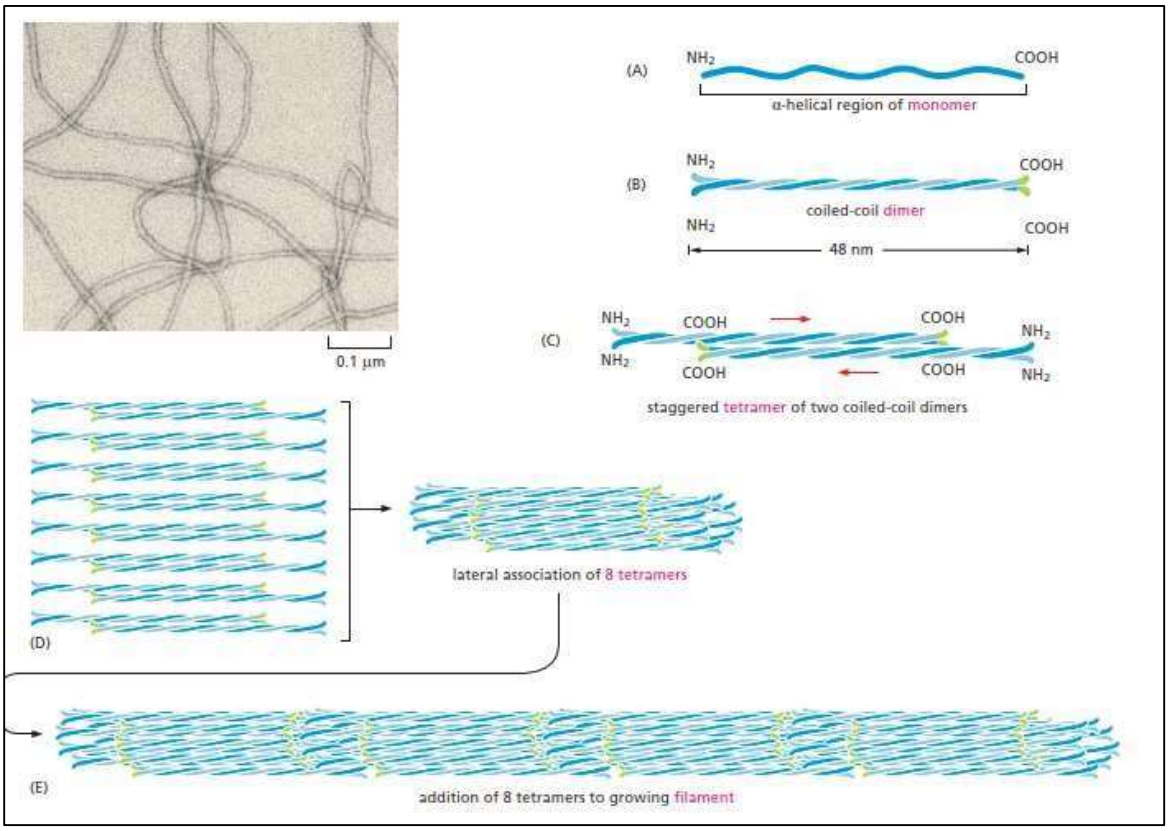


Figure 31: Assembly of Intermidiates filaments (Lodish, 2008).

2.2.3 Functions of Ifs

The majority of intermediate filaments are primarily responsible for giving the cell and its nucleus mechanical support. In epithelia, IFs organise into a transcellular network that seems to be built to withstand outside influences. These long, thin cylinders of cytoplasm would normally shatter due to forces from the animal's motion, but the neurofilaments in the nerve cell axons likely withstand these strains. Vimentin filaments encircle and most likely support the big fat droplets in the fat cells, whereas desmin filaments provide the sarcomeres in muscle cells mechanical support.

2.3 Microfilaments:

Thin, solid actin protein microfilaments, with a diameter of 5 to 7 nm, comprise the active or motile portion of the cytoskeleton. They seem to be important for amoeboid motility and cyclosis. High voltage electron microscopy has produced a three-dimensional picture of microfilaments, or an image of the microtrabecular lattice. The alkaloid cytochalasin-B can attach to these microfilaments and stop a number of cell functions, such as heartbeat, migration, cytokinesis, endocytosis, and exocytosis. People often think of the cytochalasin-B-sensitive microfilaments as the contractile apparatus of non-muscle cells.

2.3.1 Distribution:

Typically, microfilaments are found in the cell's cortical areas, directly below the plasma membrane. On the other hand, deeper and subcortical areas of the cell include microtubules and intermediate filaments. Additionally, microfilaments penetrate cell processes, particularly in areas where movement occurs. As a result, they are present in intestinal epithelial brush border microvilli as well as cell types that exhibit cytoplasmic streaming and amoeboid migration.

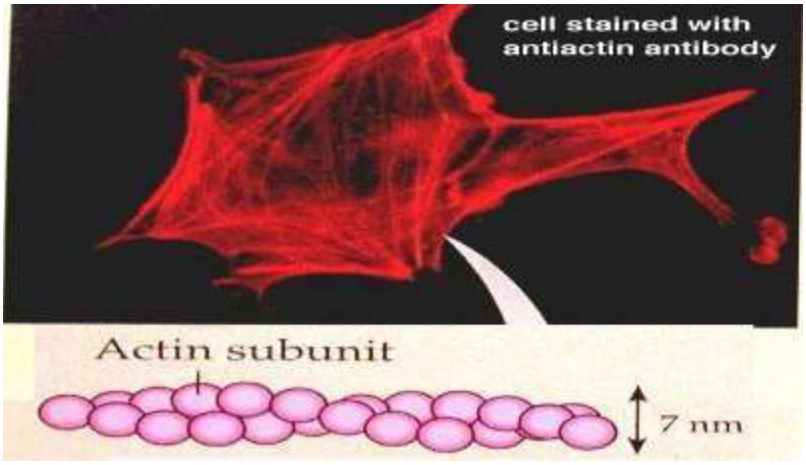
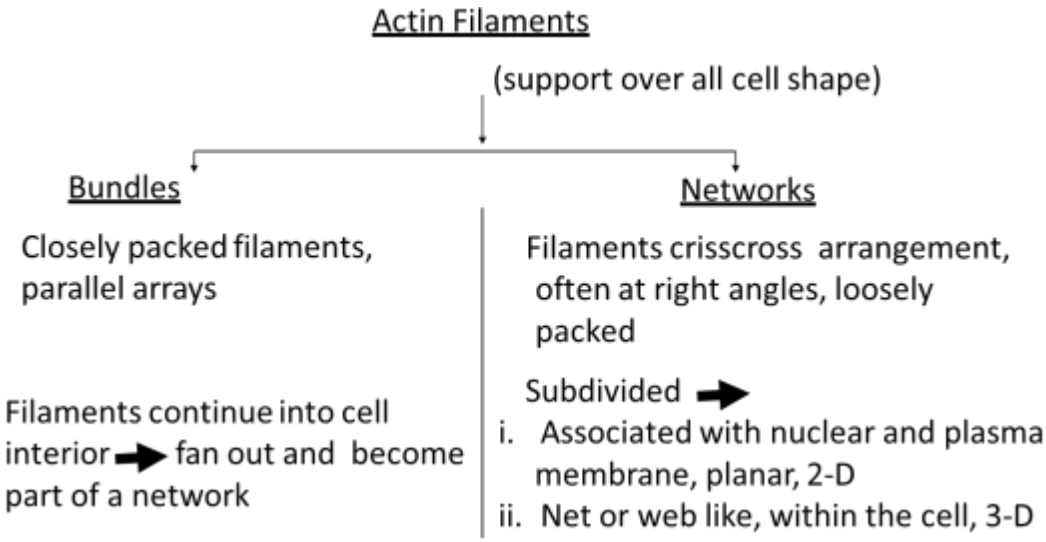


Figure 32 Distribution of microfilaments in cell (Alberts et al., 2015).

2.3.2 Organisation



2.3.3 Microfilament Assembly

- Filament formation- head to tail polymerization of Actin monomers (**Globular or G-actin**)
- **Filamentous or F-actin** à Linear chain of G-actin subunit (accompanied by addition of ions, Mg^{2+}, K^{+})
- Two helical interlaced strands of subunits

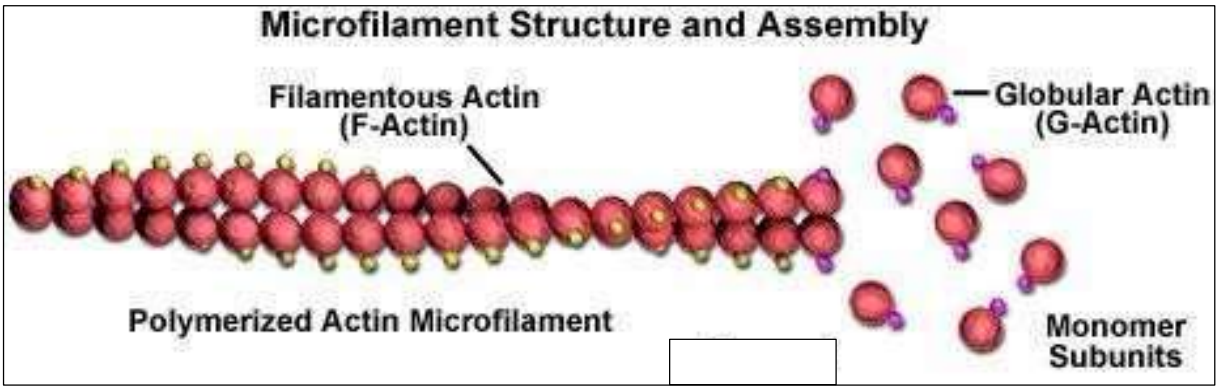


Figure 33 : Microfilaments structure and assembly (Lodish, 2008).

2.3.4 Function

Microfilaments are found to be involved in movement associated with furrow formation in cell division, cytoplasmic streaming in plant cells (e.g., Nitella and Chara) and cell migration during embryonic development.

Chaptter 4: Cell Adhesion and the Extracellular Matrix

1 Introduction:

Multicellular organisms exist because cells can bind to each other. The process by which cells attach to a cell or a substance is called **cell adhesion**. Cells may adhere directly to each other, a process called **cell-cell adhesion.** Cells also bind to extracellular components that provide a structural framework for cell binding. These extracellular components are collectively called the **extracellular matrix (ECM).** The binding of cells to the ECM is termed **cell-matrix** or **cell-substratum adhesion.**

Cell adhesion and the ECM are, together, crucial for the development and maintenance of tissue structure and function.

In a single tissue, there are multiple types of cells at work taking for example the lumen of gut

- ✓ Epithelial cell forms the epithelium
- ✓ Fibroblasts forms the connective tissue
- ✓ Smooth muscle cells epithelial cell forms that smooth muscle

The question that is posed is how do these tissue form – since they are not random how-to cells adhere to each other and become a tissue all having specific locations and functions The answer: cells due to stress transmissions that come from within multicellular organisms will adhere together (Alberts et al., 2018).

2 Cell Adhesion

To understand cell adhesion, one must know about the molecules that mediate cell adhesion **(cell adhesion molecules, CAMs),** organization of these molecules into multiprotein adhesion complexes, and regulation of protein-protein interactions by cell signaling pathways. The domain structures of **CAMs** determine their precise organization into specific cell-cell and cell-substratum junctions (Alberts et al., 2018).

Cellular adhesion is essential

- ✓ In cell recognition, one cell specifically binds to another cell of a certain type.
- ✓ In cell adhesion, the relationship between the two cells is “cemented”.
- ✓ Tissue-specific and species-specific aggregation occur because of plasma membrane recognition proteins.

2.1 2.2. Cell Adhesion Molecules (CAMs)

Most of CAMs belong to one of four gene families, **the cadherins**, **immunoglobulin superfamily CAMs** (IgCAMs), **selectins**, and **integrins**. Proteoglycans may be considered as another class of CAMs. CAMs can also be classified as calcium-dependent and calcium independent CAMs.

Adhesive properties of **cadherins and selectins are calcium dependent**, whereas **integrins and IgCAMs associations are independent of calcium**. CAMs are typically single-pass transmembrane proteins with:

- An extracellular domain that participates in adhesion,
- A transmembrane domain that anchors the protein in the cell membrane,
- A cytoplasmic domain that mediates attachment to the cytoskeleton.

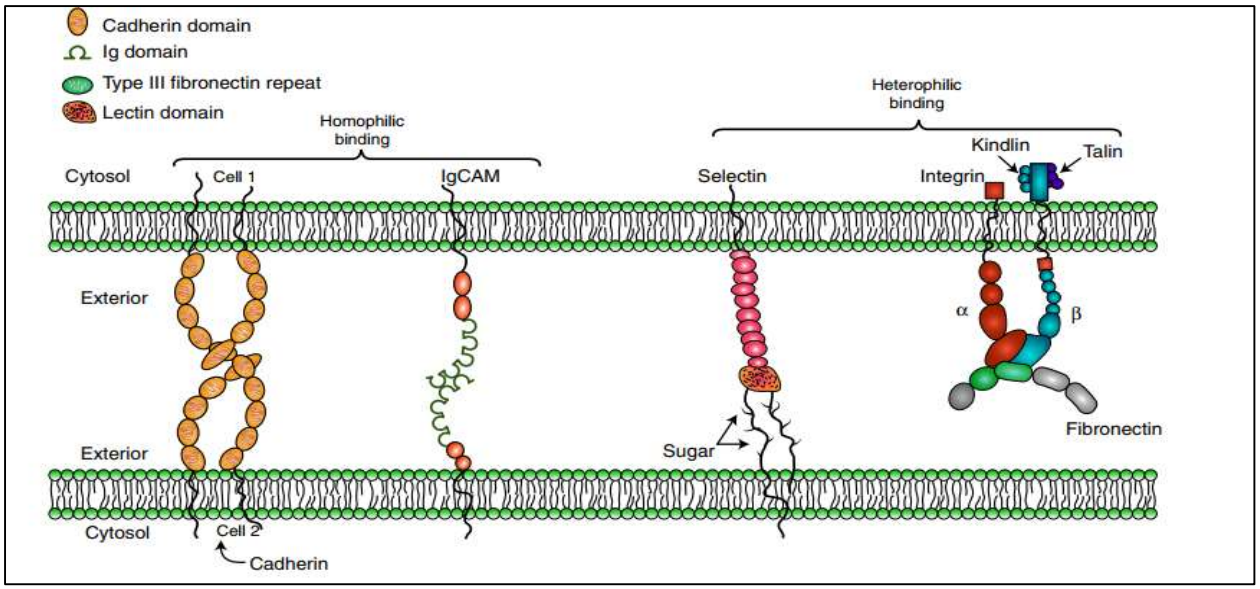


Figure 34 : Types of cell adhesion molecules (Alberts et al., 2018).

The adhesive binding of adhesion molecules is either **homophilic** or **heterophilic**.

- **Homophilic adhesion** means the adhesion is mediated by the interaction between the extracellular domains of the same type of CAM molecules.
- **Heterophilic binding** refers to the adhesion mediated by the interaction of the extracellular domain of a CAM with the extracellular domain of a different type of molecule in another cell or ECM

2.1.1 Cadherins

Are Calcium-Dependent Cell-Cell Adhesion Molecules. The cadherins are members of a superfamily of calcium-dependent cell-cell adhesion molecules. They are classified as:

- Type I (e.g., E-cadherin and N-cadherin) and

- Type II (e.g., cadherin-6 and 11)
- Calcium-dependent transmembrane proteins, 720 to 740 amino acids
- Responsible for cell-cell interactions
- Carried by many cells: neurons, muscles, osteoclasts and by the membranes of epithelial cells
- Are essential for the formation of adhesion junction complexes (zonula adherens and Desmosome).
- There are 40 types of Cadherins. Ex: E-cadherin found on the lateral faces of epithelial cells, P-cadherin found in the Placenta, N-cadherin found in the central nervous system.

If there is a drop in cadherin concentration, there is a drop in intercellular coherence. The cells therefore detach from the original tissue, and then migrate to form metastases at the origin of tumors.

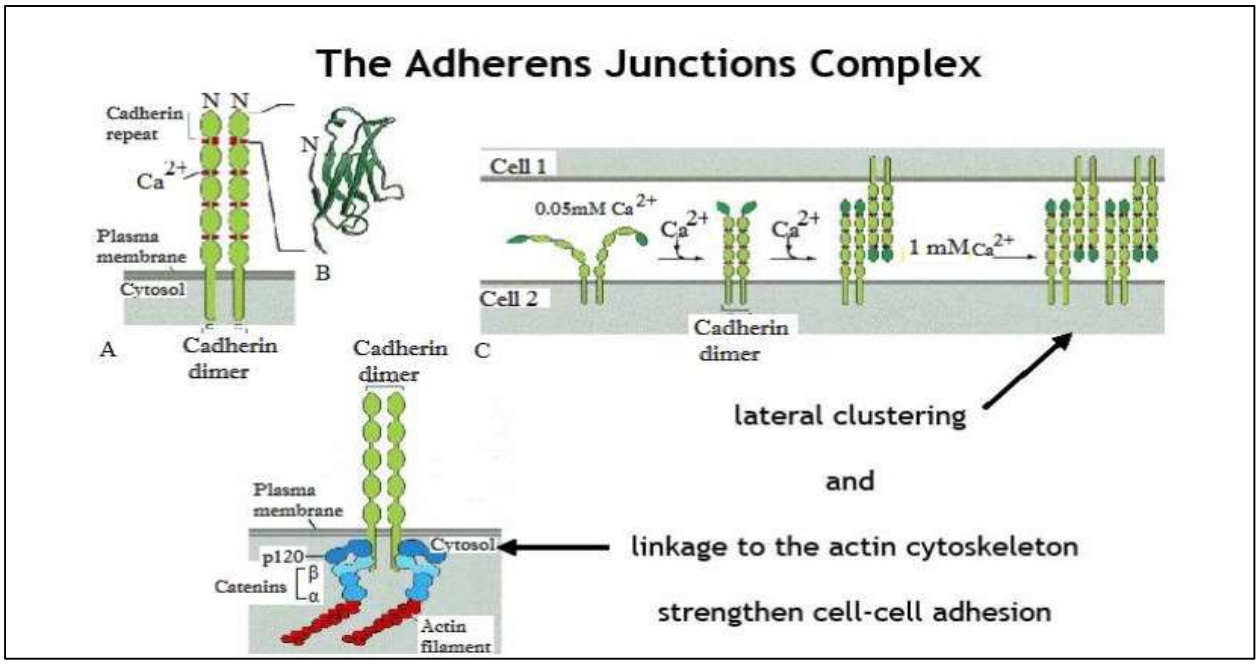


Figure 35 : The adhérens junctions complex (Alberts et al., 2015).

2.1.2 Integrins

- As the name indicates, integrins play a role in the integration of cells into tissues.
- All integrins are calcium or magnesium dependent.
- Integrins function as cell surface receptors that interact with components of the extracellular matrix.
- integrins are **heterodimeric** transmembrane proteins that consist of one ***α-subunit*** and one ***β-subunit(Alberts et al., 2018)***

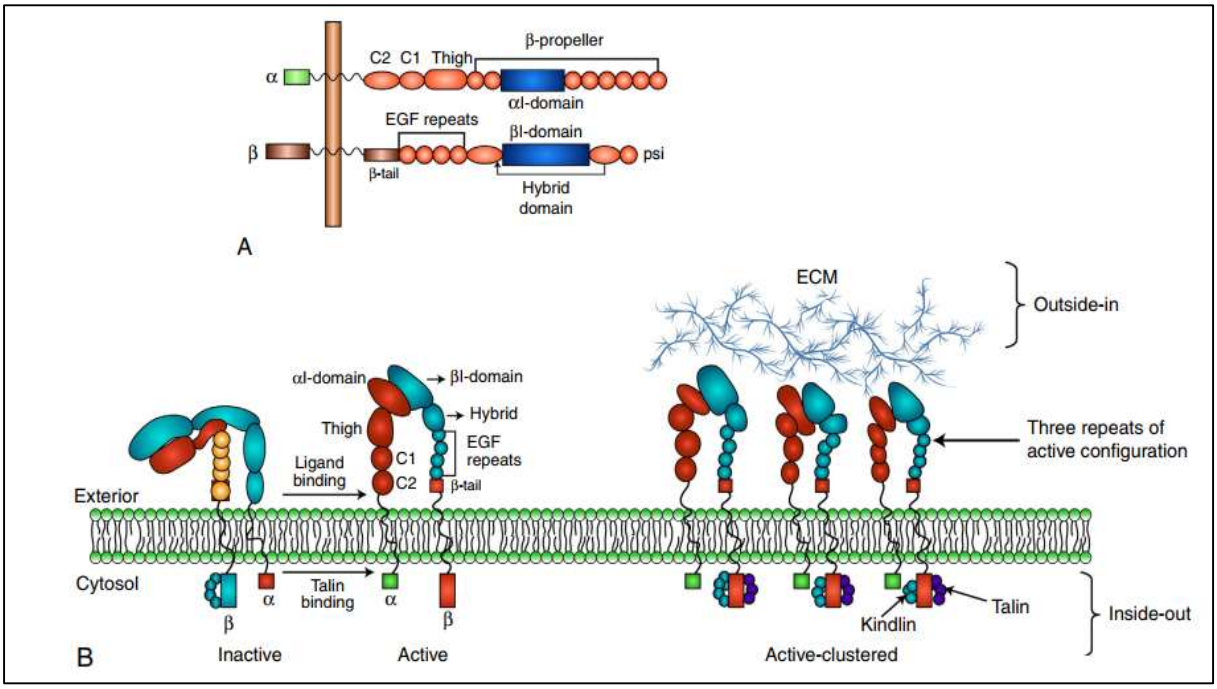


Figure 36: Integrin activation and clustering. (A) Domain structure of integrin subunits, (B) activation and clustering of integrins (Alberts et al., 2015).

2.1.3 Selectins:

- ✓ Selectins are a family of three proteins that mediate adhesive interactions between endothelium, platelets and leukocytes.
- ✓ They regulate the first reversible interaction between leukocytes and endothelial cells, a process commonly referred to as rolling.
- ✓ The selectins, as indicated by their name, participate exclusively in **heterophilic cell-cell binding** because they have a lectin-like domain at their NH2 terminus that binds to specific carbohydrate residues on the opposite cell surface
- ✓ There are three members of selectins (named on the basis of cellular expression), P-selectin, E-selectin, and L-selectin localized on the surface of platelets, endothelial cells, and leukocytes, respectively
- ✓ The extracellular domains of all three selectins are composed of a lectin domain, epidermal growth factor (EGF) domain, and consensus repeats. Three selectins differ in the number of consensuses repeats: The longest P-selectin has nine consensus repeats, the medium E-selectin has sixconsensus repeats, and the shortest L-selectin has only two consensus repeats
- ✓ Selectin are engaged in binding numerous oligosaccaride ligands.
- ✓ The role that selectins and their ligands is dramatically expressed in patients with leukocyte adhesion deficiency (Lodish, 2008).

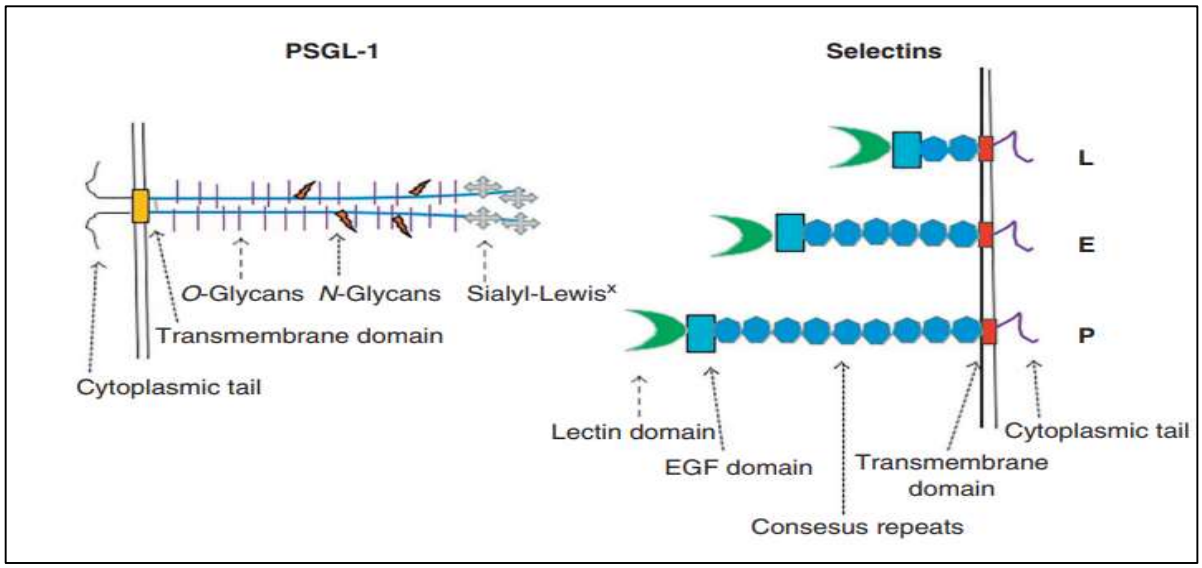


Figure 37: Structural features of selectins and PSGL-1. (Lodish, 2008).

2.1.4 Immunoglobulin Family of Cell Adhesion Molecules:

The IgCAM family includes hundreds of adhesion proteins that bind ligands on the surfaces of other cells. Some interactions are **homophilic** binding to the same IgCAM on another cell; others are **heterophilic** with different IgCAMs, integrins, other proteins or proteins with sialic acid. These interactions help specify interactions between different cell types in developing and mature animals.

Like other cell adhesion proteins, IgCAMs participate in signaling processes. Best understood are interactions of lymphocytes with antigen-presenting cells during immune responses. IgCAMs reinforce the interaction of T-cell receptors with major histocompatibility complex molecules carrying appropriate antigens on other cells (see Fig. 27.8). Although individual interactions are weak, the combination of specific (T-cell receptor) and nonspecific (CD2 and CD4) interactions with the target cell suffices to initiate signaling.(Lodish, 2008)

3 Extracellular matrix (ECM).

The ECM is a complex structural entity surrounding and supporting cells that are found within mammalian tissues. It is also found in plants. The ECM is often referred to as the connective tissue. The ECM is composed of 3 major classes of biomolecules:

- **Structural proteins:** collagen and elastin.
- **Specialized adhesion proteins;** which are also important matrix fibrillin, fibronectin, and laminin.
- **Proteoglycans:** molecule contributing to the mechanical behavior of the tissue. These are composed of a protein core to which is attached long chains of repeating disaccharide units

termed of glycosaminoglycans (GAGs) forming extremely complex high molecular weigh components of the ECM

3.1 Functions of Extracellular matrix

- ✓ Forms a supporting framework.
- ✓ Helps in holding the cells and tissues together
- ✓ In animals, it provides an organized environment within which migratory cells can move and interact with one another in orderly ways

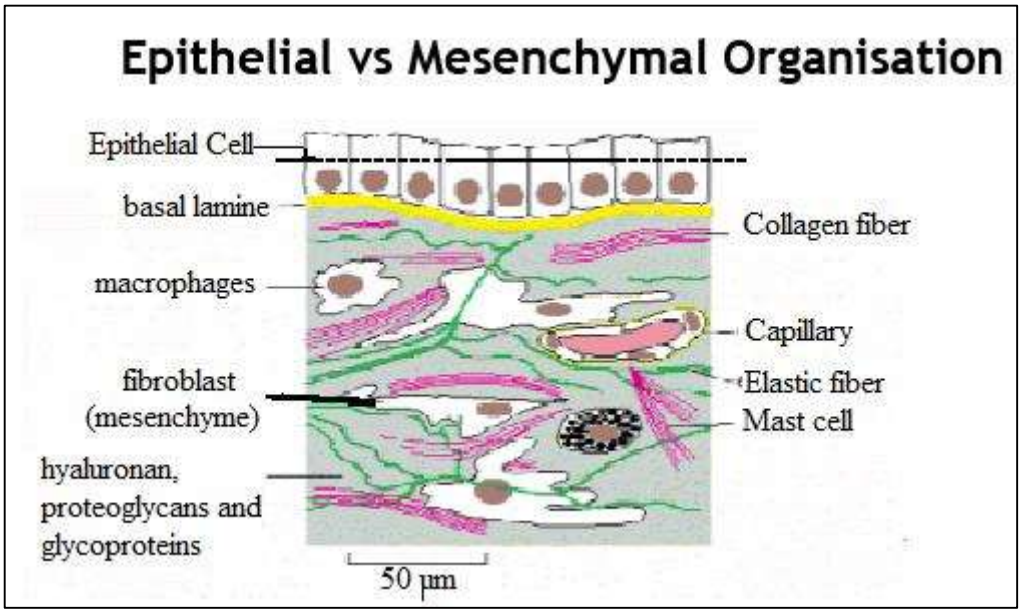


Figure 38: The connective tissue underlying an epithelium. This tissue contains a variety of cells and extracellular matrix components. The predominant cell type is the fibroblast, which secretes abundant (Lodish, 2008).

3.2 Structural proteins

3.2.1 Collagen

Collagens is a long and thin diameter rod-like protein e.g. type I collagen is 300nm long, 1.5nm in diameter.

- ➢ **Characteristics**
- ➢ Collagens are the most abundant proteins found in the animal kingdom.
- ➢ It is the major protein comprising the ECM.
- ➢ Are controlled by about **30 different collagen genes** dispersed through the human genome.
- ➢ Genes code for proteins that combine in a variety of ways to create over **20 different** types of collagen fibrils (Lodish, 2008).
- ➢ Lateral interactions of collagens result in the formation of **fibrils** roughly 50nm diameter. Collagens are synthesized as **longer precursor** proteins called procollagens.
- ➢ Collagen fibers begin to assemble in the ER and Golgi complexes.

- Procollagens are processed and secreted into the extracellular space where extracellular enzymes remove the pro-domains and the collagen molecules then polymerize to form collagen fibrils. Accompanying fibril formation is the oxidation of certain lysine residues by the extracellular enzyme lysyl oxidase forming reactive aldehydes. These reactive aldehydes form specific cross-links between two chains thereby, stabilizing the staggered array of the collagens in the fibril (Lodish, 2008).

3.2.2 Elastic Fibers

Rubber-like elastic fibers are found throughout the body and are prominent in the connective tissue of skin, the walls of arteries, and the lung. They are entropic springs that recoil passively after tissues are stretched. For example, each time the heart beats; pressurized blood flows into and stretches the large arteries. Energy stored in elastic fibers pushes blood through the circulation between heartbeats

- Main component: elastin (70kDa) non-glycosylated protein rich in proline, glycine and tropoelastin (monomer)
- Microfibrils composed of several glycoproteins including fibrillin
- Elastin molecules linked together by MAGP glycoproteins (microfibrill associated glycoprotein)
- Biosynthesis and renewal: synthesized by fibroblasts or muscle cells, half-life time approximately 70 years then degradation by elastase (MMP12) (Lodish, 2008).

3.3 Proteoglycans and Glycosaminoglycans

Glycosaminoglycans (GAGs, formerly called mucopolysaccharides) are long polysaccharides made up of repeating disaccharide units. All vertebrate cells synthesize proteoglycans. Most are secreted into the extracellular matrix, where they are major constituents of cartilage, loose connective tissue, and basement membranes.

Four main types

- hyaluronic acid
- chondroitin sulfate
- heparan sulfate
- keratan sulfate

3.4 Adhesive Glycoproteins

3.4.1 Fibronectin

Fibronectins are large proteins composed of two polypeptides of approximately 235 kD linked by disulfide bonds near their C-termini, Fibronectin presents in soluble form in the ECM. These adhesion functions are due to its binding capacities to numerous ECM proteins (polysaccharides and structural proteins such as collagen) and to membrane receptors of the integrin family.

- Cell adhesion.

- Organization of the matrix (forms a fibrillar network which promotes adhesion and arrangement of matrix proteins together).
- Synthesis by fibroblasts or other connective tissue cells.
- Synthesis by hepatocytes is released into the bloodstream.
- The circular shape is different from the tissue shape even though there is only one gene.

This is possible through the phenomenon of alternative splicing (variable assembly of products resulting from the transcription of different exons (Alberts et al., 2015).

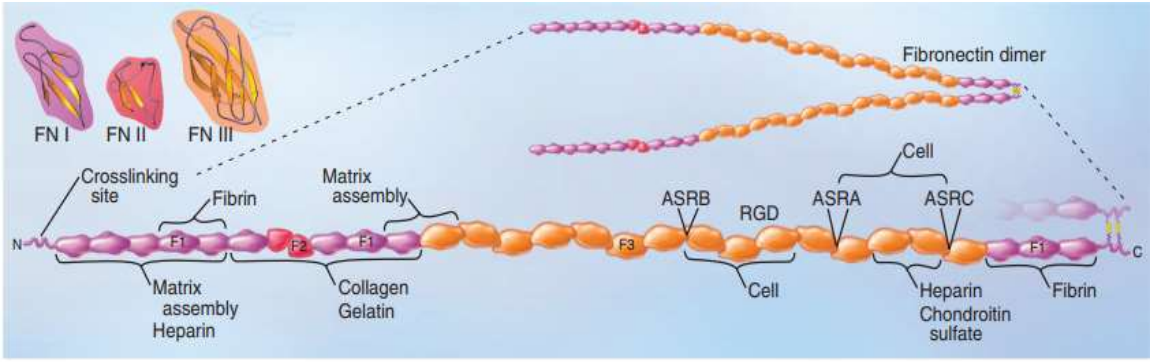


Figure 39: The different type of fibronectin (Alberts et al., 2015)

3.4.2 Laminine:

Three cross-shaped chains. It is an adhesion protein present mainly in the basal laminae and which binds certain polysaccharides such as hyaluronic acid as well as membrane receptors of the integrin family (Alberts et al., 2015).

Chapter 5: Chromatin, Chromosomes, and the Interphase Nucleus

1 Introduction

Chromatin and nucleosomes are fundamental elements of a eukaryotic cell's genetic organization, playing a main role in the structuring and packaging of DNA within the nucleus. Nucleosomes, which consist of DNA wound around histone proteins, serve as the fundamental units that assemble to form chromatin. This arrangement enables the extensive DNA molecules to be efficiently compacted, ensuring that the genetic material fits within the limited space of the cell nucleus while also facilitating the regulation of vital nuclear processes such as transcription, replication, and repair

1 Chromatin

1.1 Definition:

In all eukaryotic cells, except for a few, a nucleus is present. Generally, cells have a single nucleus, but some cells can have two or more (multinucleated). The shape of the nucleus depends on the cell type and is most often centrally located, though some cells have a peripheral nucleus.

In the nucleus of eukaryotic cells lies the genetic material, which is made up of DNA and proteins and is called chromatin. The human genome contains about 3×10^9 nucleotide pairs, which can be visualized as small structures: chromosomes. Each chromosome contains a single DNA molecule. Humans, as diploid organisms, have two copies of each type of chromosome: one inherited from the mother and one from the father. Thus, a human diploid cell contains about 6×10^9 DNA base pairs, corresponding to roughly 2 meters of DNA packed into a nucleus with an average diameter of a few micrometers. This physical constraint requires the DNA to be folded (Wiser).

1.2 Composition of Chromatin

Chromatin consists of a double helix of DNA tightly bound to an equal mass of proteins called histones (present exclusively in eukaryotes). The histones are organized into an octamer formed by two molecules of each of the following four types: H2A, H2B, H3, and H4. The DNA double helix (146 base pairs) wraps twice around the octamer. This structure is called the nucleosome (11 nm in diameter). The linear DNA segment between two nucleosomes is called the internucleosomal linker. The fifth histone, H1, is extranucleosomal and functions to maintain the stacking of adjacent nucleosomes, thereby ensuring the supercoiling of DNA molecules (Alberts et al., 2015).

1.3 Structure of Chromatin

Under electron microscopy, chromatin appears in two forms:

1.3.1 Heterochromatin:

Dense, dark, and condensed; defined as a structure that does not change its condensation state during the cell cycle.

- **Constitutive heterochromatin:** Mainly made of repetitive sequences and contains few genes. It is generally concentrated near centromeres and telomeres.
- **Facultative heterochromatin:** Contains coding regions that can adopt the structural and functional characteristics of heterochromatin, such as the inactive X chromosome in females.

1.3.2 Euchromatin:

Less dense and appears decondensed during interphase. It has a "beads-on-a-string" structure, with each bead representing a nucleosome core particle (Urry et al., 2017).

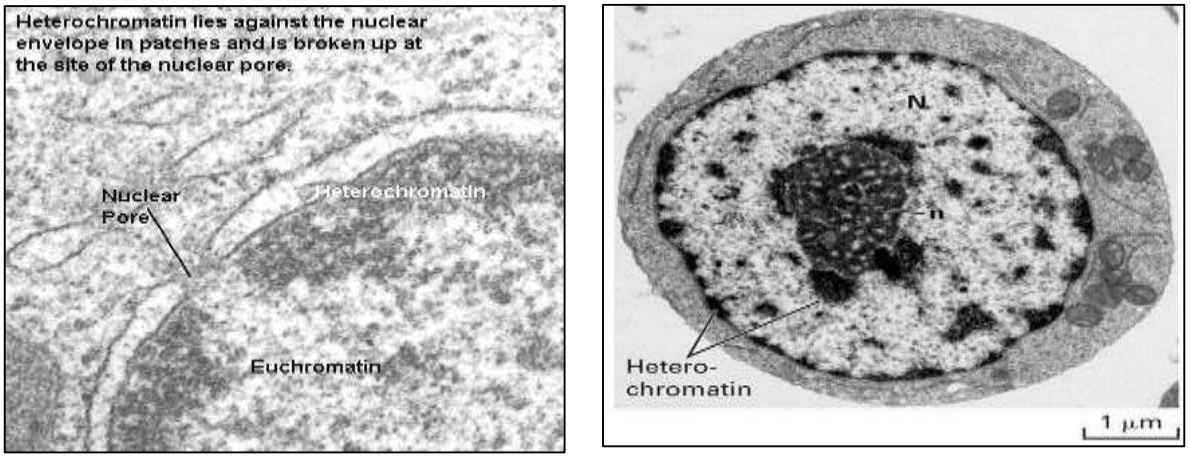


Figure 40: Ultrastructural Organization of Chromatin in the Eukaryotic Cell Nucleus: Distribution of Heterochromatin and Euchromatin (Alberts et al., 2018).

1.4 DNA Compaction

1.4.1 The First Level of DNA Folding "Beads-on-a-String (Primary Structure):

- ✓ This level involves the association of DNA with small basic proteins called histones (H2A, H2B, H3, H4), which organize into octamers.
- ✓ The DNA double helix wraps almost twice around the octamer, with a small free segment on each side called the nucleosomal linker.
- ✓ The DNA + histone complex forms the nucleosome.
- ✓ A succession of nucleosomes creates the nucleofilament.

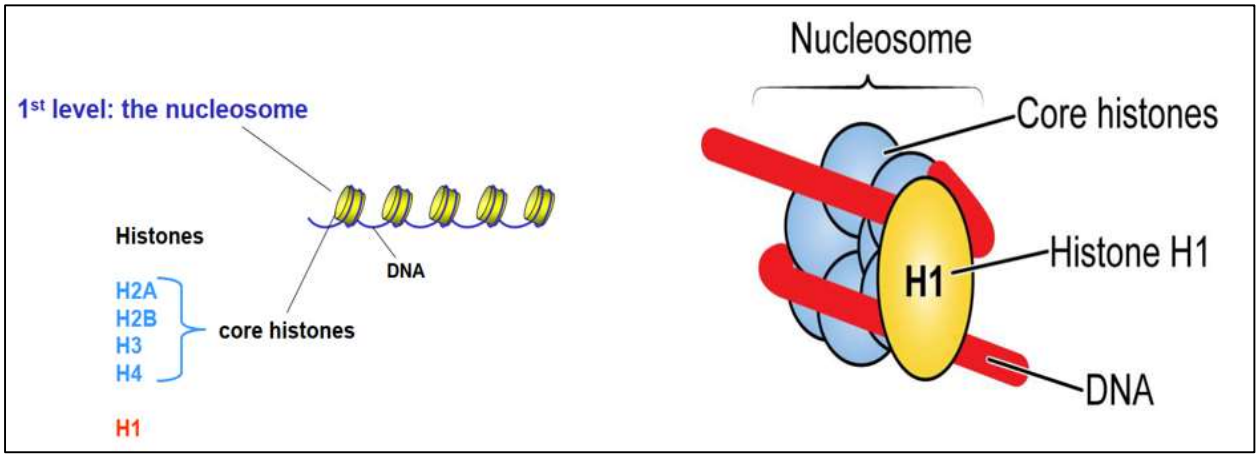
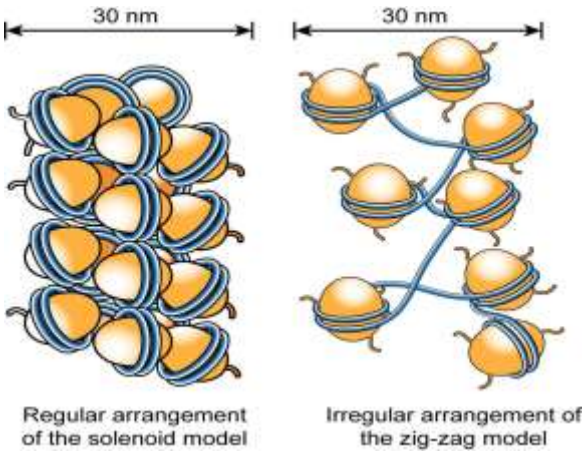


Figure 41: Representative schema of nucleosome

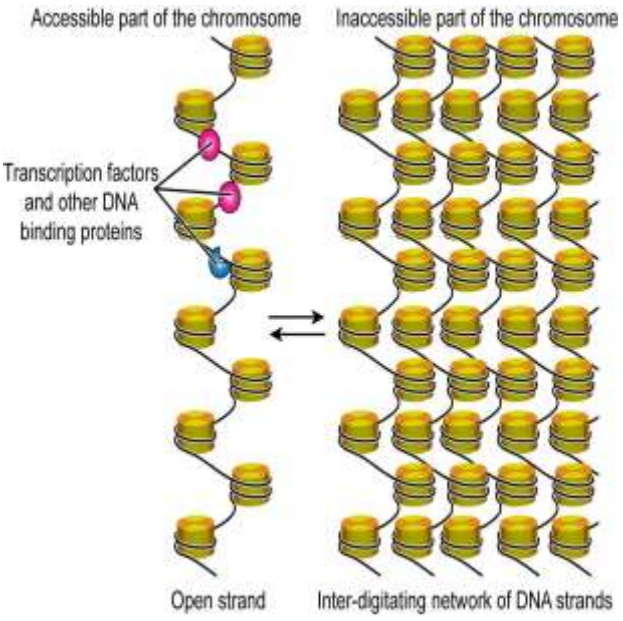
1.4.2 The Second Level of DNA Folding "The 30 nm Fibre (Secondary Structure):

The nucleofilament undergoes a second level of folding through the action of a fifth histone: **histone H1**. This histone binds to the DNA linking two nucleosomes and helps further coil the DNA into a **30 nm chromatin fiber** called the **solenoid**. Each turn of the solenoid contains **six nucleosomes**.



1.4.3 Higher Levels of Folding:

A higher order structure is recognized as the tertiary structure when the genome is arranged in individual chromosomes. Essentially, chromosome depicts a tertiary arrangement. This is made due to interdigitation of independent DNA strands in a beads-on-a-string. With the help of proteins that can change the structure of chromatin, one entire beads-on-a-string DNA can move out of the compacted chromosome and be accessible for transcription factors to carry out transcription.



1.4.4 Proteins Involved in Chromatin Compaction:

- **HMG (High Mobility Group) proteins:** Non-histone chromatin proteins that specifically bind to DNA and can affect nucleofilament spacing and folding.
- **Histone chaperones:** Acidic factors that can form complexes with histones, facilitating their assembly into nucleosomes.
- **Chromatin remodeling factors:** Require ATP to induce conformational changes in nucleosomes and broader chromatin domains.

2 Chromosomes

2.1 Description of Chromosomes

Chromosomes are small rod-shaped bodies made of long double-stranded DNA molecules associated with two types of proteins: basic proteins (histones) and acidic proteins (non-histones).

In the human genome, chromosomes vary in size. The smallest is chromosome 21 (about 50 million base pairs), and the largest is chromosome 1 (up to 250 million base pairs).

Cytogenetics is the study of chromosomes, their structure, and transmission. Establishing a chromosomal formula for a species allows for the detection of structural or numerical chromosome anomalies (Urry et al., 2017).

2.2 Chromosome Number

The number of chromosomes is a species-specific characteristic, vital for phylogeny and taxonomy. Gametes (sperm and ova) contain a haploid set of chromosomes, known as the genome, while somatic cells are diploid, containing two sets formed by the union of male and female gametes during sexual reproduction.

In humans, the chromosome count is 46 (23 pairs), consisting of 44 autosomes and two sex chromosomes. Females have two morphologically similar X chromosomes, while males have one X and one morphologically distinct Y chromosome.

2.3 Chromosome Morphology

Chromosomes vary in size and shape. The smallest chromosomes are about 0.25 μm (found in fungi and birds), while the largest can reach 30 μm (as in Trillium plants). Organisms with fewer chromosomes tend to have larger ones, and plants generally have larger chromosomes than animals. Chromosome shape is dynamic, changing throughout the cell cycle. In interphase, chromosomes are thin, coiled, and thread-like (chromatin threads). During metaphase and anaphase, they become thick and filamentous (Urry et al., 2017).

The position of the centromere -a clear zone along the chromosome- divides it into two arms and determines its shape. Chromosomes are classified based on centromere position as telocentric (centromere at the end), acrocentric (centromere near one end), submetacentric (centromere slightly off center), and metacentric (centromere in the middle, forming two equal arms) (Urry et al., 2017).

2.4 Chromosome Structure

Each metaphase chromosome consists of two symmetrical chromatids, each containing a single DNA molecule. The chromatids are joined at the centromere and separate during anaphase. Chromonemata are the thin filaments visible during prophase, representing chromatids in early condensation. Chromomeres are bead-like accumulations of chromatin visible along interphase chromosomes, especially clear in polytene chromosomes. The centromere, or kinetochore, is the region where spindle fibers attach during cell division.

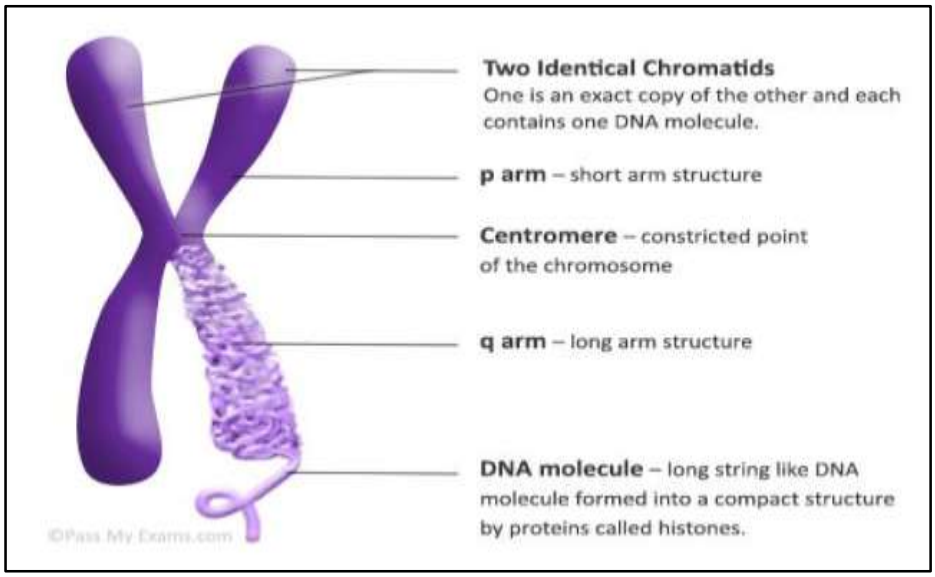


Figure 42: Structure of a Metaphase Chromosome and Its Key Components (Alberts et al., 2018).

2.5 Chromosome Analysis

Dividing human cell chromosomes are best analyzed during metaphase or prometaphase of mitosis. Chromosomes are classified and analyzed after staining.

Each chromosome has a primary constriction or centromere that joins the two sister chromatids and attaches the chromosome to the mitotic spindle. On either side of the centromere, a chromatid has a short arm (p arm) and a long arm (q arm).

Based on centromere position, chromosomes are classified as:

- **Metacentric:** centromere in the middle

- **Submetacentric:** centromere slightly off center
- **Acrocentric:** centromere near one end

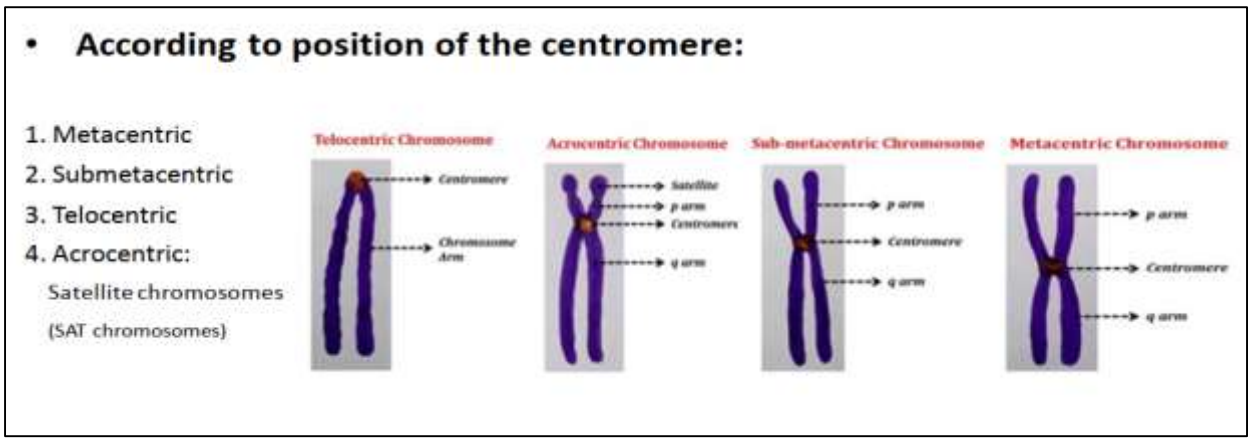


Figure 43: Types of Chromosomes Classified by Centromere Position (Alberts et al., 2018)

Telomeres are at the ends of chromosomes. These highly specialized nucleoprotein structures protect chromosome ends and are rich in GC repeats, making the double strand very stable. Telomeres shorten with each cell division (Urry et al., 2017).

Members of a chromosomal pair (homologous chromosomes) carry homologous genetic information, meaning their loci sequences are identical, though each locus may have different or identical forms of a gene, called alleles.

3 The Interphase Nucleus

3.1 Introduction to the Nucleus

The nucleus is a specific organelle found in eukaryotic cells, delimited by the nuclear envelope, which separates its content from the rest of the cytoplasm, acting as the control center by housing genetic material and orchestrating all hereditary and metabolic activities. Its presence distinguishes eukaryotes from prokaryotes, which lack a true nucleus. The nucleus is typically the most prominent organelle, occupying about 10% of the cell's volume, and is visible under a light microscope as a spherical or oval structure. It is bounded by a double membrane called the nuclear envelope, which separates its contents from the cytoplasm (Verma and Agarwal, 2004).

3.2 History

The nucleus was the first organelle to be discovered by Robert Brown in 1833 in plant cells, and the nucleolus was noted by Fontana in 1781 and later described by Schleiden. The term chromatin was introduced by Flemming in 1879, and the nuclear envelope was demonstrated by O. Hertwig in 1893. The role of the nucleus in heredity was firmly established by Hammerling's experiments

with Acetabularia in the 1950s, showing that the nucleus controls cell morphology and genetic traits.

3.3 Nucleus: Occurrence, Number, and Position

3.3.1 Occurrence

The nucleus is found in almost all eukaryotic cells, with exceptions such as mature mammalian erythrocytes and sieve tube elements in higher plants, which lose their nuclei during maturation.

3.3.2 Number

- Mononucleate cells: Most cells contain a single nucleus.
- Binucleate cells: Some, like liver cells or certain protozoa, have two nuclei.
- Polynucleate cells: Muscle fibers, osteoclasts, and some plant cells (coenocytes) may have many nuclei.

3.3.3 Position

The nucleus is usually centrally located but may shift depending on cell type and metabolic activity. In glandular cells, it is often basal. (Alberts et al., 2018).

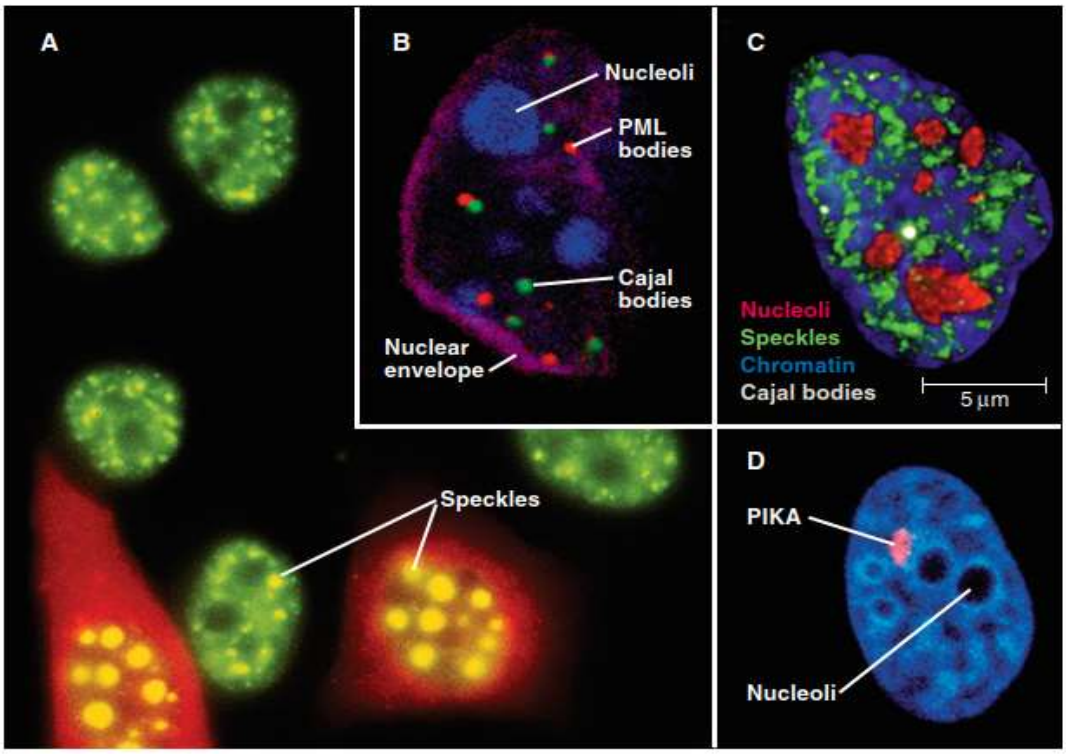


Figure 44: Examples of major subnuclear structures (Lodish, 2008).

3.4 Morphology of the Nucleus

3.4.1 Shape

The shape of the nucleus often mirrors the cell's shape:

- Spherical in isodiametric cells,
- Ellipsoidal in cylindrical cells,
- Discoidal in squamous epithelial cells,
- Irregular in leukocytes and some glandular cells.

3.4.2 Size

Nuclear size varies from 3 to 25 μm in diameter and is generally proportional to cell size and ploidy (DNA content). Polyploid cells have larger nuclei.

3.5 Structure and Ultrastructure

3.5.1 Nuclear Envelope

The nuclear envelope consists of two concentric membranes (each 6–10 nm thick) separated by a perinuclear space (10–50 nm wide), which is continuous with the rough endoplasmic reticulum (RER). The outer membrane bears ribosomes, while the inner membrane is lined by the nuclear lamina -a meshwork of intermediate filaments (lamins) providing structural support and anchoring chromatin (Lodish, 2008).

3.5.2 Nuclear Lamina

The nuclear lamina is composed mainly of lamins A, B, and C, which form a dynamic scaffold. It is essential for nuclear assembly, chromatin organization, and nuclear stability. Mutations in lamins can cause laminopathies, including premature aging syndromes.

3.5.3 Nuclear Pores

The nuclear envelope is perforated by nuclear pores—large protein complexes (nuclear pore complexes, NPCs) that regulate the bidirectional exchange of molecules between the nucleus and cytoplasm. Each pore is about 100 nm in diameter and allows passive diffusion of small molecules while actively transporting proteins, RNAs, and ribosomal subunits. The number of pores correlates with the cell's transcriptional activity (Verma and Agarwal, 2004).

3.6 Nucleoplasm

The nucleoplasm (karyolymph) is the semi-fluid matrix filling the nucleus, analogous to cytoplasm. It contains:

- **Nuclear matrix:** A fibrous network supporting nuclear shape and organizing chromatin.
- **Ions, nucleotides, enzymes, and ribonucleoproteins:** Essential for DNA/RNA synthesis and processing.

- **Proteins:** Histones, non-histone proteins, enzymes for DNA replication and transcription, and structural proteins.

3.7 Nucleocytoplasmic Transport

Nuclear pores mediate selective transport:

- **Import:** Proteins with a nuclear localization signal (NLS) are imported via importins.
- **Export:** mRNAs, tRNAs, and ribosomal subunits are exported via exportins.
- **Energy:** Transport is energy-dependent, often involving GTP hydrolysis.

This regulated traffic ensures that only properly processed RNAs and proteins enter or exit the nucleus, maintaining compartmentalization and gene expression control.

3.8 The Nucleolus

3.8.1 Structure

The nucleolus is a prominent, non-membrane-bound structure within the nucleus, visible as a dense, spherical region. It forms around nucleolar organizer regions (NORs) on certain chromosomes.

3.8.2 Ultrastructure

The nucleolus has three main regions:

- **Fibrillar centers (FC):** Contain rDNA and are sites of rRNA transcription initiation.
- **Dense fibrillar component (DFC):** Surrounds FCs; site of early rRNA processing.
- **Granular component (GC):** Periphery; site of late rRNA processing and ribosome assembly.

3.8.3 Function

- **Ribosome Biogenesis:** The nucleolus synthesizes and processes rRNA, assembles ribosomal subunits (40S and 60S), and exports them to the cytoplasm.
- **Other Functions:** Involvement in cell cycle regulation, stress response, and assembly of ribonucleoproteins.

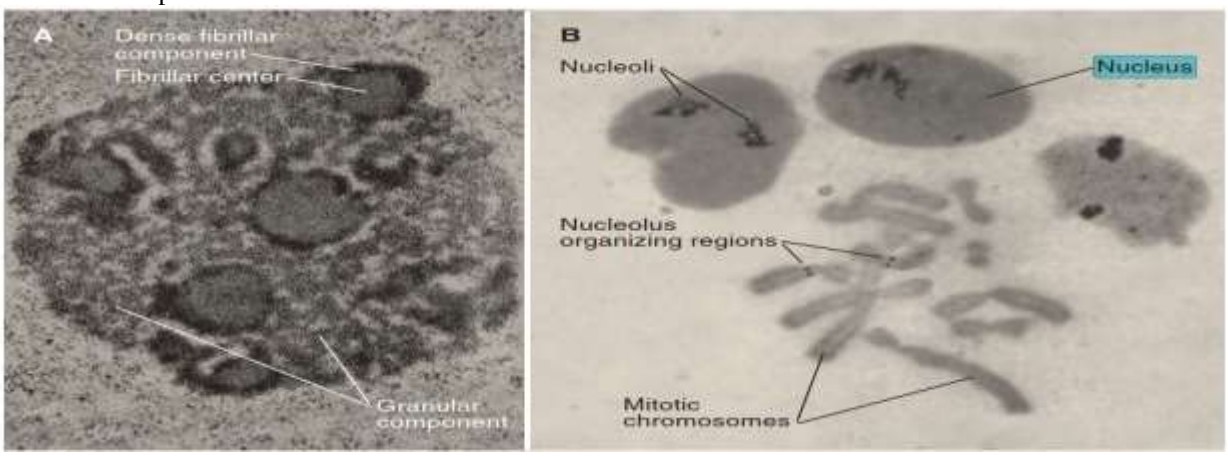


Figure 45: Nucleolus and nucleolar organizer region (Alberts et al., 2018).

3.9 Functions of the Nucleus

The nucleus performs several vital functions:

- **Genetic Information Storage:** Houses DNA, the hereditary material, organized as chromatin and chromosomes.
- **Control of Gene Expression:** Regulates which genes are transcribed and when, controlling protein synthesis and cell specialization.
- **DNA Replication:** Duplicates DNA during the S phase of the cell cycle, ensuring each daughter cell receives an exact copy during cell division.
- **RNA Synthesis and Processing**: Site of transcription (DNA → RNA). And Pre-mRNA is processed (splicing, capping, polyadenylation) before export to the cytoplasm for translation.
- **Ribosome Production**: Nucleolus synthesizes rRNA and assembles ribosomal subunits.
- **Regulation of Cell Division**: Coordinates cell cycle progression and ensures accurate chromosome segregation.

4 Nuclear Dynamics and Cell Cycle

The nucleus is dynamic, with its structure and components changing during the cell cycle:

- **Interphase**: Chromatin is decondensed, nucleolus is present.
- **Prophase:** Chromatin condenses, nucleolus disappears.
- **Metaphase:** Chromosomes are maximally condensed.
- **Telophase:** Nuclear envelope re-forms, nucleolus reappears.

Chapter 6: Ribosome and Protein Synthesis

1 Introduction :

In eukaryotes, genetic information encoded in DNA is transcribed into RNA, which undergoes post-transcriptional processing to become functional. There are three major classes of RNA: messenger RNA (mRNA), which carries genetic information for protein synthesis; non-coding RNAs like ribosomal RNA (rRNA) and transfer RNA (tRNA), which play roles in protein synthesis and ribosome biogenesis; and small regulatory RNAs such as microRNAs (miRNAs), which regulate gene expression by repressing mRNA translation. These RNA species are crucial for various cellular processes, and their processing ensures the proper functioning of the cell.

1 Ribosomes

The ribosomes are small, dense, rounded and granular particles of the ribonucleoprotein. They occur either freely in the matrix of mitochondria, chloroplast and cytoplasm (i.e., cytoplasmic matrix) or remain attached with the membranes of the endoplasmic reticulum and nucleus.

They occur in most prokaryotic and eukaryotic cells and are known to provide a scaffold for the ordered interaction of all the molecules involved in protein synthesis.

1.1 History of Ribosome Discovery and Study

- ✓ **1930s**: Ribosomes studied before discovery.
- ✓ **1940s**: Discovered and isolated.
- ✓ **1950s**: Scrutinized and characterized.
- ✓ **1958**: Ribosomes officially named.
- ✓ **1960s**: Dissociated and reconstituted.
- ✓ **1970s**: Sequenced and studied topographically.
- ✓ **1980s-Present**: Continual focus of extensive research.

1.2 Ribosome Distribution in Cells

- **Prokaryotes:** Ribosomes are typically free in the cytoplasm.
- **Eukaryotes:** Ribosomes may be free in the cytoplasm or attached to the rough ER.

- **Cells with High Ribosome Density:** Rapidly dividing or highly active cells—such as yeast, reticulocytes, lymphocytes, meristematic plant tissues, embryonic nerve cells, and cancer cells—have abundant free ribosomes. Cells specialized for secretion (e.g., pancreatic, plasma, hepatic, and glandular cells) have many ribosomes attached to the ER. Cells focused on intracellular protein synthesis (e.g., erythroblasts, developing muscle, skin, and hair cells) also contain numerous ribosomes (Alberts et al., 2015).

1.3 Isolation and Sedimentation of Ribosomes

Ribosomes are isolated from cells using differential centrifugation, which separates cellular components based on size and density. The sedimentation coefficient, measured in **Svedberg units (S),** reflects both the size and shape of the ribosome. This property is essential for distinguishing between ribosomes from different organisms and organelles.

1.4 Types of Ribosomes Based on Size and Sedimentation Coefficient

- ✓ **70S Ribosomes:** Smaller, with a sedimentation coefficient of 70S and a molecular weight of about 2.7 million daltons. Found in prokaryotes (bacteria, blue-green algae) and in mitochondria and chloroplasts of eukaryotes.
- ✓ **80S Ribosomes:** Larger, with a sedimentation coefficient of 80S and a molecular weight of about 40 million daltons. Found in the cytoplasm of eukaryotic cells. Mitochondrial ribosomes are smaller (e.g., 77S in fungi, 60S in mammals), and chloroplast ribosomes resemble prokaryotic 70S ribosomes**.**

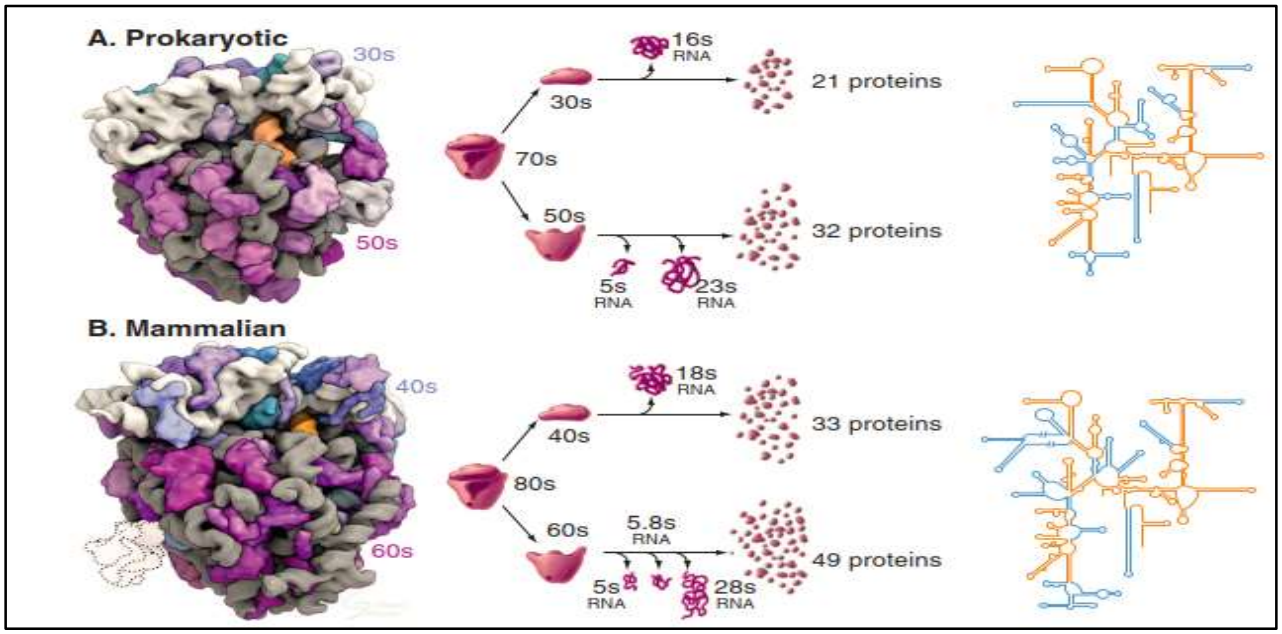


Figure 46: Types of Ribosomes Based on Size and Sedimentation Coefficient (Alberts et al., 2018).

1.5 Structure of Ribosomes

Ribosomes consist of two subunits—a small subunit and a large subunit—that come together during protein synthesis. Each subunit contains ribosomal RNA (rRNA) and numerous ribosomal proteins. The subunits are measured in Svedberg units: for example, in eukaryotes, the small subunit is 40S and the large is 60S; in prokaryotes, they are 30S and 50S, respectively (Davis, 2012).

Functional Sites

- A (Aminoacyl) Site: Binds incoming tRNA carrying amino acids.
- P (Peptidyl) Site: Holds the tRNA carrying the growing polypeptide chain.
- E (Exit) Site: Where empty tRNAs exit the ribosome.

The interface between the subunits forms a cavity lined with rRNA, where mRNA decoding and peptide bond formation occur. The growing polypeptide chain exits through a tunnel in the large subunit.

1.6 Chemical Composition of Ribosomes

Ribosomes are composed of roughly equal parts rRNA and protein, though the exact proportions differ:

- **70S Ribosomes (Prokaryotes):** 60–63% rRNA, 37–40% protein (e.g., *E. coli* ribosomes: 63% rRNA, 37% protein).
- **80S Ribosomes (Eukaryotes):** 40–44% rRNA, 56–60% protein (e.g., yeast ribosomes: 40–44% rRNA, 56–60% protein).(Davis, 2012)

a. rRNA Components

- **70S Ribosomes:** 23S and 5S rRNA in the large subunit; 16S rRNA in the small subunit.
- **80S Ribosomes:** 28S, 5.8S, and 5S rRNA in the large subunit; 18S rRNA in the small subunit

b. Ribosomal Proteins

70S Ribosomes: About 53 distinct proteins (21 in the small subunit, 32 in the large subunit).

80S Ribosomes: 70–80 proteins, larger and more numerous than in prokaryotes.

c. Metallic Ions

Divalent cations such as Mg^{2+}, Ca^{2+}, and Mn^{2+} are essential for ribosome stability and function.

1.7 Biogenesis of Ribosomes

The process begins in the nucleolus, where ribosomal DNA (rDNA) is transcribed by RNA polymerase I to produce a large precursor ribosomal RNA (pre-rRNA). This pre-rRNA undergoes extensive processing, including 2'-O-methylation and pseudouridylation, guided by small nucleolar RNAs (snoRNAs), and is further modified and cleaved into mature rRNA components. Simultaneously, 5S rRNA is transcribed outside the nucleolus. Ribosomal proteins, synthesized in the cytoplasm, are imported into the nucleus and nucleolus, where they assemble with rRNAs to form pre-ribosomal particles (preribosomes). These preribosomes undergo additional structural reorganization and maturation as they transit from the nucleolus to the nucleoplasm. After passing through the nuclear pore complex, the nearly mature ribosomal subunits enter the cytoplasm, where they complete their final maturation steps and become fully functional ribosomes capable of

participating in protein synthesis. Throughout this process, various processing and assembly factors are recycled or shuttled between the nucleus and cytoplasm to ensure efficient ribosome production (Davis, 2012).

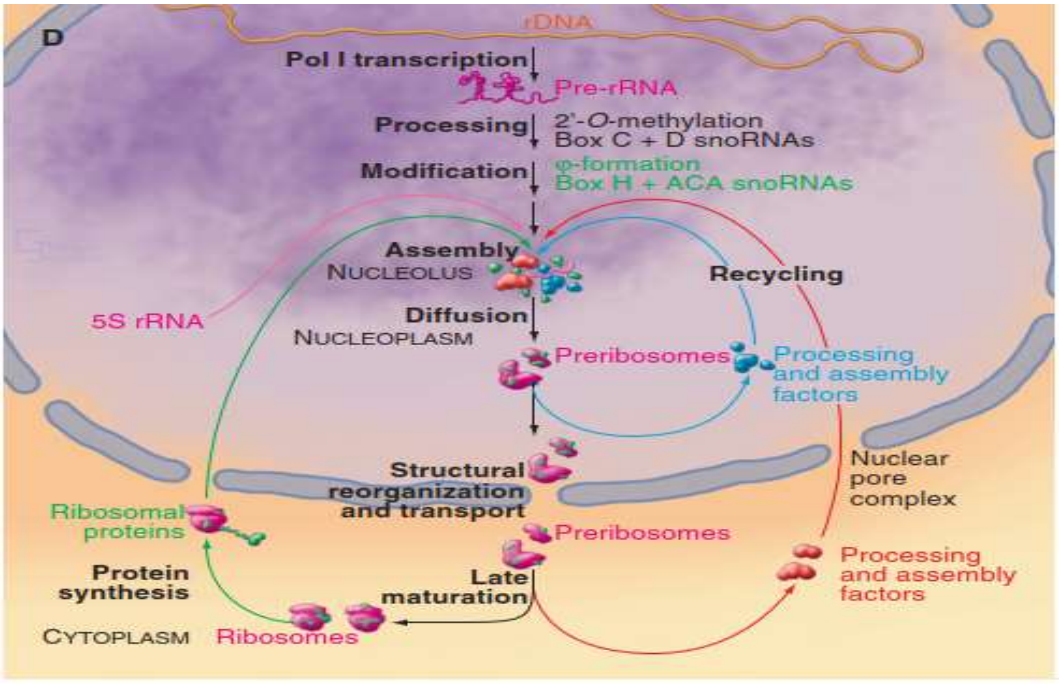


Figure 47: Biogenesis of Ribosomes (Alberts et al., 2018).

2 Protein Synthesis

Protein synthesis is the set of biochemical mechanisms that, using **amino acids** as building blocks, leads to the formation **of proteins**. These macromolecules are characteristic of the species and differ by the arrangement of amino acids. For a given protein in an individual, the amino acid order is always the same.

Genes are **DNA fragments** carrying genetic information necessary for the assembly of amino acids. The genetic code in DNA consists of **triplets** (codons of 3 bases). **Leucine**, for example, is coded by the triplets **CUU, CUC, CUA**, and **CUG**. The genetic code is redundant (several triplets can code for the same amino acid).

The information stored in DNA can be replicated as DNA, transcribed into RNA, and then translated into an amino acid sequence in proteins.

Genetic information is preserved as a code based on the fact that each DNA strand is composed of sequences (nitrogenous bases): Adenine (A), Cytosine (C), Guanine (G), Thymine (T), and Uracil (U) for RNA (Alberts et al., 2018).

A purine on one strand always pairs with a pyrimidine on the other:

- Cytosine pairs with guanine (C–G).
- Adenine pairs with thymine in DNA and with uracil in RNA (A–T and A–U).

Nucleic acids are oriented molecules. One end has a phosphate (5'P end), the other a sugar (3'OH end). Nucleic acids consist of:

- A phosphoric acid,
- A sugar,
- A nitrogenous base (Adenine, Thymine, Guanine, Cytosine, and Uracil).

A nucleoside is a sugar plus a base. A nucleotide is a nucleoside plus a phosphate. Depending on the sugar involved—either deoxyribose (a cyclic pentose) or ribose—there are two types of nucleic acids:

2.1 Deoxyribonucleic Acid (DNA)

DNA is a polymer, the largest macromolecule in living organisms, formed of two complementary, antiparallel helical strands of nucleotides. **Their 5'-3' orientations are opposite (3'-5' and 5'-3').** The sugar carbons are numbered 1' to 5'. A nitrogen atom of the base attaches to C1' (glycosidic bond), and the phosphate attaches to C5' (ester bond) to form the nucleotide. Thus, a nucleotide is: **phosphate–C5' sugar–C1' base**.

Hydrogen bonds (2 between A–T and 3 between C–G) hold the two DNA strands together, allowing nucleic acids to form stable three-dimensional structures—the DNA double helix, 20 Å in diameter. This rule ensures the conservation of base sequences and thus the information they carry.

In prokaryotes, DNA lacks proteins for compaction. The DNA helix coils on itself and is kept compact by a mechanism still not well understood, forming the nucleoid.

Structurally, replication and transcription require chromatin decondensation. Condensed chromatin prevents replication or transcription complexes from accessing DNA, as RNA polymerase II is twice the size of a nucleosome (Alberts et al., 2015).

2.2 Ribonucleic Acids (RNA)

RNA polymers are ribonucleotides and serve as functional intermediates between DNA and protein synthesis. They are grouped into three classes by function: mRNA (messenger), tRNA (transfer), and rRNA (ribosomal).

- **mRNA:** Carries genetic information from the nucleus to the cytoplasm via the nucleoplasmic cytoskeleton.
- **tRNA:** A small, globular molecule (~70 nucleotides) that carries the anticodon (complementary to the codon) at its 3' end and brings an amino acid matching the codon on the mRNA, pairing via hydrogen bonds.
- **rRNA:** (Discussed in the ribosome section).

2.3 Protein Synthesis in Eukaryotes Occurs in Three Steps

- ✓ Transcription
- ✓ Maturation
- ✓ Translation

First Step: Transcription (in the nucleus)

- Begins with the transcription of a complementary nucleotide sequence (mRNA) from a DNA gene sequence.
- RNA polymerase II binds to DNA and unwinds it at a protein-coding gene in the presence of transcription factors.
- One of the two DNA strands (the template or transcribed strand) serves as a template for mRNA synthesis.
- Each DNA nucleotide attracts a complementary RNA nucleotide, except uracil replaces thymine in RNA.
- The order of nucleotides in mRNA is dictated by the DNA sequence.
- DNA strands re-associate after RNA polymerase detaches.

DNA consists of alternating coding (exons) and non-coding (introns) sequences. Each exon is followed by an intron, and their nucleotide lengths vary (Meyers, 1995).

Second Step: mRNA Maturation

- Pre-mRNA undergoes maturation before leaving the nucleus for the cytoplasm, involving excision and splicing:
  - Excision: Enzymatic removal of introns.
  - Splicing: Joining of exons.
- The pre-mRNA receives:

- A 7-methylguanosine triphosphate cap at the 5' end.
- A poly-A tail (50–250 adenines) at the 3' end, which:
    - Stimulates transcription termination,
    - Assists mRNA migration to the cytoplasm,
    - Protects mRNA from rapid degradation,
    - Helps initiate translation.
    - Mature mRNA detaches and exits the nucleus through nuclear pores.

Third Step: Translation (in the cytoplasm at the ribosome with tRNAs)

Translation is divided into three phases:

- Initiation
- Elongation (chain extension)
- Termination

Initiation:

Requires:

- Both ribosomal subunits,
- mRNA,
- Initiator tRNA (Met-tRNA),
- Three initiation factors,
- GTP (energy).

The initiation codon is an AUG

- Is towards the 5’ end of the mRNA molecule that is being translated.
- NOT the first 3 nucleotides!
- It determines the reading frame.

In prokaryotes, there is a conserved region about 7 nucleotides upstream from the initiating AUG:

- This region contains a 6-nucleotide sequence
- Shine-Dalgarno box: AGGAGG.

The Shine-Dalgarno sequence is complementary to a region at the 3’ end of the 16 rRNA of the small subunit;

- Base pairing between these complementary sequences stabilizes the binding of the small ribosomal subunit to the mRNA for proper assembly (Meyers, 1995).

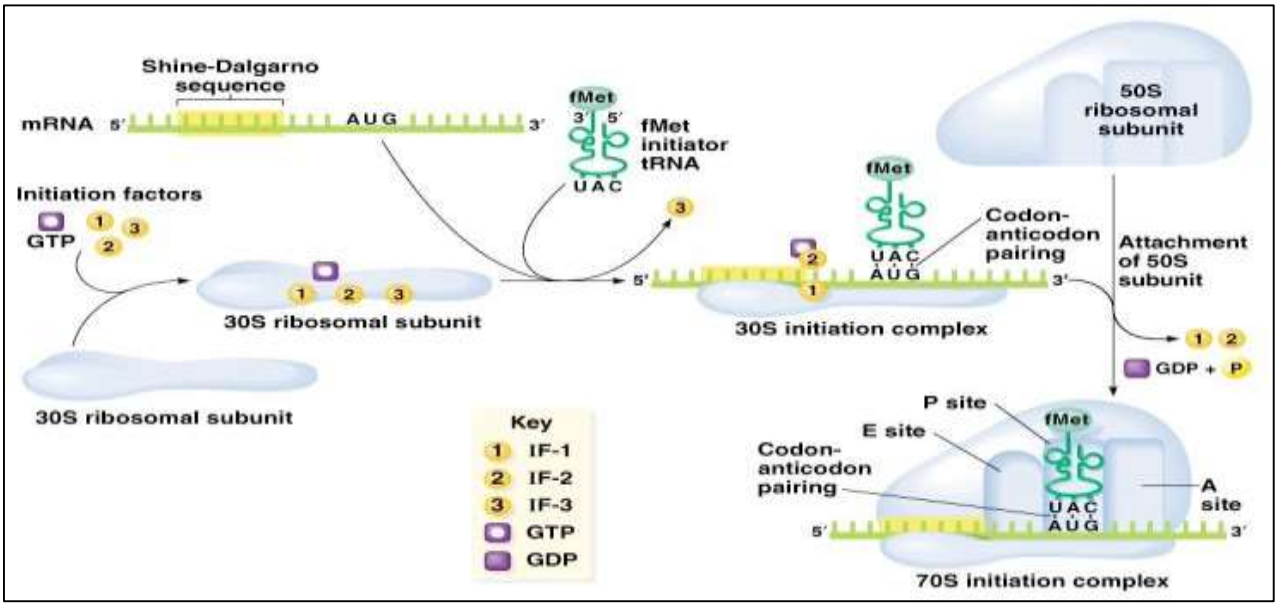


Figure 48: Initiation of protein synthesis in prokaryotes (Alberts et al., 2018).

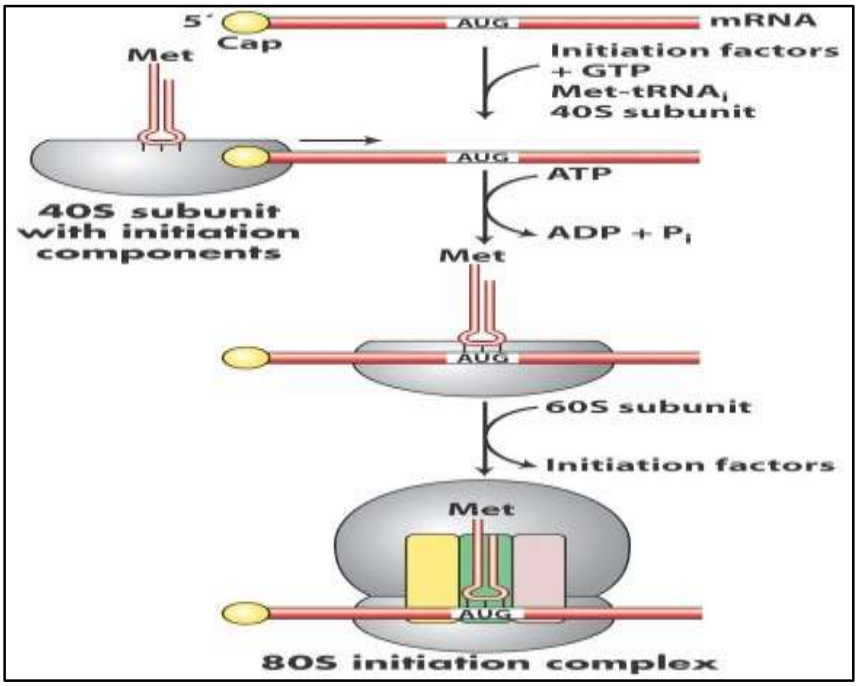


Figure 49: Initiation of protein synthesis in Eucaryotes (Alberts et al., 2018).

Elongation:

- A second tRNA carrying the next amino acid binds to the A site, matching the second mRNA codon.
- A peptide bond forms between the two amino acids via peptidyl transferase.
- The initial tRNA detaches from its amino acid and mRNA and returns to the cytoplasm.
- The ribosome translocates one codon, positioning the next tRNA at the P site and a new aminoacyl-tRNA at the A site.
- The chain elongates from the N-terminal to the C-terminal end.
- This step requires GTP and elongation factors.

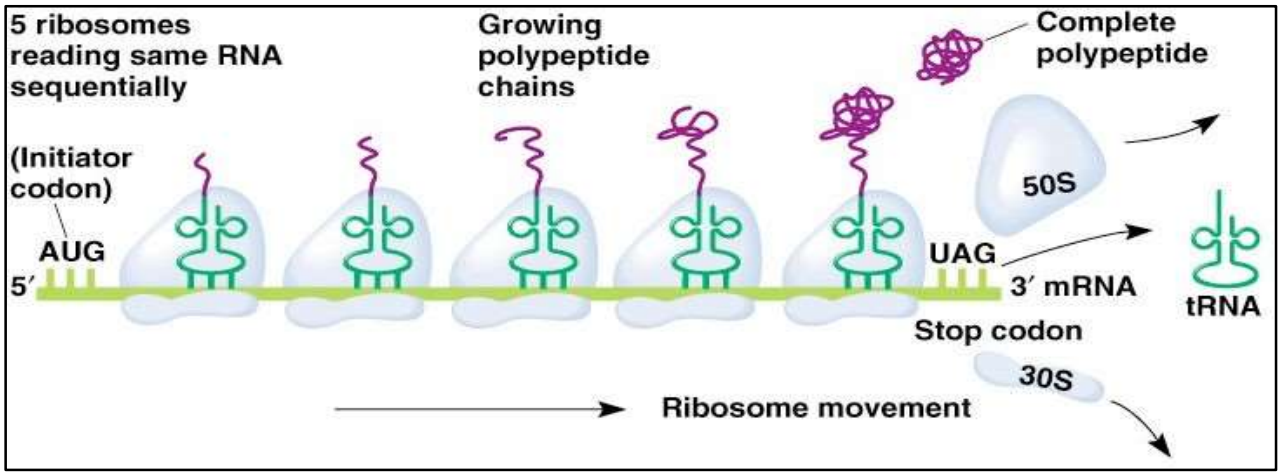


Figure 50: Elongation phase (Alberts et al., 2018).

Termination:

- Occurs when the A site of the ribosome encounters a STOP or nonsense codon (UAA, UAG, UGA), for which no tRNA exists.
- A release factor recognizes these sequences and occupies the A site, causing hydrolysis of the bond between the newly synthesized protein and the tRNA. The protein chain is released from the ribosome.
- The tRNA is released into the cytoplasm, and the ribosome dissociates into subunits, releasing the mRNA.
- Most newly synthesized cytoplasmic proteins are handled by chaperone proteins, which help establish the final tertiary structure.

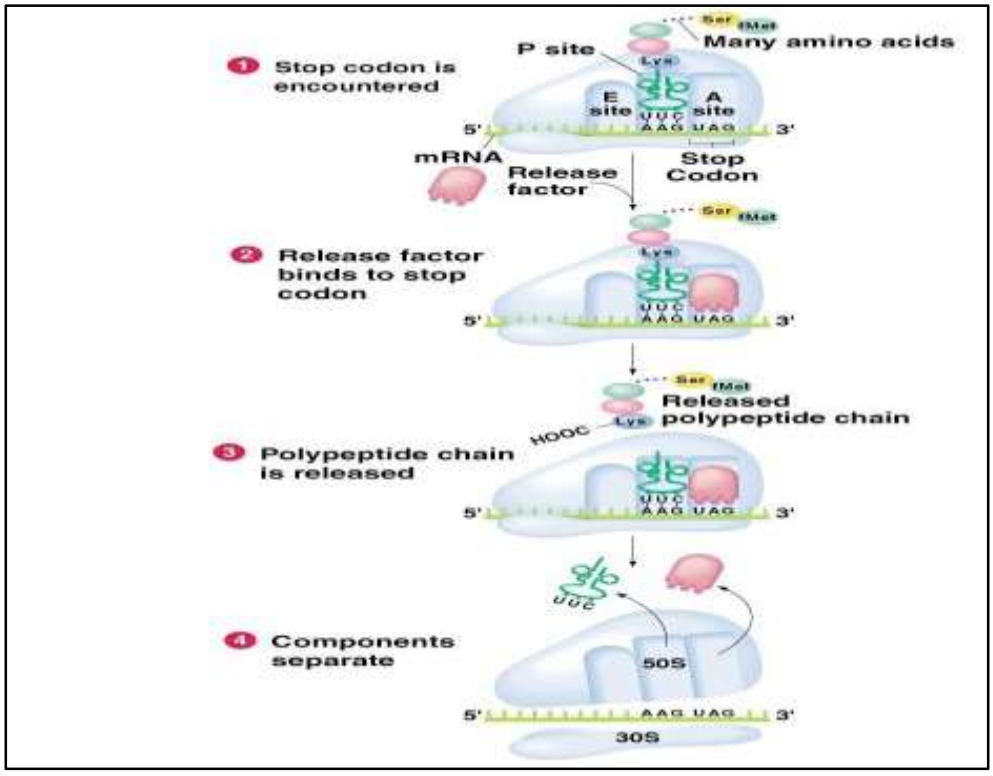


Figure 51: Termination of translation (Alberts et al., 2018).

Chapter 7: The Endomembrane System

1 Introduction to the Endomembrane System

The endomembrane system, present only in eukaryotic cells, is composed of cytoplasmic cavities bounded by membranes that communicate with each other through vesicles or small channels. The different compartments of this system are: the endoplasmic reticulum, the Golgi apparatus, phagosomes and endosomes, lysosomes, and the plant vacuole. The endomembrane system is highly dynamic, with constant movement and exchange of materials via vesicular transport

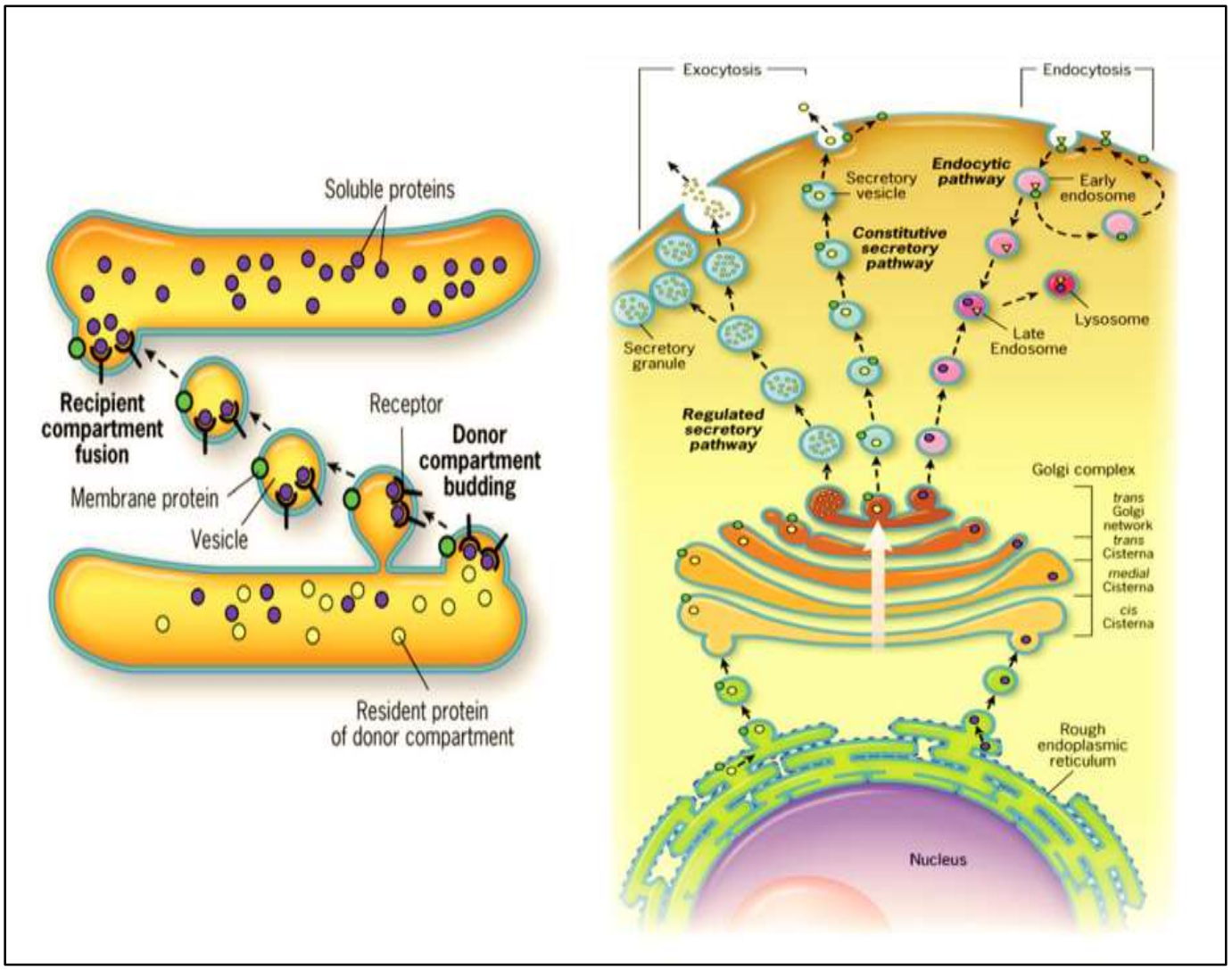


Figure 52: Membrane-bound compartments of the cytoplasm (Alberts et al., 2018).

1.1 The Endoplasmic Reticulum (ER): Structure and Types

1.1.1 Discovery and Morphology

The ER was first visualized by Porter in the 1940s and named in 1953. Under the light microscope, it appears as a network (reticulum) within the cytoplasm. Electron microscopy reveals an extensive network of interconnected cisternae (flattened sacs), tubules, and vesicles traversing the cytoplasm. The ER membrane is continuous with the outer nuclear envelope and often closely associated with the Golgi apparatus and plasma membrane.

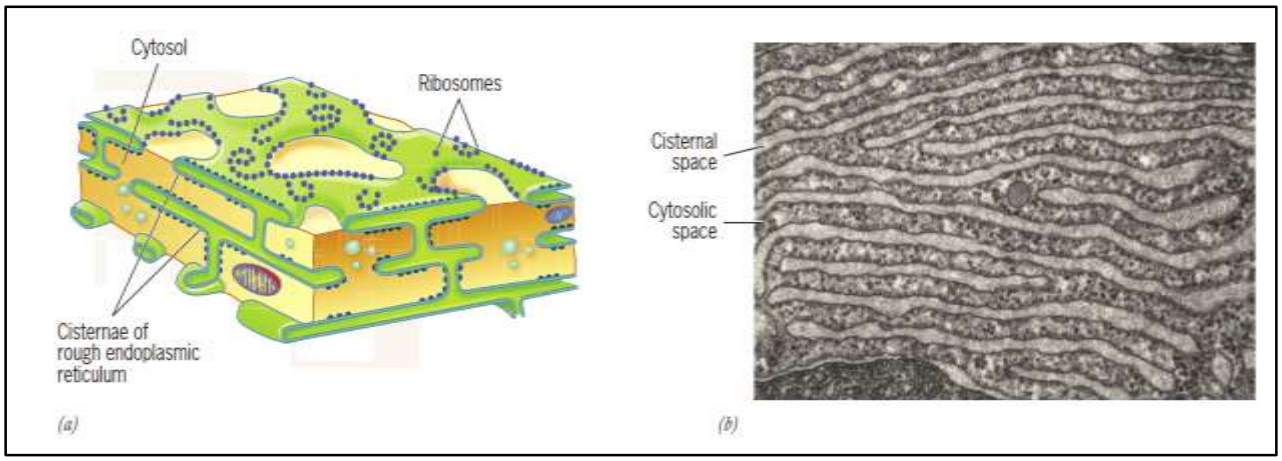


Figure 53: The rough endoplasmic reticulum (RER).

1.1.2 Forms of ER

- **Cisternae:** Long, flattened, unbranched sacs (40–50 µm diameter), often arranged in parallel stacks. Prominent in cells with active protein synthesis (e.g., pancreas, brain).
- **Vesicles:** Oval, membrane-bound structures (25–500 µm diameter), abundant in smooth ER regions.
- **Tubules:** Branched, forming a dynamic reticular system (50–190 µm diameter), especially in smooth ER.

1.1.3 Types of ER

1.1.3.1 Rough Endoplasmic Reticulum (RER)

- **Structure:** Studded with ribosomes on the cytoplasmic side, giving a "rough" appearance. Composed mainly of cisternae.
- **Location:** Prominent in cells engaged in protein synthesis for export or membrane insertion (e.g., hepatocytes, pancreatic acinar cells, plasma cells).

- **Function:** Synthesis and initial modification (folding, glycosylation) of proteins destined for secretion, membranes, or lysosomes.

1.1.3.2 Smooth Endoplasmic Reticulum (SER)

- **Structure:** Lacks ribosomes, appears smooth, composed mainly of tubules and vesicles.
- **Location:** Abundant in cells involved in lipid metabolism, detoxification, and steroid synthesis (e.g., liver, adrenal cortex, gonads, muscle—where it is called sarcoplasmic reticulum).
- **Function:** Lipid and steroid biosynthesis, carbohydrate metabolism, detoxification, calcium storage and release.

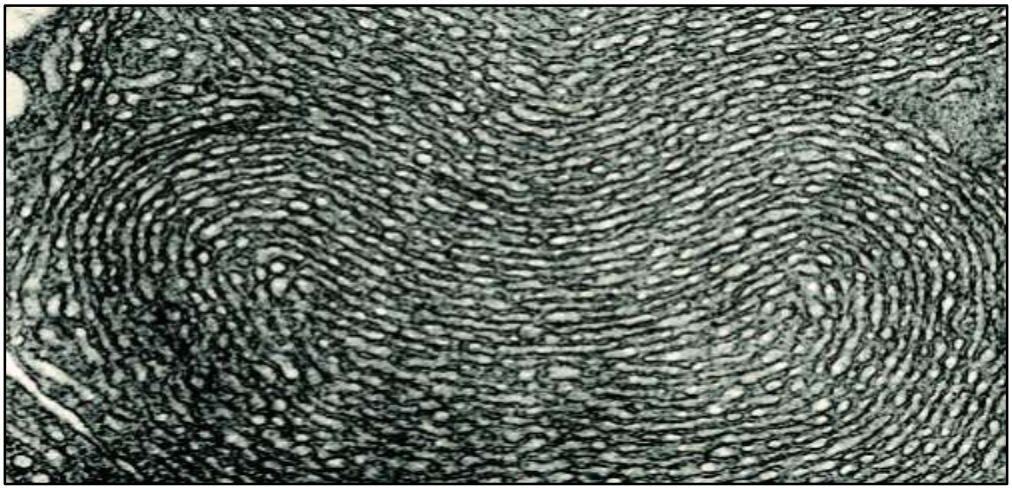


Figure 54: The smooth ER (SER). Electron micrograph of a Leydig cell from the testis showing the extensive smooth ER where steroid hormones are synthesized.

1.1.4 Chemical Composition and Enzymes of the ER

- **Membrane:** Fluid-mosaic model; phospholipid bilayer with embedded proteins.
- **Proteins:** ER membranes are rich in proteins (60–70% by weight in rough ER), including enzymes for lipid and carbohydrate metabolism, protein folding, and detoxification.
- **Enzymes:** Key enzymes include stearases, NADH-cytochrome C reductase, glucose-6-phosphatase (marker for SER), and cytochrome P-450 (detoxification).

1.1.5 Functions of the Endoplasmic Reticulum

1.1.5.1 Common Functions

- **Structural Support:** Provides a skeletal framework for the cytoplasm.
- **Compartmentalization:** Divides the cytoplasm into functional compartments, facilitating specialized metabolic activities.
- **Transport:** Acts as an intracellular circulatory system, transporting proteins and lipids to other organelles via vesicles.

- **Membrane Biogenesis:** Major site for the synthesis of new membrane phospholipids and proteins.

1.1.5.2 Functions of Smooth ER

- **Lipid Synthesis:** Produces phospholipids, cholesterol, and steroid hormones.
- **Carbohydrate Metabolism:** Involved in glycogenolysis (breakdown of glycogen) via glucose-6-phosphatase, maintaining blood glucose homeostasis.
- **Detoxification:** Modifies drugs and toxins to make them more water-soluble for excretion; proliferation of SER is observed in cells exposed to drugs (e.g., phenobarbital).
- **Calcium Storage:** Sarcoplasmic reticulum in muscle stores and releases Ca^{2+} ions for muscle contraction.
- **Other Roles:** Synthesis of triglycerides, visual pigments, and plant cell wall components.

1.1.5.3 Functions of Rough ER

- **Protein Synthesis:** Ribosomes on RER synthesize proteins destined for secretion, membranes, or lysosomes.
- **Protein Folding and Modification:** Newly synthesized polypeptides enter the RER lumen, where they are folded and undergo co-translational modifications (e.g., N-linked glycosylation).
- **Quality Control:** Misfolded proteins are retained in the ER for refolding or degradation.

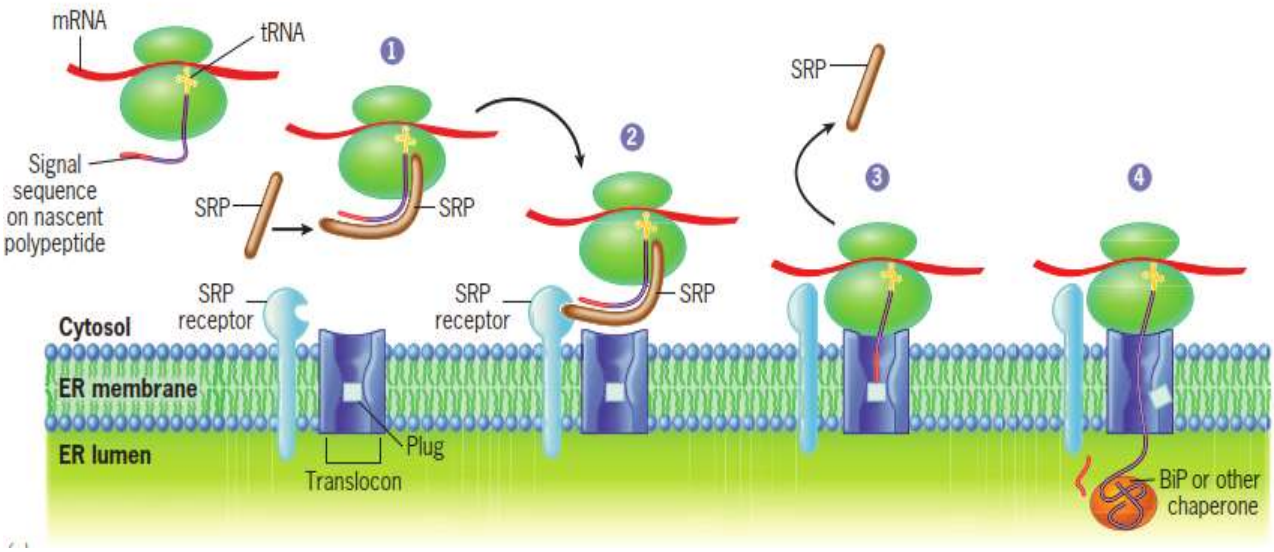


Figure 55: A schematic model of the synthesis of a secretory protein (or a lysosomal enzyme) on a membrane-bound ribosome of the RER (Alberts et al., 2018).

1.1.6 Protein Targeting and the Signal Hypothesis

- **Signal Peptide:** Proteins destined for secretion or membranes have an N-terminal signal sequence.
- **SRP (Signal Recognition Particle):** Binds the signal peptide, pauses translation, and directs the ribosome-mRNA complex to the ER membrane.
- **Translocation:** The complex binds to the SRP receptor on the ER membrane, translation resumes, and the nascent polypeptide is translocated into the ER lumen or membrane.
- **Signal Peptidase:** Cleaves the signal peptide; the protein is then folded and modified in the ER.

1.1.7 Glycosylation in the ER

- **N-linked Glycosylation:** Addition of a pre-assembled oligosaccharide to the asparagine residue of a nascent protein in the ER lumen.
- **Dolichol Carrier:** The oligosaccharide is assembled on a lipid carrier (dolichol) and transferred en bloc.
- **Processing:** Initial trimming of sugars occurs in the ER; further modification happens in the Golgi apparatus.

1.2 The Golgi apparatus: Structure and Organization

1.2.1 Discovery and Morphology

- Discovered by Camillo Golgi in 1898 using silver staining.
- **Shape:** the shape of Golgi is quite variable in somatic cell types of animals, even in the same cell, there are variation with functional stages. In some cases, it occurs as dense reticulum of anastomosing trabeculae while in others as an irregular fenestrated plaque a ring hollow spheres united together. In nerve cells it occurs as a reticular of wide meshes around the nucleus.
- **Size:** The size of Golgi is variable, small in muscle cell and large in nerve and the gland cell.
- **Numbers:** The number of Golgi apparatus per cell is also variable. Some cells have recorded as having a single apparatus, other cells with dispersed Golgi may have hundred.
- Position: The position of Golgi is relatively fixed for each cell type. In the cells which are ectodermal in origin, the Golgi is polarized from the time of embryonic stage between the nucleus and the periphery of the cell.

1.2.2 Electron Microscope Structure:

1.2.2.1 Structure

Under a light microscope, after impregnation with silver nitrate, the Golgi apparatus appears as small scales near the nucleus.

1.2.2.1.1 Organisation

In the TEM, a stack of saccules and small vesicles. Each stack of 4 to 8 saccules is a dictyosome (on average 20 dictyosomes per cell). Each dictyosome comprises cis saccules (close to the ER); the input side supplied by the ER, median saccules and trans saccules (output side) in continuity with a network of canaliculi called the Trans-Golgi Network (TGN).

1.2.2.1.2 Golgi membranes

In the TEM, the membrane is tripartite; in the SEM, integrated globular particles are present. The thickness of the membranes is variable and intermediate between those of the GER (or RER) and the plasma membrane (cis saccule: 6nm and trans saccule: 7,5nm).

1.2.3 Functions of the Golgi Apparatus

1.2.3.1 Protein Modification and Sorting

- **Glycosylation:** Continues and modifies N-linked glycosylation begun in the ER; adds O-linked oligosaccharides to serine/threonine residues.
- **Phosphorylation:** Adds phosphate groups to certain proteins (e.g., lysosomal enzymes).
- **Sulfation, Acetylation, Proteolysis:** Additional post-translational modifications.

1.2.3.2 Packaging and Secretion

- **Sorting Center:** Directs proteins to their correct destinations (plasma membrane, lysosomes, secretory vesicles).
- **Vesicle Formation:** Packages proteins into vesicles for transport; secretory vesicles fuse with the plasma membrane to release contents (exocytosis).
- **Lysosome Formation:** Involvement in the production of lysosomes and their enzymes.

1.2.3.3 Plant Cell Functions

- **Cell Wall Synthesis:** Synthesizes and exports complex polysaccharides for cell wall formation (e.g., pectins, hemicellulose).
- **Cytokinesis:** Golgi-derived vesicles form the cell plate during plant cell division.

1.2.4 Dynamics and Models of Transport

- **Vesicular Transport Model:** Cargo moves forward in vesicles between stable cisternae.

- **Cisternal Maturation Model:** Cisternae themselves mature and progress from cis to trans, carrying cargo with them.
- **Combined Model:** Both vesicular and cisternal maturation mechanisms operate, with retrograde vesicles recycling Golgi enzymes.

Table 4: Differences between ER and Golgi apparatus

Feature	**Endoplasmic Reticulum (ER)**	**Golgi Apparatus**
Structure	Network of tubules, cisternae, vesicles	Stacks of flattened cisternae
Types	RER (with ribosomes), SER (no ribosomes)	Only one type
Location	Continuous with nuclear envelope	Near nucleus, not continuous with envelope
Ribosomes	Present on RER, absent on SER	Absent
Main Functions	Protein/lipid synthesis, detoxification, transport	Protein modification, sorting, packaging
Association with Lysosomes	Synthesizes lysosomal hydrolases	Produces lysosomes
Size	Largest organelle	Smaller than ER

2 Clinical and Biological Relevance

- **Drug Metabolism:** Proliferation of SER in liver cells in response to drugs increases detoxification capacity.
- **Genetic Disorders:** Defects in glycosylation enzymes (in ER or Golgi) can cause congenital disorders of glycosylation.
- **Muscle Function:** Sarcoplasmic reticulum's role in calcium handling is critical for muscle contraction and relaxation.
- **Secretion Disorders:** Malfunction of the Golgi apparatus can disrupt hormone and enzyme secretion, affecting multiple organ systems.

2.1 Endosome or receptosome.

Recently it has been found that in the cells exists a complex set of heterogeneous membrane-bound tubes and vesicles, called **endosome**, which extends from the **periphery of the cell** to the **peri-nuclear** region, where it lies quite close to Golgi apparatus. Thus, endosomes may be of two types:

- **Peripheral endosomes** just beneath the plasma membrane and
- **Peri-nuclear** or internal endosomes.

The interior of the endosome is **acidic** (**pH 5-6**) due to the presence of ATP-driven proton (H+) pumps in its membrane that pumps H+ ions into the lumen from the cytosol (Sly and Doisy, 1984). Endosomes lack in degradative enzymes.

Thus, via receptor-mediated coated-vesicles, the ligands are delivered to the peripheral endosomes which slowly move inward to become perinuclear endosomes. These perinuclear endosomes are converted into endolysosomes and then into lysosomes due to following three activities :

- The fusionof transport vesicles from the Golgi apparatus,
- Continuous membrane retrieval
- Increased acidification

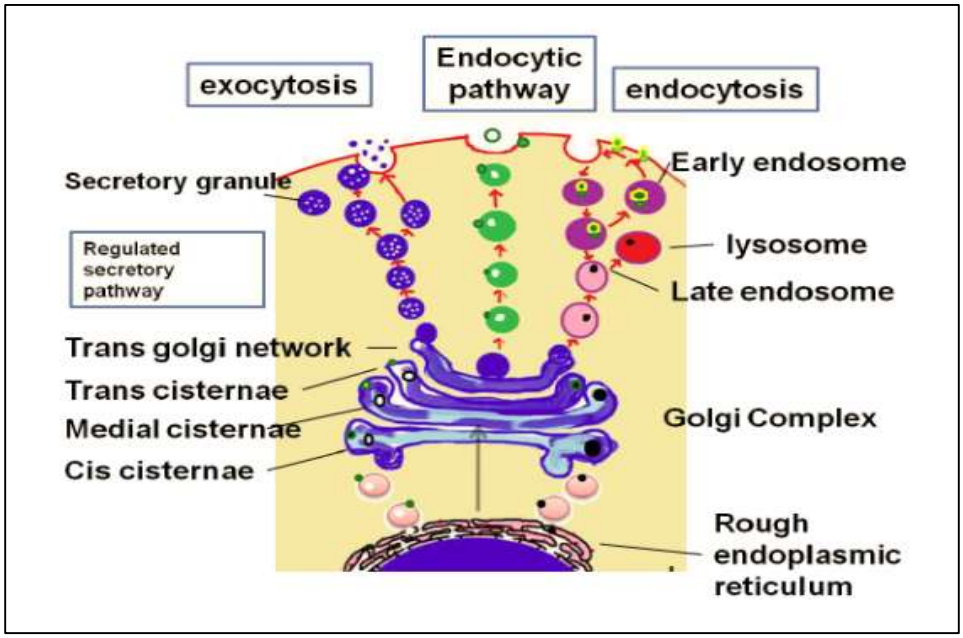


Figure 56 : Intra-Cellular Vesicular Trafficking System of Cell

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2.2 Lysosomes

In the cytoplasmic matrix of the cells, there occur variously shaped bodies usuallybounded by a single surface membrane and containing hydrolytic enzymes. Theseare called lysosomes. These enzyme containing bodies play important role in thedigestion or lysis of intracellular substances, so they are called lysosomes.

2.2.1 Occurrence of Lysosomes

Lysosomes appear to be **absent** in prokaryotes. Cyto-chemical and electron microscopic studies have revealed the **presence of membrane bound** enzyme-containing bodies in animal tissues. It is not certain whether the structures equivalent to animal Lysosomes are present in plant cells.

The presence of lysosomes has been demonstrated in several slime moulds, fungal hyphae and algae. In 1964, P. Matile reported the occurrence of lysosomes in neumspora. Among the algae acid phosphatase has been located in lysosomes of Euglena and a few other species.

2.2.2 Structure of Lysosomes

Lysosomes represent a class of morphologically heterogeneous cytoplasmic particles. The polymorphic nature of lysosomes has been attributed to specific functions, substances they contain and stage of digestion of those substances.

Their size ranges from 0.25 to 0.8µ in diameter. In mammalian kidney cells theymay be as large as 5µ and they may be even larger in phagocytes.

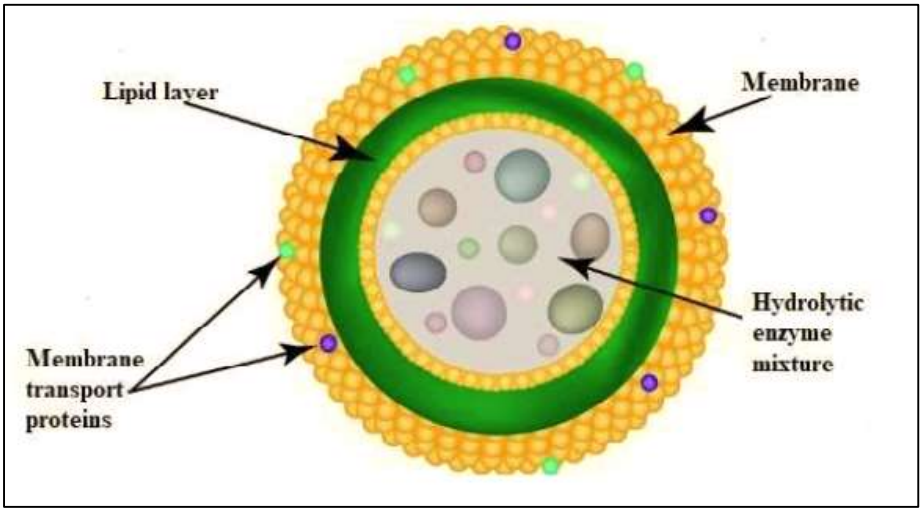

Figure 57 : Structure of Lysosome

Based on morphological and functional criteria, a variety of lysosomes can be recognised in different cells as well as within a single cell. **Two basic forms** of lysosomes have been distinguished:

- The primary lysosomes; and
- The Endoplasmic Reticulum secondary lysosomes.

2.2.2.1 Primary Lysosomes (Storage Granules)

They originate from the endoplasmic reticulum or are cut off indirectly from the tips of Golgi saccules and have not yet been involved in digestive process.

2.2.2.2 Secondary Lysosomes

These are digestive vacuoles, which are sites of digestive activity. Lysosomes belonging to this group may be classified into two separate types;

- Heterophagic
- Autophagic on the basis of exo or endogenous origin of the material undergoing digestion

Each of these types may be further sub-divided as follows:

- Pre-Lysosomes whose enzymes have never been engaged in hydrolysis.
- Lysosomes which are sites of present digestive activity.
- Post-Lysosomes which have lost their enzymes.

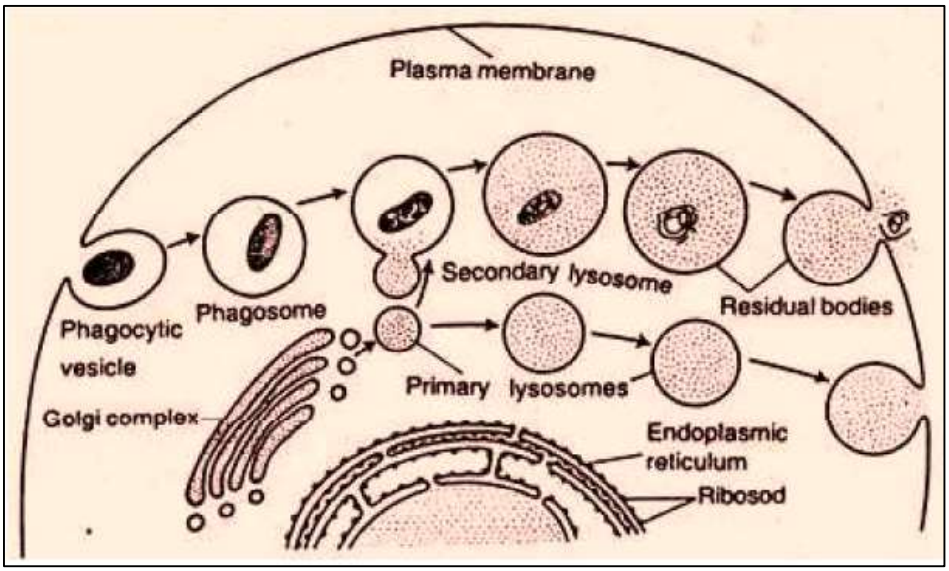

Figure 58 : Formation of Primary and secondary Lysosomes

2.2.3 Functions of Lysosomes

2.2.3.1 Extracellular Digestion

Lysosomes are small bags containing **digestive enzymes**. They behave like tiny time bombs waiting for their explosion in the cytoplasm. When the limiting membrane ruptures, the digestive enzymes are released which take part in the digestion.

Sometimes lysosomal enzymes may be released outside the cell where they digest extracellular substances. Saprophytic fungi and other micro-organisms utilize extracellular digestion of complex substrates in the habitat and degrade them into simpler soluble forms which are then absorbed.

2.2.3.2 Intracellular Digestion

The digestive enzymes released in the cytoplasm may be involved in **autophagy** or **heterophagy.**

- **Autophagy**: refers to digestion of endogenous materials or breakdown of molecules and pieces of cytoplasmic materials within the cell. The simpler substances formed after the digestion are then utilized in the synthesis of some other substances.
- **Heterophagy**: refers to intake of extraneous matter into the cell and subsequent break-down of that material by acid hydrolases. The bulk intake of exogenous material is called endocytosis.

2.2.3.3 Role in the Release of Hormones

There is evidence that lysosomal acid hydrolases are involved in release of certain hormones from secretory cells of certain glands, e.g., thyroid hormones are released by hydrolysis of thyroglobulin.

2.2.3.4 Role in the Penetration of Sperm Nucleus into the Egg

The enzymes released from acrosome vesicle, the giant lysosomes of sperms, dissolve the cortical granules, the structure surrounding the egg nucleus and help in the penetration of sperm nucleus into the egg.

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