Faculty of Medicine – Department of Medicine – Cytology Course – First Year of Medicine – Academic Year 2025/2026 – Academic Coordinator of the Cytology Module: Prof.W.AYAD

PLASMA MEMBRANE

I- STRUCTURE

The plasma membrane is an essential structure that defines all living cells and separates the cell from its environment. It acts as a selectively permeable barrier that regulates the transport of molecules between the intracellular and extracellular compartments. The plasma membrane plays a key role in protecting the cell and maintaining its integrity, as well as in cell recognition, signaling, and adhesion. Under transmission electron microscopy, the plasma membrane, with an average total thickness of about 7.5 nm, appears as three distinct layers that differ in electron density: two dense layers approximately 2 nm thick each, separated by a lighter layer of about 3.5 nm. This trilaminar structure is also observed in the membranes of organelles within the cell.

II- BIOCHEMICAL COMPOSITION

The plasma membrane is an assembly of protein and lipid molecules held together mainly by non-covalent interactions. Membrane carbohydrates, which form the glycosylated fraction of glycoproteins and glycolipids, constitute the **cell coat** or **glycocalyx**.

1. Membrane Lipids

Lipid molecules are organized into a **lipid bilayer**, which represents the fundamental structural framework of all cellular membranes. Membrane lipids are **amphipathic**, with polar head groups oriented outward and hydrophobic fatty acid tails facing inward.

The lipids include:

Phosphoglycerides, such as *phosphatidylcholine*;

Sphingosine-based lipids, such as *sphingomyeline*;

Glycolipids, including *cerebrosides* and *gangliosides*;

Cholesterol, a sterol molecule with a rigid ring structure, a single polar hydroxyl group, and a short nonpolar hydrocarbon tail. Cholesterol molecules orient within the lipid bilayer so that their hydroxyl group lies close to the polar heads of adjacent phospholipids. Glycolipids contain a sugar residue or oligosaccharide attached to the polar head group and are found exclusively in the **non-cytosolic (outer) leaflet**. Glycolipids are present in all animal plasma membranes, where they account for about **5%** of the lipid molecules in the outer monolayer.

2. Membrane Proteins

Membrane proteins include all proteins that contribute to the structure of the plasma membrane: **intrinsic (integral or transmembrane) proteins**, **peripheral (extrinsic)** proteins, and **lipid-anchored** proteins.

a. Intrinsic (Transmembrane) Proteins

These proteins are firmly embedded in the plasma membrane, penetrating the lipid bilayer. They are **amphipathic**, possessing both hydrophobic and hydrophilic regions. The hydrophobic domains are intramembranous and typically composed of nonpolar amino acids forming the **transmembrane segment**, whereas the hydrophilic regions are exposed to the aqueous environments on the cytosolic and extracellular sides.

Most intrinsic membrane proteins function as:

Receptors, binding specific ligands at the membrane surface;

Channels or transporters, mediating the passage of ions and solutes across the membrane;

Single-pass transmembrane proteins traverse the bilayer only once. They possess two hydrophilic ends—one facing the extracellular space and the other the cytoplasm—connected

by a hydrophobic segment embedded in the lipid layer. These proteins generally act as **receptors** that detect chemical signals (e.g., hormones) or physical stimuli and convert them into intracellular responses.

Multi-pass transmembrane proteins cross the bilayer several times, forming multiple regular α-helices, each composed of roughly thirty amino acids.

b. Peripheral Membrane Proteins

Peripheral membrane proteins are hydrophilic and do not penetrate the hydrophobic interior of the bilayer. They are associated with the membrane through non-covalent interactions, attaching either to the cytosolic or extracellular surface, to the polar head groups of lipids, or to hydrophilic regions of intrinsic proteins extending beyond the bilayer. Peripheral proteins, especially those on the cytosolic side, provide mechanical support, serve as anchoring points for other membrane proteins, and act as mediators of signal transduction. Their association with the membrane is dynamic—they can attach or detach depending on cellular conditions.

c. Lipid-Anchored Membrane Proteins

These proteins are located outside the lipid bilayer—either on the extracellular or cytosolic side, but are covalently linked to lipid molecules embedded in the bilayer. Many proteins on the inner surface of the plasma membrane are attached via a short oligosaccharide chain linked to **phosphatidylinositol** within the outer leaflet. Such proteins are known as **GPI-anchored proteins** (*Glycosylphosphatidylinositol-anchored*). Other cytosolic membrane proteins are tethered to the bilayer by one or more long hydrocarbon chains inserted into the inner leaflet.

3. Membrane Carbohydrates

Membrane carbohydrates occur as oligosaccharide residues of glycoproteins and glycolipids. These carbohydrate chains are always located on the extracellular surface of the membrane, forming the cell coat (glycocalyx).

The cell coat contains:

Intrinsic components, such as glycoproteins and glycolipids embedded in the membrane;

Extrinsic components, such as adsorbed extracellular matrix proteins (e.g., **fibronectin** and **laminin**).

The carbohydrate composition of the glycocalyx varies among cell types and provides each cell with a specific identity, enabling cell recognition and adhesion. For example, antigens within the glycocalyx of red blood cells determine the ABO blood groups, with cells of the same group not aggregating together. Cell recognition and adhesion are essential for tissue formation. The glycocalyx also serves as a protective barrier against mechanical, chemical, and enzymatic damage, and contributes to maintaining membrane asymmetry.

III. MEMBRANE FLUIDITY AND MOBILITY OF MEMBRANE COMPONENTS

The lipid bilayer is **fluid**, with lipid molecules able to diffuse rapidly within their own leaflet (**lateral diffusion**). The movement of most lipid molecules within one leaflet is independent of that occurring in the opposite leaflet. Some lipids undergo **flip-flop movement**, transferring from one side of the bilayer to the other with the help of specific **translocator enzymes** that maintain membrane asymmetry:

Flippases (ATP- and calcium-dependent) catalyze the transfer of **phosphatidylserine** and **phosphatidylethanolamine** from the outer leaflet to the cytosolic leaflet of the plasma membrane.

Membrane proteins do not flip from one side of the bilayer to the other, but they can **rotate** around an axis perpendicular to the plane of the bilayer (**rotational diffusion**). Moreover, many membrane proteins can move **laterally** within the membrane (**lateral diffusion**), contributing to the dynamic nature of the membrane.

IV. MEMBRANE ASYMMETRY

The distribution of lipids between the two leaflets of the bilayer is highly asymmetric.
Sphingolipids and phosphatidylcholines are more abundant in the outer leaflet, whereas phosphatidylethanolamines and phosphatidylserines predominate in the inner leaflet.
This asymmetric distribution reflects the distinct functional roles of the two membrane surfaces and is crucial for cellular signaling, particularly the conversion of extracellular signals into intracellular responses. Membrane proteins also exhibit an asymmetric distribution between the two sides of the membrane, which determines many of the physiological properties of the membrane.
Asymmetry is further influenced by carbohydrates:
Glycosylation of proteins and lipids occurs within the lumen of the endoplasmic reticulum and the Golgi apparatus, thus, sugar residues are found only on the extracellular side of the plasma membrane, forming the cell coat (glycocalyx).
This glycocalyx plays an essential role in cell adhesion and cell recognition.

V. PERMEATIVE TRANSPORTS OF THE PLASMA MEMBRANE

Membrane transport mechanisms include:
Passive transport, which depends on the energy provided by the concentration gradient of the substance being transported. This process does not require cellular energy.
Active transport, which relies on membrane pumps that consume energy derived from the hydrolysis of cellular ATP to move molecules against their concentration gradient.

V. TRANSPORT MECHANISMS ACROSS THE PLASMA MEMBRANE

1. Passive Transport

a. Simple Diffusion

Simple diffusion is the transmembrane passage of molecules from a region of higher concentration to one of lower concentration, that is, **down their concentration gradient**, without any expenditure of cellular energy. The movement of substances by simple diffusion across the membrane depends on several factors:

Molecular size

Molecules with a molecular mass greater than 150 Da cannot cross the membrane freely. The rate of penetration is inversely proportional to molecular volume (this rule applies mainly to small molecules).

Partition coefficient (P.C.)

$$P.C. = \frac{\text{Lipid solubility}}{\text{Water solubility}}$$

The higher this ratio, the easier the molecule can pass through the membrane. Lipid-soluble molecules (such as alcohols or anesthetics) diffuse rapidly across the plasma membrane.

Concentration gradient

If a molecule can move freely through the membrane, its rate of diffusion is proportional to the concentration difference across the membrane—it moves from regions of high concentration to regions of low concentration.

Electrical charge:

Charged molecules with a high degree of hydration, even if very small, cannot penetrate the lipid bilayer.

b. Facilitated diffusion

Certain molecules such as ions, sugars, amino acids, and many cellular metabolites cross membranes through selective transport proteins that mediate facilitated diffusion. These

proteins enable specific solutes to cross the membrane without contacting the hydrophobic core of the lipid bilayer.

Aquaporins (AQP):

Embedded in the plasma membrane, aquaporins allow water to move rapidly in both directions across the membrane. They are particularly abundant in cells specialized for water transport, such as renal epithelial cells.

Carrier Proteins (Transporters):

Also known as permeases or translocases, these transmembrane proteins mediate facilitated diffusion, moving molecules across the membrane without cellular energy expenditure, the driving force being the concentration gradient. They are specific and saturable.

Example: **GLUT transporters (Glucose Transporters),** particularly GLUT1, responsible for glucose uptake in red blood cells and many other cells.

Ion Channels:

These proteins form water-filled pores in the membrane, allowing ions of suitable size and charge to move along their electrochemical gradient. They are highly selective, with selectivity determined by pore diameter. Channels can open or close in response to stimuli and contain gates that transiently open upon specific membrane disturbances.

2. Active Transport

Cells also rely on carrier proteins functioning as pumps that actively move certain solutes across membranes against their concentration gradients, consuming energy derived from cellular ATP hydrolysis.

Ion Pumps:

Example: the **sodium–potassium pump (Na^+/K^+-ATPase)**.

This pump operates continuously in all cells, exporting **3 Na^+ ions** and importing **2 K^+ ions** against their electrochemical gradients.

ABC Transporters (ATP-Binding Cassettes):

These proteins possess an ATP-binding domain and use ATP hydrolysis energy to transport a wide variety of molecules, including **sugars, amino acids**, and **toxic compounds**.

3. Cotransport Systems

Some transport systems combine **active** and **passive** mechanisms — known as **cotransporters**, which can operate as **symports** or **antiports**.

a. Symports

Symports couple passive and active transport in the **same direction**, typically driven by an ion flux following its electrochemical gradient.

Example: The **Na^+/glucose cotransport** in intestinal epithelial cells.

At the **apical membrane** of enterocytes, two Na^+ ions and one glucose molecule bind to the **SGLT1 (Sodium–Glucose Transporter 1)** and enter the cell together. The resulting rise in intracellular glucose concentration drives its export through **GLUT2** transporters at the **basal membrane**, allowing glucose to enter the bloodstream.

A **Na^+/K^+-ATPase** pump maintains the sodium gradient by extruding intracellular Na^+, enabling the Na^+/glucose symport to continue functioning.

b. Antiports

Antiports transport two substances in **opposite directions** — one into the cytoplasm and the other outward.

Examples include:

Na^+/Ca^{2+} antiporter: regulates the strength of cardiac muscle contraction.

Na^+/H^+ exchanger: maintains intracellular pH homeostasis.

VI. MEMBRANE TRANSPORT OF MACROMOLECULES AND PARTICLES

Most cells ingest and secrete macromolecules via specialized mechanisms.

1. Endocytosis

Endocytosis encompasses pinocytosis and phagocytosis, processes by which cells internalize extracellular substances or microorganisms. Invagination of the plasma membrane forms vesicles or vacuoles containing the ingested material.

Pinocytosis

Pinocytosis captures macromolecules and solutes in small vesicles that bud inward from the plasma membrane. Four main types of vesicles exist, differing in size, coating, and mechanism:

Smooth (uncoated) vesicles
Clathrin-coated vesicles
Macropinosomes
Caveolae (raft-derived vesicles)

A. Smooth vesicle pinocytosis:

A non-specific uptake of extracellular fluid droplets, mainly involved in transcellular transport. These vesicles deliver their contents upon fusion with early endosomes.

B. Receptor-mediated pinocytosis:

A highly specific and selective form of endocytosis involving membrane receptors that recognize extracellular ligands. The receptor–ligand complexes accumulate in specialized membrane regions known as clathrin-coated pits (about 2% of total plasma membrane area) and are internalized via adaptin-dependent mechanisms.

C. Macropinocytosis:

A type of endocytosis initiated by cytoplasmic extensions rather than invaginations, leading to the formation of macropinosomes, large uncoated vacuoles.

D. Raft-mediated endocytosis:

Involves the formation of caveolae, small flask-shaped invaginations derived from lipid rafts or Detergent Insoluble Glycolipid-enriched domains (DIGs), rich in cholesterol and glycosphingolipids. Caveolae contain caveolin, proton pumps, Ca^{2+} channels, and molecules involved in signal transduction.

Phagocytosis

Phagocytosis is the uptake of solid particles or pathogens into large vesicles. It occurs mainly in defense cells such as macrophages and neutrophils.

Exocytosis

The reverse process of endocytosis. In exocytosis, the contents of transport or secretory vesicles are released into the extracellular space upon fusion with the plasma membrane.

There are two main exocytic pathways:

Regulated (triggered) exocytosis:

Occurs in specialized secretory cells. Molecules are concentrated within secretory vesicles that remain in the cytoplasm until receiving an external signal (e.g., a hormone or neurotransmitter). The signal triggers vesicle fusion and content release.

Constitutive exocytosis:

Operates continuously in all cells, transporting soluble proteins, lipids, and transmembrane proteins from the trans-Golgi network (TGN) to the plasma membrane. It maintains membrane renewal and supplies secreted molecules.

Depending on their nature, exocytosed molecules may integrate into the plasma membrane or be released extracellularly.

VII. SPECIALIZATIONS OF THE CELL PERIPHERY

A. Microvilli, Stereocilia, Cilia, and Flagella

Microvilli:
Fine, cylindrical cellular projections located on the apical surface of certain epithelial cells. They form a striated border in intestinal epithelium or a brush border in renal tubules. Their function is to increase the surface area for absorption and exchange.

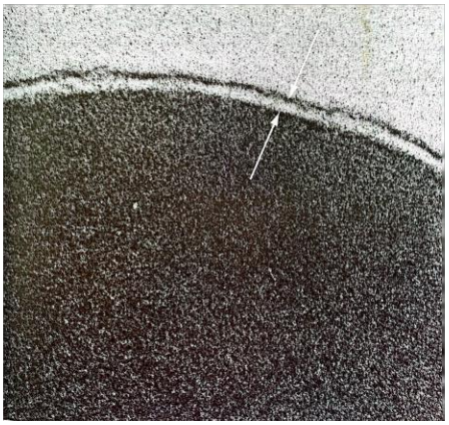
Stereocilia:
Long, irregular, and sometimes branched apical extensions of epithelial cells. They are immotile and often form intertwined tufts.
Example: stereocilia of the cochlear duct in the inner ear, essential for hearing and balance perception.

Cilia:
Motile cytoplasmic extensions composed of microtubules, found in certain bacteria and multicellular organisms such as humans (e.g., respiratory epithelium).

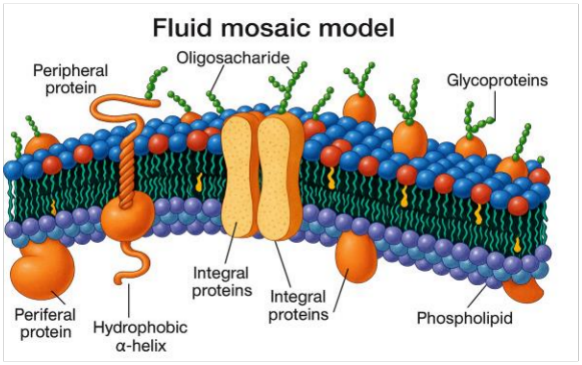
Flagella:
Structurally similar to cilia but much longer, as seen in sperm cells.
Both cilia and flagella enable cell motility or movement of surrounding fluids to facilitate nutrient capture or clearance.

B. Intercellular Junctions
In multicellular organisms, the lateral surfaces of adjacent cells (e.g., intestinal epithelial cells) are connected by various structures called intercellular junctions, which ensure tissue cohesion. These junctions may be punctate (macular) or form continuous belts (zonular) around the cell.
There are **four main types** of intercellular junctions:

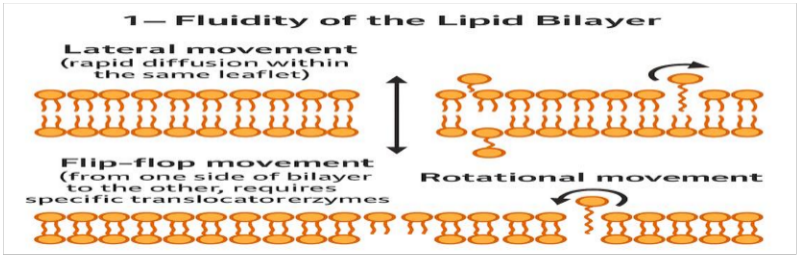
1. **Tight junctions (Zonula occludens):**
Found mainly in **simple epithelia**; they completely obliterate the intercellular space by forming multiple contact points between adjacent membranes, preventing paracellular leakage.
2. **Gap junctions (Macula occludens):**
Present in various tissues (e.g., nervous and muscular). They link adjacent cells through small tubular channels formed by hexameric proteins called connexins, enabling the passage of ions and small molecules for intercellular communication.
3. **Anchoring junctions (Desmosomes or Macula adherens):**
Found primarily in mechanically stressed tissues (e.g., muscle, skin). They mechanically link the cytoskeleton (intermediate filaments) of one cell to that of another or to the extracellular matrix.
4. **Adherens junctions (Zonula adherens):**
Form **continuous belts** around certain epithelial cells, helping maintain cell shape and stabilize tissue architecture.

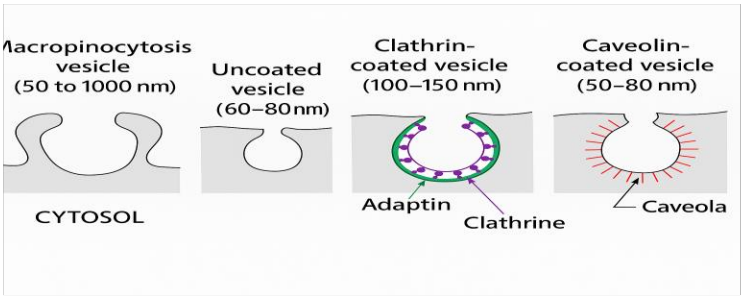


Trilamellar appearance of the plasma membrane



Biochemical composition of the plasma membrane





The different forms of pinocytosis.