Int. J. Sci. R. Tech., 2026 3(11)
A Multidisciplinary peer-reviewed Journal
www.ijsrtjournal.com [ISSN: 2394-7063]

Original Article

Nuclear Phospholipids in Genome Regulation: Structure, Signaling And Emerging Functional Roles

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ABSTRACT

In addition to their well-known structural function in cellular membranes, phospholipids are now understood to be essential for signal transmission, metabolism, and cellular homeostasis. But when it comes to phospholipid biology, the nucleus is frequently disregarded. Specialized roles are implied by the dynamic abundance and accurate control of nuclear phospholipid turnover by specialized kinases, phosphatases, and phospholipases. The nuclear membrane, similar to the cytoplasm, is the site of or the initiator for many of these biological processes. However, soluble and dynamic lipoprotein complexes appear to mediate a number of aspects of nuclear phospholipid biology that originate in the nucleoplasm. Technical challenges likely lead to an underestimation of nuclear phospholipid physiology and a lack of clarity regarding their specific molecular mechanisms of action and functional regions. New evidence, however, suggests that nuclear phospholipids influence genome structure and function in a more nuanced and varied manner. This study summarises recent findings about the biological roles and interactions of phospholipids as they pertain to nuclear physiology, gene regulation, and chromatin. Within the context of the nuclear membrane and the nucleoplasm, two important functional areas, we also discuss these functions. We argue that a better understanding of the molecular mechanisms of nuclear phospholipids is crucial for a full scientific understanding of these molecules. This is especially true in light of the fact that studying nuclear phospholipid biology and dysregulation could lead to new treatments for various genome-linked disorders.

Keywords: Phospholipid structure and composition , phospholipid in the nucleus , membrane specialization , Ion permeability, transport across cell membrane , endocytosis and exocytosis , Receptors.

INTRODUCTION

Varied class of hydrophobic and amphiphilic chemicals, lipids are crucial for cellular structure, signaling, and energy storage. Phospholipids are a large class of complex lipids that have rather wide-ranging biological importance. Amphipathic compounds are those that have a phosphate group in addition to two hydrophobic fatty acid chains and a hydrophilic head group. The structural variation of phospholipids is influenced by factors such as their length, the degree of acyl chain saturation, and the type of polar head groups they contain. Sphingophospholipids and glycerophospholipids are the two main types of phospholipids. Because phospholipids are amphipathic, they spontaneously organize into micelles in an aqueous environment, forming the lipid bilayer, the fundamental structure of biological membranes[1]. Membranes define the organelles within eukaryotic cells and divide the external and intracellular environments. In addition to these structural tasks, phospholipids are directly and through their metabolites engaged in a number of other biological processes, including gene expression, cellular signaling, and chromatin modeling. The 1960s saw the discovery of phospholipids in the cell nucleus[2, 3]. Although their presence and significance in this compartment were previously believed to be unfounded or anecdotal, nuclear phospholipids play crucial roles in maintaining nuclear architecture and function.

This is mostly due to the fact that nuclear phospholipids are now recognized to be functionally active not only in the nuclear envelope but also within the nucleoplasm. With an emphasis on their

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

functional activities within the nuclear membrane and nucleoplasm in relation to their impacts on the genome, we examine the varied biology of nuclear phospholipids in this review[4,5].

Phospholipids are special and adaptable compounds. Both naturally occurring and essential, they make up the bulk of cellular membranes. A lipid bilayer composed of phospholipids is essential for the formation and function of cellular membranes. Their hydrophilic head group and lipophilic/hydrophobic tail make them amphiphilic[6].

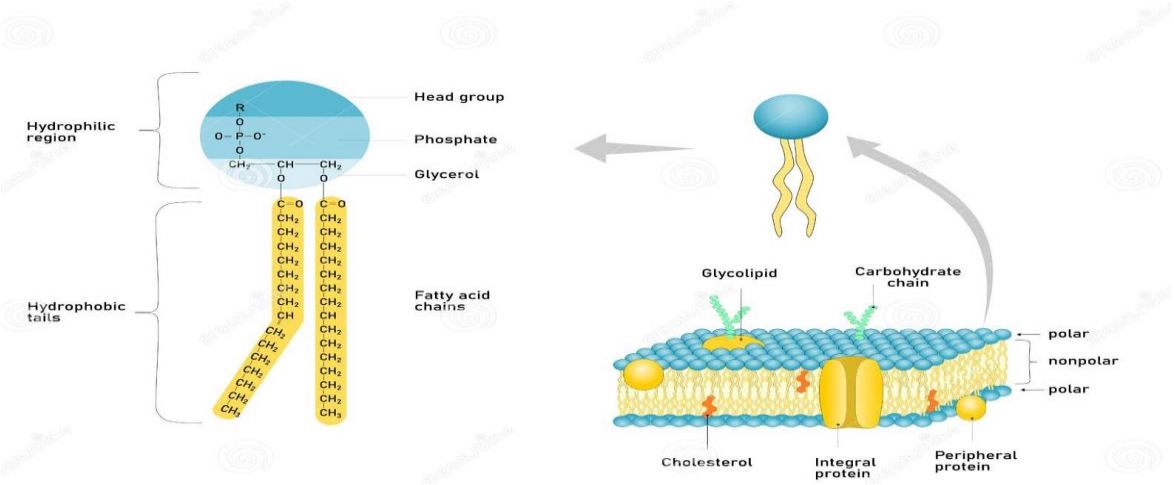


Figure 1: Cell Membrane Structure

illustrates the molecular blueprint of a phospholipid, as shown by 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) and the different possible headgroups that vary with the alcohol type: phosphatidylinositol (PI) with inositol, phosphatidylserine (PS) with serine, phosphatidylglycerol (PG) with glycerolamine (PE) with ethanolamine, and phosphatidylinositol (PI) with inositol.

2. STRUCTURE AND COMPOSITION

Plasma membranes are extremely adaptable structures composed of a phospholipid bilayer that separates the intracellular and extracellular fluid compartments. Even while other proteins buried in the membrane perform a variety of unique functions, cholesterol is primarily responsible for the membrane's fluidity. A phospholipid molecule is composed of two parts: the head and the tail. In contrast to the two neighbouring fatty acid chains that compose the tail, the head consists of a hydrophilic (negatively charged) phosphate group. Here in the bilayer, the polarised head allows for interactions with water on both the internal and external membranes. In contrast, lipid tails are hydrophobic because they are uncharged or non-polar. This membrane's fluidity is also influenced by the mixture of unsaturated and saturated fatty acid tails. As a result, the phospholipids that make up the bilayer are referred to as amphipathic [7,8].

Figure 2 shows the phospholipid bilayer structure, which includes consecutive layers and the orientation of the lipid tails of the molecules facing inward (Figure 2). Consequently, the heads are pointing outward, with one set of cells facing the inside of the cell and the other set facing the outside. This enables the bilayer's interior hydrophobic portion to be kept out of the intracellular and extracellular compartments. Because they "float" in or across the membrane, membrane proteins and other lipids, such as cholesterol, also pass through this region and give the cell membrane additional activities that contribute to cell homeostasis without compromising the fluidity of the bilayer[9].

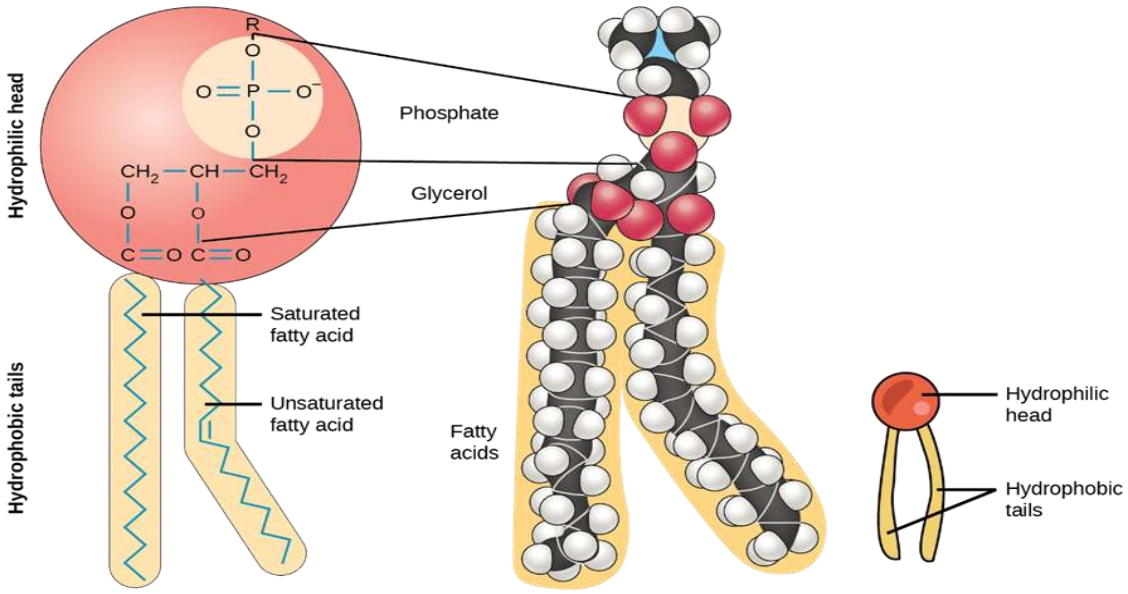


Figure 2 :Structure Of Phospholipid Molecule

The "head" of a phospholipid molecule is a polar phosphate and is hydrophilic; the "tail" is a non-polar lipid and is hydrophobic. Hydrophobic tails become twisted as a consequence of unsaturated fatty acids.

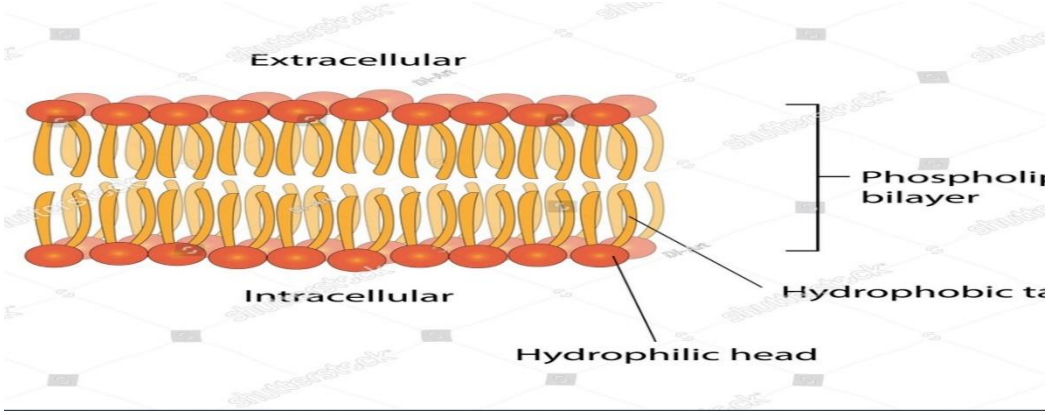


Figure 3 : Phospholipid bilayer

Two adjacent phospholipid sheets, organised tail-to-tail, make up the phospholipid bilayer. Interacting with each other, the hydrophobic tails construct the membrane's interior. Both the intracellular and extracellular fluids are touched by the polar heads.

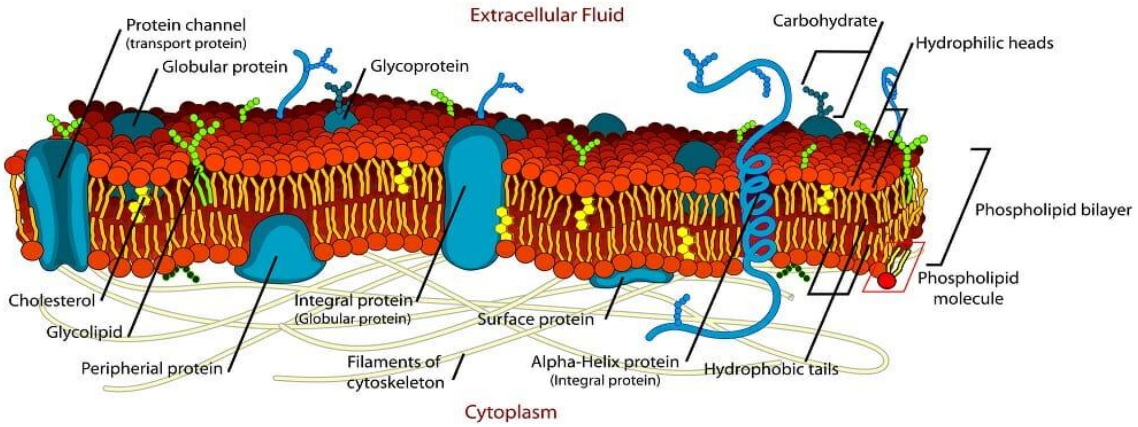


Figure 4 : Cell membrane

Phospholipid bilayers make up the cell membrane, which contains a wide variety of molecular components such as proteins, cholesterol, and various carbohydrate groups.

The physicochemical properties of the cell membrane cause it to be selectively permeable. The size and solubility of the substance determine its capacity to pass across the membrane. Oxygen, carbon dioxide, and lipid-soluble compounds can all flow through with ease. Transmembrane proteins or channels are necessary for the free passage of water-soluble glucose and other charged molecules, such ions, into and out of the cell [7].

3.Membrane proteins

Integral and peripheral proteins make up the bulk of the proteins found in the plasma membrane's lipid bilayer. Integral proteins are anchored in the membrane (Figure 3).

Examples of integral proteins are:

• Channel or transport proteins: they selectively permit substances, like ions, to pass across the plasma membrane.

• Receptors: often referred to as cell recognition proteins, which enable the selective attachment of molecules external to the cell. The cell's second messenger systems are typically activated when a molecule binds. For other cells and proteins to detect cells, these receptors function similarly to cell labels.

• Glycoproteins: The extracellular matrix is accessible through the carbohydrate groups that are connected to these proteins. The carbs have 'tags' on them, which helps in cell-to-cell recognition as well. Additionally, they are an integral component of the glycocalyx, a crucial mechanism that incorporates lipids from outside the cell membrane [7].

The glycocalyx has many roles that include:

• Receptors for hormone binding

• Cell-to-cell binding

• Enzymatic breakdown of nutrient.

4. Membrane Specialization:

Parts of the plasma membrane give the membranes of specialized cells particular functions:

The microvilli, which are extensions of the cell membrane that resemble fingers, enhance the surface area of the cell, allowing for maximum absorption. They are present in small intestinal cells.

A unique class of proteins called junctions (Figure 4) firmly packs and joins cells. There are three primary kinds:

• Tight junctions: prevent anything from moving between cells by holding neighboring cells firmly together.

• Desmosomes, also known as anchoring junctions, are fibers that hold cells together while permitting some mobility without separation.

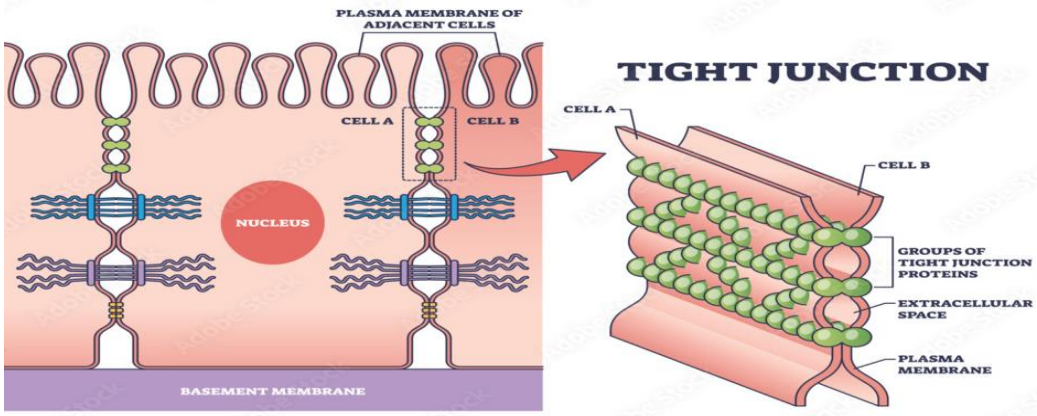
• Gap junction: These proteins allow specific chemicals to move between cells across gap junctions, which are open spaces in the plasma membrane between two cells [1].

5. Ion Permeability:

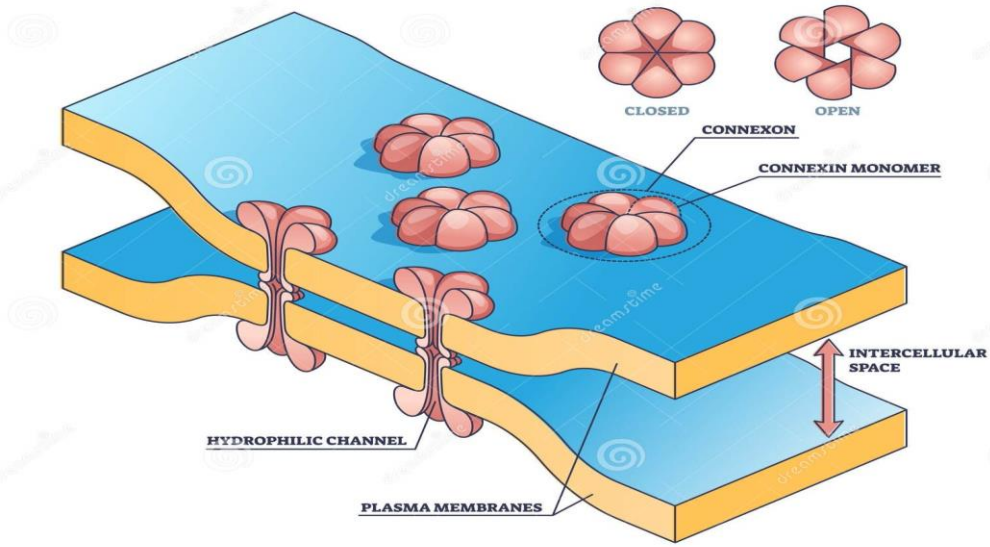
Because of selective ion transport and the resulting difference in concentrations (electrical charge) on either side of the cell membrane, a potential difference can be established across the membrane because of the semipermeable nature of the membrane. Since a charge transfer is theoretically possible, the bilayer can double as a capacitor. The resting membrane potential of cells is typically 70–80 mV lower than that of extracellular fluid [8, 10].

The cell is permeable to potassium, so it can leave the cell at will along a concentration gradient. Thus, the resting membrane potential drops, balancing the electrical and chemical gradients and preventing additional potassium loss from the cell.

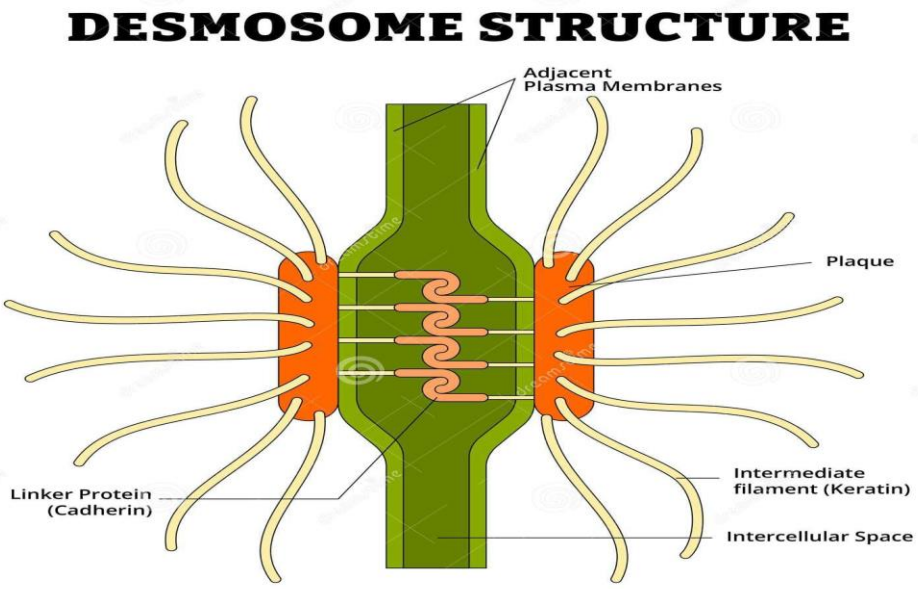
Other cations cannot pass through the cell, although Na+ does gradually seep down its concentration gradient [7].



GAP JUNCTION



ANCHORING JUNCTION



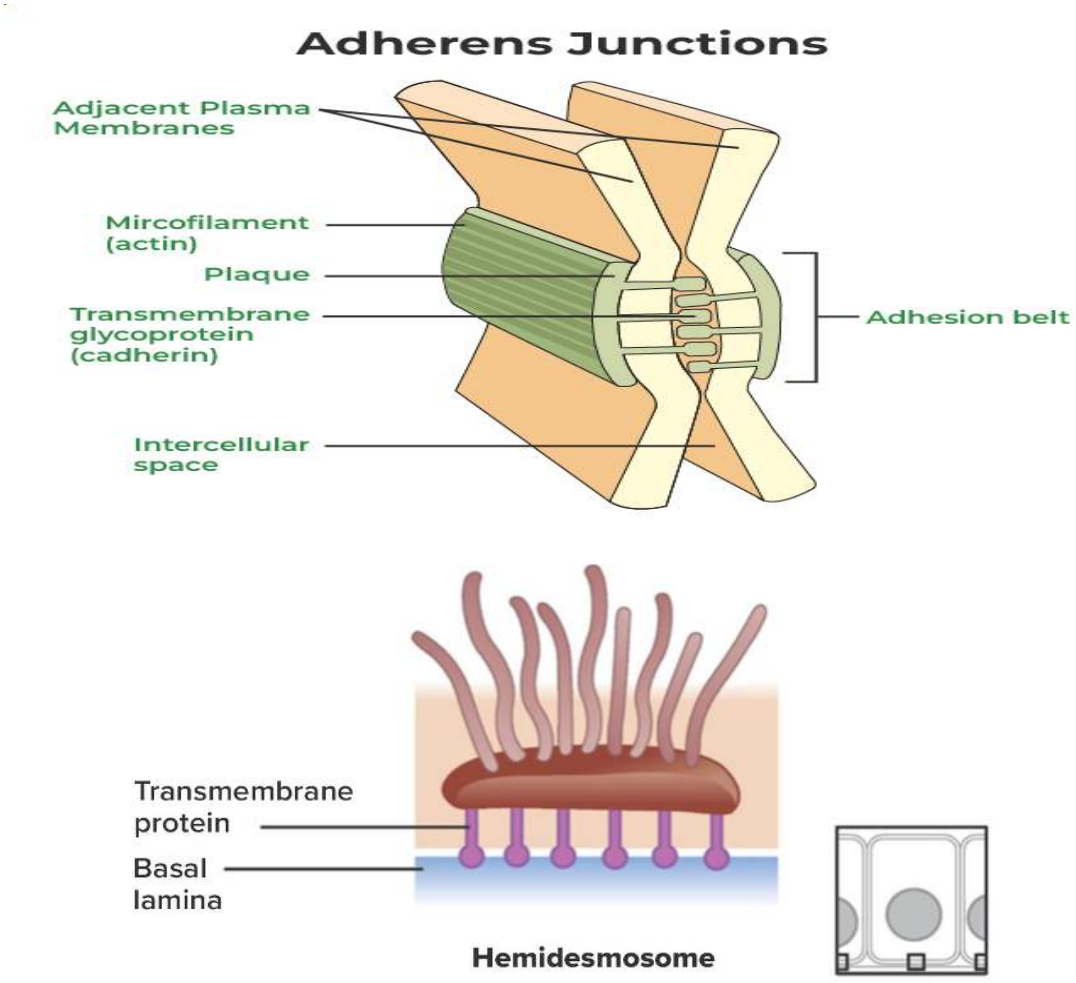


Figure 5 : Three major types of junctions

The electrochemical gradient is produced by the NA+/K+-ATPase pump, which is electrogenic due to the unequal ion exchange:

- There are three sodium ions released by the cell's pump, and
- Two potassium ions are injected into the cell.

Ion	Intracellular	Extracellular
Cl	10	100
K	150	4.5
Na	15	140

6. Membrane potential

As indicated earlier, the resting membrane potential is created by the negative charge that permeable potassium produces as it moves along its own diffusion gradient, which counteracts the diffusion of potassium. For these two forces to be considered in equilibrium, they must be equal [7,10].

If the ion in issue is permeable and present across the membrane in electrochemical equilibrium at changing quantities, the potential difference that the ion produces can be calculated using the Nernst equation.

If the potential difference of one permeable ion across a membrane is described by the Nernst equation, then the true membrane potential must be determined by considering allions with different permeabilities across the same membrane. The Goldman-Hodgkin-Katz equation does this. If the potential difference of a single permeable ion across a membrane can be explained by the Nernst equation, then the real membrane potential must be found by taking into consideration allions with varying permeabilities across those same membranes. To do this, the Goldman-Hodgkin-Katz equation is employed [9,11].

$$V_m = \frac{(g_{Na})(E_{Na}) + (g_K)(E_K) + (g_{Cl})(E_{Cl})}{g_{Na} + g_K + g_{Cl}}$$

It is crucial to remember that this equation, in contrast to the Nernst equation, ignores valency and that the concentration of negative ions is the opposite of that of positive ions [1]

7. Action potential:

Both chemical (mediated by cholinergic receptors, which open Na+ channels) and physical (mediated by pressure receptors, which deform Na+ channels) mechanisms allow excitable cells to change their membrane potential in reaction to stimuli. Therefore, the membrane potential is raised (becoming more negative) when the excitable cell is activated because Na+ permeability is increased. When the threshold potential is satisfied, an action potential is generated. It is at this voltage point, typically -55 mV that fast Na+ channels, also called voltage-gated Na+ channels, open. An all-or-nothing effect results from this. Sodium and potassium are essential components of cell membranes that generate an action potential [7,9,12] .

There are three states of the Na+ channels that cause depolarization:

1. Closed and Na+ impermeable.

2. When threshold probable is reached, it becomes open and permeable to Na+.

3. Immediately upon entering the open state, it becomes inactivated and impermeable to Na+. This state lasts until the potential falls below -50 mV.

The slow opening of voltage-gated potassium channels during depolarisation reduces the membrane potential and increases potassium permeability; these channels are crucial for repolarisation.

By diffusing across the cell membrane and raising the membrane potential above the resting potential in neighbouring cells, an increase in sodium in one region causes the action potential to spread. Afterward, the cell experiences a depolarisation and repolarisation wave due to the opening of fast Na+ channels. The maintenance of cell membrane potentials and the importance of the sodium-potassium ATPase pump within cell membranes are highlighted by this process [7]

8.Transport cell membrane

The cellular membrane allows for the regulation of intracellular material concentrations. The cell membrane maintains a stable concentration of ions such as Na+, K+, Ca+2, and Cl-as well as waste products such as carbon dioxide, carbs, fatty acids, amino acids, and ions. As a result of their hydrophobic interior and dense packing, phospholipids give the first degree of control within the phospholipid bilayer. Because of this structure, the selective permeability property is described. Oxygen, carbon monoxide, lipids, and alcohol are examples of small, non-polar molecules that meet the criteria for selective permeability and can therefore flow through the membrane unimpeded. However, because the hydrophobic phospholipid tails reject water-soluble molecules, they require aid to cross the membrane[7 ,10 11,13].

There are two main ways in which molecules might penetrate a membrane: passively and actively.

By utilising concentration gradients and diffusion, molecules can be transported to areas with lower concentrations in this manner.

A variety of processes contribute to diffusion across cell membranes, including:

- simple diffusion
- Osmosis
- Facilitated diffusion(uniporters)

Diffusion rate and intensity are affected by gradients caused by hydrostatic pressure, concentration of solutes, and electrical charg.

• Simple diffusion:

The permeability of the membrane determines whether a chemical with a concentration gradient can travel across it via simple diffusion. Some substances are very fluid, such as gases such as oxygen and carbon dioxide. Since cell uses oxygen quickly, its internal concentrations are often substantially lower, resulting in a concentration gradient that permits continuous diffusion into the cell. In contrast, high

intracellular amounts of carbon dioxide migrate from the cytoplasm to the interstitial fluid compartment, where the concentration is lower (Figure 6) [7].

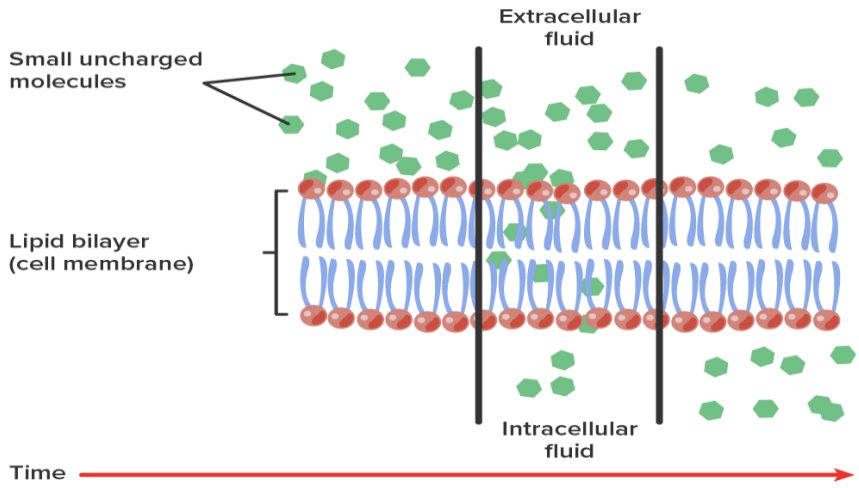


Figure 6 : Simple diffusion across the cell (plasma) membrane

Lipid bilayer architecture restricts diffusion across cell membranes to tiny, non-polar molecules like carbon dioxide and oxygen, which can move down concentration gradients.

• Osmosis :

As shown in Figure 6, osmosis allows water to diffuse across a semipermeable barrier. Water can diffuse across all cell membranes by either penetrating protein channels or sliding between the lipid tails of the membrane. When the concentration of solutes across the cell membrane is unequal, osmosis takes place. The concentration gradient across membranes, etc., determines how much water moves through a solution. The osmotic pressure that the solutes in the solution generate is essentially what pulls water, as illustrated in the figure below. The effect is concentration-dependent; an increase in osmotic pressure results from a more concentrated solution. Isotonicity ensures the structural and functional integrity of the cell and maintains homeostasis in the cellular environment, both of which are dependent on this effect. Maintaining homeostasis is an important function of the kidneys [7].

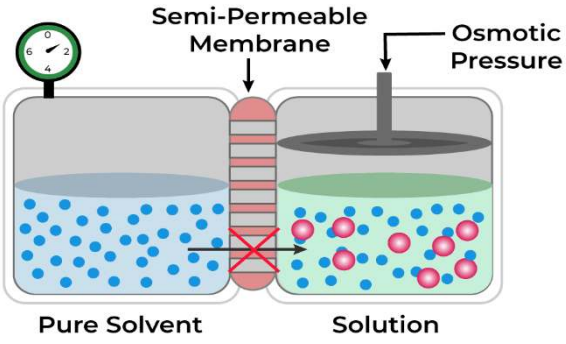


Figure 7 : Osmosis

Water diffuses through a semipermeable membrane following a concentration gradient; this process is called osmosis. When a membrane allows water to pass through but not a solute, the water will diffuse to the side with a lower concentration, bringing its own concentration level to the same as the solute's. The hypertonic solution can be seen on the right side of the membrane in the left-hand beaker.

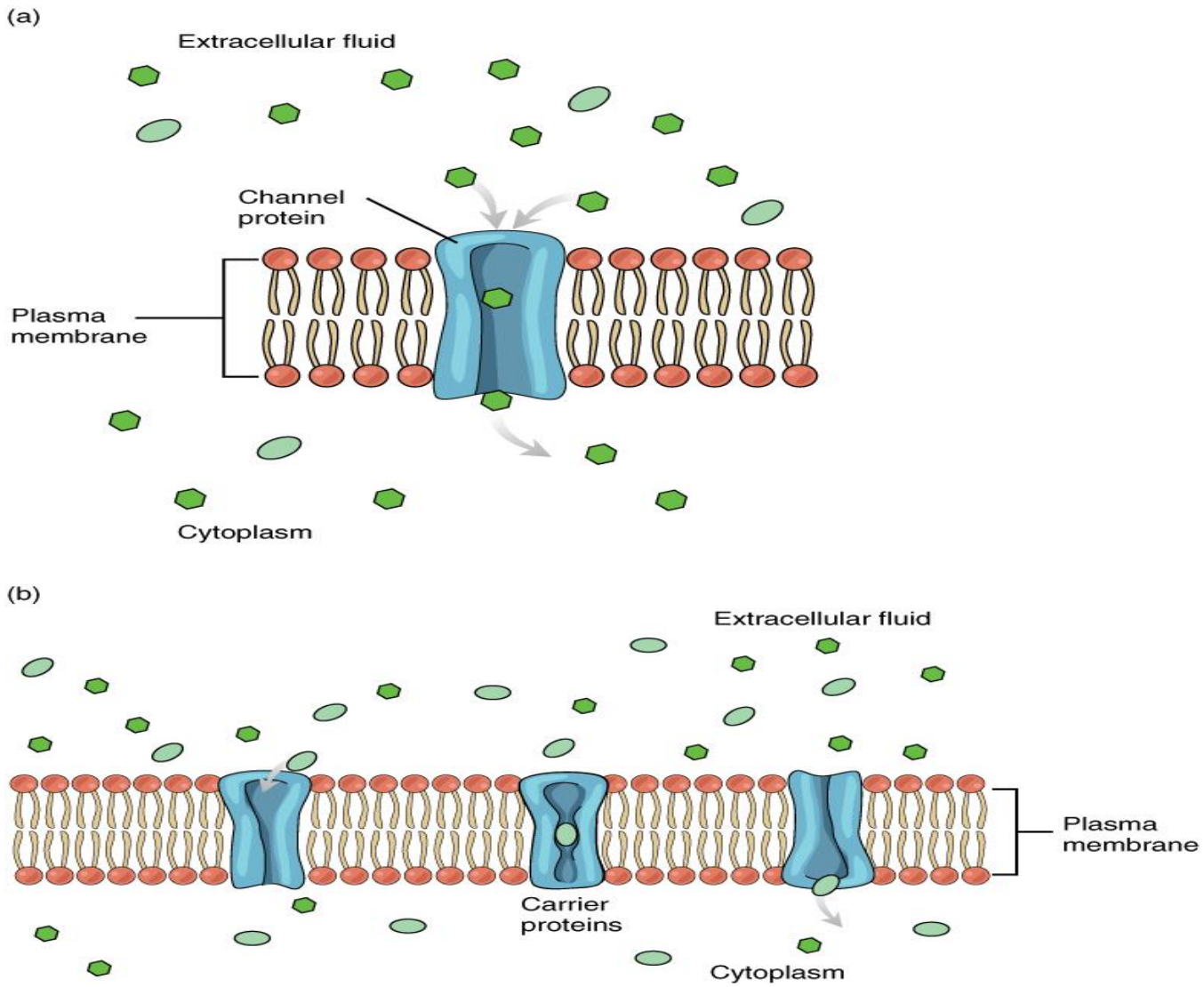


Figure 8 : Facilitated diffusion

(a) Proteins called channel proteins and carrier proteins help chemicals diffuse across the cell membrane, also known as the plasma membrane. Typically, channel proteins only slightly differentiate between their cargo according to size and charge, making them less selective than carrier proteins. (b) Carrier proteins are notoriously picky, letting through far fewer molecules than other types.

• Facilitated diffusion:

Help is needed for substances whose physicochemical characteristics (size, shape, polarity, etc.) prevent them from passing through the cell membrane. One common example of a chemical that requires enhanced diffusion to enter the cell and produce ATP is glucose. Enhanced inward diffusion of glucose requires a specialised carrier protein called the glucose transporter (Figure 7). Glucose is too large and polar to pass through the cell membrane alone, even when there is a concentration gradient. Amino acids and some metabolic byproducts can't be transported without these carrier proteins. Crucially, assisted diffusion does not require ATP because it is a passive process[7,10, 11,13].

9. Active diffusion :

To overcome a concentration gradient, molecules must undergo active transport, which uses ATP for energy. The following are examples of active transport mechanisms:

- Material movement is the main form of active travel.
- Connections between substances and the active movement of other ions against concentration gradients allow them to migrate

along electrochemical gradients, a process known as secondary active transport. Common examples include ions of hydrogen and sodium.

- Sodium and amino acids are two examples of chemicals that can be transported across a membrane by carrier proteins called co-transporters or symporters.
- A process is considered passive if the energy required to lower one substance's concentration gradient is greater than the energy required to raise the other substance's concentration gradient.
- Counter-transporters, also known as antiporters, use carrier proteins to carry two chemicals in opposite direction.

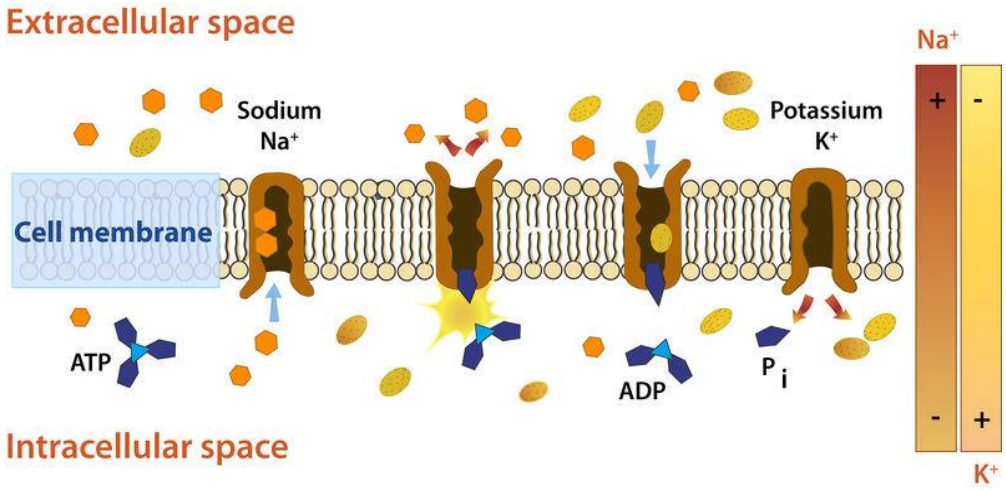


Figure 9 : Sodium-potassium pump

Many cell membranes contain the sodium-potassium pump. The sodium-potassium ion pump works by transferring ions in the opposite direction of their concentration gradients, using ATP as its power source. A single pump cycle causes the cell to expel three sodium ions and import two potassium ions.

The most common example of cellular active transport is the sodium-potassium pump, sometimes called Na+/K+ ATPase (Figure 9). This pump, found in the membranes of many different kinds of cells, is responsible for the intracellular transport of two potassium ions and the extracellular release of three sodium ions. This pump is extensively dispersed in nerve cells to keep an electrical gradient across the membrane of the cell. This electrical charge difference accounts for most of the ATP consumption in tissues; it generates an intracellular charge that is relatively negative (-70 mV), which is essential for the proper functioning of nerve cells. This pump helps maintain cellular homeostasis among its many other functions [7,10,13,14].

The pump has numerous different roles, one of which is maintaining cellular homeostasis.

- The net loss of osmoles keeps the cell volume constant.
- It has been shown in the previous situation that the potential difference across the membrane is preserved.
- Making chemical gradients that can be used in S-GLUT and other secondary active transport systems.

10. Endocytosis and exocytosis :

In order to move materials inside cells, these activities entail the creation of a vesicle.

As shown in Figure 9, endocytosis occurs when a material is absorbed into a cell by means of the cell membrane invaginating around it, which is then pinched off such that the membrane portion and its contents form a distinct intracellular vesicle. Two subtypes of endocytosis are phagocytosis and pinocytosis.

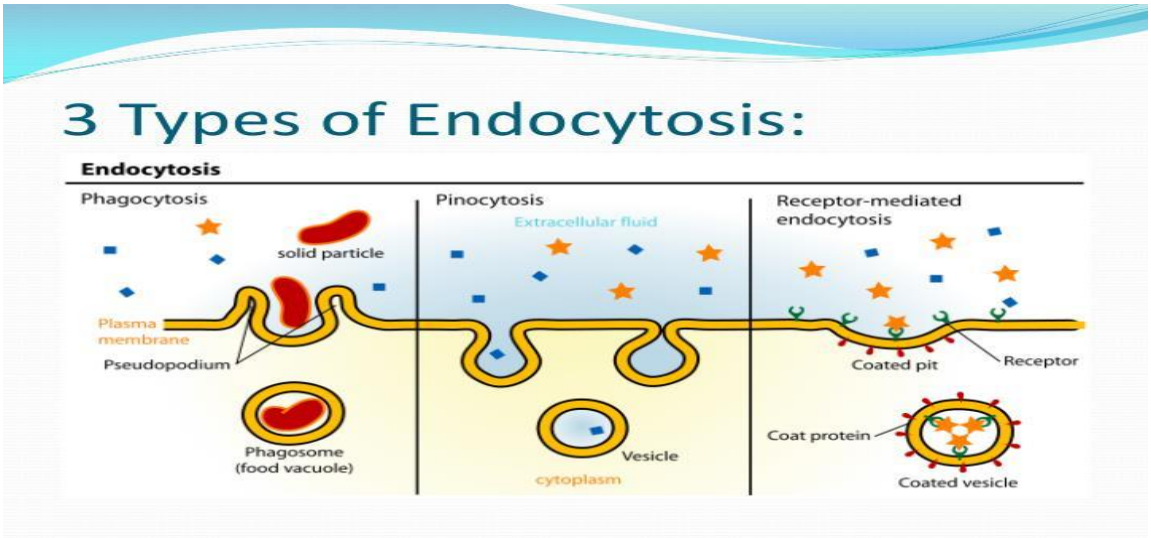


Figure 10 : Three forms of endocytosis

As a type of active transport, endocytosis involves the encasing of external substances by means of the cell membrane. (a) Nonselective phagocytosis involves the cell taking in a big particle. (b) Pinocytosis captures fluid-borne particles as small as a single molecule. (c) On the other hand, endocytosis mediated by receptors is highly selective. Endocytosis is the cell's reaction when an external receptor binds a particular ligand.

Phagocytosis is the process by which larger particles are taken up into the cell. By generating a vacuole inside the leukocyte, immune cells absorb germs and subsequently consume them. When substances that contain fluid are endocytosed but do not generate a vacuole, this process is called pinocytosis. Such two types of endocytosis do not necessarily "ingest" very selective large extracellular particles. However, receptor-mediated endocytosis is a mechanism that certain cells employ to regulate this process. After binding with specific substances, receptor-ligand complexes are able to regulate the substance's entrance into the cell through endocytosis. This is the standard mechanism for regulating iron entry into RBCs [7,10].

Exocytosis is an active calcium-dependent process that occurs when vesicles containing contents merge with the plasma membrane (Figure 10). The pancreatic and stomach cells, which secrete digestive enzymes and hormones, provide an example of this.

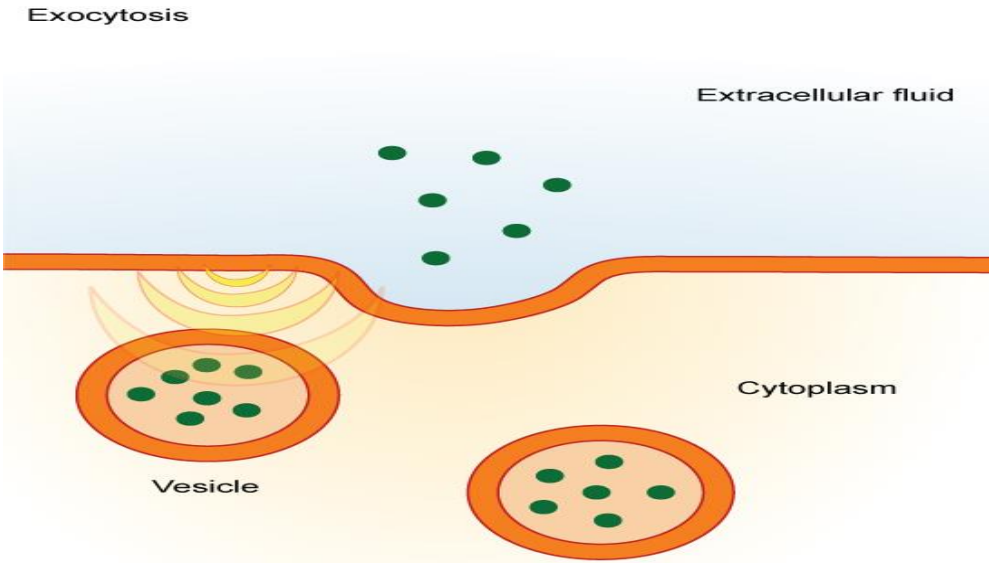


Figure 11: Exocytosis

In many ways, exocytosis is just the opposite of endocytosis. A vesicle is formed within the cell to contain materials that are about to be exported. The vesicle's contents are discharged into the extracellular space once its membrane fuses with the cell membrane.

Gibbs – Donnam effect

If non-diffusible ions are present in a solution, the Gibbs-Donnan effect will cause the ions to diffuse unevenly across a semipermeable membrane.4 At the point of Gibbs-Donnan equilibrium, which occurs when:Both sides of the membrane have an electrically neutral solution.

The product of the diffusible ion concentrations on either side of the membrane is equal to the product of those concentrations on the other side.

$[Na+]A \times [Cl-]A = [Na+]B \times [Cl-]B$

The transmembrane potential difference, which results from electrochemical gradients induced by an uneven distribution of charged ions, can be calculated using the Nernst equation.

An osmotic diffusion gradient, brought about by a change in tonicity on one side of the membrane, draws water into a compartment [10,14,15].

The Gibbs-Donnan effect is caused by two main factors: sodium and protein. Cell membranes are almost impermeable to sodium because of the Na+/K+ ATPase pump, and they are impermeable to protein when there are significant amounts of protein inside the cell. To sum up, the Gibbs-Donnan effect is crucial for preserving cell volume, plasma oncotic pressure, and resting membrane potential. However, there is a difference between the Gibbs-Donnan effect and the processes that maintain the resting membrane potential:

• The Donnan equilibrium is a passive process since no active transporters are involved.

• In a Donnan equilibrium, the concentrations of ions across the barrier are equal.

• When the Donnan equilibrium is entirely attained, cells swell due to the osmotic influx of water.

• At Donnan equilibrium, the resting membrane potential is only about -20 mV. This potential would persist regardless of whether or not all ions exhibited the same level of membrane permeability.

Because the resting membrane potential depends on different permeabilities for potassium and sodium and is constantly maintained by constant Na+/K+ ATPase activity, the Goldman-Hodgkin-Katz equation is usually the best choice for explaining the electrochemical behaviour of biological membranes, especially those of nerve cells. [10,14,15].

11. Phospholipid in the cell nucleus :

organelle that sets eukaryotic cells apart and contains the organism's genetic code is the nucleus. Lipides are an essential but minor component of the nucleus, which is defined by a nuclear envelope rich in lipids and a nucleoplasm lacking in lipids. Phospholipids are the most common kind of nuclear lipids. According to reports, the total phospholipid concentration in rat liver nuclei was 3.2% by weight, whereas the protein and DNA contents were 74.6% and 22.2%, respectively [16,17]. Phospholipids make roughly 65% of the nuclear envelope's total lipid content, which is approximately 50% of the protein by weight.

The most prevalent phospho-lipid in nuclei is phosphatidylcholine, which is followed in large quantities by phosphatidylethanolamine and phosphotidylinositols. On the other hand, sphingomyelin and phosphatidylserine are present at lesser concentrations. Phosphophatidylinositol (PtdIn)-containing nuclear phospholipids are notable because of their vital biological functions. An sn-3 position of the glycerol group on a hydrophobic diacylglycerol (DAG) tail is joined to the hydrophilic myo-inositol head group by a phosphodiester bond to form PtdIns. In phosphoinositides (PIPs), phosphatidylinositol is the primary component [18].

Seven different poly-acidic phospholipids, or phosphoinositides, can be formed by reversibly phosphorylating the hydroxyl group on the myo-inositol ring at the C3, C4, and C5 positions: PtdIns3P, PtdIns4P, PtdIns5P, and PtdIns(3,4). P2, PtdIns(3,5)P2, PtdIns(4,5)P2, and PtdIns(3,4,5)P3. The nuclear environment and nucleoplasm have been found to include phosphatidylinositol and the

majority of its derivatives, with the exception of PtdIns(3,5)P2 [19 - 22].

12. Biology of nuclear phospholipid in shaping genome:

Phospholipids, in their abundant and hydrophobic forms, are encased in hydrophobic protein pockets, incorporated inside the lipid bilayer, or aggregated to avoid the watery milieu of cells. Most of the known functions of nuclear phospholipids, especially those associated with signalling, rely on the polar headgroups and the interactions between them and proteins and nucleic acids. Although little research has been done on the biology of the hydrophobic tails [23,24], it is possible that the acyl portions of nuclear phospholipids, in addition to the extensively studied polar head groups, could have important signaling potential (e.g., due to variations involving length/saturation of the acyl chain .The functional areas in which phospholipids function have rarely been discussed, despite the fact that many elements of nucleus phospholipid biology have been outlined in recent literature [25 – 30]. To fully grasp the role of nuclear phospholipids in genome biology as a whole, we believe it is important to investigate the functional domains of these proteins inside the nuclear membrane and the nucleoplasm.

13.Membrane bound roles of nuclear phospholipid :

The structural integrity of the nuclear envelope is ensured by phospholipids, which also control nuclear pore functions, interact with proteins or factors linked with the nuclear membrane, and generate lipid microdomains. Nuclear phospholipids are related with the nuclear membrane as a dynamic platform for genome control, and here we focus on their biological functions.

14.Nuclear phospholipid signaling in the nucleus :

Nuclear phospholipids have functional domains that go beyond their conventional functions in lipid bilayers. Indeed, it appears that a sizable pool of nuclear phospholipids, especially nuclear phosphoinositides, are separated from the nuclear membrane [31]. Nucleoplasmic phospholipids are known to either function in phase-separated structures or to be solubilised with nuclear proteins.

Function of phospholipid withn nuclear speckles and other phase -separated domains

Nuclear speckles are dynamic, sub-nuclear membrane-free structures that include a variety of enzymes that do post-transcriptional modifications, polyadenylating polymerases, and pre-mRNA splicing factors [32]. Phosphoinositides are abundant in these crucial functional structures, indicating that phospholipids have an effect on mRNA processing [25]. These structures allow phospholipids to conceal their hydrophobic tails, allowing them to remain functionally accessible in the nucleoplasm. The nuclear speckles in mammalian cell nuclei contain as much as 40% of the nuclear phosphoinositides [66]. Notably, PtdIns(3,4,5)P3 and PtdIns(4,5)P2 have emerged as critical elements of the machinery involved in pre-mRNA splicing and mRNA export.

15 . Receptors :

Membrane receptors are specialized integral proteins that cause an intracellular reaction (signal transduction) by binding to particular external signaling molecules (ligands), such as hormones, neurotransmitters, or growth factors.

Membrane receptors belong to three primary structural and functional classes despite the wide variety of ligands:

1. Ligand-gated ion channel (ionotropic receptors)

• Structure:

These proteins produce pores. They are made up of several subunits organized to form a central pore that crosses the membrane.

• Mechanism: The pore is closed when they are at rest. The receptor experiences a conformational (shape) change that opens the pore when a particular ligand attaches to the extracellular binding site. This permits certain ions, such as Na+, Ca2+, and Cl-, to rush into or out of the cell along their electrochemical gradients. The cellular signal is the resultant shift in membrane voltage.

• Speed: Very quick (milliseconds).

• Example :

° The nicotinic acetylcholine receptor opens a channel for Na+ to trigger muscle contraction by binding acetylcholine at the neuromuscular junction.

° Glutamate receptors : The main excitatory receptors in the central nervous system, (such as NMDA and AMPA) are essential for memory and learning[31,32].

2. Metabotropic receptors, or G-Protein Coupled Receptors (GPCRS)

• Structure : The human body's largest family of membrane receptors, GPCRs, include over 800 different types. Their unique alpha-helical shape that oscillates inside the lipid bilayer is characterised by seven transmembrane segments (7TM) in both.

• Mechanism:

The receptor on inside of cell changes shape when a ligand attaches to the extracellular side. It can function as a Guanine Nucleotide Exchange Factor for a neighboring G-protein because to this shape alteration. After exchanging GDP for GTP and splitting into two active subunits, the G-protein regulates downstream effectors such as ion channels or enzymes (such as Adenylyl Cyclase, which generates the secondary messenger cAMP).

• Speed :Moderate speed (seconds to minutes).

• Example :

° Adrenaline is bound by beta-adrenergic receptors, which raise heart rate.

° Rhodopsin: In the retinal cells of the eye, it absorbs light.

° Endorphins and analgesics like morphine are bound by opioid receptors[31,32].

3 .Enzymes linked receptor :

• Structure:

These are typically transmembrane proteins with a single pass. The intracellular domain is either an enzyme or is directly linked to one, while the extracellular domain binds the ligand.

• Mechanism:

Ligand interaction often results in the dimerization of two receptor molecules as well as the activation of the intracellular enzyme domain. To properly activate the enzyme, dimerization is frequently necessary.

• Subtypes :

The most prevalent kind are receptor tyrosine kinases (RTKs). They phosphorylate (add a phosphate group to) particular tyrosine amino acids on one another when they dimerize (autophosphorylation).These phosphates serve as intracellular signaling protein docking sites, initiating large-scale cascades such as the MAPK pathway, which regulates cell division and proliferation.

° Receptor serine / threonine kinase : Like RTKs, receptor serine/threonine kinases phosphorylate distinct amino acids (such as TGF-beta receptors).

° **Receptor guanylyl cyclase** : Cyclic GMP (cGMP) is produced by receptor guanylyl cyclases, such as the ANP receptor in the heart, which reduces blood pressure.

• Examples: include the epidermal growth factor (EGF) receptor, which promotes cell proliferation, and the insulin receptor, an RTK that initiates glucose uptake[33,34].

4. Adhesion receptors, or integrin receptors

• Structure:

Integrins do not have huge external "classic" ligand-binding pockets or intracellular enzymatic domains, in contrast to other receptors. Instead, integrins are heterodimers made up of two distinct subunits, alpha and beta, that pierce the membrane just once each.

• Mechanism:

They attach to the actin cytoskeleton on the inside and bind to extracellular matrix (ECM) proteins (such as collagen or fibronectin) on the outside. They convey both "inside-out" and "outside-in" messages as well as mechanical forces.

Usually, they recruit adaptor proteins to create massive signaling complexes (focal adhesions) rather than initiating chemical cascades on their own.

• Examples : include platelet integrins, which attach to fibrinogen and are essential for blood clotting[33,34].

CONCLUSION

In conclusion, phospholipids are no longer viewed merely as passive structural barriers, but as essential dynamic regulators of cellular signaling, homeostasis, and genomic architecture. While their roles in the plasma membrane—such as maintaining selective permeability, establishing membrane potentials, and hosting complex receptor systems—are fundamental to cell survival, recent evidence highlights their vital, active presence within the cell nucleus. Operating within both the nuclear envelope and the nucleoplasm, specialized nuclear phospholipids actively orchestrate the cell's genetic framework.

REFERENCES

1. Alberts B, Lewis JA. The lipid bilayer. In: Alberts B, et al. Molecular Biology of the Cell. 4th ed. New York: Garland Science; 2002.
2. Torres TE-BAA. Phospholipids: physiology. In: Encyclopedia of Food and Health. Vol. 3. Brazil: Elsevier; 2016. p. 352–359.
3. Dowhan W. The role of phospholipid in cell function. In: Gross RW, editor. Advances in Lipobiology. Vol. 2. Elsevier; 1997. p. 79–107.
4. Manzoli FA, et al. Chromatin phospholipids in normal and chronic lymphocytic leukemia lymphocytes. Cancer Res. 1977;37(3):843–849.
5. Rose HG, Frenster JH. Composition and metabolism of lipids within repressed and active chromatin of interphase lymphocytes. Biochim Biophys Acta. 1966;126(3):577–591.
6. Khandwala AS, Kasper CB. The fatty acid composition of individual phospholipids from rat liver nuclear membrane and nuclei. J Biol Chem. 1971;246(20):6242–6246.
7. Lumen Learning. Anatomy and physiology: the plasma membrane \[Internet\]. 2020 Oct 12 \[cited 2020 Oct 12\]. Available from: [https://courses.lumenlearning.com/atd-biology2/chapter/the-cell-membrane/](https://courses.lumenlearning.com/atd-biology2/chapter/the-cell-membrane/?utm_source=chatgpt.com)
8. Barrett KE, Barman SM, Boitano S, Brooks HL. Ganong's Review of Medical Physiology. 24th ed. New York: McGraw-Hill; 2012.
9. Chambers D, Huang C, Matthews G. Basic Physiology for Anaesthetists. Cambridge: Cambridge University Press; 2015. doi:10.1017/CBO9781139226394.
10. Life in the Fast Lane. Part One: Cellular Physiology \[Internet\]. \[cited 2020 Oct 6\]. Available from: [https://partone.litfl.com/the_cell_membrane.html](https://partone.litfl.com/the_cell_membrane.html?utm_source=chatgpt.com)
11. Karn P, Power I. Principles of Physiology for the Anaesthetist. 3rd ed. Hodder Education; 2012.
12. Deranged Physiology. Cellular physiology: mechanisms responsible for the cell resting membrane potential \[Internet\]. \[cited 2020 Oct 12\]. Available from: [https://derangedphysiology.com/main/cicm-primary-exam/required-reading/cellular-physiology/Chapter%20118/mechanisms-responsible-cell-resting-membrane-potential](https://derangedphysiology.com/main/cicm-primary-exam/required-reading/cellular-physiology/Chapter%20118/mechanisms-responsible-cell-resting-membrane-potential?utm_source=chatgpt.com)
13. Eaton DC, Pooler JP. Vander's Renal Physiology. 6th ed. (Revised). McGraw-Hill Education Europe; 2004.
14. PhysiologyWeb. Secondary active transport \[Internet\]. \[cited 2020 Oct 12\]. Available from: [https://physiologyweb.com/lecture_notes/membrane_transport/secondary_active_transport.html](https://physiologyweb.com/lecture_notes/membrane_transport/secondary_active_transport.html?utm_source=chatgpt.com)
15. Deranged Physiology. Cellular physiology: the Gibbs-Donnan effect \[Internet\]. \[cited 2020 Oct 12\]. Available from: [https://derangedphysiology.com/main/cicm-primary-exam/required-reading/cellular-physiology/Chapter%20121/gibbs-donnan-effect](https://derangedphysiology.com/main/cicm-primary-exam/required-reading/cellular-physiology/Chapter%20121/gibbs-donnan-effect?utm_source=chatgpt.com)

16. Khandwala AS, Kasper CB. The fatty acid composition of individual phospholipids from rat liver nuclear membrane and nuclei. J Biol Chem. 1971;246(20):6242–6246.
17. Neitcheva T, Peeva D. Phospholipid composition, phospholipase A2 and sphingomyelinase activities in rat liver nuclear membrane and matrix. Int J Biochem Cell Biol. 1995;27(10):995–1001.
18. Ledeen RW, Wu G. Nuclear lipids: key signaling effectors in the nervous system and other tissues. J Lipid Res. 2004;45(1):1–8.
19. Cocco L, et al. Synthesis of polyphosphoinositides in nuclei of Friend cells. Evidence for polyphosphoinositide metabolism inside the nucleus which changes with cell differentiation. Biochem J. 1987;248(3):765–770.
20. Divecha N, Banfic H, Irvine RF. The polyphosphoinositide cycle exists in the nuclei of Swiss 3T3 cells under the control of a receptor (for IGF-I) in the plasma membrane, and stimulation of the cycle increases nuclear diacylglycerol and apparently induces translocation of protein kinase C to the nucleus. EMBO J. 1991;10(11):3207–3214.
21. Jacobsen RG, et al. Polyphosphoinositides in the nucleus: roadmap of their effectors and mechanisms of interaction. Adv Biol Regul. 2019;72:7–21.
22. Mazloumi Gavgani F, et al. Nuclear phosphatidylinositol 3,4,5-trisphosphate interactome uncovers an enrichment in nucleolar proteins. Mol Cell Proteomics. 2021;20:100102.
23. Barger SR, Penfield L, Bahnmanyar S. Coupling lipid synthesis with nuclear envelope remodeling. Trends Biochem Sci. 2022;47(1):52–65.
24. Barlow CA, Laishram RS, Anderson RA. Nuclear phosphoinositides: a signaling enigma wrapped in a compartmental conundrum. Trends Cell Biol. 2010;20(1):25–35.
25. Vidalle MC, et al. Nuclear phosphoinositides as key determinants of nuclear functions. Biomolecules. 2023;13(7):1049.
26. D'Santos CS, Clarke JH, Divecha N. Phospholipid signalling in the nucleus. In: Een DAG Uit Het Leven Van de Inositide Signalering in de Nucleus. Biochim Biophys Acta. 1998;1436(1–2):201–232.
27. Irvine RF. Nuclear lipid signalling. Nat Rev Mol Cell Biol. 2003;4(5):349–360.
28. Martelli AM, et al. Re-examination of the mechanisms regulating nuclear inositol lipid metabolism. FEBS Lett. 2001;505(1):1–6.
29. Payrastre B, et al. Phosphoinositides: key players in cell signalling, in time and space. Cell Signal. 2001;13(6):377–387.
30. Bryant JM, Blind RD. Signaling through non-membrane nuclear phosphoinositide binding proteins in human health and disease. J Lipid Res. 2019;60(2):299–311.
31. Alberts B, Johnson A, Lewis J, et al. Molecular Biology of the Cell. 6th ed. New York: Garland Science; 2014.
32. Nelson DL, Cox MM. Lehninger Principles of Biochemistry. 8th ed. New York: W.H. Freeman; 2021.
33. De Robertis EDP, De Robertis EMF. Cell and Molecular Biology. Lea & Febiger; 2004.
34. Cooper GM, Hausman RE. The Cell: A Molecular Approach. 7th ed. Sunderland (MA): Sinauer Associates.

HOW TO CITE: Sanchita Sachin Hajare*, Gayatri Mallinath Godale, Sayali Ananda Chougule, Dr. Mahesh Babanrao Thorat, Dr. Dhanraj Raghunathrao Jadge, Nuclear Phospholipids in Genome Regulation: Structure, Signaling And Emerging Functional Roles, Int. J. Sci. R. Tech., 2026, 3 (11), 571-586. https://doi.org/10.5281/zenodo.24214752