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BEYOND LITTLE HANDSHAKE: ROLE OF PHOSPHOLIPIDS IN HEALTH AND DISEASE

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ABSTRACT

Analogous to the large sized protein and carbohydrate based macromolecules, the large macro-sized bio-membrane assemblies are primarily derived from the monomeric phospholipids (PL). Besides offering protection from outside environment, the PLs play important role in regulation of cellular structure, signalling, and various other related metabolic processes. In addition to regulating membrane integrity, curvature, and compartmentalization, they sustain architecture and function of various cellular organelles, such as mitochondria, where the major phospholipids namely phosphatidyl-ethanolamine (PE) and cardiolipin (CL) are indispensable not only for cristae organization, however, also to play important role in the regulation of efficient oxidative phosphorylation as well. On the other hand, the phospholipids such as phosphatidylcholine (PC) are essential for lipoprotein assemblage and lipid transport, thereby linking membrane biogenesis to whole-body metabolic homeostasis. Beyond their structural roles, PLs function as central signalling platforms. They act as precursors of lipid-derived second messengers, orchestrate the spatial organization of membrane-associated protein complexes, and directly modulate the activity of enzymes and receptors. The phosphoinositides (PI) confer membrane identity and enable the precise recruitment of signalling proteins, while enzymatic remodelling of phospholipid headgroups and acyl chains generates bioactive mediators. Consequently, altered PL homeostasis has been implicated in cardiovascular and neurodegenerative diseases and more importantly in many types of cancer as well. This review synthesizes current insights into the multifaceted roles of phospholipids in health and disease and also underscores significance of phospholipids in diagnostic biomarkers and therapeutic targets.

List of abbreviations: PI (4,5) P_2, phosphatidylinositol 4,5-bisphosphate; PI (3,4,5) P_3, phosphatidylinositol 3,4,5-triphosphate, IP_3, inositol 1,4,5-trisphosphate; DAG, diacylglycerol; OxPLs, oxidized phospholipids; LPC, lysophosphatidylcholine; LPA, lysophosphatidic acid; PLA_2, phospholipase A2; AA, arachidonic acid.

INTRODUCTION

Biomacromolecules are considered as the chemicals that form backbone of the life. Among various classes of biomacromolecules, the proteins boast peptide bonds linking monomeric amino acids into lengthy chains. Similarly, in the carbohydrates, glycosidic bonds string sugars together to form large sized carbohydrates. Nucleic acids, as represented by DNA or RNA, are basically comprised of modest monomeric units that are known as nucleotides.

Lipids don't play that game. Their monomers—the fatty acids and glycerol—aren't constantly linking into repeating long chains. Instead, they form distinct molecules, such as triglycerides or phospholipids. Despite their large size and biological importance, fats, particularly triglycerides, are generally not considered true macromolecules in the strict biochemical sense. This distinction arises because they are not polymers formed from the repetitive linking of identical or similar monomer units; a triglyceride is assembled from a single glycerol molecule and three distinct fatty acid molecules. Unlike other classical biomacromolecules, fats do not consist of a long chain of repeating monomers, still these are larger in terms of their size and molecular weight. The structural assembly differs fundamentally from the polymeric structure that defines most other biological macromolecules. The term "macromolecule" is sometimes used more broadly to include any large biological molecule, which can lead to confusion about lipids.

Biological membranes, particularly the plasma membrane, are not merely the static barriers that limits cell boundary, however, considered as an assembly of a sophisticated, dynamic composites of lipids, proteins, and carbohydrates. As the foundational architecture of a typical bilayer, the amphipathic core phospholipids spontaneously orient themselves in a fashion so that hydrophilic head-groups face the aqueous surrounding on its either side, where as hydrophobic tails form a sealed inner core, ensemble in the form of a selectively permeable cell barrier.[1] The mammalian membrane matrix is functionally modulated by cholesterol, a lipid with core sterol nucleus. The cholesterol intercalates between phospholipids to fine-tune fluidity, mechanical stability, and the formation of functional micro-domains of the specific membrane.[2] Protein based macromolecules are embedded within this lipid bilayer in a pattern best described by the Fluid Mosaic Model.[3] In general, the integral trans-membrane proteins serve as channels, transporters, and receptors, while peripheral proteins associate dynamically with the membrane surfaces to facilitate signalling and structural support. The wholesome structural accomplishment of membrane assembly is achieved by covalent linkage of sugar moieties with both lipids (glycolipids) as well as proteins (glycoproteins). The sugar-rich coat is critical for intercellular recognition, adhesion, and more importantly in the immune compatibility of the parent cell.[4] Collectively, this dynamic organization enables the plasma membrane to define cellular identity, regulate material exchange, transduce signals, and undergo remodelling for essential processes like endocytosis and cell motility.

While phospholipids constitute the essential architectural foundation of cellular membranes, ensuring integrity and compartmentalization, their role generally encompass numerous vital biological activities of the cell as well. Our scientific insight visualises phospholipids as dynamic regulators of cellular physiology. The chemical diversity, in terms of variations in the head-groups (e.g., choline, ethanolamine, serine, inositol *etc*.) or the presence of multi-composite acyl chains, or the asymmetric distribution of specific PL across bilayer leaflets, and finally their constant enzymatic remodelling enable them to function not only as structural components, however, also as a versatile signalling intermediaries.[5] For instance, phosphatidylinositol (PI) and its phosphorylated derivatives (PIPs) are pivotal in directing membrane trafficking and cell signalling,[6] while phosphatidylserine (PS) externalization serves as a key signal for clearance of apoptotic bodies.[7]

Any commotion in phospholipid metabolism reverberates not only in the form of membrane composition; however, many vital biological activities are also manipulated. At the organelle scale, they impair membrane trafficking, fusion, and eventually energy regulation processes. While compromised communication between compartments and disturb signalling cascades may ensue at the cellular level. Systemically, such perturbations manifest in the form of pathological states that span cardiovascular dysfunction,[8] metabolic disorders,[9] neurodegeneration,[10] inherited genetic syndromes,[11] and chronic inflammatory complications.[12] This review, therefore, explores the multifaceted contributions of phospholipids to systemic health at cellular level. It highlights their indispensable roles in maintaining physiological homeostasis and examines how their dysregulation serves as a critical nexus for the onset and progression of diverse human diseases, underscoring their potential as therapeutic targets.

1. Primary Functions of Phospholipids in Health

1.1. Structural and functional role in living system

Phospholipids constitute the universal architectural foundation of biological membranes, forming a semi-permeable bilayer that demarcates cellular and organellar boundaries, and govern essential properties such as membrane fluidity, permeability, and curvature *etc*.[5] Beside core function as basic structural unit, the asymmetric distribution of the PL across the membrane bilayer has been considered indispensable for specialized physiological functions. For example, the aminophospholipid, phosphatidylethanolamine (PE) and the dimeric phospholipid cardiolipin (CL) are highly enriched in the inner membrane of the mitochondria. CL is particularly critical for the organization and stabilization of respiratory chain complexes, optimization of oxidative phosphorylation, regulation of membrane dynamics and apoptotic signalling, thereby directly supporting mitochondrial energy production.[13]

Phospholipids are also central to lipid transport in the systemic circulation. Phosphatidylcholine (PC) forms the dominant component of the phospholipid monolayer surrounding circulating lipoproteins, including high-density HDL, and low-density LDL particles. The PC enriched surface is essential for lipoprotein assembly, stability, and solubility in plasma, enabling efficient transport of cholesterol, triglycerides, and fat-soluble vitamins.[14] Further, specialized phospholipids perform critical tissue-specific functions. In the lungs, 1, 2-dipalmitoyl-sn- glycerol-3-phosphorylcholine (DPPC) acts as a potent pulmonary surfactant. By markedly reducing alveolar surface tension, DPPC prevents end-expiratory alveolar collapse and is essential for normal respiratory mechanics.[15] The PLs are equally vital for structural integrity and signalling in the nervous system. PS, enriched in the inner leaflet of the plasma membrane, supports synaptic function by facilitating membrane trafficking and serving as a platform for signalling proteins, while its regulated externalization acts as a key apoptotic signal promoting the clearance of dying cells.[16]

1.2. Phospholipids as a precursor of second messengers

Far from being passive structural components, the membrane lipids are continuously remodelled by stimulus-activated phospho-lipases, enabling signal initiation, amplification, diversification, and termination with remarkable spatial and temporal precision. This organization embeds signal transduction within the context of membrane identity, curvature, and protein composition, thereby integrating biochemical signalling with cellular architecture. In fact, membrane phospholipids function as dynamically regulated signalling reservoirs, coupling extracellular stimuli to precisely orchestrated intracellular responses through the controlled generation of lipid-derived second messengers.[5,17]

The canonical paradigm of phospholipid-derived signalling involves regulated hydrolysis of phosphatidylinositol 4,5-bisphosphate (PI (4,5) P_2), a quantitatively minor yet functionally dominant phosphoinositide enriched in the cytosolic leaflet of the plasma membrane(6) (**Fig. 1).** Activation of phospholipase C cleaves PI (4, 5) P_2 into two chemically distinct and spatially segregated second messengers: inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). This bifurcation divides the signal into diffusible and membrane-confined components.[18] IP_3 propagates intracellular signals by inducing Ca^{2+} release from the endoplasmic reticulum via specific receptors, generating oscillatory and wave-like calcium dynamics that encode stimulus intensity and duration (19). DAG, the other hydrolysis product of PI, remains membrane-associated, and activates protein kinase C (PKC) isoforms[20] as well as other C1-domain–containing effectors, including RasGRPs and chimaerins.[21] RasGRPs and chimaerins represent two families of DAG-responsive regulatory proteins that connect membrane lipid signalling to small GTPase regulation, but they act on distinct GTPases and drive divergent biological outcomes. This dual-output architecture coordinates detection between lipid and calcium signals, conferring robustness and specificity to downstream pathways that govern proliferation, secretion, differentiation, and survival.

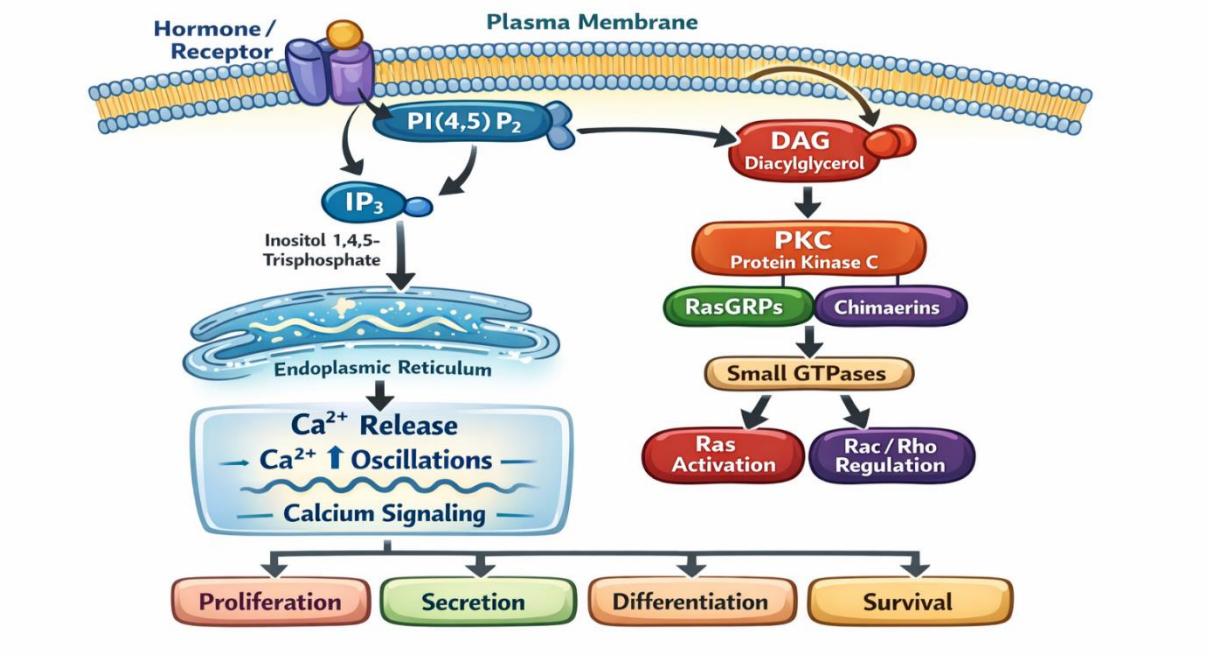

Figure 1: PLC-mediated phosphoinositide signalling downstream of hormone receptor activation.

Ligand binding to a plasma membrane hormone receptor stimulates phospholipase C (PLC), which hydrolyses phosphatidylinositol 4,5-bisphosphate (PI (4,5) P_2) into two second messengers: inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 diffuses to the endoplasmic reticulum (ER), where it binds to specific receptors and triggers Ca^{2+} release into the cytosol, generating Ca^{2+} oscillations and downstream calcium-dependent signalling. In parallel, DAG remains in the plasma membrane and activates protein kinase C (PKC) as well as DAG-responsive effectors such as RasGRPs and chimaerins, leading to modulation of small GTPases. These pathways promote Ras activation and regulate Rac/Rho signalling. Together, Ca^{2+}- and DAG-dependent signalling cascades coordinate key cellular responses, including proliferation, secretion, differentiation, and survival.

Beside phosphoinositides, the phospholipids, such as PC and PE, may also act as substrates for alternative phospholipase-driven pathways and help in sustaining the signalling outputs.[22] Hydrolysis of PC by phospholipase D (PLD) generates phosphatidic acid (PA), a versatile lipid messenger that regulates membrane curvature, vesicle trafficking, and cytoskeletal dynamics, while serving as a central metabolic and signalling hub[23] **(Fig.2)**. PA directly modulates key effectors, including mTOR, Raf kinases, and phosphatidylinositol kinases, and its enzymatic conversion to diacylglycerol (DAG) provides a mechanism for sustained or delayed DAG signalling. This process fine-tunes signal amplitude, duration, and pathway crosstalk beyond the initial phospholipase C response.[24]

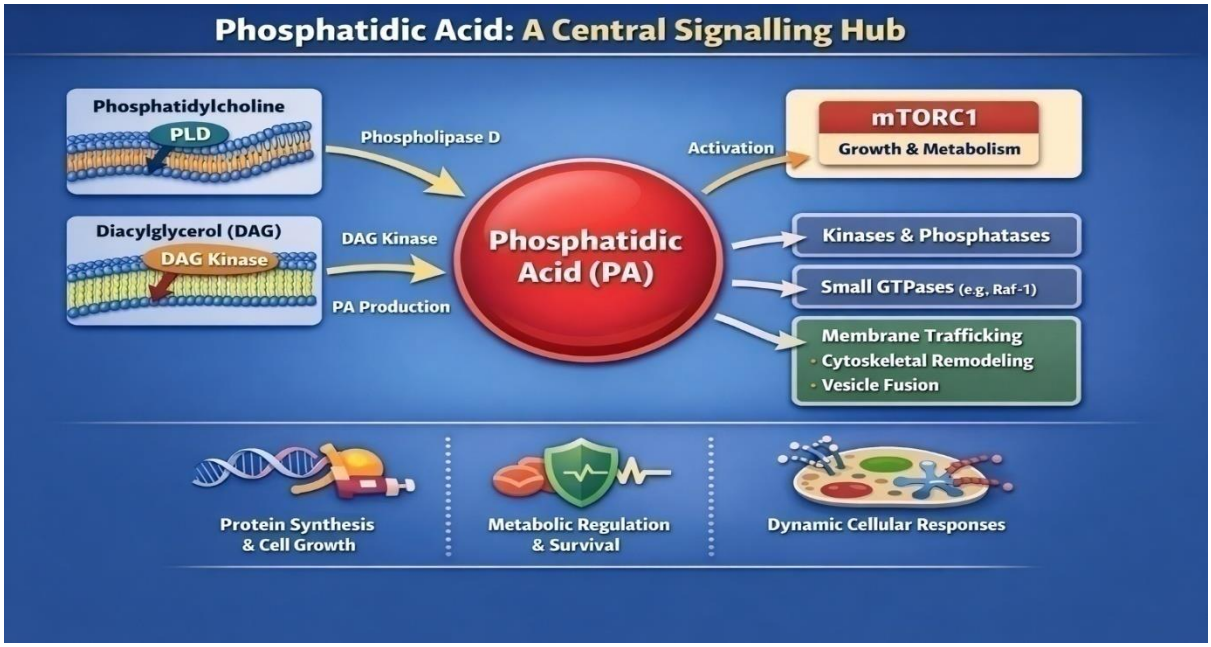

Figure 2: Phosphatidic acid (PA) as a central signalling hub integrating lipid metabolism with cellular growth and dynamics.

Phosphatidic acid, a hydrolyzed product, is generated by two principal enzymatic pathways: (i) hydrolysis of phosphatidylcholine by phospholipase D (PLD), and (ii) phosphorylation of diacylglycerol (DAG) by DAG kinase. The resulting PA functions as a bioactive second messenger that recruits and modulates multiple effector proteins. A major downstream target is mTORC1, whose activation promotes protein synthesis, cell growth, and metabolic regulation. PA also regulates diverse kinases and phosphatases, small GTPases (e.g., Raf-1), and me mbrane-associated processes including vesicle trafficking, cytoskeletal remodelling, and membrane fusion. Through these coordinated interactions, PA integrates lipid-derived signals to control metabolic adaptation, cell survival, and dynamic cellular responses.

Another important enzyme, phospholipase A_2 (PLA_2) can also hydrolyze membrane phospholipids to release polyunsaturated fatty acids, most notably arachidonic acid, thereby coupling phospholipid turnover to the generation of diffusible lipid mediators.[25,26] As the rate-limiting step in eicosanoid biosynthesis, this process led to the formation of prostaglandins, leukotrienes, and thromboxanes—potent regulators of inflammation, thereby help in regulation of vascular tone, immune activation, and tissue repair[27] **(Fig.3).** The stimulus-specific activation and compartmentalization of distinct PLA_2 isoforms ensure precise spatial and temporal control, preventing excessive or pathological inflammatory signalling.

The fatty acid in the sn-1 position is usually saturated (e.g. palmitic acid, stearic acid) and the fatty acid in the sn-2 position is usually unsaturated, particularly Arachidonic acid which is an omega-6 fatty acid.[28] Phospholipase enzymes mediate the hydrolysis of membrane phospholipids, with Phospholipase A1 (PLA1) and Phospholipase A2 (PLA2) being the most important in membrane remodelling and inflammatory signalling.[28,29]

PLA1 cleaves the ester bond at the sn-1 position of phosphatidylcholine, releasing a saturated free fatty acid and producing 2-lysophosphatidylcholine. Lysophospholipids have detergent-like properties and tend to disrupt membrane integrity. This transformation can affect membrane fluidity and stability. In contrast, PLA2 targets the sn-2 position and, in general, releases arachidonic acid with the formation of 1-lysophosphatidylcholine. PLA2 is the most important enzyme in inflammatory signalling among the phospholipases, because arachidonic acid is the precursor of several potent inflammatory mediators.

The released arachidonic acid is metabolised primarily through the cyclooxygenase (COX) and lipoxygenase (LOX) pathways. Arachidonic acid is converted to prostaglandins and thromboxanes through the action of cyclooxygenase enzymes (COX-1 and COX-2). Prostaglandins such as PGE2 are responsible for pain, fever, vasodilation and inflammation while thromboxanes are involved in platelet aggregation and vasoconstriction. Alternatively arachidonic acid can be metabolised via the LOX pathway to form leukotrienes which contribute to bronchoconstriction, allergic responses and recruitment of inflammatory cells. Therefore, activation of PLA2 results in an “arachidonic acid cascade” that augments inflammatory responses in tissues.[30]

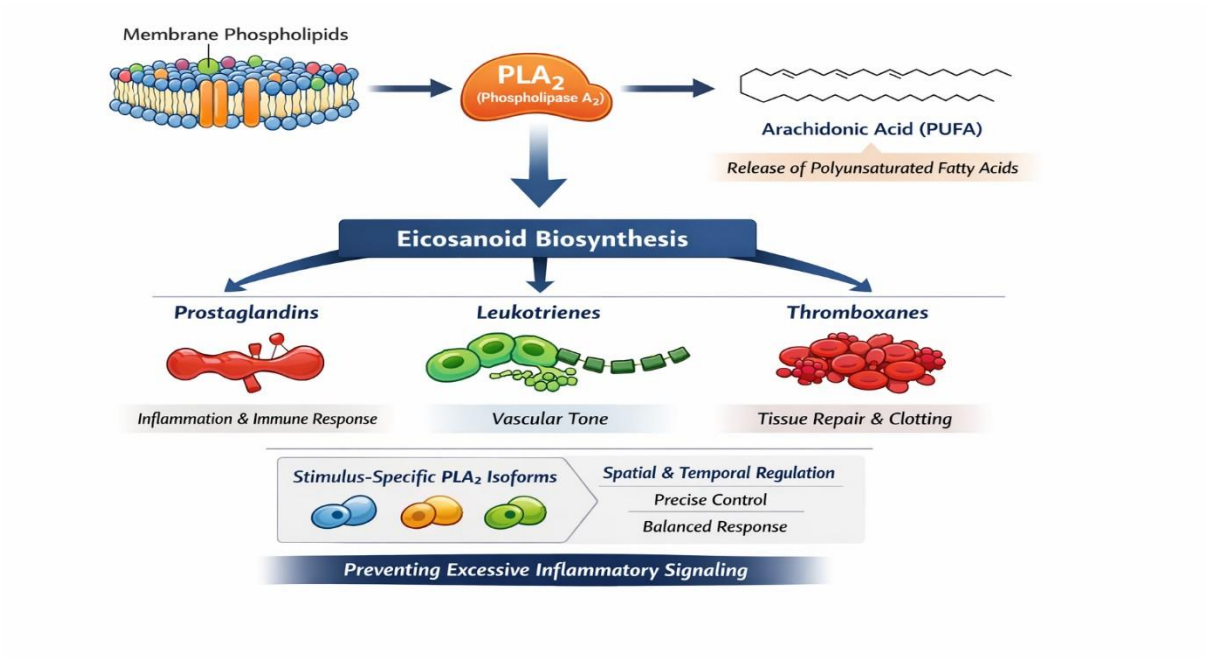

Figure 3: Phospholipase A2–mediated initiation of eicosanoid biosynthesis and its physiological outcomes.

Membrane phospholipids serve as reservoirs of polyunsaturated fatty acids (PUFAs). Upon cellular stimulation, phospholipase A_2 (PLA_2) hydrolyses the sn-2 acyl bond of membrane phospholipids, releasing arachidonic acid, a key PUFA substrate. Arachidonic acid is subsequently metabolized through eicosanoid biosynthetic pathways to generate distinct lipid mediators, including prostaglandins, leukotrienes, and thromboxanes. These eicosanoids regulate diverse biological processes: prostaglandins mediate inflammation and immune responses; leukotrienes modulate vascular tone

and leukocyte activity; and thromboxanes promote tissue repair and platelet aggregation. Stimulus-specific PLA_2 isoforms provide spatial and temporal regulation of arachidonic acid release, ensuring precise control of eicosanoid production and preventing excessive inflammatory signalling.

Together, these enzymatic pathways position membrane phospholipids as central integrators of cellular signalling networks, capable of producing chemically diverse second messengers with distinct diffusion ranges, lifetimes, and mechanisms of action. Coordinated phospholipid remodelling thus provides a unifying framework through which cells translate membrane-localized events into scalable physiological responses, spanning rapid signal transduction to longer-term transcriptional and metabolic reprogramming. Disruption of these lipid signalling circuits has profound pathological consequences, underscoring phospholipids as fundamental determinants of cellular communication and compelling targets for therapeutic intervention.[31]

1.3. Phospholipids as direct allosteric regulators of protein function

Phospholipids act as direct, instructive regulators of protein function, exerting precise control through chemically specific interactions at the membrane–protein interface. A dominant regulatory mechanism involves electrostatic coupling between anionic headgroup of the PL and clusters of basic residues (lysine and arginine) within protein domains, a process that governs membrane recruitment, stabilizes active conformations, and enables lipid-dependent allosteric activation.[32] Among anionic phospholipids, PS functions as a critical signalling cofactor, serving as an obligate lipid determinant for the canonical activation of multiple kinase families (**Fig.4**). PS is required for productive membrane engagement and catalytic activation of protein kinase C (PKC),[33] and also for signal propagation within the MAPK cascade.[34] Further, it is indispensable for the phosphorylation and full activation of Akt/PKB, thereby directly linking membrane lipid composition to cell survival and metabolic signalling.[35]

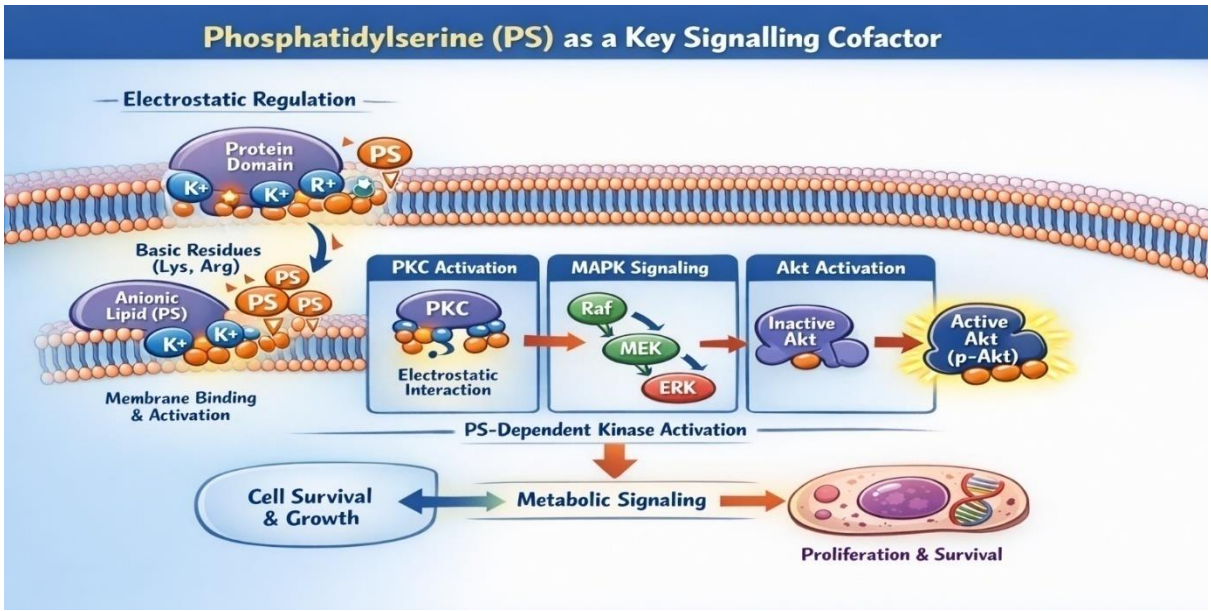

Figure 4: The role of phospholipid PS as a key signalling cofactor at the plasma membrane.

Phosphatidylserine (PS), an anionic phospholipid enriched in the inner leaflet of the plasma membrane, regulates signalling proteins through electrostatic interactions. Negatively charged serine residue of PS interacts with clusters of basic residues (lysine and arginine) within protein domains, promoting membrane recruitment, stable membrane

association, and conformational activation. The executed electrostatic regulation facilitates activation of multiple kinase pathways. PS-dependent membrane binding enhances protein kinase C (PKC) activation via direct lipid–protein interactions, supports MAPK cascade signalling through sequential activation of Raf, MEK, and ERK, and promotes Akt phosphorylation and activation. Collectively, PS-dependent kinase activation integrates membrane localization with downstream metabolic signalling, leading to enhanced cell survival, growth, proliferation, and survival outcomes.

Beyond individual lipid–protein interactions, the broader phospholipid landscape, most notably the spatially and temporally regulated phosphoinositide network [e.g., PI (4,5) P_2 and PI (3,4,5) P_3], confers exquisite signalling specificity. In fact, phosphoinositides function as molecular zip codes that orchestrate protein targeting, scaffold assembly, and pathway insulation through selective engagement of specialized lipid-binding domains (6) **(Fig.5).** This mode of regulation extends well beyond cytosolic kinases to integral membrane proteins. Numerous ion channels and transporters are directly gated or stabilized by PI (4,5) P2, which modulates channel opening frequency, conductance, and coupling to downstream signalling pathways.[36] Similarly, for G protein–coupled receptors (GPCRs), the local phospholipid milieu acts as an allosteric regulator that shapes receptor conformational ensembles, tunes signalling bias between G-protein and β-arrestin pathways, and regulates both desensitization as well as re-sensitization dynamics.[37]

Collectively, these mechanisms establish phospholipids not as passive membrane constituents, but as dynamic, information-encoding cofactors that directly program protein activity and signalling outcomes.

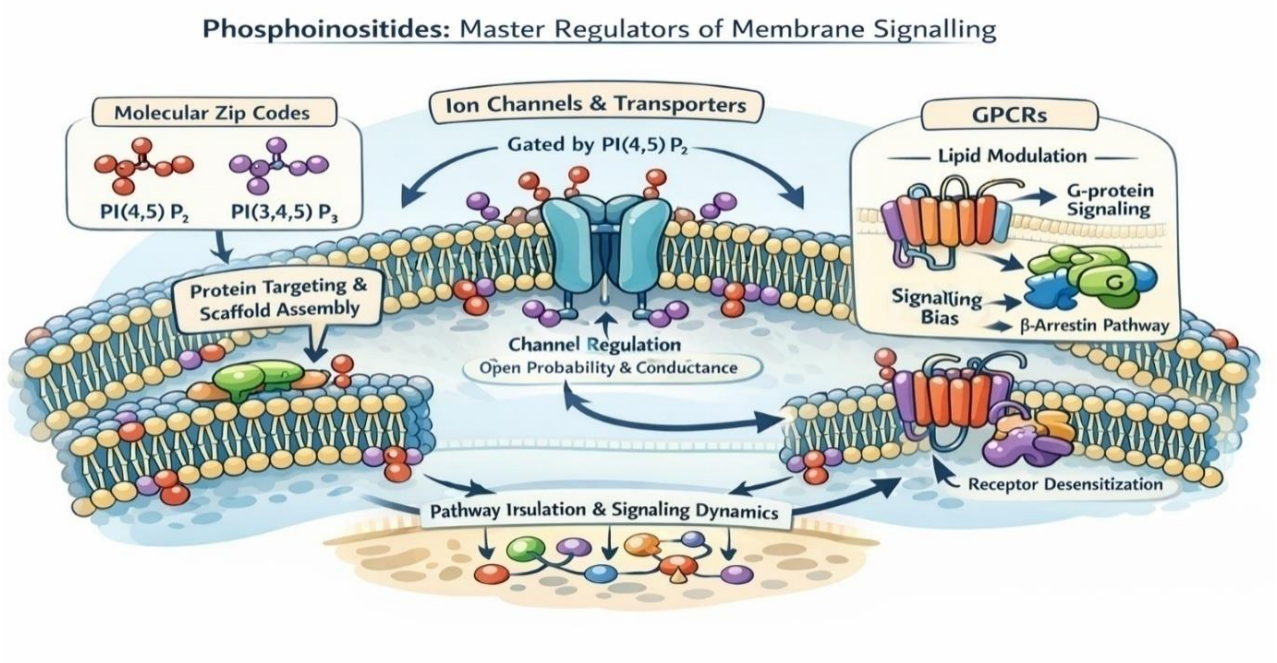

Figure 5: Phosphoinositides as master regulators of membrane signalling.

Schematic representation of the plasma membrane highlighting the central roles of phosphoinositides in coordinating signalling specificity and dynamics. Distinct phosphoinositide species, including PI(4,5)P_2 and PI(3,4,5)P_3, function as "molecular zip codes" that define membrane identity and recruit effector proteins to discrete subdomains. These lipids regulate protein targeting and scaffold assembly at the cytoplasmic leaflet, thereby organizing signalling complexes.

PI(4,5)P_2 directly gates ion channels and transporters, modulating channel open probability and conductance.

Phosphoinositides also modulate G protein–coupled receptors (GPCRs), influencing G-protein activation, β-arrestin pathway engagement, signalling bias, and receptor desensitization. Through dynamic synthesis and turnover, phosphoinositides insulate pathways and fine-tune signalling amplitude, spatial confinement, and temporal responses, collectively orchestrating membrane-associated signalling networks.

1.4. Membrane microdomains and signal compartmentalization

The plasma membrane is a laterally heterogeneous, metastable assembly whose organization arises from collective lipid–lipid and lipid–protein interactions rather being a uniform bilayer architecture. A central organizing principle underlying this heterogeneity is the cooperative association of specific phospholipid species with cholesterol and sphingolipids, which gives rise to sterol-enriched, liquid-ordered membrane microdomains, classically referred to as lipid rafts.[2,38] These domains are distinguished by increased acyl-chain order, reduced lateral diffusion, and enhanced thickness relative to the surrounding liquid-disordered phospholipid matrix, thereby creating physico-chemically distinct membrane environments.

Lipid rafts behave as the selective molecular hubs that organize signalling components within the cell membrane. Proteins with saturated lipid modifications, such as glycosylphosphatidylinositol (GPI) anchors or S-palmitoylation, tend to cluster within these ordered lipid regions. In contrast, proteins carrying unsaturated acyl chains or large transmembrane domains are excluded because of the thermodynamically unfavourable interactions.[39,40] This selective sorting creates nanoscale platforms with ensemblance of selective receptors, kinases, and adaptor proteins, with exclusion of inhibitory or competing molecules. As a result, lipid rafts prearrange the signalling environment even before binding of the approaching ligand **(Fig.6).**

In fact, lipid rafts are not static entities but transient nanoscale assemblies whose formation as well as half-life are generally regulated by protein scaffolding, membrane curvature, and cortical actin dynamics.[41,42] Within this framework, raft-associated lipids act as organizing scaffolds that lower the energy barrier for signalosome assembly, facilitating rapid, stimulus-dependent coalescence of signalling complexes. This model is best exemplified in immune signalling, where antigen-induced clustering of the T-cell receptor promotes its recruitment into cholesterol-dependent nanodomains, enabling efficient coupling to Src-family kinases and downstream signalling cascades.[43,44]

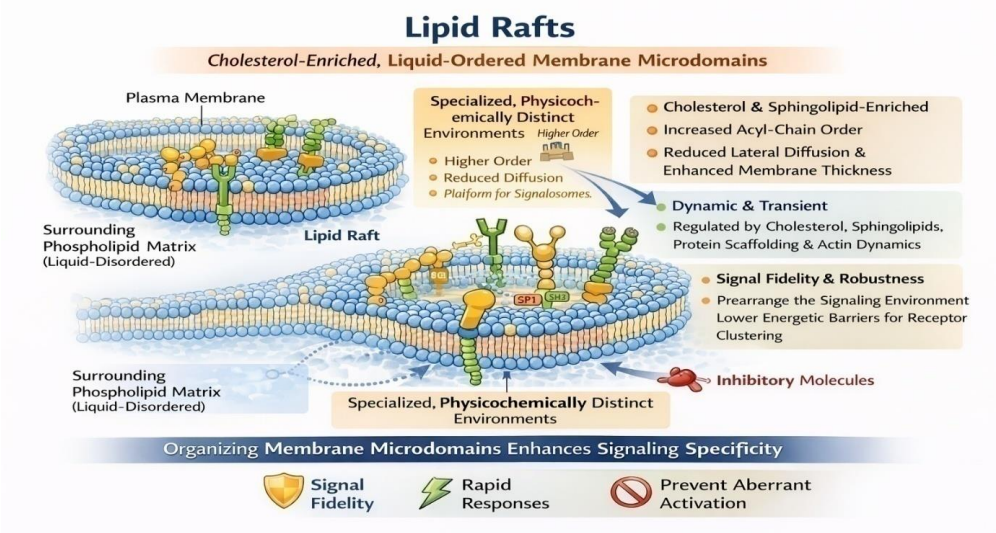

Figure 6: Structural and functional organization of lipid rafts in the plasma membrane.

Lipid rafts are cholesterol- and sphingolipid-enriched, liquid-ordered microdomains embedded within the surrounding liquid-disordered phospholipid matrix of the plasma membrane. Compared with the bulk membrane, rafts exhibit increased acyl-chain order, enhanced membrane thickness, and reduced lateral diffusion, creating specialized physico-chemically distinct environments. These domains are dynamic and transient, regulated by cholesterol content, sphingolipids, protein scaffolding interactions, and actin cytoskeletal dynamics. Lipid rafts serve as platforms for signalosome assembly by concentrating receptors, adaptor proteins (e.g., SH2/SH3 domain–containing proteins), and downstream signalling molecules while excluding inhibitory components. By prearranging signalling machinery and lowering the energetic barrier for receptor clustering, rafts enhance signal fidelity, promote rapid and robust cellular responses, and prevent aberrant activation.

More broadly, membrane microdomains represent a spatial regulatory layer that complements classical biochemical control mechanisms. By restricting signal propagation to defined lipid environments, microdomains enhance signalling fidelity, accelerate kinetic responses, and insulate parallel pathways from aberrant cross-activation.[45] Emerging models suggest that lipid-driven phase separation at the plasma membrane is analogous to biomolecular condensates, integrating membrane composition, protein multivalency, and cytoskeletal constraints to dynamically tune signalling output.[46,47] Thus, membrane micro-domains are increasingly recognized not merely as passive lipid assemblies but as active determinants of signal specificity, robustness, and cellular decision-making.

1.5. Phospholipid asymmetry: A dynamic platform for cellular signalling and homeostasis

The asymmetric distribution of phospholipids across the plasma membrane bilayer is a fundamental and actively regulated feature of eukaryotic cells, with critical implications for cellular signalling and homeostasis.[48] Under steady-state conditions, aminophospholipids, primarily PS and PE, are enriched in the inner, cytosolic leaflet. This asymmetry is maintained by ATP-dependent flippases (e.g., P4-ATPases), while opposing movements are mediated by floppases and scramblases, establishing a dynamic equilibrium.[49] The cytosolic leaflet, enriched in PS and PE, creates a distinct lipid environment that directly regulates intracellular signalling pathways. Both the lipids facilitate the recruitment, conformational change, and full activation of key signalling proteins. A canonical example is the direct binding of PS to the C2 domains of PKC and to specific sites on Akt kinase, interactions that are essential for their activation and downstream functions.[50] In this way, maintained asymmetry provides a permissive lipid landscape that supports vital signal transduction cascades **(Fig.7).**

The collapse of phospholipid asymmetry is itself a tightly controlled signalling mechanism, most prominently during apoptosis. Caspase activation leads to the proteolytic cleavage and activation of specific scramblases (e.g., XKR8), concurrent with the inhibition of flippases, resulting in the rapid externalization of PS.[51] The surface-exposed PS offers a “eat-me” signal, enabling efficient recognition and phagocytic clearance of apoptotic cells by macrophages and other phagocytes.[7] Beyond facilitating clearance, PS externalization actively modulates immune responses.

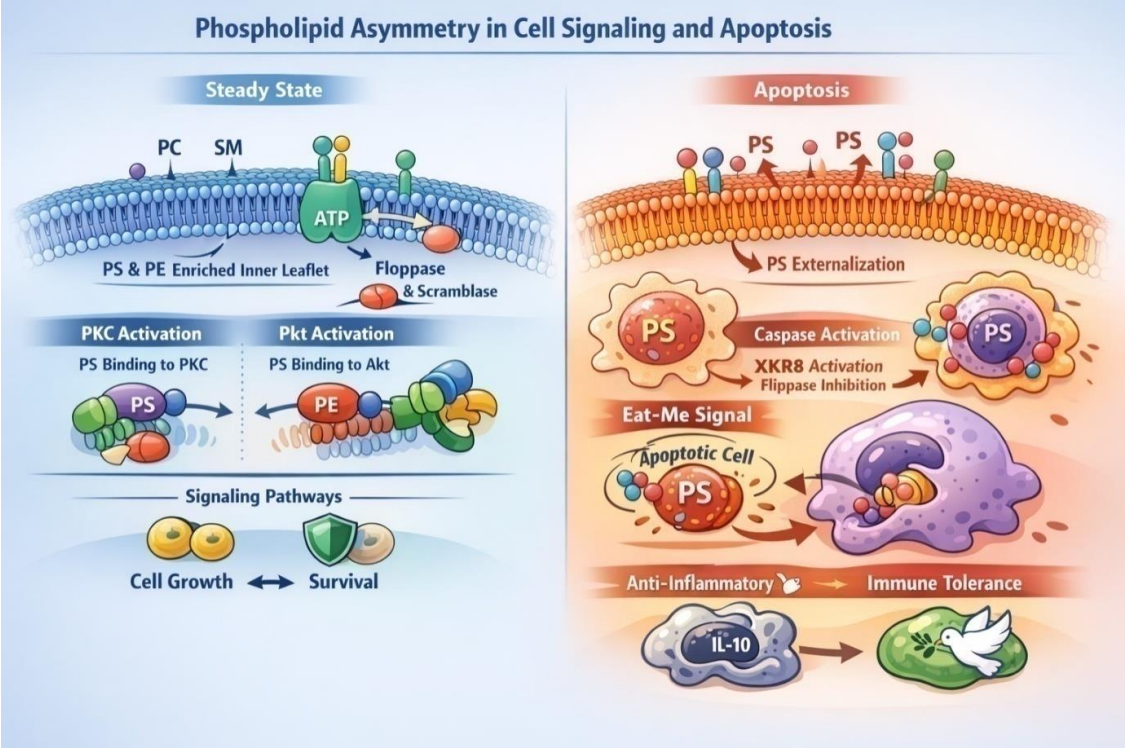

Figure 7: Phospholipid Asymmetry in Cell Signaling and Apoptosis.

Schematic representation of the asymmetric distribution of phospholipids across the plasma membrane and its functional implications in eukaryotic cells. Under steady-state conditions (left), aminophospholipids—phosphatidylserine (PS) and phosphatidylethanolamine (PE)—are enriched in the inner leaflet through ATP-dependent flippase activity, counterbalanced by floppases and scramblases. This maintained asymmetry creates a signaling-competent lipid environment that facilitates membrane recruitment and activation of key kinases such as protein kinase C (PKC) and Akt, supporting cell growth and survival pathways. During apoptosis, caspase-mediated activation of scramblases (e.g., XKR8) and inhibition of flippases lead to PS externalization. Surface-exposed PS acts as an "eat-me" signal recognized by phagocytic receptors (TIM-4, Stabilin-2), promoting apoptotic cell clearance and inducing anti-inflammatory, tolerogenic signaling that preserves immune homeostasis.

Engagement of PS by receptors on phagocytes, such as TIM-4 and Stabilin-2, triggers intracellular signalling that promotes anti-inflammatory and tolerogenic outcomes, thereby preventing autoimmunity and excessive inflammation.[52] Thus, the disruption of asymmetry is not a passive breakdown but an active process that transmits critical extracellular signals.

In summary, phospholipid asymmetry serves as a dynamic, dual-purpose signalling platform. Its preservation is essential for propagating intracellular signals, while its regulated dissipation transmits extracellular cues that coordinate tissue homeostasis and immune regulation. The transition between these two states represents a decisive event in cellular life and death, underscoring the central role of lipid dynamics in physiology and pathology.

1.6. Lipid-derived mediators in cellular stress signalling

The stimulus-dependent enzymatic remodelling of membrane phospholipids represents a central mechanism by which cells generate bioactive lipid mediators that translate environmental stress, inflammatory cues, and immune challenges

into coordinated intracellular responses. Far from serving merely as structural components, phospholipids act as dynamically regulated reservoirs of signalling molecules. The rapid PL liberation as well as their inter-conversion confer both temporal precision and spatial specificity to stress-adaptive signalling networks.[53,25]

1.6.1 ***Phosphatidic acid (PA) as a central signalling hub*****:** PA occupies a pivotal position within lipid signalling hierarchies. It is produced primarily through phospholipase D -mediated hydrolysis of PC or via phosphorylation of DAG by DAG kinases, thereby tightly coupling PA generation to receptor-activated signalling cascades.[23] Acting as a second messenger, PA directly engages and regulates key stress-responsive pathways, most notably the mechanistic target of rapamycin complex 1 (mTORC1). The mTORC1 signalling pathway integrates nutrient availability, energy status, and growth factor signals to control cellular metabolism, survival, and protein synthesis.[54,55] Beyond mTOR signalling, PA exerts broad regulatory influence by modulating the membrane recruitment, activity, and conformational state of diverse effector proteins, including kinases, phosphatases, and small GTPase regulators such as Raf-1. Through these interactions, PA orchestrates membrane trafficking, vesicle fusion, and cytoskeletal remodelling, enabling rapid structural and functional adaptation during cellular stress.[56]

1.6.2 ***Eicosanoids as master regulators of inflammatory stress responses*****:** A second major class of lipid-derived stress mediators arises from phospholipase A_2–driven hydrolysis of membrane phospholipids, which liberates arachidonic acid (AA) from the sn-2 position. AA serves as the principal substrate for the biosynthesis of eicosanoids, a diverse family of short-lived yet highly potent lipid mediators.[12] Through the coordinated actions of cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, AA is converted into prostaglandins, thromboxanes, and leukotrienes, each exerting distinct but overlapping biological effects.

Eicosanoids function predominantly through both autocrine and paracrine signals that fine-tune inflammatory and immune responses. They regulate fundamental processes such as vasodilation, vascular permeability, leukocyte recruitment and activation, nociception, and fever, thereby shaping both acute and chronic responses to physiological stress and tissue injury.[26,27] Dysregulated eicosanoid production is a hallmark of inflammatory, metabolic, and cardiovascular diseases, underscoring the central role of lipid mediator signalling in stress-associated pathology.[57]

PLA2 activation can be triggered by a range of stimuli, including infections, oxidative stress, cytokine ambience, tissue damage, and certain toxins or venoms. An overactive PLA2–arachidonic acid pathway has been associated with a variety of pathological conditions such as Rheumatoid Arthritis, Asthma, Psoriasis, inflammatory bowel disease, cardiovascular issues, neurodegenerative diseases like Alzheimer's Disease, and cancer progression.[58] Due to its crucial involvement in inflammation, the pathway offers a significant target for therapeutic intervention. Non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and aspirin work by inhibiting COX enzymes, thereby decreasing the synthesis of prostaglandins, while corticosteroids indirectly lower PLA2 activity by preventing the release of AA from membrane phospholipids.[27]

1.7. Lipid-modifying enzymes as a dynamic regulator

Cellular signal transduction is orchestrated by a highly dynamic network of lipid-modifying enzymes that continuously remodel membrane phospholipid composition in response to extracellular and intracellular cues.[6] Phosphoinositide kinases and phosphatases, phospholipases, and lipid transfer proteins act in concert to regulate both the abundance and spatial distribution of bioactive lipids across distinct membrane compartments.[31] This enzymatic control enables rapid,

reversible, and compartmentalized remodelling of key signalling lipids, including phosphatidylinositol phosphates (PIPs), PA, DAG, and lysophospholipids.

A hallmark of lipid-mediated signalling is the exceptional temporal and spatial precision with which lipid species are generated and removed. Upon receptor stimulation at the plasma membrane, class I phosphoinositide 3-kinases (PI3Ks) catalyse the localized conversion of PI(4,5)P_2 into PIP_2, creating transient membrane microdomains enriched in this low-abundance but high-impact signalling lipid.[59] PIP_2 serves as a recruitment platform for proteins containing pleckstrin homology (PH) and related lipid-binding domains, thereby coupling membrane identity to downstream effector activation. Signal termination and spatial confinement are achieved through the opposing activity of lipid phosphatases such as PTEN, which dephosphorylates PIP_3 back to PI (4,5)P_2, sharpening signalling gradients and preventing inappropriate pathway propagation.[60]

Similarly, phospholipase C enzymes mediate stimulus-dependent hydrolysis of PI (4,5)P_2 to generate DAG and inositol 1,4,5-trisphosphate, converting a structural membrane lipid into both diffusible and membrane-retained second messengers with distinct signalling outputs. In parallel, lipid transfer proteins facilitate the non-vesicular exchange of phospholipids between organelles, sustaining localized lipid pools and enabling signalling reactions at membrane contact sites with no perturbation of membrane composition (**Fig.8).**[61]

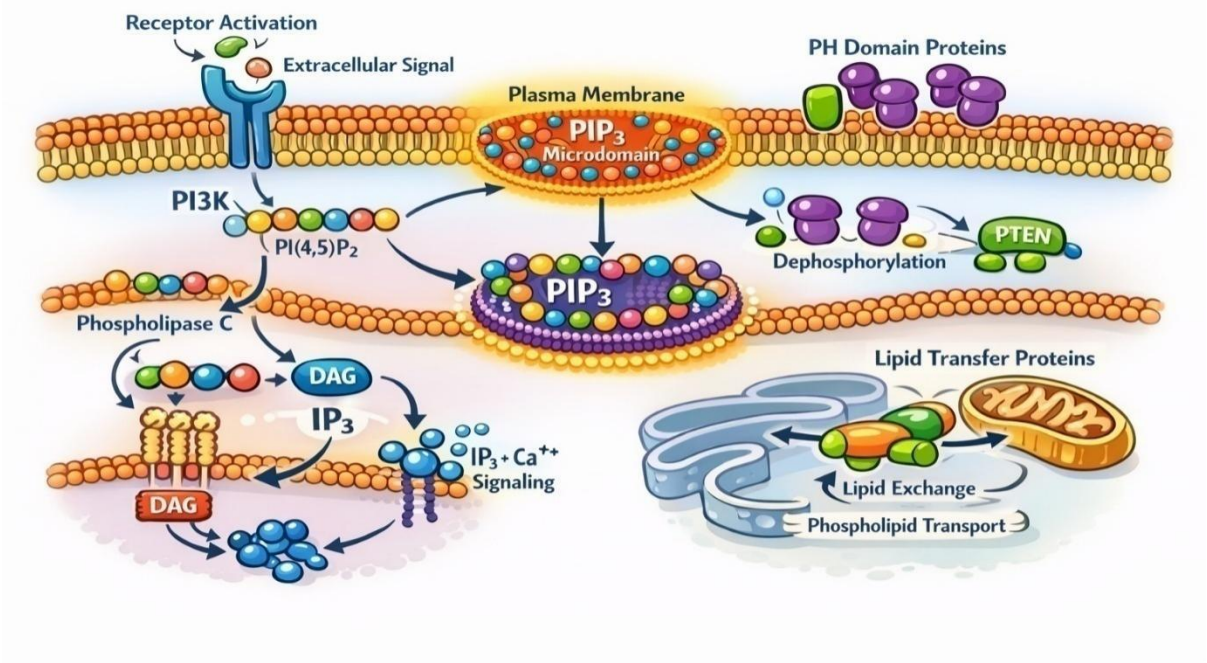

Figure 8: Phosphoinositide-mediated signalling at the plasma membrane.

Extracellular ligand binding induces receptor activation at the plasma membrane, leading to recruitment and activation of phosphoinositide 3-kinase (PI3K). PI3K phosphorylates phosphatidylinositol 4, 5-bisphosphate [PI(4,5)P_2] to generate phosphatidylinositol 3,4,5-trisphosphate (PIP_3), which accumulates in membrane microdomains. PIP3 serves as a docking site for pleckstrin homology (PH) domain–containing proteins, promoting their membrane recruitment and downstream signal propagation. The lipid phosphatase PTEN counteracts this pathway by dephosphorylating PIP3 back to PI(4,5)P2, thereby attenuating signalling. In parallel, phospholipase C (PLC) hydrolyses PI (4,5)P2 to produce diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). DAG remains membrane-associated to activate protein

kinase C and related effectors, whereas IP3 triggers intracellular Ca^{2+} release, amplifying Ca^{2+}-dependent signalling cascades. Lipid transfer proteins facilitate phospholipid exchange between organelles, including the endoplasmic reticulum and mitochondria, maintaining membrane lipid homeostasis and supporting sustained signal transduction.

Together, these enzymatic processes establish dynamic, short-lived lipid landscapes that encode information in both space and time. The subcellular targeting, regulated activation, and coordinated turnover of lipid-modifying enzymes generate transient "lipid codes" that govern protein recruitment, conformational activation, and signal integration.[62]

Through this mechanism, lipid metabolism constitutes a fundamental layer of cellular information processing, underpinning diverse processes such as membrane trafficking, cytoskeletal remodelling, and cell fate determination.

2. Phospholipids and Disease Mechanisms

Phospholipids are more than structural scaffolds of cellular membranes—they are dynamic regulators of signalling, metabolism, and immunity. Their dysregulation fuels the onset and progression of diverse pathologies, from neurodegeneration and cancer to cardiovascular and metabolic disorders. By bridging molecular architecture with cellular dysfunction, phospholipids emerge as pivotal players in disease mechanisms, offering both challenges and opportunities for therapeutic intervention.

2.1. Phospholipid dysregulation in cardiovascular disease

Alterations in phospholipid composition and lateral membrane organization disrupt fundamental bilayer properties, including fluidity, curvature stress, and phase behaviour. These changes impair essential membrane-dependent processes such as signal transduction, vesicular trafficking, and cellular compartmentalization, thereby compromising cardiovascular cell function.[5] Mitochondrial phospholipids are particularly critical in this context. PE and CL preserve inner mitochondrial membrane architecture and facilitate respiratory chain supercomplex assembly.[63]

Defective synthesis or remodelling of these lipids destabilizes oxidative phosphorylation, elevates reactive oxygen species production, and drives mitochondrial dysfunction, a central pathogenic mechanism in cardiomyopathies as well as neurodegenerative and mitochondrial disorders.[13,64] At the systemic level, disrupted phospholipid metabolism,particularly impaired PC availability, compromises hepatic very-low-density lipoprotein (VLDL) assembly and secretion. The resulting dyslipidaemia promotes hepatic steatosis and accelerates the development of atherosclerotic cardiovascular disease.[65]

Beyond their structural roles, phospholipids function as bioactive mediators in cardiovascular pathology. Phospholipase A_2–dependent hydrolysis generates eicosanoids and platelet-activating factor, key regulators of inflammation, thrombosis, and vascular tone.[66,67] In parallel, oxidative modification of phospholipids produces pro-inflammatory species that trigger endothelial dysfunction, monocyte recruitment, and foam cell formation, thereby amplifying atherogenesis.[68,69] Moreover, dynamic remodelling of phospholipid pools following myocardial injury modulates inflammatory resolution, fibrosis, and tissue repair. These lipid-dependent processes critically shape post-infarction remodelling and functional recovery.[70]

In summary, phospholipid homeostasis integrates membrane biophysics, mitochondrial bioenergetics, lipid transport, and inflammatory signalling. Its disruption represents a unifying mechanistic axis linking cellular membrane dysfunction to cardiovascular disease pathogenesis.[5,68]

2.2. Phospholipids as pathogenic drivers and diagnostic biomarkers in metabolic and liver diseases

Phospholipids are now recognized as dynamic mediators and markers in metabolic and liver diseases, playing central roles in both pathogenesis and clinical assessment.[71] Their involvement extends from initiating cellular injury to serving as measurable indicators of disease progression. Altered phospholipid metabolism had been directly correlated to hepatocyte dysfunction and liver injury. A pivotal mechanism is the generation of oxidized phospholipids (OxPLs), which are potent inducers of oxidative stress and inflammation.[8] OxPLs derived from damaged hepatocytes and lipid peroxidation activate both Kupffer as well as hepatic stellate cells, promoting a pro-inflammatory and pro-fibrogenic microenvironment that drives progression of non-alcoholic steato-hepatitis (NASH) disease.[72] Concurrently, imbalances in hepatic PC synthesis critically influence lipid homeostasis. Specifically, impaired PC synthesis via the phosphatidyl-ethanolamine N-methyltransferase (PEMT) pathway reduces the hepatic pool of PC necessary for assembling and secreting very-low-density lipoproteins (VLDL).[14] This impairment leads to intra-hepatic triglyceride retention, directly promoting the development of non-alcoholic fatty liver disease (NAFLD).[73]

The metabolic disturbances in these diseases are reflected systemically, making specific phospholipid species promising non-invasive biomarkers. Plasma phospholipid profiling has revealed distinct signatures that correlate with disease states. For instance, a reduced ratio of phosphatidylcholine to phosphatidylethanolamine (PC/PE) in circulation is associated with hepatic insulin resistance and NAFLD severity.[9] Furthermore, specific phospholipid classes, such as lysophosphatidylcholines (LPCs), show consistent alterations in conditions of metabolic stress, including obesity and sepsis, highlighting their potential for diagnostic and prognostic applications.[74,75]

The pathogenic role of phospholipids extends beyond the liver, forming a key molecular link between metabolic liver disease and cardiovascular complications. Oxidized phospholipids, particularly those contained within oxidized low-density lipoprotein (LDL) like 1-palmitoyl-2-(5-oxovaleroyl)-*sn*-glycero-3-phosphocholine (oxPOVPC, a component of oxPAPC mixtures), are established promoters of atherosclerosis (76). These OxPLs drive endothelial dysfunction by activating pro-inflammatory pathways, and facilitate foam cell formation by enhancing the uptake of modified LDL by macrophages, thereby accelerating plaque development (8, 77). Phospholipids are, thus, far more than structural components of cellular membranes; they are active signalling molecules involved in the pathogenesis of metabolic and liver diseases and valuable biomarkers reflecting systemic metabolic health. Targeting phospholipid pathways or utilizing their signatures for diagnosis represents a promising frontier for therapeutic and clinical intervention.

2.3. Phospholipids in neurodegenerative disorders

Phospholipids are fundamental to neurological function, fulfilling two powerful and seemingly opposing roles: they are indispensable structural constituents of neural membranes and, simultaneously, precursors of highly bioactive signalling molecules. Structurally, phospholipids form the bilayer framework of every neuronal membrane and represent the predominant lipid component of myelin. This architecture, which is not mere a passive scaffolding, is essential for neural performance.[78] The myelin sheath enables rapid saltatory conduction along axons, ensuring efficient electrical transmission and precise, coordinated neural communication.[79] The integrity, fluidity, and organization of phospholipid bilayers directly influence membrane excitability, synaptic function, and axonal stability.[80] Metabolically, however, these same membrane phospholipids serve as dynamic reservoirs of signalling potential. Species enriched in polyunsaturated fatty acids, particularly arachidonic acid, can be hydrolysed by phospholipase A_2 to release potent lipid mediators, including prostaglandins and leukotrienes.[25] Under physiological

conditions, this pathway is tightly regulated and supports normal cellular signalling. When excessively activated, however, it amplifies inflammatory cascades, promotes oxidative stress, and contributes to chronic neuroinflammation, a hallmark of many neurodegenerative disorders.[81] Thus, phospholipids embody a central biological paradox within the nervous system: they provide the structural foundation required for neural integrity and rapid communication, yet they also constitute a molecular source of inflammatory signals that, when dysregulated, can actively drive neuropathology.

Disruptions in phospholipid homeostasis are not passive epi-phenomenon of neurodegeneration; they are active, mechanistic drivers of disease progression. Among the earliest and most reproducible lipid abnormalities is the selective depletion of plasmalogens, a brain-enriched subclass of ether phospholipids that serve both structural and antioxidant functions.[82-84] In Alzheimer's disease, plasmalogen loss occurs at prodromal stages and correlates closely with synaptic dysfunction, cognitive decline, and overall disease severity. This consistent association across independent cohorts.[82] supports a contributory, rather than incidental, role in pathogenesis. Concurrently, the precisely maintained asymmetry of the neuronal plasma membrane becomes destabilized. Under physiological conditions, phosphatidylserine (PS) is restricted to the cytosolic leaflet. Its translocation to the extracellular surface constitutes a highly conserved and early apoptotic signal.[85] Externalized PS functions as an “eat-me” cue, promoting microglial recognition and phagocytic clearance of stressed or compromised neurons (16, 86. In this way, disruption of phospholipid organization does not merely reflect cellular distress—it actively orchestrates neuronal elimination, thereby linking membrane lipid dysregulation directly to neurodegenerative progression.

Collectively, impaired phospholipid metabolism establishes a pathological continuum. It undermines membrane integrity, compromises axonal stability, and perturbs synaptic function, while simultaneously amplifying neuroinflammatory cascades and accelerating structural neuronal loss. This convergence of membrane instability, inflammatory signalling, and programmed clearance mechanisms positions phospholipid dysregulation as a central nexus in the pathogenesis of neurodegenerative disorders.

2.4. Phospholipid dysregulation in genetic, rare, and acquired diseases

Phospholipids are indispensable structural and signalling constituents of cellular membranes, and their tightly regulated synthesis, remodelling, intracellular trafficking, and homeostasis are essential for organelle integrity, bioenergetic efficiency, and cellular survival. Disruption of these processes, whether through inherited mutations or acquired immune and inflammatory mechanisms, contributes to a broad spectrum of human diseases.

Inherited defects in phospholipid metabolism frequently present early in life and are characterized by profound organelle dysfunction. A canonical example is Barth syndrome, an X-linked condition caused by loss-of-function mutations in the *TAZ* gene.[87] *TAZ* encodes tafazzin, a phospholipid transacylase required for cardiolipin remodelling.[88,89] Cardiolipin is a mitochondria-specific phospholipid critical for maintaining inner mitochondrial membrane architecture and stabilizing respiratory chain supercomplexes.[89,90] Tafazzin deficiency results in abnormal cardiolipin composition, disrupted cristae morphology, impaired oxidative phosphorylation, and increased apoptotic susceptibility, culminating clinically in cardiomyopathy, skeletal myopathy, neutropenia, and growth delay.[91] These findings illustrate how defective phospholipid remodelling translates into systemic mitochondrial dysfunction.

Interestingly, phospholipid homeostasis also depends on their precise intracellular distribution. Non-vesicular lipid transport at membrane contact sites between the endoplasmic reticulum (ER), mitochondria, and other organelles is essential for metabolic coordination.[92] Mutations in lipid transport proteins disrupt this spatial organization and induce organelle stress. For example, defects in *VPS13A* impair lipid transfer at ER contact sites and cause Chorea-acanthocytosis.[93-95] Experimental studies demonstrated that VPS13 proteins function as lipid transport bridges facilitating bulk phospholipid movement between membranes.[95] Similarly, impaired phosphatidylserine decarboxylase activity compromises mitochondrial phosphatidylethanolamine production, leading to defects in mitochondrial respiration and membrane integrity.[96] Together, these studies underscore that disruption of phospholipid trafficking could be as pathogenic as defects in their synthesis.

Beyond inherited disorders, phospholipids and their associated proteins are central to acquired autoimmune and inflammatory diseases. In Antiphospholipid syndrome, pathogenic autoantibodies target phospholipid-binding proteins, most notably β2-glycoprotein I (β2GPI).[97-98] Anti-β2GPI antibodies induce endothelial and platelet activation, amplify procoagulant signalling, and disrupt anticoagulant pathways, producing the characteristic clinical manifestations of arterial and venous thrombosis and pregnancy morbidity.[99] These findings establish phospholipid–protein complexes as central immunologic targets driving thrombosis.

Under conditions of oxidative stress, phospholipids undergo enzymatic or non-enzymatic modification to generate oxidized phospholipids (OxPLs), which function as bioactive danger-associated molecular patterns rather than passive markers of lipid peroxidation.[8,100] OxPLs activate scavenger receptors such as CD36[101] and cooperate with Toll-like receptors to amplify inflammatory signalling.[102] Through these pathways, oxidized phospholipids promote cytokine production and sustain sterile inflammation.[8] This mechanism contributes to autoimmune pathogenesis in disorders such as Systemic lupus erythematosus[99,103-105] and Rheumatoid arthritis,[105] where oxidative stress and lipid per-oxidation enhance autoantibody formation and tissue injury.

Collectively, the literature supports two principals —yet sometimes intersecting—mechanistic axes of phospholipid-mediated disease: first, monogenic disorders resulting from inherited defects in phospholipid biosynthesis or inter-organelle transport, leading to mitochondrial structural and bioenergetic failure; and second, acquired disorders in which phospholipids or their oxidized derivatives become targets of pathogenic autoimmunity or active drivers of chronic inflammation. In both contexts, phospholipids emerge not as passive membrane constituents but as dynamic regulators of cellular integrity and immune signalling.

2.5. Cancer and proliferation

Aberrant phospholipid metabolism is now recognized as a core metabolic hallmark of cancer, functioning not merely as a by-product of transformation but as an active driver of tumor progression. Lipid metabolic reprogramming supports rapid membrane biogenesis, sustains oncogenic signalling, and remodels the tumor microenvironment (TME) to favour malignant growth.[106,107]

To sustain uncontrolled proliferation, cancer cells markedly upregulate the Kennedy pathway for phosphatidylcholine (PC) synthesis. A pivotal step in this pathway is catalysed by choline kinase-α (CHKα), which phosphorylates choline to generate phosphocholine. Elevated CHKα expression and accumulation of phosphocholine and total PC are consistently observed across multiple malignancies, including breast, ovarian, and lung cancers. These alterations

correlate with aggressive phenotype and poor prognosis, reflecting both the increased demand for membrane biosynthesis and the generation of lipid-derived second messengers that amplify growth signalling.[108]

In parallel, lysophosphatidic acid (LPA) signalling represents a major phospholipid-derived oncogenic axis. LPA engages its G protein–coupled receptors (LPAR1–6), triggering downstream pathways such as PI3K/AKT, RAS/MAPK, and Rho/ROCK that collectively promote proliferation, migration, invasion, and resistance to apoptosis. This autocrine–paracrine signalling loop is frequently intensified in tumors through increased activity of secretory phospholipase A_2 (sPLA$_2$) and autotaxin (ATX), the lysophospholipase D that converts lysophosphatidylcholine into LPA, thereby establishing a feed-forward circuit that sustains malignant progression.[109]

Phospholipid-derived mediators also directly suppress apoptosis. Molecules such as platelet-activating factor (PAF) and specific oxidized phospholipids can activate pro-survival transcription factors, including NF-κB, enhancing tumor cell resilience under metabolic and therapeutic stress.[106] Beyond tumor cells themselves, these lipid signals profoundly reshape the TME. Cancer-derived LPA and prostaglandins—generated from arachidonic acid released by phospholipase A_2—promote angiogenesis, activate cancer-associated fibroblasts, and polarize immune populations toward immunosuppressive phenotypes such as M2 macrophages and regulatory T cells. These changes foster metastasis and contribute to therapeutic resistance.[107-110]

Collectively, these interconnected disturbances in phospholipid metabolism establish a self-reinforcing metabolic and signalling network that supports malignant growth, enhances survival under stress, and undermines therapeutic efficacy.

3. Phospholipids in Diagnostics and Therapeutics: Emerging Frontiers

Phospholipids are increasingly recognized as central molecules in both diagnostics and therapeutics owing to their fundamental roles in membrane architecture, intracellular signalling, and metabolic regulation. Disease-specific alterations in phospholipid composition, distribution, and turnover are now being translated into clinically actionable strategies, positioning these molecules at the interface of pathophysiology and precision medicine.

Therapeutically, phospholipids contribute through both direct replacement approaches and targeted modulation of metabolic pathways. A landmark example is the clinical introduction of synthetic pulmonary surfactants enriched in dipalmitoylphosphatidylcholine (DPPC) by Tetsuro Fujiwara in 1980, which dramatically improved survival in neonatal respiratory distress syndrome.[111] This pioneering work provided compelling proof that restoration of phospholipid balance can reverse life-threatening physiological dysfunction.

Nutritional supplementation strategies further illustrate their therapeutic potential. Polyunsaturated phosphatidylcholine (PPC) has demonstrated hepatoprotective effects and improvements in lipid metabolism in chronic liver disease.[112]

Likewise, phosphatidylserine (PS) supplementation has been investigated for mitigating age-related cognitive decline, with clinical evidence suggesting potential neurocognitive benefits.[113]

Beyond supplementation, pharmacological targeting of phospholipid-metabolizing enzymes represents a powerful and rapidly expanding therapeutic avenue. Cytosolic phospholipase A_2 (cPLA$_2$), which releases arachidonic acid for the generation of pro-inflammatory eicosanoids, has been extensively characterized and is strongly implicated in

inflammatory disease pathogenesis.[114] Autotaxin (ENPP2), the enzyme that converts lysophosphatidylcholine (LPC) into lysophosphatidic acid (LPA), has emerged as a promising target in fibrosis and cancer.[115] More broadly in oncology, lipid kinases such as phosphoinositide 3-kinase (PI3K), which phosphorylates phosphatidylinositol lipids to drive oncogenic signalling, could emerge as established drug targets.[116,117]

In the diagnostic and prognostic arena, alterations in phospholipid metabolism have emerged as robust and clinically informative biomarkers across a broad spectrum of diseases. In oncology, magnetic resonance spectroscopy (MRS) frequently reveals an elevated "choline peak" in tumors, reflecting enhanced phosphatidylcholine synthesis driven by upregulated choline kinase activity—now recognized as a metabolic hallmark of malignant transformation and progression.[107]

In autoimmune disease, the detection of anti-cardiolipin and anti-β_2-glycoprotein I antibodies—collectively termed antiphospholipid antibodies—constitutes a central laboratory criterion for the diagnosis of antiphospholipid syndrome under the international consensus guidelines.[97]

Within cardiovascular medicine, oxidized phospholipids (OxPLs), particularly those bound to apolipoprotein B-100–containing lipoproteins, are strongly implicated in the pathogenesis of atherosclerosis and have demonstrated significant value in cardiovascular risk stratification.[117] Moreover, in systemic inflammatory states such as sepsis and acute pancreatitis, distinct phospholipidomic profiles—most notably reduced phosphatidylcholine (PC) and elevated lysophosphatidylcholine (LPC) levels—correlate closely with disease severity and adverse clinical outcomes.[75]

Although certain mechanistic pathways remain incompletely defined, the centrality of phospholipids to cellular homeostasis and disease pathobiology is unequivocal. The convergence of high-resolution lipidomics with targeted pharmacologic innovation is rapidly advancing translational medicine, positioning phospholipids not merely as structural membrane components but as dynamic biomarkers and actionable therapeutic targets at the forefront of precision healthcare.

CONCLUSIONS

Phospholipids occupy a central position in cellular physiology, integrating membrane architecture with signaling, various crucial metabolic processes, and immune regulation. Their functions extend far beyond structural support: through tightly regulated synthesis, remodelling, and spatial organization, phospholipids encode information that governs protein activity, organelle function, and cellular fate. Disruption of these lipid networks destabilizes membranes, distorts signal transduction, and perturbs metabolic homeostasis, thereby driving the onset and progression of cardiovascular, metabolic, neurodegenerative, genetic, and malignant diseases.

Considering above specified facts, it is tempting to place phospholipids at the forefront of translational opportunity. Disease-specific alterations in phospholipid composition and turnover are emerging as robust biomarkers for diagnosis, prognosis, and therapeutic monitoring, while enzymes controlling phospholipid metabolism represent tractable and clinically validated drug targets. As lipidomics, structural biology, and cell signalling continue to converge, phospholipids are poised to serve as critical molecular bridges between fundamental membrane biology and precision medicine.

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