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REVIEW

Adaptive regulation of glycerophospholipid metabolism

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ABSTRACT

Lipid membranes form the essential barriers that compartmentalize life, separating intracellular processes from the external environment. To maintain cellular function and viability, both the plasma membrane and internal organelle membranes undergo continuous compositional and functional remodeling in response to environmental fluctuations. Traditionally, glycerophospholipids have been primarily considered structural components of these membranes. However, their dynamic synthesis plays a crucial role in modulating membrane functions and, consequently, cellular adaptability. This Review discusses how cells orchestrate complex glycerophospholipid metabolism to adapt to diverse environmental challenges. By examining membrane adaptation to various changes, including temperature shifts, pH imbalances and nutrient availability, we propose that responsive alterations in glycerophospholipid synthesis act as a central metabolic hub. This hub influences overall cellular metabolism and regulatory networks. This Review highlights an often overlooked aspect of lipid biology: the pivotal role of glycerophospholipid metabolism in modulating cellular adaptability and resilience.

KEY WORDS: Glycerophospholipid, Cellular adaptability, Lipid membranes, Metabolism, Metabolic regulation, Phospholipid synthesis

Introduction

Cell membranes across the three domains of life – archaea, bacteria and eukaryotes – are primarily composed of glycerol phosphate phospholipids, despite significant variations in lipid chirality, chemical composition and biosynthesis across different organisms (Lombard et al., 2012; Wächtershäuser, 2003). Such lipid commonality supports the concept of a last common ancestor and has sparked debates about the evolutionary origins of phospholipid biosynthesis, particularly in relation to the divergence between archaeal and bacterial–eukaryotic pathways (Lombard et al., 2012). From the perspective of the origins of life, lipid compartmentalization likely provided primordial boundaries that enabled the emergence of individuality in early cells. These boundaries would have allowed primitive cells to concentrate metabolites, including replicating materials necessary for inheritance, while maintaining interactions with the surrounding environment (Edidin, 2003). However, early vesicle-like membranes, formed through the self-assembly of simple, single-chain amphiphilic molecules, such as monocarboxylic acids, are highly unstable under extreme conditions, such as the high temperatures associated with volcanic environments, which likely reflect where life evolved (Monnard and Deamer, 2002; Wächtershäuser, 1992). The subsequent emergence of phospholipids might have provided a selective advantage, leading to the development of environmentally adapted phospholipid membranes with increasingly complex metabolic and transport systems (Budin and Szostak, 2011; Liu et al., 2020).

Over billions of years since the origin of life, lipid biosynthesis has co-evolved with cellular adaptability to environmental shifts. This evolutionary process likely enabled organisms to adjust lipid synthesis, fine-tuning membrane function to thrive in dynamic environments. A striking example of this adaptability is observed in phytoplankton, which increase the synthesis of non-phosphorus betaine lipids in response to phosphorus scarcity in the ocean (Van Mooy et al., 2009). This adaptation allows them to substitute phospholipids, sparing phosphorus utilization and sustaining growth despite phosphorus limitation (Van Mooy et al., 2009).

Organismal metabolism is crucial in cellular adaptation (Rothman et al., 2023), as is the remodeling of boundary biomembranes in response to the environment (Chwastek et al., 2020; Ernst et al., 2018; Lipowsky, 2022). However, phospholipid biosynthesis has a high energetic cost (Ortega-Arzola et al., 2024). Therefore, there remains a crucial knowledge gap: how are phospholipid biosynthesis, membrane function and intersecting metabolic pathways integrally regulated under diverse environmental and physiological conditions? Recent findings indicate that phospholipid synthesis for cellular membrane compartments is coupled strongly with the environment. In response to environmental challenges, cellular adaptation is intertwined with phospholipid biosynthesis involving precursor metabolites (Ye et al., 2017), the choice of biosynthetic routes (Zhu et al., 2025) and the temporal orchestration of phospholipid production (Yang et al., 2025b). Such a connection highlights a previously underappreciated regulatory function of phospholipids in constructing cellular compartments. This Review focuses on eukaryotic models, summarizes recent advancements in this area, and posits that phospholipid biosynthesis acts as a central regulator of cellular adaptability by orchestrating the remodeling of both cellular membranes and metabolism.

Eukaryotic biomembranes are composed of phospholipids with varied chemical structures

Biological membranes are dynamic assemblies built upon a broad spectrum of lipid species, including glycerophospholipids, sphingolipids and sterols (van Meer et al., 2008). It is the collective diversity and asymmetric distribution of these lipids that ultimately dictates the physical properties – such as fluidity and curvature – and functional dynamics of the membrane, influencing crucial processes like signal transduction and protein trafficking (Janmey and Kinnunen, 2006). Phospholipids are phosphorus-containing lipids characterized by a molecular architecture featuring a backbone of either glycerol or sphingosine, grouping them into two major classes: glycerophospholipids and sphingophospholipids (Fig. 1) (Harayama and Riezman, 2018). This backbone links a hydrophilic head group to one or more hydrophobic fatty acid tails, typically

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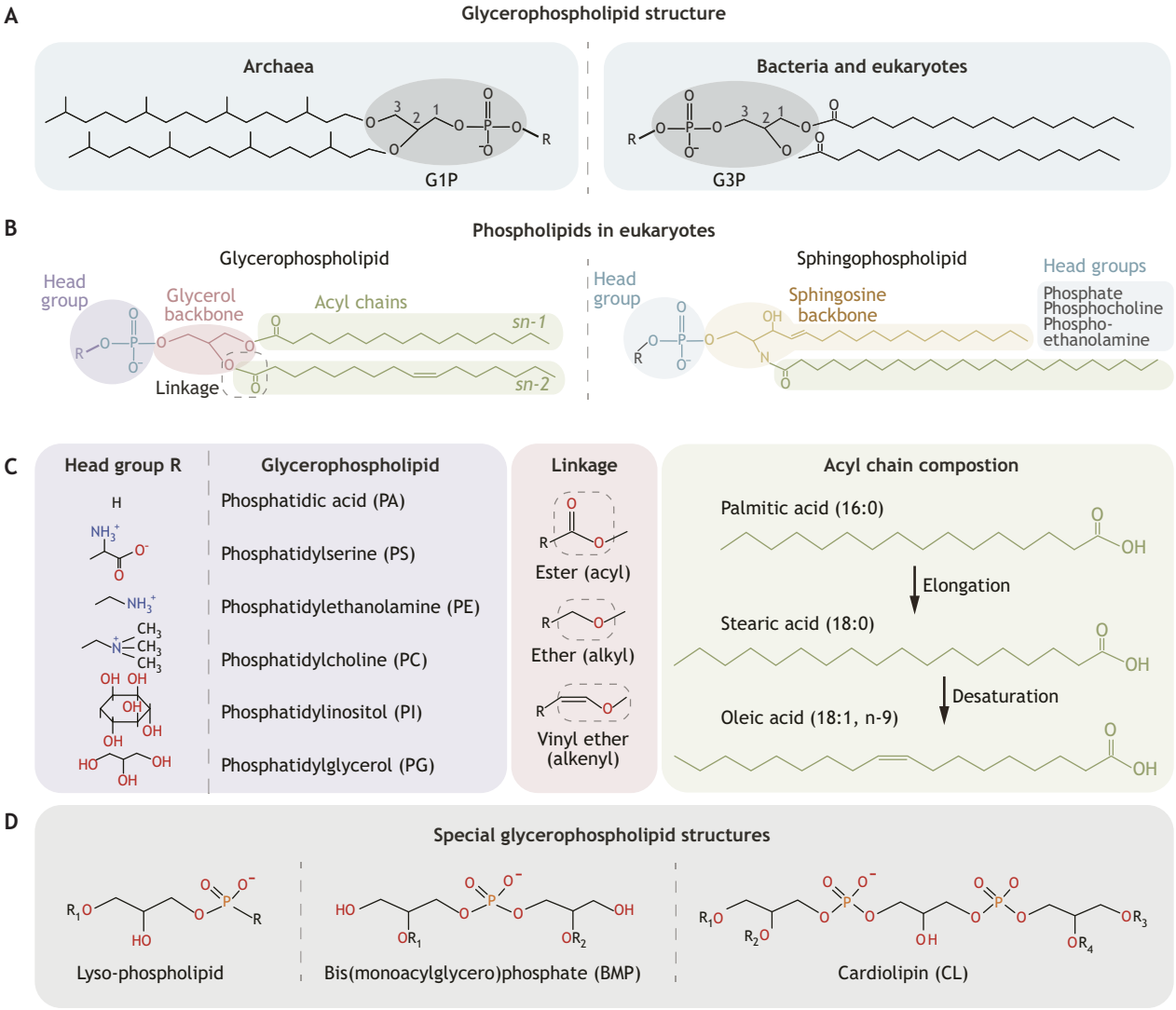

Fig. 1. Phospholipid chemical structures. (A) Glycerophospholipids in archaea feature ether-linked isoprenoid chains and a G1P backbone, in contrast to bacterial and eukaryotic phospholipids, which use a G3P backbone. (B) Phospholipids in eukaryotes are composed of a glycerol (left) or sphingosine (right) backbone, a hydrophilic head group, and one or more hydrophobic acyl chains. Classical glycerophospholipids and sphingophospholipids typically comprise two acyl chains. Although the head groups of glycerophospholipids are highly variable, the most commonly observed head groups of sphingophospholipids are phosphate, phosphocholine and phosphoethanolamine. The fatty acyl chains are typically attached to the glycerol backbone via ester linkages, and the single fatty acid chain is attached to the amino group of the sphingosine backbone via an amide linkage. The top and middle carbons of the glycerol backbone are indicated by *sn-1* and *sn-2*, respectively. (C) Head groups, linkages and acyl chains can vary to create a diverse range of phospholipid structures. The nomenclature used for acyl chains, such as (16:0) and (18:1, n-9), represents the fatty acyl chain structure as (*C*:*D*), where *C* is the total number of carbon atoms, *D* is the number of double bonds, and the optional 'n' indicates the position of the first double bond counted from the methyl end of the chain. (D) Distinct phospholipid subclasses that differ from this structure include lyso-phospholipid, which contains only one fatty acid chain; bis(monoacylglycero)phosphate, which contains two monoacylglycerol units; and cardiolipin, which is characterized by four acyl chains with two phosphatidyl moieties (Harayama and Riezman, 2018).

ranging from one to four in number (van Meer et al., 2008). Archaeal phospholipids are composed of glycerol-1-phosphate (G1P) ether-linked to isoprenoid chains (Fig. 1A) (Kates et al., 1965; Langworthy et al., 1972). In contrast, in bacteria and eukaryotes, glycerophospholipids consist of glycerol-3-phosphate (G3P) with ester- or ether-linked fatty acids (Fig. 1A,B) (Caforio and Driessen, 2017). This chemical distinction underlies differences in biosynthesis pathways and is potentially driven by evolutionary selective pressures for environmental adaptation. For example, archaeal G1P-based lipid membranes effectively minimize proton leakage at elevated temperatures and sustain transmembrane electrochemical gradients under conditions of extreme pH and high salinity (Caforio and Driessen, 2017; Langworthy et al., 1972), potentially originating from hyperthermophilic ancestors that adapted to extremely hot environments. However, the evolution of G3P-based lipid membranes in bacteria and eukaryotes is associated with adaptation to more ambient environments (Lombard et al., 2012). Therefore, the broad range of habitats and complex intracellular membrane systems in these organisms suggest a high degree of fine-tuning in phospholipid functions and biosynthesis pathways, tailored to their specific environments (Lombard et al., 2012).

Eukaryotic cellular membranes are primarily composed of glycerophospholipids, hereafter referred to as phospholipids (Sud et al., 2007). The phosphate moiety of the head groups is covalently linked to polar molecules such as choline, ethanolamine, serine or inositol (van Meer et al., 2008). The linked fatty acyl chains vary

in length, saturation, and double bond number and position, as well as in the type of chemical linkage that connects them to the glycerol backbone (Fig. 1C) (Harayama and Riezman, 2018). This dual-level diversity in both head group and fatty acyl chain composition dictates the physicochemical properties of phospholipids and influences membrane structure, thereby modulating phospholipid function across cellular processes (Antonny et al., 2015; Hishikawa et al., 2014).

Phospholipids are classified by their polar head groups, which include phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidic acid (PA), cardiolipin (CL) and phosphatidylinositol (PI) and its phosphorylated derivatives, phosphoinositides (PIPs) (Fig. 1C). These phospholipids, along with sterols and sphingolipids, constitute the bulk of biomembrane lipids (van Meer et al., 2008). Structurally distinct from conventional phospholipids, certain unique lipids exhibit significant variation (Fig. 1D). These include lyso-phospholipids, possessing only a single fatty acyl chain (Tan et al., 2020); bis(monoacylglycero)phosphate (BMP), characterized by two monoacylglycerol units linked by a central phosphate group with unusual stereochemistry (Showalter et al., 2020); and cardiolipin, a dimeric lipid consisting of two phosphatidyl groups bridged by an additional glycerol molecule (Ye et al., 2016).

Phospholipid diversity across organisms and organelles

Membrane phospholipid compositions exhibit remarkable differences across organisms, evident not only in the varying percentage abundance of different phospholipid classes but also in the presence of unique lipid species in specific organisms. For example, the protozoan parasite *Toxoplasma gondii* synthesizes abundant levels of the uncommon lipid phosphatidylthreonine, which plays roles in its lytic cycle and virulence (Arroyo-Olarte et al., 2015). Meanwhile, *Caenorhabditis elegans* can synthesize monomethyl branched-chain fatty acids (mmBCFAs). When these mmBCFAs are ester-linked to glycerol, they generate unique acyl compositions of phospholipids that have also been reported as minor lipids in mammals (Witting and Schmitt-Kopplin, 2016). Other phospholipids incorporated into membranes differently between species include BMP and ether phospholipids. Although these are major lipid constituents of mammalian membranes, they are generally not found in unicellular eukaryotes such as yeast (Luquain-Costaz et al., 2020).

Phospholipid compositions also vary between organelle membranes within a eukaryotic organism. BMP, for example, is a key mammalian lipid constituent of lysosomal internal membranes, and its elevated levels are associated with lysosomal dysregulation, aging and various human diseases (Janssens et al., 2024; Medoh and Abu-Remaileh, 2024). Similarly, CL is a unique, dimeric phospholipid found in mitochondria, where it is *de novo* synthesized (Ye et al., 2014, 2016). CL is crucial for numerous mitochondrial functions, including energy generation and maintaining mitochondrial structure (Schlame et al., 2000). This is largely due to its physical interaction with a wide range of mitochondrial proteins, such as respiratory complexes, thereby facilitating the assembly of supercomplexes (Pfeiffer et al., 2003).

Beyond these examples of organelle-specific enrichment of certain phospholipids, broader lipid composition also varies significantly among organelles. In mammals and yeast, for instance, the endoplasmic reticulum (ER) is characterized by relatively low levels of cholesterol (ergosterol in yeast) and an abundance of unsaturated phospholipids (Antonny et al., 2015; Keenan and Morré, 1970; Schneiter et al., 1999), whereas the plasma membrane is rich in cholesterol and sphingolipids (van Meer et al., 2008). The Golgi, lysosomes and endosomes contain high levels of PIPs, which regulate membrane dynamics and intracellular trafficking (van Meer et al., 2008). These organelle-specific lipid compositions are crucial to the establishment of sites for sensing and regulatory control. For example, the low cholesterol content in the ER is integral to the feedback regulation initiated at this organelle in mammals (Luo et al., 2020). When ER cholesterol falls below a critical threshold, the protein SCAP changes conformation, enabling it to travel to the Golgi in complex with the sterol regulatory binding protein SREBP2 (also known as SREBF2). In the Golgi, SREBP2 is cleaved, releasing its N-terminal domain. This active fragment then enters the nucleus, binds sterol regulatory elements in the promoters of target genes, and activates gene expression for cholesterol synthesis and uptake (Luo et al., 2020). Another recent study demonstrates that, under conditions of lysosomal vacuolation, PIP signaling mediates stress-induced lysosomal lipid remodeling (Yang et al., 2025a). This action drives the transfer of PS and cholesterol, subsequently facilitating recruitment of the lysosomal vacuolator protein LYVAC (also known as PDZD8) and triggering its lipid transfer function, which leads to the osmotic membrane expansion of lysosomes (Yang et al., 2025a). Such intricate compositional diversity of organelles is governed by biosynthesis and transport mechanisms, frequently involving localized lipid metabolism (Calzada et al., 2016; Hishikawa et al., 2014; Osman et al., 2011) and dynamic membrane–membrane contact sites (Lahiri et al., 2015). Ultimately, the unique phospholipid environment of each organelle membrane dictates the localization, activity and function of its associated proteins, thereby modulating the function of corresponding cellular compartments.

Phospholipid compositions also differ across sub-membrane domains (Sezgin et al., 2017) and exhibit asymmetry between the two leaflets within lipid bilayers (Devaux, 1991). This leaflet asymmetry was initially observed in the plasma membranes of red blood cells, which lack complex internal membranes (Verkleij et al., 1973). Specifically, PC and sphingomyelin predominantly reside on the exoplasmic leaflet, whereas PE, PS, PI, PA and PE plasmalogen are abundant on the cytoplasmic leaflet in human erythrocytes (Lorent et al., 2020; Verkleij et al., 1973). Interestingly, phospholipid unsaturation also displays marked asymmetry: most lipids on the exoplasmic leaflet have fewer than two unsaturations per lipid, contrasting with an enrichment of polyunsaturated lipids on the cytoplasmic leaflet (Lorent et al., 2020). Alongside these asymmetric lipid profiles, phospholipids are surprisingly overabundant by more than 50% in the cytoplasmic leaflet compared to the exoplasmic leaflet (Doktorova et al., 2025). This phospholipid abundance imbalance necessitates the presence of cholesterol, whose rapid transbilayer diffusion enables its redistribution to buffer leaflet imbalance stresses (Doktorova et al., 2025). Such compositional asymmetry confers biophysical asymmetry to the membrane, resulting in a less fluid and more tightly packed outer leaflet (Lorent et al., 2020). Given the rising interest in lipid asymmetry, critical questions remain regarding its universality across organisms, the precise mechanisms by which phospholipid transporters (flippases, floppases and scramblases) establish and maintain this abundance asymmetry across the bilayer, and how this asymmetry responds to various environmental shifts.

Impact of phospholipids on membrane properties

Biological membranes rely on their intrinsic properties to perform functions, which are largely determined by their lipid and protein composition (Cronan and Gelmann, 1975). Because the lipidome remodels far more quickly than the proteome, lipids are thought to play a dominant role in modulating membrane properties (Ernst et al., 2018). Key membrane properties – including order, fluidity,

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compressibility, thickness, curvature and bending rigidity – collectively define the physical state of the membrane, and these properties are often interdependent (Ernst et al., 2018; Lipowsky, 2022). For example, membranes composed of tightly packed lipids tend to exhibit higher order, reduced fluidity and increased thickness (Ernst et al., 2018; Goldfine, 1984; Israelachvili et al., 1980).

The properties of membranes are directly influenced by the physical properties of their constituent lipids (Janmey and Kinnunen, 2006). Hydrophobic interactions, dictated by acyl chain length and saturation, are key determinants of membrane fluidity. Shorter acyl chains and unsaturated fatty acids introducing kinks disrupt packing, enhancing fluidity (Budin, 2018). Phospholipid fatty acyl asymmetry can lead to the formation of thinner membranes in the fission yeast *Schizosaccharomyces japonicus* (Rao et al., 2025). Importantly, the increases in asymmetric phospholipids under anoxic conditions are observed in other species, such as budding yeast (Meyer and Bloch, 1963; Panconi et al., 2023), underlying membrane adaptation in response to oxygen deprivation. Notably, the impact of a phospholipid class on membrane properties can be attributed to both its head group and its fatty acyl chain characteristics. Membrane curvature is a biophysical property that is influenced by the geometry of the constituent phospholipids. For example, cone-shaped lipids like PE can promote curvature stress, further increasing fluidity and facilitating dynamic processes such as membrane budding and fusion (Fig. 2A) (Venkatraman et al., 2024).

The phospholipid-to-cholesterol ratio also exerts bidirectional effects on membrane fluidity, a biophysical property that reflects the ability of lipid molecules and proteins to move laterally within the plane of the lipid bilayer. In loosely packed, unsaturated membranes, cholesterol reduces fluidity by restricting acyl chain motion, whereas in saturated lipid systems, cholesterol prevents excessive rigidity. This maintains an optimal fluid state that is physiologically required for the proper function of all associated membrane proteins and for key cellular processes (Fig. 2B) (Ohvo-Rekilä et al., 2002; Pöhnl et al., 2023).

However, it is important to note that even drastic changes in lipid composition do not necessarily alter overall membrane properties, with examples observed in lipidomic remodeling during postnatal development of rat synaptic membranes and during early mammalian embryo development (Tulodziecka et al., 2016; Zhang et al., 2024). This stability is achieved through homeostatic mechanisms, where the physicochemical characteristics of different lipid species compensate for one another (such as changes in tail length balancing changes in saturation). This phase maintenance ensures functional consistency by maintaining optimal membrane thickness, packing density and fluidity, despite compositional change. Furthermore, this regulation involves additional mechanisms, such as lipidation (for example, palmitoylation) of membrane proteins, which might help stabilize microdomains crucial for cellular processes, such as neuronal synapse function (Tulodziecka et al., 2016). Therefore, it is likely that environmental changes dictate the required membrane biophysics, prompting compensatory lipid alterations to maintain functional consistency or adaptive changes to modulate membrane properties (Ernst et al., 2018).

Phospholipid compositional adaptation to environmental changes

Temperature

Biological membranes are highly sensitive to temperature fluctuations due to the direct influence of thermal energy on the rotational dynamics of carbon–carbon bonds in phospholipid acyl chains (Hazel, 1995). Under physiological conditions, membranes adopt a liquid-crystalline phase (L_α), enabling efficient lateral diffusion of lipids. However, temperature deviations can disrupt this equilibrium. Reduced temperatures promote tighter lipid packing, driving a transition toward a more rigid gel phase (L_β), whereas elevated temperatures can induce non-bilayer phases (such as the H_{II} phase), compromising membrane integrity (Hazel, 1995). To maintain membrane properties under varying temperatures, organisms have evolved different mechanisms. *Escherichia coli*, for instance, modulates its membrane composition by increasing the unsaturation of phospholipid acyl chains during cold stress, thereby preserving fluidity – a process known as homeoviscous adaptation (Ernst et al., 2016; Sinensky, 1974). Similar adaptive changes are observed across various organisms. Studies of plankton from different latitudes show a

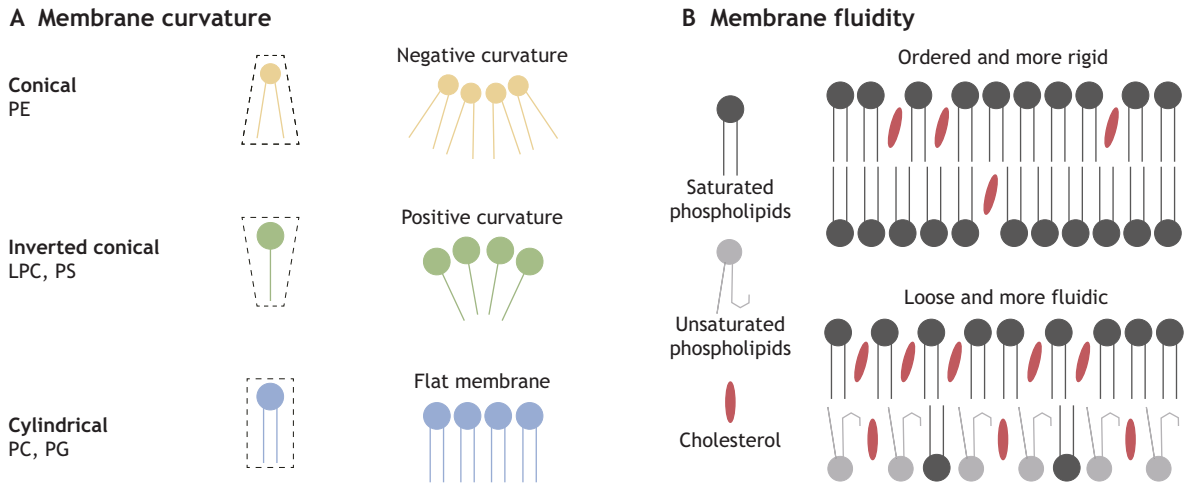

Fig. 2. Impact of phospholipids on membrane fluidity and curvature. Membrane fluidity and curvature are influenced by lipid composition. (A) Lipid geometry can influence membrane curvature: conical lipids such as PE induce negative curvature, inverted-conical lipids such as lyso-phosphatidylcholine (LPC) and PS promote positive curvature, and cylindrical lipids such as PC and phosphatidylglycerol (PG) form flat bilayers. (B) Saturated phospholipids increase membrane order and rigidity (top), whereas unsaturated phospholipids enhance membrane disorder and fluidity (bottom). Cholesterol has a dual role in regulating membrane fluidity because it can both restrict and enhance the movement of lipid molecules depending on the surrounding lipid environment.

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negative correlation between the abundance of eicosapentaenoic acid-containing lipids and temperature (Holm et al., 2022). Cold temperatures can elevate the expression of Δ9-fatty acid desaturase in organisms such as budding yeast, fruit flies and carp, which promotes the desaturation of phospholipid acyl chains (Murakami et al., 2022; Nakagawa et al., 2002; Tiku et al., 1996). In yeast, elevated membrane lipid saturation and consequent increases in packing density are detected by Mga2, a key transcription factor that regulates expression of the desaturase Ole1. This sensing mechanism involves lipid packing-dependent activation of Mga2 proteolytic processing, which is mediated through dimerization of its transmembrane helix domain (Ballweg et al., 2020; Covino et al., 2016) (Fig. 3A). Interestingly, yeast cells exhibit cold sensitivity when phospholipid synthesis from PS decarboxylation and PE methylation is spatially redirected to specific organelles (John Peter et al., 2022). This highlights that the spatial regulation of phospholipid synthesis and transport is crucial for adapting to cold stress. Homeothermic animals like mice have evolved a distinct mechanism involving thermogenic tissues, such as brown fat, to increase heat production under cold stress. Upon cold exposure, lipocalin 2 (LCN2), a PA-binding protein, can activate brown adipose tissue for continuous heat production by modulating the acyl chain composition of the mitochondrial lipid CL (Su et al., 2023).

Pressure

Pressure, much like temperature, can profoundly impact membrane phases. This sensitivity stems from both the high compressibility of fatty acyl chains and pressure-induced alterations in lipid molecular geometry (Somero, 1992; Winnikoff et al., 2024). Consequently, increasing pressure causes membranes in a liquid-crystalline phase to transition into a less fluid gel phase, an effect similar to that induced by cold temperatures (Cossins and Macdonald, 1989). Although this parallel between pressure and cold temperature effects suggests homeoviscous adaptation as the common principle governing membrane function (Cossins and Macdonald, 1989; Somero, 1992), a recent comparative study using multiple comb jelly (ctenophore) lineages has revealed that pressure adaptation is biochemically distinct from temperature adaptation at the lipid membrane level (Winnikoff et al., 2024).

Comparative lipidomic analysis of ctenophores across a 4000 m depth gradient has unveiled a striking pressure adaptation strategy involving plasmenyl phosphatidylethanolamine (PPE) (Winnikoff et al., 2024). Unlike temperature-dependent lipid remodeling, PPE accumulation shows a strong correlation with depth, reaching 73% of total phospholipids in the deepest species (Winnikoff et al., 2024). PPE contains an *sn-1* α-alkenyl ether linkage

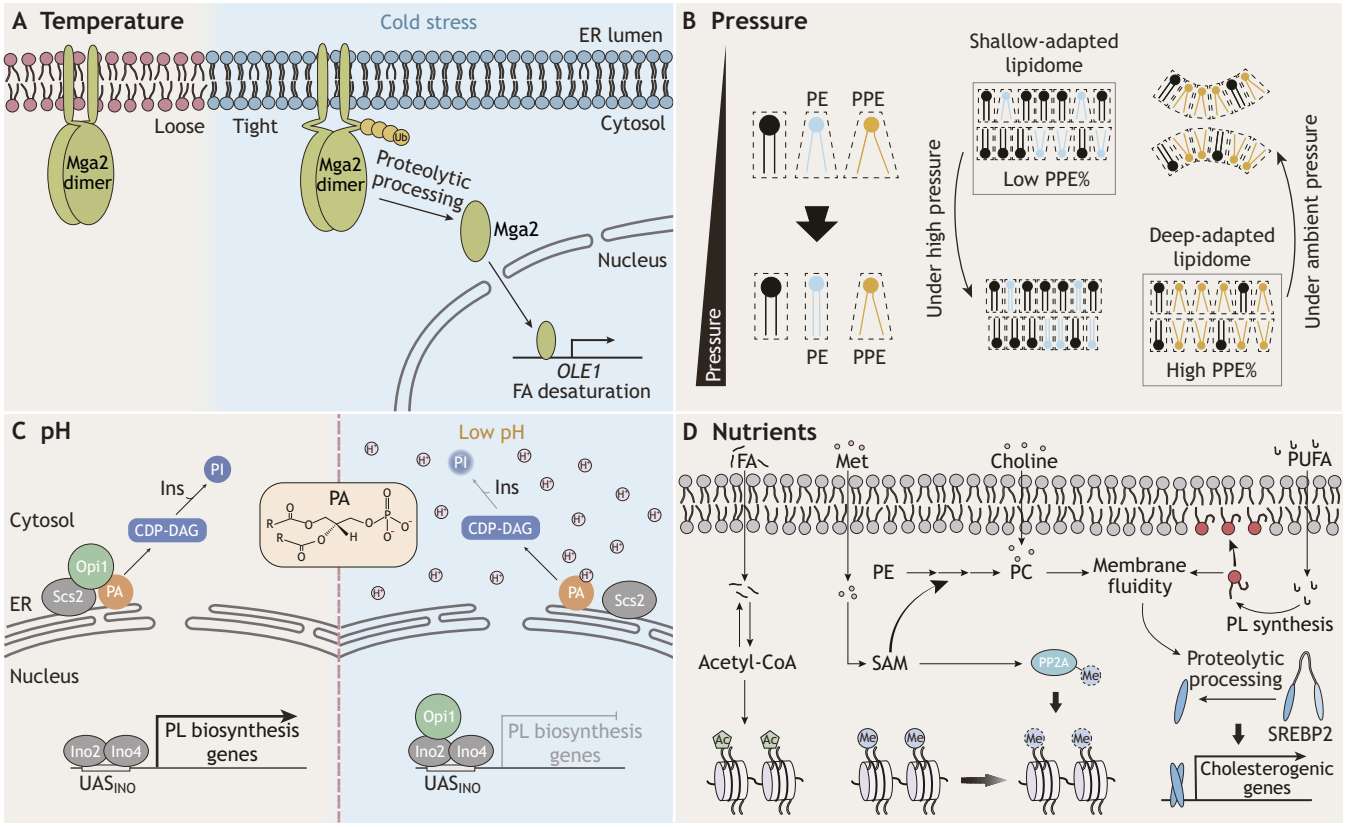

Fig. 3. Responses of phospholipid metabolism and their regulatory roles in adapting to environmental changes. (A) Cold stress adaptation: during cold stress, an increase in membrane packing density activates the otherwise membrane-bound transcription factor Mga2, leading to the upregulation of fatty acid (FA) desaturase Ole1 expression. Ub, ubiquitin. (B) Pressure: organisms adapt to high-pressure environments such as deep water by accumulating PPE in their membranes. In contrast to conventional PE, which shifts to a cylindrical shape under pressure (left), PPE maintains a conical structure under extreme hydrostatic pressure (right), preserving membrane functionality. This adaptation, however, comes at the cost of membrane stability at ambient pressure. (C) pH fluctuation sensing: in yeast, pH fluctuations are sensed by PA. PA feeds the CDP-DAG pathway and reacts with inositol (Ins) to form PI. Under acidic conditions, PA protonation disrupts the binding of Opi1 to PA in the ER membrane. The released Opi1 relocates into the nucleus and binds to the Ino2–Ino4 complex, regulating the expression of genes involved in phospholipid biosynthesis that contain the UAS$_{INO}$ regulatory sequence. (D) Nutrients: phospholipid metabolism adapts to nutrient availability. The cellular levels of methionine (Met) and SAM are transduced through the methylation of PE to generate PC, and through histone methylation via the methylation of PP2A. Analogously, FA availability integrates with acetyl-CoA and FA biosynthesis to regulate histone acetylation and cell growth. Furthermore, the incorporation of PUFA via phospholipid (PL) synthesis modulates membrane fluidity and SREBP2-mediated activation of cholesterol biosynthesis genes. Ac, acetylation; Me, methylation.

(Dean and Lodhi, 2018), which confers strong negative spontaneous curvature compared to diacyl PE. Whereas conventional PE undergoes pressure-induced conformational changes towards a cylindrical geometry, PPE maintains its conical shape even under extreme hydrostatic pressure (Fig. 3B) (Winnikoff et al., 2024). This structural stability, along with other lipidomic profiles, appears crucial for preserving membrane functionality in deep-sea environments, where pressure-induced distortion of typical lipid geometries would otherwise compromise essential cellular processes (Winnikoff et al., 2021, 2024). However, this specialized adaptation also comes at the cost of membrane stability under ambient pressure (Fig. 3B) (Winnikoff et al., 2024). Such adaptation represents a novel homeocurvature principle that is fundamentally different from the temperature-driven control of membrane fluidity. This distinction arises because pressure is a stronger modulator of lamellar to non-lamellar phase transitions, as it compresses phospholipid tails more effectively than head groups, thereby leading to a dominant change in membrane biophysical dynamics (So et al., 1993). Further experimental support for this concept comes from engineered *E. coli* expressing PPE lipids, which demonstrate significantly enhanced pressure tolerance (Winnikoff et al., 2024).

pH

Extreme pH causes problems for membranes primarily because changes in pH alter the ionization state of phospholipid polar groups, leading to immediate changes in the surface charge of the membrane (McLaughlin et al., 1970; Siliakus et al., 2017). This altered surface charge consequently influences lipid interactions and packing, increasing membrane stress and potentially membrane permeability to ions and metabolites (Davis, 2003; Siliakus et al., 2017). In particular, extreme low pH poses a major challenge by overwhelming the cellular ability to maintain electrochemical gradients across the plasma membrane, which are necessary for energy production and nutrient transport (Davis, 2003; Foster, 1995). Therefore, pH adaptation serves as a key mechanism for stabilizing bacterial communities (Mougi, 2024). Microorganisms thriving in extreme pH environments illustrate evolved mechanisms whereby specialized membrane structures maintain cellular integrity and function. In acidophilic bacteria, an adaptive strategy involves reducing proton permeability through lipid modifications that alter plasma membrane composition (Siliakus et al., 2017). This often includes incorporating high levels of branched-chain fatty acids, such as iso- and anteiso-forms, along with saturated and monounsaturated fatty acids (Siliakus et al., 2017). Additionally, these membranes often contain unusual fatty acid derivatives like β-hydroxy, ω-cyclohexyl and cyclopropane fatty acids, which further stabilize the membrane under acidic conditions (Siliakus et al., 2017). Despite these adaptations, bacteria are generally unable to grow at pH levels below 1, unlike certain archaea that dominate ultra-acidic environments (Siliakus et al., 2017). The unique content of tetraether lipids with methyl branches in archaea is likely a crucial factor for extreme pH adaptation (Macalady et al., 2004), as these membrane-spanning lipids with multiple methyl groups confer greater proton resistance to the membrane.

While bacteria and archaea utilize specialized lipid species for adaptation to extreme pH environments, many eukaryotes instead respond to subtle pH fluctuations by altering their lipid composition to modulate membrane properties (Shin and Loewen, 2011). In *Saccharomyces cerevisiae*, PA, a ubiquitous precursor lipid for phospholipid synthesis, acts as a key intracellular pH sensor to coordinate phospholipid production through a well-defined transcriptional mechanism (Fig. 3C) (Young et al., 2010). When intracellular pH drops, protonation of PA disrupts its binding to the transcriptional repressor Opi1, releasing Opi1 from its nuclear ER-bound anchor, Scs2 (Loewen et al., 2004; Young et al., 2010). The liberated Opi1 then translocates to the nucleus, where it binds and inhibits the Ino2–Ino4 heterodimer, a transcriptional activator of phospholipid biosynthesis genes that binds to the UAS_{INO} regulatory sequence (Ambroziak and Henry, 1994; Henry et al., 2012). Consequently, reduced intracellular pH triggers Opi1-mediated repression of phospholipid synthesis, linking pH sensing to membrane homeostasis. However, while this pathway highlights how PA protonation couples pH shifts to transcriptional regulation, the direct biophysical effects of these changes on eukaryotic membrane organization and function remain an open question, warranting further investigation.

Nutrients

Given that phospholipid membrane production is one of the most metabolically demanding cellular processes (Ortega-Arzola et al., 2024; Qiu and Ye, 2025), it is unsurprising that phospholipid composition dynamically adapts to fluctuations in nutrient availability. In yeast, the lipidome undergoes extensive remodeling in response to changes in carbon sources, growth phases (Klose et al., 2012) and the abundance of key biosynthetic precursors such as *myo*-inositol and choline (Fig. 3D) (Gaspar et al., 2006). The absence of surrogate nutrients like methionine, choline and fatty acids can activate various adaptive responses alongside membrane lipid remodeling, underscoring the tight coupling between metabolic state and membrane architecture (Qiu and Ye, 2025). This interplay is a key focus of this Review, as growing evidence shows that metabolites influenced by phospholipid metabolism have direct regulatory roles in cellular adaptation.

Methionine acts as a sentinel nutrient that links an environmental signal to adaptive regulation in budding yeast and cultured mammalian cells via the PE methylation pathway, an alternative biosynthetic process for PC synthesis (Ye et al., 2017). This three-step methylation consumes *S*-adenosylmethionine (SAM), a major methyl donor synthesized from methionine through ATP activation (Ye et al., 2017). Upon nutrient deprivation, SAM levels decline sharply through PE methylation activity, which triggers downstream effects on chromatin regulation (Fig. 3D) (Ye et al., 2017; Ye and Tu, 2018). The resulting SAM depletion induces histone demethylation, with histone H3 methylation at K36 (H3K36) being particularly sensitive (Fang et al., 2022; Ye et al., 2017). This response is executed through SAM-sensitive carboxyl methylation of PP2A, the phosphatase controlling H3K36 demethylase phosphorylation (Ye et al., 2019). This coordination between lipid metabolism and chromatin modification under nutrient stress conditions promotes survival through two interconnected mechanisms. First, the methyl sink function facilitates SAM turnover for cysteine synthesis that fuels glutathione (GSH) production, effectively mitigating oxidative stress (Ye et al., 2017). Second, the consequent preservation of redox homeostasis enables continued operation of oxidation-sensitive phospholipid biosynthetic pathways (Fang et al., 2022). Notably, histone methylation appears to exert minimal direct effects on transcriptional regulation (Fang et al., 2022; Ye et al., 2017; Ye and Tu, 2018), underscoring the importance of metabolic function over gene regulatory function for histone methylation under these conditions.

Nutrient stress also remodels membrane composition by shifting the PC-to-PE ratio via PE methylation, which reduces levels of PE, elevates PC and ultimately increases plasma membrane order (Fig. 3D) (Fang et al., 2022). These lipid alterations are associated with dramatic subcellular reorganization, manifested by

the formation of a distinctive 'subcellular bearing' structure – where an expanded vacuole engulfs the nucleus while maintaining physical connection to an orbiting array of lipid droplets (Qiu et al., 2025). This striking architectural rearrangement, mediated by multiple membrane contact site proteins, facilitates lipid droplet biogenesis and turnover for metabolic adaptation (Qiu et al., 2025). These findings collectively demonstrate how lipid biosynthetic pathways can simultaneously regulate membrane physical properties, metabolic homeostasis and inter-organelle spatial relationships during stress responses.

As crucial nutrient sources, fatty acids and their availability drive significant metabolic and membrane reprogramming in cells (Levental et al., 2016). Mammalian cells can maintain membrane homeostasis despite dietary fluctuations in polyunsaturated fatty acids (PUFAs) (Levental et al., 2020). When incorporated into membrane phospholipids, PUFAs increase membrane fluidity and permeability, posing a challenge to cellular function (Fig. 3D) (Levental et al., 2020). To counteract these effects, mammalian cells undergo lipidomic remodeling, upregulating saturated lipids and cholesterol to restore membrane biophysical properties by normalizing permeability and lipid packing (Levental et al., 2020). This adaptive response is mediated in part by the SREBP2 pathway, which regulates cholesterol synthesis. Disruption of SREBP2 impairs lipidomic and biophysical homeostasis, leading to increased membrane permeability and non-apoptotic cell death (Levental et al., 2020). This demonstrates the necessity of this adaptive mechanism for cellular fitness. A diet rich in PUFAs induces substantial membrane remodeling in mouse tissue (Cao et al., 2006; Metcalf et al., 2007), where elevated PUFA incorporation into phospholipids triggers a compensatory increase in saturated lipids to offset their fluidizing effects (Levental et al., 2020). These findings provide evidence of homeoviscous adaptation in homeothermic animals, illustrating how cells dynamically sense and adjust their lipidomes in response to dietary inputs.

Metabolic impact of phospholipid biosynthesis during cellular adaptation

To adapt to environmental changes, shifts in phospholipid composition activate biosynthetic and remodeling processes that modulate membrane properties and functions. This activation unavoidably alters cellular metabolism and metabolite abundance, both directly and indirectly. Given the substantial energetic and metabolic resources required for maintaining lipid membranes, important questions arise: how do alterations in membrane phospholipid metabolism influence overall cellular metabolism? How do cells coordinate this metabolic influence during adaptation? Does this coordination elicit cellular signals and regulatory functions? Recent studies have shown that as cells adjust their membrane lipidome during environmental fluctuations, the metabolic impact from phospholipid biosynthesis itself couples membrane function and metabolic regulation to facilitate adaptation.

The intersectional pathways of phospholipid biosynthesis

Phospholipid production is deeply interconnected with core metabolic networks (Fig. 4), requiring diverse small-molecule precursors and energy investment. The head group moieties of major phospholipids are derived from choline, ethanolamine, serine and *myo*-inositol, which are incorporated into PC, PE, PS and PI, respectively (Carman and Han, 2011). The glycerol backbone originates from glycolytic intermediates G3P and dihydroxyacetone phosphate (DHAP) (Henry et al., 2012), whereas the fatty acid components are supplied through acetyl-CoA-dependent synthesis (Barritt et al., 2024). This process also demands significant energetic and reducing equivalents. NADPH serves as an essential electron donor for fatty acid synthesis and elongation (Chandel, 2021), whereas NADH participates in fatty acid desaturation reactions (Nakamura and Nara, 2004). SAM provides methyl groups for the conversion of PE to PC and contributes to

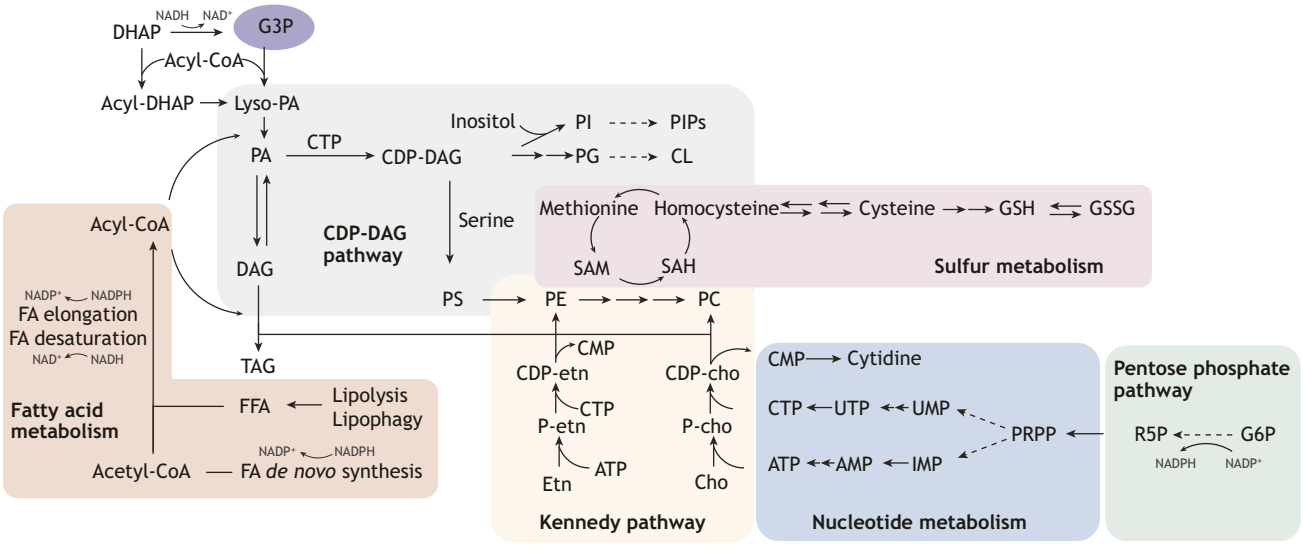

Fig. 4. Phospholipid biosynthesis and its intersectional metabolic pathways in yeast. The CDP-DAG pathway converts PA into CDP-DAG, which is subsequently used to synthesize PI, phosphatidylglycerol and CL. The synthesis of phospholipids is intricately connected with broader metabolic networks: fatty acid metabolism supplies acyl-CoA; nucleotide metabolism provides CTP, which acts as an energy carrier for phospholipid head group attachment; sulfur metabolism generates SAM, which donates methyl groups for phospholipid class conversion; and the pentose phosphate pathway generates NADPH, which is essential for lipid biosynthesis. In the Kennedy pathway, the polar head group precursors are first phosphorylated using ATP and then activated by CTP to form CDP-choline or CDP-ethanolamine, which subsequently react with DAG to generate PE and PC, respectively. AMP, adenosine monophosphate; CDP-cho, CDP-choline; CDP-etn, CDP-ethanolamine; Cho, choline; Etn, ethanolamine; FA, fatty acid; FFA, free fatty acid; G6P, glucose-6-phosphate; GSSG, glutathione disulfide; IMP, inosine monophosphate; lyso-PA, lyso-phosphatidic acid; P-cho, phosphocholine; P-etn, phosphoethanolamine; PG, phosphatidylglycerol; PRPP, phosphoribosyl pyrophosphate; R5P, ribose-5-phosphate; SAH, *S*-adenosylhomocysteine; UMP, uridine monophosphate; UTP, uridine triphosphate.

sterol methylation (Oehlschlager et al., 1984; Vance, 2014). Cytidine triphosphate (CTP) plays a dual role by activating both lipid precursors like PA and polar head groups such as choline and ethanolamine (Chang and Carman, 2008).

As illustrated by the depiction of yeast metabolic pathways in Fig. 4, phospholipid synthesis begins with the acylation of G3P or DHAP, leading to the formation of PA (Athenstaedt and Daum, 1999). PA can be dephosphorylated to produce diacylglycerol (DAG), which serves as a substrate for either triacylglycerol (TAG) synthesis via further acylation, or reconversion to PA through phosphorylation (Pascual and Carman, 2013). This PA–DAG interconversion acts as a metabolic junction, directing lipid precursors towards membrane biogenesis or energy storage, respectively (Pascual and Carman, 2013; Zadoorian et al., 2023). The subsequent attachment of polar head groups to these lipid precursors is energetically driven by CTP, which facilitates phospholipid synthesis through two principal biosynthetic routes (Kennedy and Weiss, 1956). In the CDP-DAG pathway, CTP primes PA to generate cytidine diphosphate (CDP)-DAG, which then reacts with *myo*-inositol, serine or glycerol to produce PI, PS or PG, respectively (Fischl and Carman, 1983; Osman et al., 2010). PS undergoes decarboxylation to yield PE, a process that occurs predominantly within the mitochondria in eukaryotes (Acoba et al., 2020). PE can be subsequently methylated in the ER to produce PC (Vance and Ridgway, 1988). An alternative route, the Kennedy pathway, involves the phosphorylation of ethanolamine and choline followed by their CTP-dependent activation to form CDP-ethanolamine and CDP-choline. These activated intermediates then react with DAG to produce PE and PC, respectively, with concomitant release of cytidine monophosphate (CMP) (Carman and Henry, 1999; Gibellini and Smith, 2010). Notably, PS biosynthesis exhibits evolutionary divergence between yeast and mammals. Whereas yeast synthesize PS through the condensation of CDP-DAG and serine, mammals primarily employ a base-exchange mechanism mediated by phosphatidylserine synthases PSS1 and PSS2 (also known as PTDSS1 and PTDSS2, respectively), which convert PC or PE into PS (Kuge and Nishijima, 1997; Vance and Vance, 2004).

These metabolic intersections create a sophisticated regulatory network where phospholipid biosynthesis both influences and responds to cellular metabolic states. Many key metabolites such as SAM, CTP and GSH are dynamically altered under adaptive conditions that require membrane remodeling (Fang et al., 2022; Ye et al., 2017; Zhu et al., 2024). Because phospholipid biosynthesis both depends on and modulates the abundance of these metabolites, the activation of phospholipid biosynthesis can drive both metabolic reactions – for example, promoting GSH production – and regulatory signals such as SAM depletion. These metabolic consequences help coordinate metabolic activity with membrane demands. We propose that, through this integrative mechanism, cells maintain metabolic flexibility while preserving proper membrane architecture and function to support cellular adaptation.

Adaptive mechanisms driven by intermediary metabolites

Intermediary metabolites can serve as critical nodes linking cellular metabolism with adaptive responses, enabling dynamic regulation of lipid biosynthesis, chromatin modification and redox balance. Acetyl-CoA exemplifies this through its dual role as both a precursor for fatty acid synthesis and a substrate for histone acetylation, coupling metabolic state with transcriptional regulation. Fluctuations in acetyl-CoA availability influence histone acetylation patterns, shifting gene expression between growth-promoting and stress-responsive programs (Cai et al., 2011; Hsieh et al., 2022). Similarly, SAM connects phospholipid methylation with chromatin dynamics, where SAM consumption for PE-to-PC conversion modulates histone methylation and downstream signaling through PP2A phosphatase regulation (Figs 3D and 4) (Ye et al., 2017, 2019; Ye and Tu, 2018). Therefore, alterations in cellular levels of acetyl-CoA and SAM resulting from changes in phospholipid metabolism can modulate other vital processes sensitive to these metabolites, such as histone modification and PP2A methylation. These subsequent events could serve as crucial response mechanisms that further trigger adaptive regulation across the cell through modulation of gene expression via histone modification (Ye et al., 2017) and phosphoregulation via PP2A regulation (Ye et al., 2019).

Redox cofactors NAD^+/NADH and $NADP^+$/NADPH further integrate lipid metabolism with cellular homeostasis. Whereas NAD^+ supports energy production and sirtuin-mediated deacetylation (Bai and Cantó, 2012), NADPH drives fatty acid synthesis and antioxidant defense (Ju et al., 2020; TeSlaa et al., 2023). Notably, phospholipid biosynthesis influences NAD^+ regeneration through G3P shuttle activity (Fig. 4) (Liu et al., 2021), potentially impacting nuclear processes like ADP ribosylation. Additionally, CTP – a key energy carrier in phospholipid synthesis – bridges nucleotide and lipid metabolism (Figs 4 and 5) (Zhu et al., 2025). Constraints in the Kennedy pathway reroute metabolic flux toward *de novo* nucleotide synthesis, elevating NADPH and GSH levels to enhance oxidative stress resistance (Zhu et al., 2025). The responsive inhibition of the Kennedy pathway under oxidative stress, aging or choline deficiency reveals a novel antioxidant defense mechanism. This mechanism operates by switching between alternative pathway routes for phospholipid and nucleotide synthesis, thereby enhancing cellular reductive capacity to combat oxidative stress (Fig. 5) (Zhu et al., 2025).

Temporal oscillation of phospholipid abundances promotes metabolic efficiency

During cell division, many metabolic processes are temporally segregated. As demonstrated in the yeast metabolic cycle (YMC), such a precisely organized metabolic hierarchy is energetically optimal for efficient utilization of metabolic resources, thereby promoting cell growth (Kaspar von Meyenburg, 1969; Murray et al., 2007; Tu and McKnight, 2006). Our recent study reveals that phospholipid abundances oscillate rhythmically throughout the YMC, coordinating membrane biogenesis with cell growth and division (Yang et al., 2025b). The most abundant phospholipids, PE and PC, display opposing oscillations that are independent of fatty acyl chain composition. Conversely, PI and PS exhibit acyl chain-dependent temporal shifts (Yang et al., 2025b). Crucially, these dynamic changes align with biophysical needs: phospholipids that promote fluidity peak at budding onset to enable membrane remodeling, whereas those stabilizing rigidity increase during bud growth. This temporal compartmentalization ensures that the membrane properties are precisely adjusted to support cell cycle progression. The resulting rhythmic phospholipid fluctuation allows cells to maintain energy efficiency by avoiding competitive synthesis of all phospholipid types, instead prioritizing specific classes when needed. The yeast ultradian clock not only synchronizes metabolic pathways but also optimizes membrane composition thermodynamically (Yang et al., 2025b). By temporally segregating phospholipid production, cells minimize unnecessary energy expenditure while ensuring precise membrane adaptation for growth and division. This cell-intrinsic rhythm exemplifies how

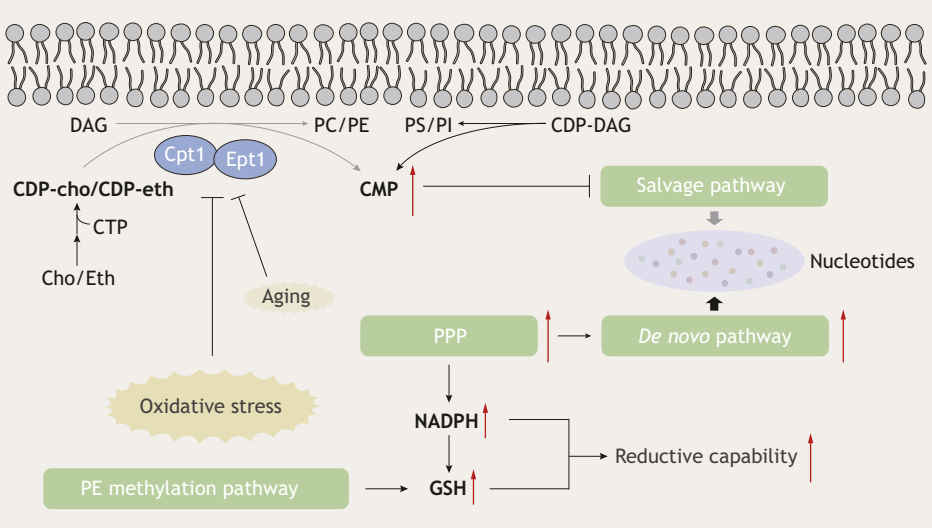

Fig. 5. The oxidative inhibition of the Kennedy pathway modulates nucleotide biosynthesis and cellular reductive capacity. In *S. cerevisiae*, metabolic adaptation is triggered by inhibition of the Kennedy pathway, either at the penultimate step due to choline deficiency or at the final step under oxidative stress and aging; this final step is mediated by amino alcohol phosphotransferases Cpt1 and Ept1, which catalyze the reaction between the activated precursors, CDP-choline or CDP-ethanolamine, and DAG to produce PC or PE. This limitation activates PE methylation and leads to the accumulation of CMP via the CDP-DAG pathway. CMP accumulation, in turn, suppresses the nucleotide salvage pathway, shifting metabolic flux toward *de novo* nucleotide synthesis and stimulating the pentose phosphate pathway to elevate NADPH production. Concurrently, enhanced PE methylation elevates GSH levels. Collectively, these phospholipid-mediated responses culminate in enhanced reductive capability, conferring increased cellular resistance to oxidative stress. CDP-cho, CDP-choline; CDP-eth, CDP-ethanolamine; Cho, choline; Eth, ethanolamine; PPP, pentose phosphate pathway.

temporal organization of lipid metabolism enhances metabolic efficiency in a proliferating system.

Summary

It is unsurprising that the synthesis of phospholipids is crucial for establishing the chemical and compositional diversity of cellular membranes, thereby dictating membrane morphology and properties. Such membrane remodeling serves at least a dual function in cellular adaptation. At the membrane level, alterations in membrane composition directly modulate function and signaling. For instance, changes in phospholipid composition can regulate organelle function and dynamics, enhancing cellular adaptability in fluctuating environments (Joshi et al., 2012; Qiu et al., 2025; Venkatraman et al., 2023). Furthermore, phospholipid synthesis can generate signaling lipids that initiate crucial signal transduction cascades, including the activation of cytosol–nucleus shuttling transcription factors that regulate gene expression to ensure adaptive transitions (Qiu and Ye, 2025). Concurrently, at the metabolite level, the membrane remodeling inherent to cellular adaptation invariably necessitates phospholipid biosynthesis. This process generates significant metabolic consequences that can feed back into complex regulatory networks. Although these metabolic impacts are an integral part of adaptive responses, their implications remain largely underappreciated. We emphasize that the membrane phospholipid coordination mechanisms enabling cellular adaptation are likely accompanied by a range of potentially unforeseen processes, crucially driven by the metabolic connections stemming from phospholipid synthesis. Given the observed dysregulation of phospholipid levels in various disease states, these metabolic connections likely hold significant implications for human physiology and pathology.

Competing interests

The authors declare no competing or financial interests.

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