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Phosphopholipid Biosynthesis: An Unforeseen Modulator of Nuclear Metabolism

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ABSTRACT

Glycerophospholipid biosynthesis is crucial not only for providing structural components required for membrane biogenesis during cell proliferation but also for facilitating membrane remodeling under stress conditions. The biosynthetic pathways for glycerophospholipid tails, glycerol backbones, and diverse head group classes intersect with various other metabolic processes, sharing intermediary metabolites. Recent studies have revealed intricate connections between glycerophospholipid synthesis and nuclear metabolism, including metabolite-mediated crosstalk with the epigenome, signaling pathways that govern genome integrity, and CTP-involved regulation of nucleotide and antioxidant biosynthesis. This review highlights recent advances in understanding the functional roles of glycerophospholipid biosynthesis beyond their structural functions in budding yeast and mammalian cells. We propose that glycerophospholipid biosynthesis plays an integrative role in metabolic regulation, providing a new perspective on lipid biology.

1 | Introduction

Glycerophospholipids, usually referred to as phospholipids, are essential components of cell membranes and are synthesized during membrane expansion and remodeling, supporting cell growth and adaptation to environmental changes. The biosynthesis of phospholipid bilayers demands substantial energy, often representing a significant portion of cellular energy expenditure (Ortega-Arzola et al. 2024). This high-energy cost necessitates energy-efficient coordination between phospholipid synthesis and various metabolic processes. Thus, phospholipid biosynthesis is integral to both the structural and metabolic aspects of cell growth and stress adaptation.

Despite the separation of the nucleus from the cytoplasm by the nuclear envelope (NE), metabolites can pass through the nuclear pores, enabling homeostatic regulation of metabolism between the nuclear and cytoplasmic compartments (Boon et al. 2020). As such, membrane biogenesis can influence nuclear metabolism through the coordination of phospholipid biosynthesis. Additionally, phospholipid synthesis that occurs in the inner membrane of the nucleus may directly impact nuclear metabolism without spatiotemporal constraints associated with nucleocytoplasmic exchange (Barbosa et al. 2019, Bahmanyar and Schlieker 2020). The biosynthesis of phospholipids during cell growth or under environmental stress not only supplies essential structural components for the expansion or remodeling of biomembranes but also influences nuclear metabolism (Ye et al. 2017; Papsdorf

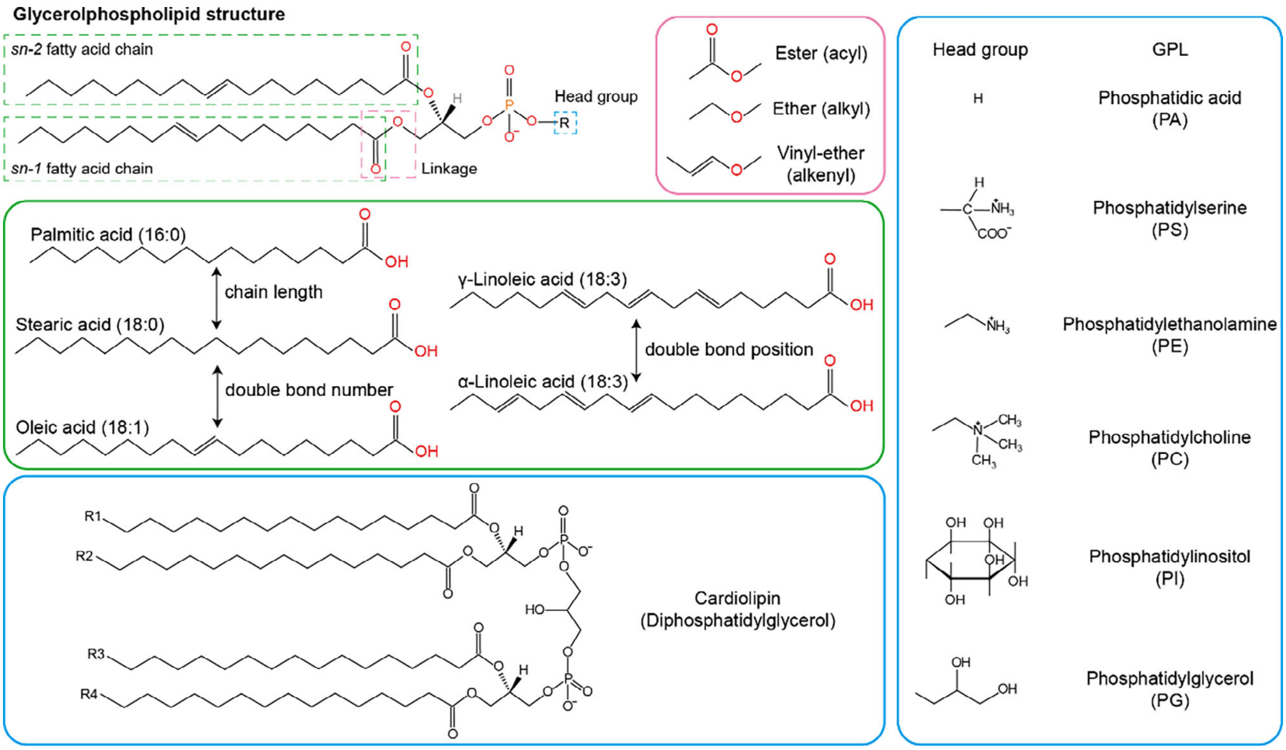

FIGURE 1 | Chemical diversity of phospholipids. Phospholipids generally consist of a hydrophilic head group and two hydrophobic fatty acid chains. Cardiolipin, however, is an exception, containing four acyl chains with two phosphatidyl moieties. Glycerophospholipids (GPLs) vary in their head groups (blue), fatty acid tails (green), and the chemical linkage between the fatty acid chains and the glycerol backbone (pink).

and Brunet 2019; Fang et al. 2022). This metabolic impact can affect critical nuclear activities such as DNA replication and RNA synthesis, thereby playing a crucial role in maintaining genome integrity and modulating transcriptional responses. In this review, we emphasize the impact of phospholipid synthesis on nuclear metabolism and propose a regulatory mechanism whereby cells exploit intersectional metabolism between phospholipid synthesis and nuclear metabolism for regulation.

2 | Chemical and Compositional Diversity of Phospholipids

Glycerophospholipids are the most common phospholipids, consisting of a glycerol molecule linked to a phosphate group, which is modified by an alcohol, and aliphatic fatty acid tails with varying compositions. As illustrated in Figure 1, the chemical diversity in phospholipids arises from various combinations of polar head groups and fatty acid tails (Harayama and Riezman 2018). For example, the length of the fatty acid chain, the number of double bonds, and the specific locations of these double bonds within the fatty acid chain all contribute to this diversity (Kaneko et al. 1998). Phospholipid species are further diversified by the number of fatty acid tails, the type of chemical bonds linking the fatty acid tails to the glycerol backbone (ester vs. ether) (Figure 1), and additional modifications such as oxidation (Harayama and Riezman 2018). For signaling phospholipids, such as phosphatidylinositol (PI) phosphates, their structural diversity is crucial for the specific recognition by effector proteins in signal transduction (Di Paolo and De Camilli 2006; Kutateladze 2010). However, the functional significance of the diversity among the most abundant structural phospholipids remains largely unknown.

Nonetheless, it is clear that phospholipid compositions vary at multiple levels, including across organisms, cell types, organelles, bilayer-leaflets, and membrane subdomains (Harayama and Riezman 2018). This compositional diversity is generated by the biosynthesis and transportation of phospholipids (Harayama et al. 2014), indicating that the metabolic impact of phospholipid biosynthesis is likely context-dependent. In different organisms and compartments or regions of cells, the biophysics of phospholipids and the characteristics of phospholipid metabolic enzymes—such as their expression levels, localization, substrate specificity, and kinetic activity—affect compositional diversity (Imae et al. 2012; Harayama et al. 2014). The context-specific coordination of metabolism ensures that phospholipid composition is finely tuned to meet specific functional needs in different biological contexts. This integral role of phospholipid coordination provides a plausible explanation for the chemical and compositional diversity of phospholipids.

3 | Integration of Metabolite Pathways in Phospholipid Synthesis

The most abundant phospholipids in eukaryotic cells are phosphatidylcholine (PC), phosphatidylethanolamine (PE), and PI. Less abundant phospholipids include phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylglycerol (PG), and cardiolipin. While the cellular composition of phospholipids varies across eukaryotes, from fungi to mammals, the pathways for

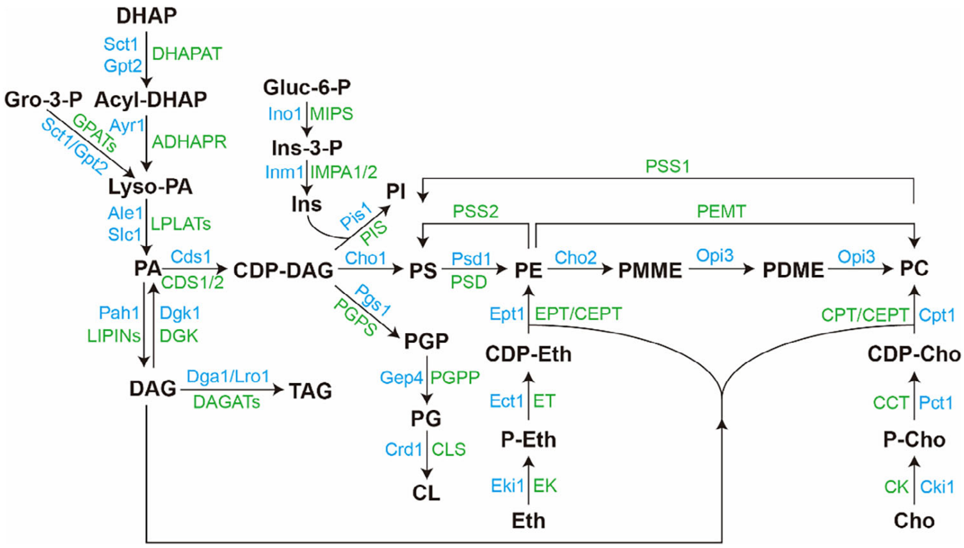

FIGURE 2 | Pathways of phospholipid biosynthesis in budding yeast and mammalian cells. Phospholipids are synthesized from two lipid precursors: PA and DAG. In the CDP-DAG pathway, PA is used to synthesize PI, PS, and PG in budding yeast. DAG participates in the Kennedy pathway to produce PE and PC, a process conserved across eukaryotic cells. In contrast to budding yeast, where PS is synthesized from CDP-DAG, mammalian cells synthesize PS from PE and PC via base exchange reactions. The enzymes responsible for phospholipid biosynthesis are shown in blue for *Saccharomyces cerevisiae* and in green for mammalian cells. CDP-DAG, cytidine diphosphate diacylglycerol; DAG, diacylglycerol; PA, phosphatidic acid; PG, phosphatidylglycerol; PI, phosphatidylinositol; PS, phosphatidylserine.

their synthesis are largely conserved (Figure 2). The diacylglycerol (DAG) unit in a phospholipid molecule is derived from the acylation of glycerol-3-phosphate or dihydroxyacetone phosphate, ultimately yielding a PA molecule (Athenstaedt and Daum 1999). PA is dephosphorylated by the phosphatase lipin to produce DAG, which can be either acylated into the storage lipid triacylglycerol (TAG) or regenerated to PA by phosphorylation (Pascual and Carman 2013). The interconversion between PA and DAG represents a metabolic branch that channels different lipid precursors for cell growth or lipid storage (Pascual and Carman 2013; Zadoorian et al. 2023). The energy carrier cytidyltriphosphate (CTP) mediates the attachment of head groups through two pathways, utilizing either DAG or PA as lipid precursors (Kennedy and Weiss 1956). In the CDP-DAG pathway, CTP activates PA to generate CDP-DAG, which subsequently condenses with inositol, serine, and glycerol to produce PI, PS, and PG (Figure 2) (Fischl and Carman 1983; Osman et al. 2010). In the budding yeast *Saccharomyces cerevisiae*, PS is decarboxylated to produce PE, which can then be further converted to PC through methylation (Figure 2) (Vance and Ridgway 1988; Ye et al. 2017). This PE methylation pathway is conserved in both yeast and mammalian cells. In budding yeast, the enzymes Cho2 and Opi3 are responsible for the sequential three-step methylation process, while in mammals, all three steps of PE methylation are catalyzed by phosphatidylethanolamine N-methyltransferase (PEMT), with significant activity notably observed in liver tissue (Vance and Ridgway 1988; Vance 2014). However, the biosynthesis of PS differs between yeast and mammalian cells. In mammals, PS synthesis does not occur through the condensation of CDP-DAG and serine. Instead, it is produced through a base exchange from PC or PE, catalyzed by phosphatidylserine synthase 1 (PSS1) and PSS2, respectively, as observed in rat hepatoma cells and mouse liver cells (Figure 2) (Kuge and Nishijima 1997; J. E. Vance and D. E. Vance 2004). In the Kennedy pathway, ethanolamine and choline are first phosphorylated and then activated by CTP to form CDP-ethanolamine and CDP-choline (Gibellini and Smith 2010). These intermediates then condense with DAG to produce PE and PC, respectively, with the release of CMP in the process (Figure 2) (Carman and Henry 1999).

Numerous small-molecule metabolites, including high-energy compounds, participate in phospholipid synthesis, intertwining with various critical metabolic pathways. For example, choline, ethanolamine, serine, and inositol act as head group precursors for the phospholipids PC, PE, PS, and PI (Carman and Han 2011), respectively. The glycolytic intermediates glycerol-3-phosphate and dihydroxyacetone phosphate provide the glycerol backbone for phospholipids (Henry et al. 2012). Moreover, phospholipid biosynthesis also demands several high-energy metabolites, such as acetyl-CoA, S-adenosylmethionine (SAM), NADH, NADPH, and CTP. Acetyl-CoA provides carbon units for fatty acid synthesis (Barritt et al. 2024). NADPH acts as a reducing agent in fatty acid synthesis and elongation, supplying electrons for reduction reactions (Chandel 2021). NADH is required for fatty acid desaturation processes (Nakamura and Nara 2004). SAM donates methyl groups in the conversion of PE to PC (Vance 2014), as well as for sterol methylation (Oehlschlager et al. 1984). CTP acts as an energy input that activates the lipid precursor PA or polar metabolites choline and ethanolamine (Chang and Carman 2008).

Because these metabolites are also extensively involved in one-carbon metabolism, amino acid metabolism, nucleotide metabolism, and redox metabolism, the significant investment of shared metabolite materials in phospholipid synthesis has a broad impact on cellular metabolism. By consuming or transforming common metabolites, phospholipid synthesis can respond to and signal cellular metabolic states through interconnected pathways, ensuring that metabolic processes are coordinated with membrane dynamics.

4 | Nuclear Metabolism Is Exploited for Integrative Regulation of Chromatin

The cell nucleus houses the genome, regulates gene expression, and compartmentalizes metabolic reactions (Li et al. 2018). Nucleotide metabolism is particularly active in the nucleoplasm, with pools of deoxyribonucleotides and ribonucleotides essential for the catalysis of DNA replication and RNA transcription by DNA polymerases and RNA polymerases (Lane and Fan 2015). Nuclear metabolism further influences genome and gene regulation through the chemical modification of chromatin, observed on histones and nucleic acids. These chromatin marks are crucial for maintaining cell identity and can influence chromatin accessibility, condensation, and the recruitment of transcriptional factors. Because biochemical reactions responsible for the addition and removal of these marks are sensitive to the nuclear concentrations of metabolites that serve as substrates, cofactors, or inhibitors (Li et al. 2018), metabolic fluctuations can be translated into changes in chromatin modification. This can result in feedback regulation from the nucleus. Besides epigenetic regulation dictated by metabolite levels, chromatin also serves as a reservoir of metabolites (Ye and Tu 2018; Karimian et al. 2023). For example, acetyl groups installed on chromatin can be recycled for metabolic needs and chromatin regulation (Charidemou et al. 2024). The crosstalk between metabolism and epigenetic modification emphasizes the role of metabolic pathways in generating specific regulatory outputs from the nucleus. In the context of phospholipid synthesis, this metabolic process may play a regulatory role by coordinating cell membrane dynamics with nuclear biology.

5 | How Does Phospholipid Synthesis Impact Nuclear Metabolism and Chromatin Regulation?

The boundary of the nucleus, known as the NE, creating the barrier between the genome and the cytoplasm, comprises two closely juxtaposed phospholipid membranes, with the outer nuclear membrane (ONM) being continuous with the endoplasmic reticulum (ER). This structure forms a protective shell for the genome. At the junctions between the inner nuclear membrane (INM) and the ONM, the nuclear pore complexes (NPCs) create nuclear pores for nucleocytoplasmic communication. The ONM, contiguous with the ER, is an active site for phospholipid synthesis. Interestingly, recent research has demonstrated that the INM is also metabolically active for lipid synthesis in budding yeast cells (Romanauska and Köhler 2018, 2023). This close proximity of phospholipid synthesis to the nucleus suggests several potential ways in which nuclear metabolism and chromatin regulation can be influenced by this biosynthetic activity:

5.1 | Metabolite Utilization and Availability

5.1.1 | Acetyl-CoA

Acetyl-CoA is a central metabolic intermediate involved in numerous anabolic and catabolic processes, including the biosynthesis of fatty acids and steroids, as well as the breakdown of carbohydrates, fatty acids, and amino acids (Pietrocola et al. 2015; Sivanand et al. 2018; Ye and Tu 2018). As an energy-rich metabolite, acetyl-CoA also serves as an acetylating agent of protein substrates such as histones (Figure 3). The acetylation of lysine residues on histone tails neutralizes their positive charges, leading to transcriptional activation of genes (Choudhary et al. 2014). Therefore, cellular acetyl-CoA abundance, influenced by fatty acid synthesis and oxidation, can act as a metabolic signal linking phospholipid metabolism to the nuclear control of gene transcription through histone acetylation.

In yeast cells, hyperacetylated histones are specifically enriched at growth-related genes involved in lipogenesis, amino acid biosynthesis, and ribosome biogenesis (Cai et al. 2011). Under glucose starvation, when acetyl-CoA is limited, acetyl marks are transferred from growth-related genes to those required for gluconeogenesis and fat metabolism, preferentially activating their expression to provide energy under starvation conditions (Hsieh et al. 2022). In mammalian cells, hyperacetylation of histones H3 on lysine 9, 27, and 56 (H3K9, H3K27, and H3K56) in hypoxic conditions predominantly activates lipogenic genes *ACACA* and *FASN*, promoting *de novo* lipid synthesis (Gao et al. 2016). In tumor cells, acetyl-CoA production promotes histone acetylation, thereby supporting tumor growth and metastasis (Comerford et al. 2014; Mashimo et al. 2014). For example, acetyl-CoA derived from fatty acid oxidation in breast cancer results in H3K27 hyperacetylation, leading to high expression of epithelial-to-mesenchymal transition-related genes (Loo et al. 2021). Importantly, acetyl-CoA can spontaneously react with protein lysine residues and has a relatively short half-life as a biochemically reactive, electrophilic molecule (Walsh et al. 2018).

Acetyl-CoA metabolism is highly compartmentalized, contributing to distinct metabolic activities in mitochondria, the nucleus, cytosol, and peroxisomes (Cobine et al. 2012). In mitochondria, acetyl-CoA primarily fuels the tricarboxylic acid (TCA) cycle and the electron transport chain. In the cytosol, it serves as a precursor for fatty acid and isoprenoid biosynthesis (Guertin and Wellen 2023). In peroxisomes, while acetyl-CoA is exported for lipid synthesis, it can also be directly used for polyketide biosynthesis, as observed in budding yeast (Lin et al. 2023). Nuclear acetyl-CoA is predominantly involved in histone acetylation (Guertin and Wellen 2023), which is tightly regulated by metabolic enzymes localized in the nucleus, including acetyl-CoA synthetase 2 (ACSS2), ATP citrate lyase (ACLY), and the pyruvate dehydrogenase complex (PDC) (Sivanand et al. 2018). ACSS2 and ACLY are dual-localized to the cytosol and nucleus in response to distinct environmental cues (Sivanand et al. 2018). For instance, nuclear localization of ACSS2 increases during glucose starvation and is regulated by AMPK (Li et al. 2017; Lin et al. 2023). Nuclear ACSS2 generates acetyl-CoA from acetate, supporting site-specific histone acetylation, crucial for processes such as spatial memory formation (Mews et al. 2017). ACLY, on the other hand, plays a role in DNA damage response (DDR). Upon exposure to ionizing radiation, phosphorylated ACLY at residue serine 455 is required for homologous recombination repair, providing acetyl-CoA via citrate cleavage to facilitate histone H4 acetylation (Potapova et al. 2000; Sivanand et al. 2017). Additionally, PDC, typically a mitochondrial enzyme, is also found in the nucleus, where it converts pyruvate directly into acetyl-CoA (Sutendra et al. 2014). Nuclear PDC accumulation is induced by mitochondrial stress, growth factors, and specific developmental signals (Sivanand et al. 2018). These compartment-specific roles underscore the

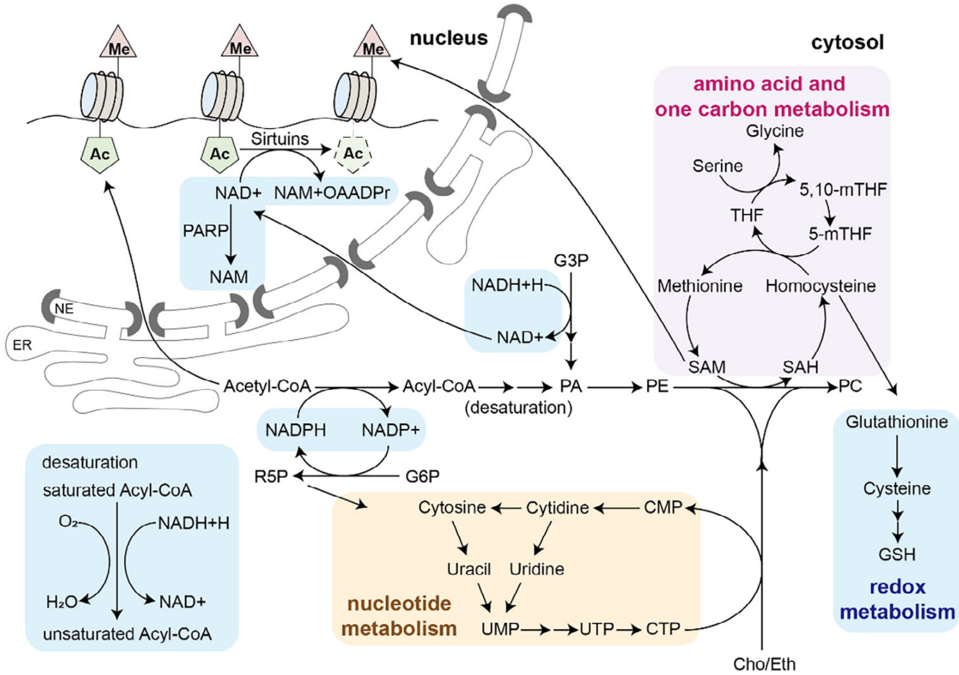

FIGURE 3 | Metabolites involved in phospholipid biosynthesis and related metabolic pathways in the nucleus and cytosol. SAM in the PE methylation pathway impacts amino acid metabolism, one-carbon metabolism, and histone methylation. CTP, which participates in the Kennedy pathway, is recycled via the salvage pathway. The synthesis of phospholipid tails and backbones requires NADH and NADPH. Related metabolites, such as NAD+, are consumed by sirtuin-mediated deacetylation and PARP-mediated ADP-ribosylation in the nucleus. CMP, cytidylmonophosphate; NAM, nicotinamide; OAADPr, O-acetyl-ADP-ribose; SAM, S-adenosylmethionine; THF, tetrahydrofolate; 5-mTHF, 5-methyl tetrahydrofolate; 5, 10-mTHF, 5, 10-methyl tetrafolate; UMP, uridylmonophosphate; UTP, uridyltriphosphate.

intricate regulation of acetyl-CoA metabolism and its integration with cellular signaling and environmental adaptation.

5.1.2 | SAM

SAM is among the most extensively used metabolites in cellular processes, akin to ATP (Thomas and Surdin-Kerjan 1997; Ye and Tu 2018). As the major methyl donor, SAM provides methyl units to a variety of cellular substrates, including lipids, proteins, nucleic acids, and small metabolites through SAM-dependent methylation reactions (Figure 3). Unlike acetyl-CoA, which can be produced from a range of metabolic pathways, SAM is synthesized solely from methionine via ATP activation. During methylation, SAM is irreversibly converted to S-adenosylhomocysteine (SAH), which is further hydrolyzed to homocysteine (Figure 3). Homocysteine can be remethylated to methionine in the methionine cycle and also serves as the sole precursor for the biosynthesis of cysteine and glutathione in higher eukaryotes (Mato et al. 2008). Similar to how acetyl marks on histones are sensitive to acetyl-CoA levels, fluctuations in cellular SAM concentration can directly influence the rate of histone methylation (Mentch et al. 2015; Ye et al. 2017).

In yeast and cultured mammalian cells, SAM is a major methyl donor, substantially consumed by phospholipid methylation, a conserved alternative biosynthetic pathway for PC via the three-step methylation of PE (Ye et al. 2017). SAM also participates in histone methylation, playing a critical role in chromatin regulation. As the major consumer of SAM, PE methylation deficiency results in a pronounced elevation in cellular SAM levels, leading to enhanced lysine methylation at histones H3, including H3K4, H3K36, and H3K79, with H3K36 being the most sensitive to hypermethylation (Berger 2007; Ye et al. 2017). While histone acetylation is generally linked to active transcription, the functional implications of histone methylation in transcriptional regulation remain less well-defined (Ye and Tu 2018). Under nutrient starvation, the reduced availability of SAM due to its consumption in phospholipid methylation creates a “low-SAM” signal, leading to histone hypomethylation, particularly impacting H3K36 (Ye et al. 2017). This low-SAM signal is transduced via the SAM-responsive carboxyl methylation of the catalytic subunit of the major protein phosphatase, PP2A. Demethylation of the PP2A catalytic subunit disrupts its assembly into the active homoenzyme, impairing its ability to dephosphorylate specific substrates. As a PP2A substrate, the H3K36 demethylase becomes hyperphosphorylated under SAM depletion, activating histone demethylation with enhanced recruitment of demethylase enzymes to chromatin (Ye et al. 2019). This SAM-sensitive regulation of PP2A further connects alterations in lipid metabolism and cellular metabolic states with chromatin modification. Interestingly, transcriptomic analyses and chromatin immunoprecipitation sequencing suggest that histone methylation dynamics may play a limited direct role in transcriptional regulation (Ye et al. 2017; Fang et al. 2022). However, SAM levels rise significantly—by 100–200-fold—when single or combinatorial methylation of H3K4, H3K36, and H3K79 is prevented in cells lacking phospholipid methylation (Ye et al. 2017). These findings highlight an unexpected metabolic function for histone methylation in regulating SAM homeostasis. This evidence underscores the influence of phospholipid synthesis on nuclear processes by modulating the availability and utilization of metabolites, revealing intricate links between cellular metabolism and chromatin regulation.

In a changing environment, it is unsurprising that phospholipid composition is altered to adjust membrane functions. Methylation converts PE, an inverted-conical phospholipid that promotes negative curvature, into PC, a cylindrical lipid that forms stable bilayers. Under nutrient starvation, wild-type cells decrease PE and increase PC levels under starvation, leading to an enhanced PC-to-PE ratio and a more ordered plasma membrane (Fang et al. 2022). However, these changes and the corresponding alteration in the PC-to-PE ratio are absent in PE methylation mutant cells (Fang et al. 2022). This suggests that the PE methylation activity, which converts PE to PC, likely accounts for these observations. Because this process consumes SAM, wild-type cells under starvation conditions exhibited SAM depletion due to an insufficient methionine supply from the environment (Ye et al. 2017). Importantly, blocking PE methylation resulted in a substantial elevation in SAM levels (Ye et al. 2017), further supporting the role of PE methylation in driving these changes. The turnover of SAM during this process also facilitates the synthesis of cysteine and glutathione (Ye et al. 2017). Thus, SAM-mediated crosstalk between phospholipid and histone methylation enables the dual regulation of membrane properties and metabolic states. Notably, sterol methylation is a crucial step in the biosynthesis of sterols in yeast and plants. Sterol methyltransferases catalyze the attachment of a methyl group from SAM to the sterol side chain, converting lanosterol and cycloartenol into ergosterol and phytosterols, respectively (Zhou et al. 2006). These enzymes have no mammalian counterparts. However, it remains unknown whether sterol methylation constitutes a major sink for SAM consumption at a comparable scale to phospholipid methylation.

Unexpectedly, the dynamic demethylation and remethylation of H3K36 are essential for cellular viability during starvation (Fang et al. 2022). A proposed model suggests that H3K36 remethylation supports nuclear GSH production, maintaining redox balance and enabling the oxidative-sensitive CDP-choline pathway for PC synthesis to proceed (Fang et al. 2022). Thus, redox status can directly influence phospholipid synthesis. As a result, aberrant phospholipid synthesis in the absence of H3K36 methylation under starvation compromises membrane integrity, leading to survival defects (Fang et al. 2022). This coordination between membrane synthesis and metabolism can be exploited as an efficient strategy to ensure adaptation to environmental stresses (Fang et al. 2022).

5.1.3 | Nicotinamide Adenine Dinucleotide (NAD) and Nicotinamide Adenine Dinucleotide Phosphate (NADP)

NAD and NADP are two pyridine nucleotides crucial for cellular redox state and metabolism (Figure 3). Both NAD and NADP exist in oxidized and reduced forms, known as NAD+/NADH and NADP+/NADPH redox couples, respectively. NAD acts as a cofactor in metabolic processes for energy production, such as glycolysis, oxidative phosphorylation, fatty acid oxidation, and the TCA cycle, with reversible interconversion between NAD+ and NADH (Katsyuba et al. 2020). Beyond its role in energy metabolism, NAD+ also participates in deacetylation by sirtuins and ADP-ribosylation during DNA damage and repair by PARP proteins (Bai and Cantó 2012). These processes consume NAD+ and release nicotinamide, which is then recovered through the salvage pathway (Cantó et al. 2015). On the other hand, NADP, the phosphorylated analogue of NAD, drives many anabolic pathways in its reduced form, such as lipid, amino acid, and nucleotide biosynthesis, as well as the production of glutathione (Ju et al. 2020). For example, in *de novo* fatty acid synthesis, fatty acid synthase utilizes NADPH to reduce the carbonyl groups of malonyl-CoA to methylene groups during chain elongation. Each cycle of fatty acid elongation consumes two molecules of NADPH (TeSlaa et al. 2023). Similarly, in cholesterol and steroid biosynthesis, NADPH is indispensable in the rate-limiting step, where HMG-CoA reductase catalyzes the reduction of HMG-CoA to mevalonate (Burg and Espenshade 2011). Additionally, while NADH is more commonly involved in fatty acid desaturation, NADPH can also serve as an electron donor in this process through NADPH-ferredoxin oxidoreductase (Martin et al. 2007).

As a critical reducing agent for antioxidant defense, NADPH is predominantly regenerated in the pentose phosphate pathway (Figure 3), by malic enzyme and isocitrate dehydrogenase in mammals (Chandel 2021). Interestingly, recent studies show that producing highly unsaturated fatty acids and generating glycerol backbones for phospholipids through the glycerol-3-phosphate shuttle both function in regenerating NAD+, thereby modulating redox homeostasis (Figure 3) (Kim et al. 2019; Liu et al. 2021). These findings suggest that the biosynthesis of phospholipid tails and glycerol backbones can modulate NAD homeostasis. It is tempting to speculate that the influence of phospholipid biosynthesis on NAD+ availability may regulate histone deacetylation and ADP ribosylation in the nucleus. Additionally, it is intriguing to consider whether fatty acid synthesis and elongation might affect NADPH homeostasis and, consequently, nuclear metabolism.

5.1.4 | CTP Utilization and Redox Balance

Nucleoside triphosphates (NTPs) perform diverse cellular functions beyond their role in nucleic acid synthesis. ATP, the primary energy currency, fuels numerous biological processes through phosphate bond hydrolysis (Alghannam et al. 2021). GTP is crucial in signal transduction processes, such as activating G-proteins and triggering downstream signaling cascades (Kostenis et al. 2024). UTP plays a key role in sugar metabolism, acting as a phosphate donor in the synthesis of sugar nucleotides like UDP-glucose, which are crucial for glycosylation (Meng et al. 2008). ATP and CTP are involved in lipid metabolism (Kennedy and Weiss 1956; Gibellini and Smith 2010). ATP donates phosphate groups during the phosphorylation of choline and ethanolamine in the initial steps of the Kennedy pathway for phospholipid synthesis (Gibellini and Smith 2010), while CTP acts as the energy carrier in head group attachment (Kennedy and Weiss 1956). NTP interconversion, often with ATP as the phosphate donor, ensures NTP availability (Lascu and Gonin 2000). CTP can also be synthesized from UTP, glutamine, and ATP by CTP synthetase (Chang and Carman 2008). This intricate network of NTP metabolism underscores its importance in supporting diverse cellular activities.

Depending on the selection of CTP for phospholipid precursor activation, cells have two strategies for adding phospholipid head groups. One strategy involves the CTP-dependent activation of water-soluble precursors, such as choline or ethanolamine, followed by condensation with DAG to produce PC and PE, in the Kennedy pathway (Figure 2). The other strategy involves the CTP-dependent activation of the lipid precursor PA, generating CDP-DAG (Figure 2). This activated lipid can react with various head group precursor metabolites to synthesize different types of phospholipids. Given the unique involvement of CTP as an energy input in phospholipid synthesis (Kennedy and Weiss 1956; Chang and Carman 2008), its broader biological significance remains underexplored.

A recent study using the eukaryotic model organism *Saccharomyces cerevisiae* reveals that CTP utilization in phospholipid synthesis allows cells to gauge the capacity of pyrimidine salvage (Zhu et al. 2024). Deficiencies in the Kennedy pathway constrain nucleotide salvage, resulting in the activation of *de novo* nucleotide synthesis as a compensatory mechanism (Zhu et al. 2024). This *de novo* synthesis, relying on the pentose phosphate pathway, increases the production of the reducing coenzyme NADPH, which in turn enhances glutathione synthesis (Zhu et al. 2024). Furthermore, defects in the Kennedy pathway compel cells to rely more heavily on the methylation of PE to synthesize PC, a process that functions as a methyl sink and further promotes glutathione synthesis (Ye et al. 2017, 2019; Fang et al. 2022). As a result, cells with Kennedy pathway deficiency exhibit greater resistance to oxidative stress due to elevated levels of antioxidants (Zhu et al. 2024).

A crucial link between phospholipid and nucleotide metabolism is the attenuation of the Kennedy pathway, which elevates pyrimidine nucleotides like CMP. This elevated CMP acts as a substrate inhibitor of nucleotidase, reducing the availability of nucleosides and nucleobases for salvage, thereby diminishing nucleotide recycling. Theoretically, for each molecule of CTP—used as the energy input in phospholipid synthesis—one molecule of CMP is generated for every phospholipid produced in cells, regardless of whether the substrates are lipidic or polar metabolites. Interestingly, Kennedy pathway-deficient mutants exhibit growth similar to wild-type cells, with a moderate increase in total phospholipid levels and a 50-fold increase in CMP levels (Zhu et al. 2024). This suggests that utilizing lipidic precursors for synthesis leads to a rapid production rate of phospholipids, facilitating the release of CMP.

The Kennedy pathway itself is inhibited at the terminal step under oxidative stress, with the formation of a pyrimidine cache that captures CTP in the form of CDP-choline and CDP-ethanolamine (Zhu et al. 2024). Under nutrient stress with choline deficiency, the rate-limiting step in the Kennedy pathway is limited by choline availability, manifesting an elevation in cellular UMP levels (Zhu et al. 2024). Biochemical evidence demonstrates that the elevated CMP and UMP levels in Kennedy pathway-deficient mutants can activate substrate inhibition, substantially reducing nucleotidase activity and thereby diminishing nucleotide recycling through the salvage pathway (Zhu et al. 2024). Oxidative stress associated with replicative aging also attenuates the terminal step in the Kennedy pathway (Zhu et al. 2024), showcasing a mechanism in which phospholipid metabolism is leveraged to combat oxidative stress. Therefore, the pivotal role of CTP in driving phospholipid synthesis underscores the integrated regulation of nucleotide metabolism, redox balance, and membrane biogenesis—all important for maintaining nuclear metabolism.

5.2 | Feedback Regulation Involving Cytosol-Nucleus Shuttling Proteins

Phospholipid synthesis can generate signaling molecules recognized by regulatory proteins that shuttle between the cytosol and the nucleus. These shuttling proteins activate transcriptional programs to regulate gene expression, enabling cells to dynamically adjust their metabolism and maintain homeostasis. PI/PIP kinases phosphorylate PI and its phosphorylated derivatives, PIPs, producing signaling lipids that mediate cytosol-nucleus communication (Anderson et al. 1999; Balla 2013). Given the intricate nature of PIP signaling, we direct readers to several excellent reviews for a comprehensive overview of its roles in nuclear metabolism, including a recent review in this collection (Hifdi et al. 2024) and others (Irvine 2003; Gonzales and Anderson 2005). Such cytosol-nucleus communications are also observed in the well-characterized the unfolded protein response (UPR) (Hetz 2012; Han and Kaufman 2016), sterol regulatory-element binding proteins (SREBPs) signaling in mammals (Shimano 2001; Shimano and Sato 2017), and the Mga2/Spt23 regulatory circuit that governs membrane lipid saturation in yeast (Chellappa et al. 2001; Covino et al. 2016). Below, we highlight a few illustrative examples to demonstrate the intersection between phospholipid signaling and nuclear metabolism.

5.2.1 | Lipid Signaling and PKC

A classic cellular lipid signaling is mediated by the activation of phospholipase C (PLC), which breaks down phosphatidylinositol-4,5-bisphosphate (PI(4,5)P_2) into DAG and inositol triphosphates (IP_3). This reaction leads to IP_3-dependent calcium release and DAG-stimulated protein kinase C (PKC) activation (Zima et al. 2007). An increase in plasma membrane DAG levels results in the activation and intracellular relocation of PKC isozymes to organelles such as the mitochondria, ER, Golgi apparatus, and nucleus (Griner and Kazanietz 2007). In addition to plasma membrane DAG-dependent PKC activation, nuclear PKC isozymes, such as PKCα and PKCβ, can be activated by the nuclear pool of DAG (Martelli et al. 2001). Nuclear DAG, generated from phosphoinositide, can promote the translocation of PKC from the cytosol into the nucleus (Divecha et al. 1991). Such PKC-mediated protein phosphorylation regulates various physiological processes, including cell proliferation and differentiation (Martelli et al. 2006). An increase in PLC-generated DAG is associated with PKC translocation to the nucleus during the early S phase (Banfić et al. 1993; York and Majerus 1994) and the G2-M transition (Sun et al. 1997; Deacon et al. 2002). For instance, PKCβII can be recruited into the nucleus to phosphorylate B-type lamins in HL60 cells, facilitating NE breakdown and cell entry into mitosis (Irvine 2003). Similar regulatory mechanisms, involving PKCα, βI, and βII isozymes, are observed in mammalian oocyte meiosis (Avazeri et al. 2004). Interestingly, PKC signaling also provides feedback regulation on the phosphoinositide pathway. For example, nuclear PKCα can phosphorylate nuclear PI-specific PLCβ on serine 887, downregulating its hydrolytic activity in Swiss 3T3 cells (Xu et al. 2001). PKC has a variety of substrates in the nucleus, including histone (Omri et al. 1987; Ajiro 2000; Huang et al. 2004; Mecklenbräuker et al. 2004), DNA polymerase (Tokui et al. 1991), DNA methyltransferase (DePaoli-Roach et al. 1986), PARP (Bauer et al. 1992; Andersson et al. 2016), and nucleolin (Zhou et al. 1997). Therefore, the DAG-PKC signaling axis can bridge lipid signaling with the regulation of nuclear processes, such as gene expression and chromatin structure.

5.2.2 | PA and Transcriptional Regulation of Phospholipid Synthesis

PA is a ubiquitous lipid intermediate that serves not only as a precursor for phospholipid synthesis, but also as a signaling lipid that regulates the process. In yeast cells, the promoters of nearly all genes involving in phospholipid synthesis contain the inositol-sensitive upstream activating element (UAS_{INO}), enabling coordinated activation of phospholipid synthesis by the Ino2-Ino4 transcription factor complex and repression by Opi1 (Carman and Han 2011; Henry et al. 2012). As a transcriptional repressor in the Henry regulatory circuit, Opi1 shuttles in and out of the nucleus in response to the availability of the phospholipid precursor PA, adjusting phospholipid synthesis transcriptionally (Carman and Henry 2007; Carman and Han 2011; Henry et al. 2012, 2014). PA, after CTP activation to form CDP-DAG, is rapidly consumed for the synthesis of PI when inositol is abundant (Gaspar et al. 2006). While Opi1 is tethered to the ER through its interaction with PA and the conserved ER integral membrane protein Scs2, the rapid depletion of PA for PI synthesis releases Opi1, which then translocates into the nucleus and binds to Ino2, leading to transcriptional repression (Loewen et al. 2004). While Opi1 translocation is responsive to inositol availability during fermentative growth, such as rapid growth in glucose medium, this Opi1-governed mechanism appears to be less sensitive to inositol levels in respiring cells. Instead, in these cells, Opi1 primarily regulates PC synthesis by modulating the balance between PE methylation and the Kennedy pathway (Fang et al. 2022).

In addition to PA availability being modulated by exogenous inositol, its signaling role is also influenced by intracellular pH (Young et al. 2010). Glucose starvation induces a rapid decrease in intracellular pH, leading to PA protonation and the subsequent dissociation of Opi1. This dissociation allows Opi1 to repress the expression of genes involved in phospholipid synthesis (Young et al. 2010), revealing a signaling mechanism that links membrane biogenesis to nutrient status. Thus, the abundance dynamics in PA, influenced by the biosynthesis and turnover of phospholipids, as well as the protonation state of PA due to pH changes, modulate its capacity to dock the transcriptional factor Opi1, connecting nutrient availability to the transcriptional coordination of phospholipid biosynthesis and thereby orchestrating membrane biogenesis (Shin and Loewen 2011).

In mammals, lipin proteins are PA phosphatase enzymes that catalyze the conversion of PA to DAG (Reue and Wang 2019). There are three mammalian lipin proteins—lipin 1, lipin 2, and lipin 3—with tissue-specific expression patterns (Wang, Airola, et al. 2017). Mutations in lipin genes are associated with severe metabolic disorders, such as rhabdomyolysis (lipin 1) (Zeharia et al. 2008), auto-inflammatory disease (lipin 2) (Ferguson 2005), and impaired intestinal lipoprotein assembly (lipin 2/lipin 3) (Reue and Wang 2019). These findings underscore the essential role of lipin activity in maintaining metabolic health and highlight the importance of understanding its regulatory mechanisms. Similar to its yeast homolog Pah1 (Hsieh et al. 2015, 2016), lipin is a phosphoprotein, with its phosphorylation status responding to nutrient availability and insulin signaling (Huffman et al. 2002). mTORC1, a central nutrient-sensing kinase, directly phosphorylates lipin, preventing its nuclear translocation. Loss of mTORC1-dependent phosphorylation enables lipin to enter the nucleus, reducing the nuclear abundance of SREBP, a key transcription factor in lipid metabolism (Peterson et al. 2011). This establishes a pathway where nutrient availability integrates the phosphoregulation of lipin with mTOR1-SERBP signaling to control lipid metabolism at the transcriptional level. Furthermore, studies have shown that the stability of mTORC complexes requires PA, the lipid substrate of lipin (Fang et al. 2001; Foster 2013; Menon et al. 2017). This suggests a reciprocal regulatory relationship between mTORC1 and PA, linking membrane lipid synthesis and nutrient sensing to ensure metabolic homeostasis. The interplay between lipin, mTORC1, and PA highlights the intricate coordination required for lipid metabolism and systemic energy balance.

5.2.3 | Phospholipid Metabolism Regulates DDR

Phosphoinositide signaling has been widely recognized as playing a crucial role in DDR. Upon genotoxic treatments, nuclear phosphoinositides such as $PI(4,5)P_2$ and $PI(3,4,5)P_3$ levels increase rapidly (Kumar et al. 2010; Wang, Hariharan, et al. 2017), suggesting a function of these PIPs in DDR. Nuclear $PI(3,4,5)P_3$ can interact with PARP1 (Mazloumi Gavgani et al. 2021), a multifunctional human ADP-ribosyltransferase with a crucial role in DDR. While PARP1 activity is required for the recruitment of repair proteins to DNA damage sites (Wang and Sheetz 2022), it remains elusive how nuclear $PI(3,4,5)P_3$ may physically affect the activation of PARP1 and DDR. During an early stage of DDR, phosphoinositides mediate a signaling cascade to activate the DDR kinase ATR (Wang, Hariharan, et al. 2017), a central regulator of the DDR signaling pathway. Following its recruitment to DNA damage sites, ATR is activated to phosphorylate Chk1 for inhibiting cell cycle progression during DNA repair. ATR activation in the DDR signaling pathway is also influenced by phospholipid synthesis and membrane availability (Kumar et al. 2014; Kidiyoor et al. 2020). Pharmacological and genetic studies suggest that increased phospholipid pools or nuclear membrane overgrowth are associated with more potent ATR activation and improved maintenance of DNA integrity during genotoxic stress (Ovejero et al. 2022).

Upon the induction of double-strand breaks in DNA, the DDR kinase ATM is also recruited to DNA damage sites, where it activates DDR through the phosphorylation of Chk2 (Sancar et al. 2004). This ATM-Chk2 activation, triggered by genotoxic stress, regulates cell cycle progression, DNA repair, and cell tolerance to DNA damage (Smith et al. 2010). Precise control of nuclear ATM is crucial, as persistent DDR activation can hinder long-range DNA end resection and repair (Clerici et al. 2013; Jinks-Robertson et al. 2013). During this process, sterol levels in the ER are depleted for the production of lipid droplets under genotoxic stress (Ovejero et al. 2023). As a result, the sterol-PI4P exchange machinery, OSBP1, is unable to relocate PI4P from the Golgi to the ER (Antonny et al. 2018). This accumulation of PI4P in the Golgi effectively retains ATM, preventing its entry into the nucleus (Ovejero et al. 2023). Therefore, the lipid-mediated mechanism finely tunes nuclear ATM levels, ensuring precise extinction of ATM signaling, which is necessary to permit the implementation of the last steps of DNA repair.

5.3 | Modulation of Nuclear Membrane Structure

The nuclear membrane serves as a critical barrier within the cell, playing a key role in regulating metabolic homeostasis and chromatin architecture. The synthesis of phospholipids not only influences nuclear metabolism and chromatin regulation through the consumption and transformation of substrate metabolites but also maintains the lipid composition crucial for the structure and integrity of the nuclear membrane.

Phospholipid composition in the nuclear membrane can be modulated by metabolic enzymes present in the nucleus, such as phosphoinositide phospholipases, lipid kinases, and phosphatases (Barlow et al. 2010). These enzymes, located in the nuclear matrix, nucleolus, and chromatin, play important roles in regulating the cell cycle, gene expression, and pre-mRNA processing (Siniossoglou 2013). A notable example of lipid enzymes regulating nuclear membrane morphology is choline phosphate cytidylyltransferase PCYT1, the rate-limiting enzyme of the CDP-choline pathway. PCYT1 is found within the nucleus of yeast, flies, and mammalian cells (Haider et al. 2018), and its activation is linked to recruitment to the INM (Haider et al. 2018). This enzyme senses membrane phospholipid composition through an amphipathic helix domain (Cornell and Ridgway 2015). In its inactive state, this domain binds to the catalytic site, leading to auto-inhibition of PCYT1 activity (Cornell and Ridgway 2015). The amphipathic helix of this domain has a strong affinity for membranes containing conically shaped lipids, such as PE and DAG (Davies et al. 2001; Taneva et al. 2005). When PC is lacking, PCYT1 is recruited to the INM, which releases the inhibitory binding and catalyzes PC synthesis (Haider et al. 2018).

Once activated on the INM, PCYT1 remodels the nuclear membrane structure, leading to the formation of nuclear membrane tubules, characteristic of the nucleoplasmic reticulum (NR) (Lagace and Ridgway 2005). Interestingly, this remodeling occurs independently of its catalytic activity but depends on the amphipathic helix membrane-binding domain (Lagace and Ridgway 2005). Additionally, this membrane remodeling requires the expression of nuclear lamins (Gehrig et al. 2007), which do not directly participate in PC synthesis (Gehrig and Ridgway 2011). This suggests that NR proliferation is mainly driven by the physical expansion and deformation of the nuclear membrane, promoting positive curvature and invagination into the nucleus. Simultaneously, PCYT1 ensures the continued synthesis of PC, providing essential components for membrane growth (Gehrig and Ridgway 2011).

The proliferation of NR is often observed in various tumor cell types (Fischer et al. 2003; Malhas et al. 2011) and in naïve T cells responding to antigen stimulation (Hale et al. 2024). NRs are proposed to play roles in chromatin regulation. For example, inhibiting histone deacetylation, which increases transcriptionally active chromatin, promotes NR proliferation, likely due to the increased need for the export and translation of abundant mRNA (Galiová et al. 2008). Additionally, the NR can facilitate the physical association between phospholipids and chromatin domains. The phosphoinositide PI(4,5)P_2 binds to the chromatin remodeling SWI/SNF complex, stabilizing actin filaments and potentially regulating higher-order chromatin structure (Rando et al. 2002; Hifdi et al. 2024). The formation of NR may spatially facilitate metabolic interplay between phospholipid synthesis and chromatin regulation, offering a platform for the exchange of metabolites with the nuclear environment.

It is worth noting that TAG synthesis can be compartmentalized by phospholipid-diacylglycerol acyltransferases within specific subdomains of the INM, particularly those adjacent to the nucleolus (Barbosa et al. 2019). Interestingly, TAGs synthesized from phospholipids at the INMs are subsequently packaged into lipid droplets associated with the ONM. While the mechanism underlying the budding directionality of lipid droplets from the nuclear membranes remains unclear, nuclear lipid droplets have been observed in both mammalian cells (Ohsaki et al. 2016) and yeast (Romanauska and Köhler 2018). These lipid droplets serve as lipid reservoirs during NE expansion (Sołtysik et al. 2021) and play a regulatory role in gene expression, such as by modulating histone acetylation (Umaru et al. 2022).

In mammalian cells, INM proteins such as Sad1p/UNC84 (SUN) domain-containing proteins, SUN1 and SUN2, regulate nuclear architecture and functions through their association with LINC (linker of nucleoskeleton and cytoskeleton) complexes (Crisp et al. 2006). These complexes mediate critical roles, including nuclear positioning within the cell, anchoring the NE at specific chromatin sites, and facilitating NE disassembly during mitosis (Krshnan et al. 2022). SUN2 is regulated by phosphorylation and dephosphorylation mediated by casein kinase 2 (CK2) and C-terminal Domain Nuclear Envelope Phosphatase 1 (CTDNEP1), respectively (Kim et al. 2007; Venerando et al. 2014). CTDNEP1 dephosphorylates SUN2, preventing its degradation and stabilizing its presence in the INM (Krshnan et al. 2022). Dysregulation of SUN2, such as the accumulation of nondegradable forms, leads to abnormal NE architecture, impaired DDR, and challenges during mitosis. These findings underscore the importance of precise regulation of SUN2 in maintaining nuclear integrity function (Krshnan et al. 2022).

Recent evidence also highlights the critical role of lipid metabolism in the formation and maintenance of NPCs (Peeters et al. 2022). NPC assembly requires the fusion of the INM and ONM at specific sites, forming highly curved structures. This process is influenced by the biophysical properties of the NE (Lone et al. 2015). Increased lipid saturation and acyl chain

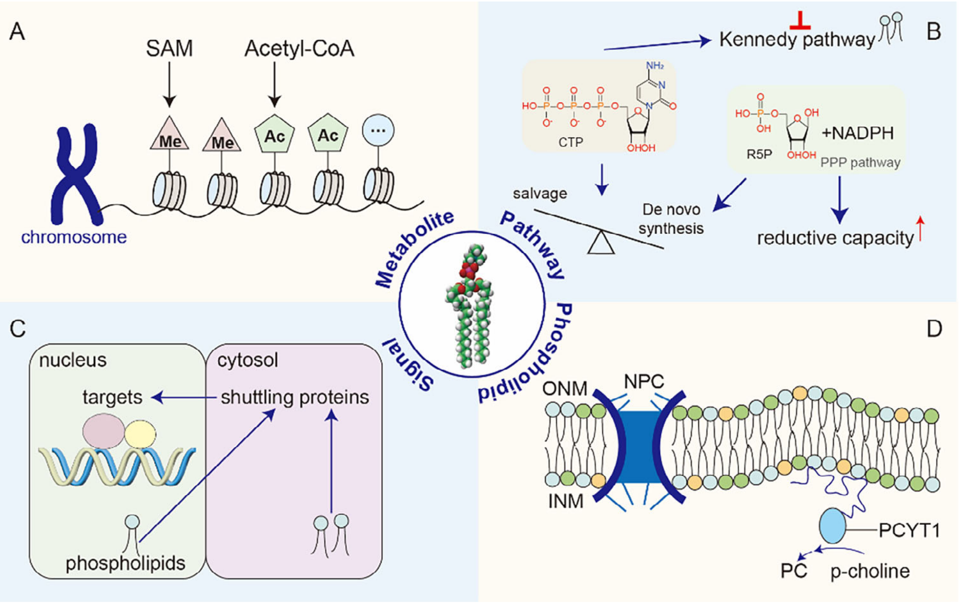

FIGURE 4 | How phospholipid synthesis modulates nuclear functions. (A) Phospholipid synthesis can influence chromatin modification by competing for shared metabolites. (B) The pathway choice of the Kennedy pathway modulates nucleotide metabolism and cellular reducing capacity via CTP utilization. (C) Signaling lipids can trigger the shuttling of regulatory proteins between the cytosol and the nucleus. (D) Phospholipid synthesis is crucial for maintaining nuclear membrane architecture. CTP, cytidyltriphosphate.

length result in a more rigid NE, which is less conducive to the membrane curvature required for NPC formation (Stankunas and Köhler 2023). Excessive lipid saturation reduces NE elasticity, transforming the spherical nucleus into a rigid polyhedron prone to rupture. These findings emphasize the need for balanced lipid saturation to maintain proper pore membrane curvature and ensure NPC integrity (Romanauska and Köhler 2023).

6 | Conclusion

Phospholipids are fundamental components of cells, forming barriers and compartments essential for metabolism, signaling, and regulation. The synthesis of phospholipids not only generates critical lipid components for cell membranes but also connects membrane biology to metabolic processes. Given that these biosynthetic processes consume substantial metabolite resources, it is plausible that phospholipid synthesis acts as an unforeseen regulatory hub, ensuring metabolic homeostasis and energy efficiency. The cell nucleus is a site of active metabolism and undergoes intensive regulatory events, making it particularly sensitive to the effects of phospholipid synthesis.

Here, we propose that phospholipid biosynthesis can exert regulatory functions on cellular and nuclear activities through four key aspects at metabolic intersections (Figure 4): (1) Small-molecule metabolite level: Functional metabolites, such as high-energy metabolites consumed or transformed by phospholipid synthesis, can influence other processes that also require these metabolites. (2) Pathway level: The utilization of different pathways for phospholipid production may be associated with specific metabolic strategies, such as how cells manage oxidative stress with the Kennedy pathway. (3) Signaling molecules: Phospholipid synthesis generates signaling molecules that activate regulatory proteins, including cytosol-nucleus shuttling proteins that regulate gene expression. (4) Membrane morphology and properties: The synthesis of phospholipids is crucial for the chemical and compositional diversity of phospholipids in cellular membranes, thereby modulating membrane morphology and properties. These functions illustrate how phospholipid synthesis is intricately linked to nuclear metabolism, providing a new perspective on the biological roles of phospholipid biosynthesis in basic science.

Author Contributions

C.Y. conceptualized this review article. C.Y. and H.Q. wrote the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

No new data were generated or analyzed in support of this review. All data referenced in this article are available from the resources cited in the references.

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