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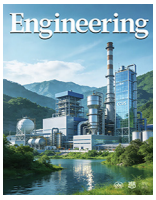

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The Phospholipid Metabolic Switch in Lung Cancer: Igniting Transformation, Fortifying Survival, and Informing Therapy

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ABSTRACT

Lung cancer, as one of the leading causes of cancer-related deaths worldwide, exhibits complex pathogenesis, with the association between inflammation and malignant transformation drawing significant attention. This paper focuses on the pivotal role of phospholipid metabolism in the inflammation-to-cancer transition of lung cancer. It systematically elucidates the molecular mechanisms by which phospholipid metabolism drives this transition, its impact on the immune microenvironment, its involvement in cell death resistance processes, and clinical translation strategies from lung cancer to pan-cancer types. Furthermore, it explores controversies and future prospects in phospholipid metabolism research. Through comprehensive analysis of relevant literature, this review aims to provide novel insights and theoretical foundations for the prevention, diagnosis, and treatment of lung cancer.

1. Introduction

1.1. The inextricable link between chronic inflammation and lung cancer

Lung cancer ranks as the second most common malignant tumor globally and the leading cause of cancer-related deaths, with approximately 2.2 million new cases and 1.8 million deaths annually [1,2]. Traditionally, lung cancer has been viewed as primarily triggered by direct gene mutations induced by carcinogens such as tobacco. The classic "inflammation-to-cancer" (ITC) model has predominantly focused on hepatocellular carcinoma (e.g., the hepatitis B virus (HBV)/hepatitis C virus (HCV) infection-induced cirrhosis-to-liver cancer pathway) [3,4] and colorectal cancer (e.g., the process from ulcerative colitis with dysplasia to malignancy) [5], which exhibit clear histological progression pathways. In contrast, lung cancer lacks a similar macro-level continuum of inflammation–hyperplasia–carcinogenesis, leading to its long exclusion from the classical ITC paradigm. However, over the past two decades, multiple studies have progressively revealed that persistent environmental or endogenous inflammation is also an independent risk factor for lung cancer development, challenging this traditional understanding. Specifically, the ITC in lung cancer refers to the process where a chronic inflammatory microenvironment drives the transformation of normal lung epithelial cells into cancer cells. Previous epidemiological evidence indicates that patients with chronic obstructive pulmonary disease (COPD) exhibit a 2- to 7-fold increased risk of lung cancer, regardless of smoking history [6–8], suggesting that inflammation itself may drive malignant transformation. Inhaled particulate matter (tobacco smoke, asbestos, and silica) can trigger persistent low-grade inflammation within the airways, which synergizes with

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genetic mutations to accelerate the development of lung cancer and mesothelioma [9,10]. In smoking-related lung cancer, inhaled particles like tobacco smoke activate the lymphotoxin β receptor (LTβR) on lung epithelial cells and its downstream non-canonical nuclear factor kappa-B (NF-κB) pathway, inducing airway fibrosis and epithelial–mesenchymal transition (EMT) to establish a persistent inflammation-transformation microenvironment [11]. A prospective study of 1148 long-term smokers followed for up to 24 years further quantified this relationship, showing that individuals with ≥30 pack-years of smoking had a 9.8-fold higher relative risk of lung cancer compared to non-smokers [12]. Among non-smokers, fine particulate matter (PM2.5) emerges as a key inflammatory trigger. A meta-analysis of 312 457 women with no smoking history revealed a 9% increase in lung cancer risk for every 10 $\mu g \cdot m^{-3}$ rise in PM2.5 concentration [13]. This mechanism is closely associated with PM2.5-induced oxidative stress and the activation of oncogene signaling pathways such as the epidermal growth factor receptor (EGFR) [14]. Furthermore, phenomena like the transdifferentiation of lung adenocarcinoma into squamous cell carcinoma provide histological evidence that the inflammatory microenvironment drives phenotypic plasticity [15]. Collectively, these data demonstrate that both smoking-related chemical inflammation and PM2.5-induced physical-oxidative stress synergize with genetic mutations to promote lung cancer development by establishing a persistent inflammatory microenvironment. These findings collectively support the novel ITC transition paradigm of "chronic inflammation–molecular mutation–malignant transformation" in lung cancer, laying a theoretical foundation for subsequent investigations into the regulatory role of phospholipid metabolic networks within this process.

1.2. Phospholipid metabolic reprogramming acts as the central driver of lung tumorigenesis and evolution

As a core component of cell membranes, phospholipids not only participate in energy storage and signal transduction but also serve as a pivotal hub in the ITC conversion axis [16]. Extensive evidence indicates that chronic inflammation drives malignant transformation by reprogramming phospholipid metabolism. Key mechanisms include inflammation-induced dysregulation of phospholipid metabolic enzymes and the release of pro-cancer signaling lipids. Pro-inflammatory factors (tumor necrosis factor-α (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6)) significantly upregulate key lipid synthesis enzymes by activating the NF-κB/signal transducer and activator of transcription 3 (STAT3) pathway. Fatty acid synthase (FASN) activity increases 5- to 8-fold in the inflammatory microenvironment, accelerating phosphatidylcholine (PC) and phosphatidylethanolamine (PE) synthesis to meet the membrane structural demands of proliferating tumor cells [17,18]. Acetyl-CoA carboxylase (ACC) and lysophosphatidylcholine acyltransferase (LPCAT) synergistically promote phospholipid remodeling, enhancing membrane fluidity and activating pro-migratory signaling receptors (e.g., EGFR and integrins) [19,20]. The transcription factor sterol regulatory element-binding protein (SREBP)/mammalian target of rapamycin (mTOR) is activated by inflammatory signals, globally coordinating the lipid synthesis network [21,22]. Inflammation induces overexpression of cyclooxygenase-2 (COX-2) and lipoxygenases (5-/12-LOX), which catalyze the conversion of arachidonic acid (AA) into pro-tumor signaling lipids like prostaglandin E2 (PGE2) and leukotriene B4 (LTB4). These lipids directly stimulate cell proliferation, migration, and angiogenesis [23–25]. Furthermore, spatial metabolomics confirmed significant enrichment of pro-tumor lipid molecules (e.g., lysophosphatidic acid (LPA)) within non-small cell lung cancer (NSCLC) lesions [26].

Notably, the core event underlying phospholipid metabolism's regulatory role in lung cancer is the "phospholipid metabolic switch," which we operationally define as follows: In lung cancer, this switch refers to the directional transformation of phospholipid metabolism from a physiological homeostatic state (maintaining cell normal function) to a pathological reprogramming state (generating pro-tumor lipids, regulating inflammation, immunity, and cell death). Driven by chronic inflammatory cues and lung cancer-specific oncogenic factors, it serves as a key hub linking inflammation to tumor progression. This definition aligns with the academic consensus of "metabolic switch" as a regulatory node triggering directional metabolic phenotype transformation (e.g., protein phosphatase 1 regulatory subunit 3B (PPP1R3B)) acts as a metabolic switch governing hepatic energy storage switching between glycogen and triglycerides [27], further validating its rationality.

1.3. Rationale and overview: A systems view of phospholipid reprogramming across the lung cancer continuum

Lung cancer exhibits distinct advantages within the "phospholipid metabolism–inflammation–mutation" axis compared to classic ITC models such as liver or colorectal cancer, providing an ideal research system for investigating how phospholipid metabolic reprogramming drives the entire tumorigenesis process. Its characteristic features include: First, different pathological subtypes of lung cancer possess specific systemic metabolic patterns detectable in peripheral blood. Patients with lung adenocarcinoma exhibit "brain–endocrine organ metabolic coordination," while those with lung squamous cell carcinoma demonstrate "systemic metabolic network disintegration" [28]. Such metabolic differences can be dynamically monitored through plasma exosomal phospholipid profiling [29]. Second, precision diagnostic and therapeutic tools for lung cancer continue to mature. For instance, low-dose computed tomography (LDCT) combined with C-reactive protein (CRP)/IL-6 testing significantly increases early-stage lung cancer detection rates by 23% while maintaining a false-positive rate below 11% [30]; the sensitivity of salivary multi-phospholipid combined models has reached 88%–91% [31]. Furthermore, the lipid ratio score (LSR score) model—developed based on four significantly altered plasma lipid biomarkers identified through non-targeted lipidomics in lung adenocarcinoma—provides a more refined tool for early screening of lung adenocarcinoma [32]. These characteristics enable the lung cancer ITC transition model to not only precisely elucidate the role of phospholipid metabolic reprogramming across the entire chain of "inflammation-to-cancer transition and tumor progression," but also provide a systematic and translatable research paradigm for the early prevention, diagnosis, and precision treatment of solid tumors. Therefore, this review will systematically connect the entire chain of mechanisms driven by phospholipid metabolic reprogramming in lung cancer initiation and progression for the first time: from the initial stage of "phospholipid metabolic reprogramming → amplified inflammatory signaling → inflammation-to-cancer conversion" to the advancing stage of "phospholipid metabolic reprogramming → resistance to cell death → microenvironment remodeling → tumor progression." By comparing similarities and differences in microenvironment remodeling between lung cancer and liver/gastric cancers, we reveal cancer-specific regulatory mechanisms of phospholipid metabolism. Ultimately, we propose personalized therapeutic strategies based on phospholipid metabolic subtyping, offering novel systems biology perspectives and translational pathways for precision prevention and treatment of lung cancer targeting phospholipid metabolism.

2. Ignites lung cancer initiation and progression through cell-autonomous phospholipid metabolism mechanisms

Chronic inflammation plays a pivotal role in the ITC transition in lung cancer by reshaping phospholipid metabolism (regulating key enzyme activity, metabolite levels, and epigenetic modifications such as histone lipidation). The core cell-autonomous mechanisms of phospholipid metabolic reprogramming driving lung cancer ITC and malignant progression are systematically illustrated in Fig. 1, and its specific mechanisms encompass the following two interconnected levels.

2.1. Pro-tumorigenic phospholipid-derived mediators drive inflammatory signaling and tumor pathogenesis

Phospholipids not only serve as components of tumor cell membranes, but abnormal phospholipid metabolism within the tumor microenvironment (TME) can also generate a series of pro-inflammatory lipid mediators that directly regulate tumor cell proliferation, migration, and immune evasion. Taking sphingosine-1-phosphate (S1P) as an example, this bioactive lipid mediator induces tumor-associated macrophages (TAMs) to produce lipocalin-2 (LCN2), which in turn activates the NOD-like receptor protein 3 (NLRP3) inflammasome, leading to the release of IL-1β and ultimately enhancing tumor lymphangiogenesis and metastatic potential [33,34] (Fig. 1). Phospholipases (PLs) are responsible for hydrolyzing phospholipids, the fundamental components of cell membranes [35]. Within the PL family, phospholipase A2 (PLA2) drives inflammation, angiogenesis, metastasis, and immune evasion in various solid tumors such as lung cancer by catalyzing the release of AA from membrane phospholipids [36]. The released AA is metabolized by COX-2 and lipoxygenase (5-/12-LOX) to generate PGE2 and LTB4, respectively. PGE2 induces human monocyte-derived dendritic cells (DCs) to upregulate the immunosuppressive cytokine IL-10 by binding to the E2 receptor subtype 4 (EP4) receptor, thereby promoting regulatory T cell (Treg) differentiation and shaping an immunosuppressive microenvironment. Conversely, LTB4 significantly enhances neutrophil infiltration, further amplifying inflammatory signaling [37] (Fig. 1). Notably, in triple-negative breast cancer, tumor cells directly reprogram tumor-associated neutrophils by secreting AA-rich lipids, leading to immune evasion and resistance to immune checkpoint inhibitors (e.g., anti-programmed cell death 1 (PD-1)) and chemotherapy. Blocking dietary omega-6 fatty acid intake or inhibiting AA synthesis restores antitumor immune responses and reverses treatment resistance [38]. Additionally, lysophosphatidylcholine (LPC) generated by PLA2 hydrolysis can be converted into LPA under the action of autocrine motility factor (ATX), which activates the Ras homolog gene/a Rho-associated coiled coil-forming protein kinase (Rho–ROCK) pathway through LPA receptors (LPARs), thereby upregulating matrix metalloproteinase matrix metalloproteinase 2 (MMP2) and MMP9 expression. This promotes EMT and invasive capacity in models of lung cancer, breast cancer, and others [37,39,40] (Fig. 1). This body of evidence demonstrates that phospholipid-derived proinflammatory mediators synergistically drive tumor progression by reshaping the immune microenvironment and modulating malignant tumor cell phenotypes, playing a crucial role in lung cancer development (Fig. 1). Interventions targeting these key mediators and pathways hold significant translational value.

2.2. Interwoven phospholipid and sphingolipid metabolism forms a coordinated network driving malignant transformation and progression

Disrupted sphingolipid metabolism represents a significant metabolic hallmark in NSCLC. This metabolism centers on a critical equilibrium involving ceramide (Cer), S1P, and sphingomyelin (SM), characterized by dynamic "apoptosis–survival" regulation. Acidic, neutral, and basic sphingomyelinases (SMase, including A-SMase, N-SMase, and B-SMase) catalyze SM hydrolysis to generate Cer. Cer activates the mitochondrial apoptosis pathway, effectively inhibiting tumor cell survival [41] (Fig. 1). Conversely, S1P concentrations are frequently elevated in experimental cancer models and patient tumor interstitial fluids. Upon binding to its receptors S1P receptors 1–5 (S1PR1–5), S1P activates multiple pro-tumor signaling pathways—including Ras/extracellular signal-regulated kinase (ERK), phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT), STAT3, and phospholipase C (PLC) pathways—thereby promoting tumor progression [42,43] (Fig. 1). Sphingosine kinase 1 (SPHK1) is frequently overexpressed in tumor cells, and its upregulation leads to increased S1P production. Notably, the S1P/S1PR1 axis has been demonstrated to play a pivotal role in mediating the transition from chronic intestinal inflammation to colitis-associated cancer. This mechanism involves the activation of master transcription factors NF-κB and STAT3, ultimately driving inflammation, angiogenesis, and tumor progression [44] (Fig. 1). Clinical data indicate that elevated SPHK1/2 expression correlates with resistance to EGFR–tyrosine kinase inhibitors (TKIs) in NSCLC patients and predicts poorer survival outcomes. Targeting this pathway, such as with the S1PR antagonist FTY720, not only reverses EGFR–TKI resistance but also enhances the efficacy of immune checkpoint inhibitors (e.g., anti-PD-1 antibodies) [45,46]. This reveals that SPHK1/2 inhibitors represent a novel therapeutic strategy to overcome treatment resistance in NSCLC, particularly in patients resistant to chemoradiotherapy.

Notably, phospholipid and sphingolipid metabolic networks are tightly intertwined, forming a complex and coordinated regulatory network in the ITC transition and tumor progression of lung cancer. In NSCLC, EGFR activation can regulate the expression of lipid metabolic enzymes such as stearoyl-CoA desaturase 1 (SCD1) and FASN via the PI3K/AKT/mTOR pathway, thereby indirectly affecting sphingolipid metabolic balance [45]. Additionally, glycosylation modifications of sphingolipids contribute to disease progression: NSCLC patients exhibiting elevated expression of β-1,3-*N*-acetylglucosaminyltransferase 5 (B3GNT5) or galactose-3-*O*-sulfotransferase 1 (GAL3ST1) or low GAL3ST1 expression in NSCLC patients is associated with poor prognosis. This suggests that the balance between lactose/galactose-derived glycolipids regulated by B3GNT5 and sulfated sphingolipid metabolism represents a critical node in regulating sphingolipid metabolic reprogramming and influencing tumor growth and progression [47]. Therefore, the interaction between phospholipid and sphingolipid metabolism plays a significant role in regulating inflammatory signaling and lung cancer development. The above cell-autonomous mechanisms of phospholipid and sphingolipid metabolic reprogramming driving lung cancer inflammation-to-cancer transition and malignant progression are systematically summarized in Fig. 1. Elucidating the specific molecular mechanisms within this network will provide a crucial foundation for developing more precise and effective diagnostic and therapeutic strategies for lung cancer.

3. Fueling tumor progression via phospholipid metabolism reprogramming-mediated TME remodeling

As delineated above, the cell-autonomous reprogramming of phospholipid metabolism constitutes a fundamental engine, fueling the abnormal proliferation, survival, and malignant phenotype of lung cancer cells themselves. Critically, this intracellular metabolic rewiring does not operate in isolation. The altered metabolic flux and the resultant bioactive lipid mediators (e.g., S1P, AA, and LPA) are not merely consumed internally; they are actively secreted or otherwise released into the immediate surroundings.

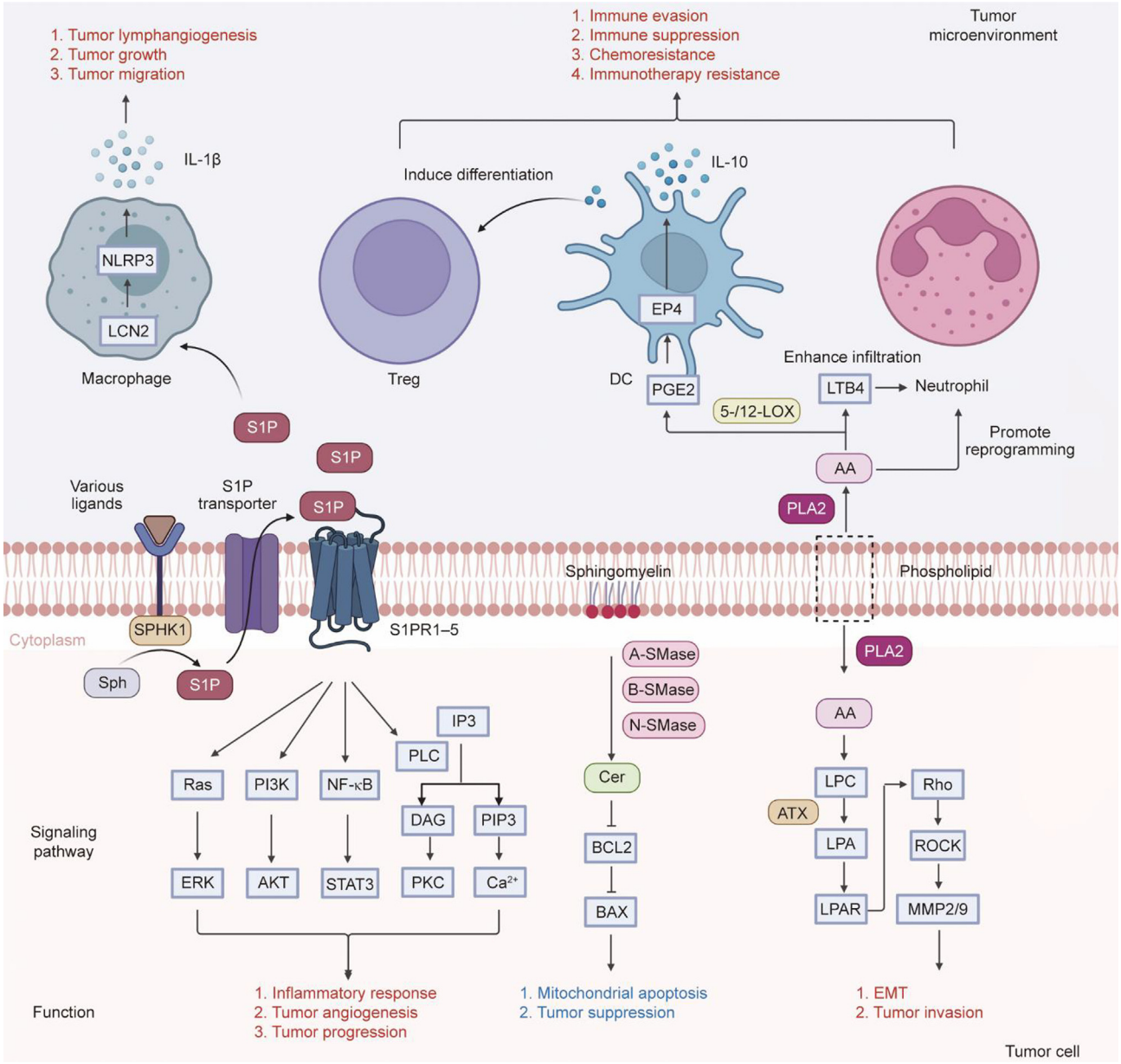


Fig. 1. Schematic of cell-autonomous mechanisms by which phospholipid metabolic reprogramming ignites ITC and sustains lung cancer malignancy. Key pathways include: Sphingolipid balance: A-/N-/B-SMase hydrolyze SM to Cer, activating mitochondrial apoptosis via the B-cell lymphoma 2 (BCL2)/BCL2-associated X protein (BAX) pathway to suppress tumor survival. Conversely, SPHK1 converts sphingosine (Sph) to S1P, which binds S1PR1–5 to activate Ras/ERK, PI3K/AKT, and NF-κB/STAT3—promoting inflammation, angiogenesis, and tumor growth. S1P-mediated immune regulation: Extracellular S1P acts on TAMs to induce LCN2, activating the NLRP3 inflammasome and IL-1β release. IL-1β drives lymphangiogenesis, facilitating tumor migration. PLA2–AA axis for immunosuppression and resistance: PLA2 releases AA from membrane phospholipids. AA is metabolized via COX-2-derived PGE2, which binds DC EP4 receptors to induce Treg differentiation and IL-10 secretion (immunosuppression) and 5-/12-LOX-derived LTB4, enhancing neutrophil infiltration and reprogramming (chemoresistance/immune checkpoint inhibitor resistance). LPC–LPA pathway for invasion: PLA2-generated LPC is converted to LPA by ATX. LPA binds LPAR to activate Rho–ROCK, upregulating MMP2/9 and promoting EMT and tumor invasion. PKC: protein kinase C; DAG: diacylglycerol; IP3: inositol 1,4,5-trisphosphate; PIP3: phosphatidylinositol (3,4,5)-trisphosphate. Created in BioRender.

Thus, tumor cells, empowered by their dysregulated phospholipid metabolism, transition from autonomous actors to dominant regulators of their microenvironment. They utilize these specific metabolic molecules as key communication signals to systematically recruit, educate, and reprogram various resident and infiltrating stromal and immune cells. The bidirectional crosstalk between phospholipid metabolic reprogramming and TME dynamics driving lung cancer progression is systematically illustrated in Fig. 2. The following section will elaborate on how this "metabolic instruction" from tumor cells reshapes the TME, fostering a pathological ecosystem that supports every stage of cancer progression.

Phospholipid metabolic reprogramming directly promotes malignant transformation in lung cancer cells by generating pro-oncogenic bioactive lipids such as LPA and oxidized phospholipids (Fig. 2). In hepatocellular carcinoma and cholangiocarcinoma, PC and LPC are significantly upregulated, accompanied by enhanced PLA2 activity, highlighting a central role for dysregulated phospholipid metabolism (as a key facet of broader lipid metabolic rewiring) in cancer progression [48]. In colorectal cancer models, cancer-associated fibroblasts (CAFs) accumulate fatty acids and phospholipids through lipid metabolic reprogramming. Secreted lipids enhance tumor cell migration upon uptake; inhibiting fatty

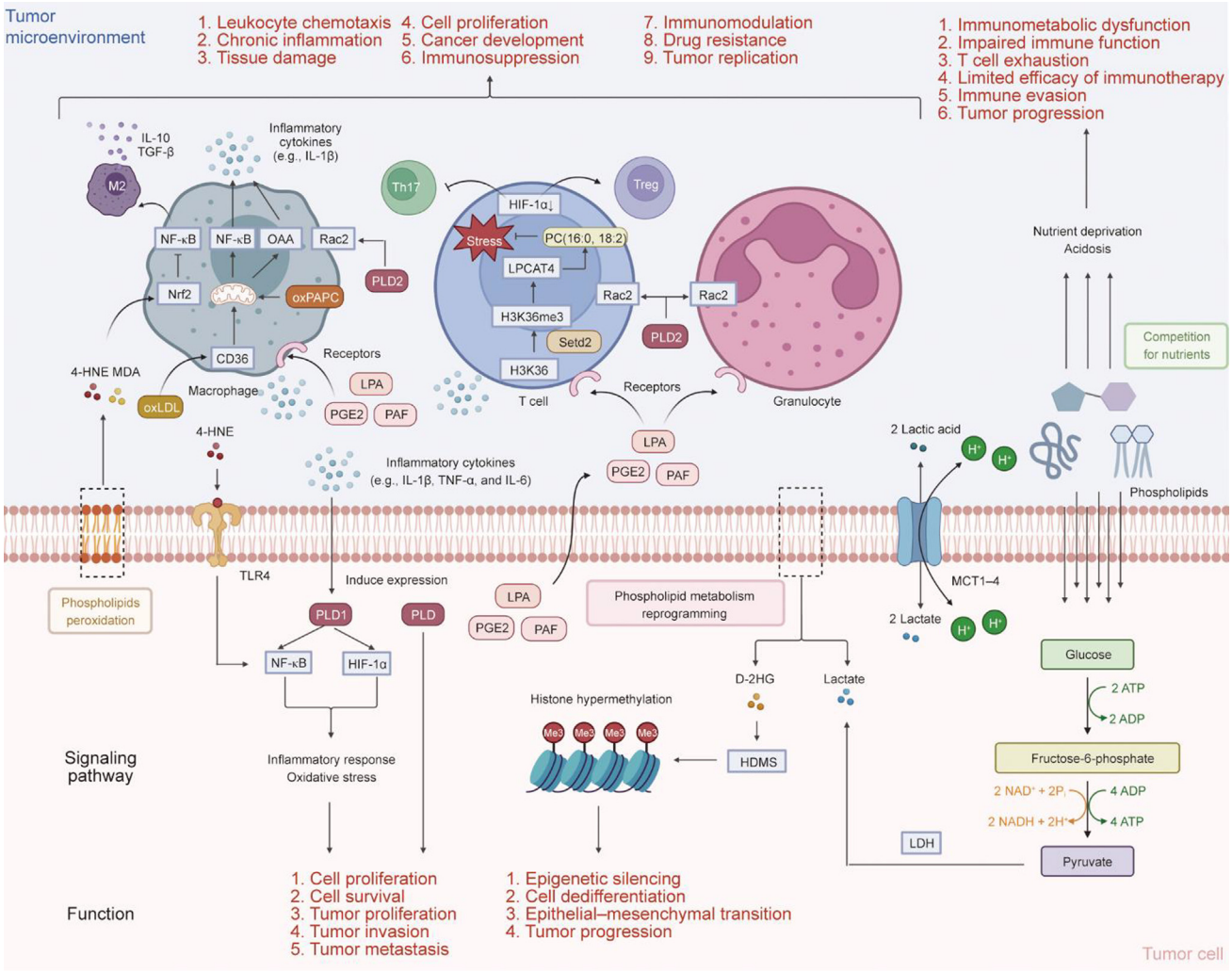


Fig. 2. Schematic of bidirectional crosstalk between phospholipid metabolic reprogramming and TME dynamics driving lung cancer progression. This framework emphasizes the bidirectional crosstalk between phospholipid metabolic reprogramming and TME dynamics: lipid-mediated inflammation fuels tumor initiation, while tumor cell metabolic rewiring (glycolysis and lactate secretion) and epigenetic regulation (histone modifications) consolidate a pro-tumorigenic TME. The cycle of phospholipid metabolic reprogramming–inflammation–oxidative stress–nutritional competition–epigenetic rewiring ultimately drives lung cancer progression and therapy resistance. Left panel: Phospholipid peroxidation (e.g., oxLDL) triggers TME dysregulation. OxLDL binds macrophage TLR4, activating NF-κB/HIF-1α to secrete pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6) and bioactive lipids (LPA, PGE2, and PAF), propagating chronic inflammation/oxidative stress. Macrophage oxLDL uptake via CD36 amplifies this loop, forming a self-reinforcing inflammation-cell damage cycle. Central panel: T cell phospholipid metabolic reprogramming—regulated by stress (HIF-1α) and histone modifications (H3K36me3)—relies on key enzymes (PLD2 and LPCAT4) to alter lipid profiles, influencing proliferation, differentiation, and granulocyte crosstalk, which shapes TME dynamics. Right panel: Tumor cells dominate TME nutrient competition via phospholipid metabolic reprogramming—enhancing synthesis/uptake to deplete microenvironmental phospholipids (e.g., PC and PE). This reduces immune cell (e.g., $CD8^+$ T cells) phospholipid levels, impairing effector functions—suppressing anti-tumor immunity. Tumor-derived lactate (monocarboxylate transporters 1–4 (MCT1–4)) exacerbates acidosis, driving T cell exhaustion and limiting immune therapy efficacy. Phospholipid metabolites (e.g., D-2HG) link metabolism to epigenetics: D-2HG inhibits HDMs, altering histone methylation to promote EMT and metastasis. This feedforward loop—phospholipid depletion→immune suppression→epigenetic rewiring—sustains tumor growth and immune evasion. H3K36: histone H3 lysine 36; NAD^+: nicotinamide adenine dinucleotide (oxidized form); NADH: nicotinamide adenine dinucleotide (reduced form); ADP: adenosine diphosphate; ATP: adenosine triphosphate. Created in BioRender.

acid synthase in CAFs or blocking lipid uptake by tumor cells eliminates this effect [49]. These findings suggest that targeting phospholipid metabolic reprogramming may offer novel therapeutic strategies for lung cancer.

3.1. Tumor cells reshape the immunosuppressive niche via phospholipid metabolism reprogramming to maintain a pro-tumorigenic soil

Phospholipid metabolic reprogramming regulates immune cell function through multiple pathways, continuously shaping and maintaining the "inflammatory soil" within the TME. Macrophages, as a crucial component of the immune microenvironment, exhibit metabolism significantly influenced by phospholipid metabolism. Within macrophages, oxidized low-density lipoprotein (oxLDL) uptake via the cluster of differentiation 36 (CD36) receptor drives a metabolic shift from oxidative phosphorylation (OXPHOS) to excessive superoxide production. This activates NF-κB and promotes inflammatory cytokine release, fueling chronic inflammation [50] (Fig. 2). Endogenous oxidized phospholipids (e.g., oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine (oxPAPC)) further reshape macrophage metabolic patterns. Under lipopolysaccharide stimulation, they simultaneously enhance glycolysis and mitochondrial respiration while supplementing the tricarboxylic acid cycle with glutamine as a carbon source. This leads to cytoplasmic accumulation of oxaloacetic acid, ultimately amplifying the production of inflammatory mediators like IL-1β [51] (Fig. 2). Beyond macrophages, phospholipid

metabolic remodeling influences the tumor immune microenvironment through multiple complementary pathways, thereby sustaining and amplifying the "inflammatory soil." Key enzymes in phospholipid metabolism, such as phospholipase D (PLD), are highly expressed in various cancers, with increased activity closely associated with tumor proliferation, invasion, and metastasis [52]. PLD2 promotes leukocyte chemotaxis by binding to Ras-related C3 botulinum toxin substrate 2 (Rac2) during early inflammation, while its expression is suppressed in later stages, leading to reduced leukocyte migration and retention (Fig. 2). Prolonged leukocyte retention may induce the pathological phase of chronic inflammation. Chronic inflammation can cause tissue damage and cell proliferation, thereby promoting carcinogenesis. Concurrently, inflammatory cytokines IL-1β, TNF-α, and IL-6 can induce PLD1 expression. PLD1 further amplifies inflammatory responses and cell survival by activating the NF-κB and hypoxia-inducible factor-1α (HIF-1α) signaling pathways, forming a positive feedback loop [53,54] (Fig. 2).

3.2. Phospholipid peroxidation fuels a vicious cycle of inflammation and oxidative stress

During tumor progression and treatment, cancer cells produce) PC-derived lipid mediators such as PGE2, platelet-activating factor (PAF), and LPA. Once released into the TME, these mediators bind to homologous receptors present on various immune cells, broadly suppressing antitumor immunity and inducing an immunoregulatory state. These lipid mediators mediate complex interactions between tumors and immune cells, contributing to therapeutic resistance and tumor recurrence [55] (Fig. 2). Notably, mitochondrial function serves as a core hub linking phospholipid metabolic reprogramming to immune checkpoint regulation in lung cancer. Phospholipids, especially PC and sphingolipids, are the major structural components of mitochondrial membranes, and their composition directly determines the stability and functional state of mitochondrial membranes. Thus, the phospholipid metabolic switch, characterized by abnormal synthesis and catabolism of PC and sphingolipids, reshapes the composition and stability of mitochondrial membranes, thereby regulating the balance between OXPHOS and glycolysis—this metabolic remodeling is the upstream driver of AMP-activated protein kinase (AMPK)/mTOR pathway activation [56]. As reported, abnormal activation of tumor mitochondria can upregulate the expression of CD276 (a B7 family immune checkpoint) through the AMPK/mTOR pathway and coordinate the expression of programmed cell death ligand 1 (PD-L1), further reinforcing the immunosuppressive microenvironment [56,57]. Conversely, disruption of mitochondrial function can inhibit the upregulation of PD-L1 and impair DNA damage repair in tumor cells, weakening the immunosuppressive niche [58]. In addition, mitochondrial dysfunction-related tumor hypoxia can exacerbate PD-L1 upregulation, forming a vicious cycle that promotes immune escape [57]. Collectively, these findings demonstrate that phospholipid metabolic reprogramming regulates the expression of immune checkpoints such as CD276 and PD-L1 by modulating mitochondrial function, forming a conserved "phospholipid metabolism–mitochondria–immun e checkpoint" regulatory axis in the TME. This axis further enhances the construction of the immunosuppressive "inflammatory soil" and provides a potential target for reversing immune tolerance in lung cancer. Phospholipid metabolism within the TME, through bidirectional signaling dialogues between immune and tumor cells, collectively constructs and reinforces the "inflammatory soil" supporting tumor growth, providing a theoretical basis for intervention strategies targeting the tumor immune microenvironment. Phospholipid peroxidation fuels a vicious cycle of inflammation and oxidative stress.

Phospholipid peroxidation is one of the major sources of intracellular oxidative stress, and its products play a pivotal role in the onset and progression of various diseases. Recent studies have revealed that phospholipid peroxidation products not only directly contribute to cellular damage but also activate inflammatory responses and oxidative stress, forming a vicious cycle that further exacerbates pathological processes. Aldehyde products generated by oxidative stress-mediated phospholipid peroxidation, such as 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA), can form adducts with intracellular proteins. These adducts alter protein structure and function, promoting inflammatory responses and cellular damage, thereby intensifying oxidative stress and perpetuating the vicious cycle. The formation of 4-HNE and MDA results from phospholipid peroxidation, and the adducts they form with proteins further exacerbate intracellular oxidative stress. This vicious cycle intensifies cellular damage and may ultimately lead to cell death [59] (Fig. 2). Concurrently, 4-HNE has been demonstrated to activate the Toll-like receptor 4 (TLR4)/NF-κB signaling pathway, significantly promoting inflammatory responses and oxidative stress, which are particularly critical in tumor progression [60] (Fig. 2). Activation of the TLR4/NF-κB pathway leads to the release of multiple pro-inflammatory factors (such as IL-1β, IL-6, and TNF-α), further amplifying inflammatory signals and exacerbating tissue damage. In chronic inflammatory diseases like metabolic dysfunction-associated steatohepatitis and rheumatoid arthritis, phospholipid peroxidation products directly drive inflammation and oxidative stress by inducing oxidized phospholipids, thereby accelerating disease progression [61]. Within the TME, phospholipid peroxidation products released by tumor cells, such as 4-HNE and MDA, exert complex effects on immune cell function. They activate the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway while simultaneously suppressing the NF-κB pathway, thereby promoting TAM polarization toward the pro-tumor M2 phenotype. M2 macrophages secrete immunosuppressive cytokines like IL-10 and transforming growth factor-β (TGF-β), which significantly inhibit anti-tumor immune responses, facilitating tumor immune evasion and growth [62] (Fig. 2). This crosstalk between Nrf2 and NF-κB signaling plays a crucial role in maintaining cellular redox homeostasis and inflammatory responses. Thus, phospholipid peroxidation products establish a complex vicious cycle between inflammation and oxidative stress, whose mechanisms in various diseases warrant further investigation. Future research should focus on developing intervention strategies to disrupt this cycle, offering new therapeutic directions for inflammation- and oxidative stress-related diseases.

3.3. Phospholipid-driven nutrient competition intensifies metabolic battle in the TME

Within the TME, intense competition for nutrients exists between tumor cells and immune cells, representing one of the key mechanisms of tumor immune evasion. Tumor cells gain a metabolic advantage through phospholipid metabolic reprogramming and enhanced nutrient uptake, thereby suppressing antitumor immune responses (Fig. 2). The unique composition of the TME, characterized by low nutrient availability and high acidity, promotes competition between tumor cells and immune cells for essential nutrients such as phospholipids, amino acids, and lipids (Fig. 2). The metabolic advantage of tumor cells makes them the "winners" in this competition, prioritizing the depletion of nutrients essential for immune cells. For example, through high lipid demand and phospholipid metabolic reprogramming, tumor cells extensively consume phospholipids and fatty acids in the microenvironment, leading to a significant reduction in phospholipid levels (e.g., decreased PC and PE) in immune cells such as $CD8^+$ T cells, thereby impairing their effector functions [63–65]. Nutritional

competition induces microenvironmental nutrient deprivation and acidosis, further precipitating metabolic dysfunction in immune cells. $CD8^+$ T cells, as primary anti-tumor effector cells, face metabolic challenges in the TME including glucose deprivation and lipid accumulation. Under conditions of nutritional deprivation, particularly in low-phospholipid environments, metabolic reprogramming occurs, shifting toward fatty acid oxidation (FAO) for energy acquisition. This process suppresses immune effector functions and promotes tumor progression [65,66] (Fig. 2). Furthermore, nutritional competition induces an "immune exhaustion" state in the microenvironment, where immune cells experience functional decline or impaired differentiation due to nutrient scarcity, severely limiting the efficacy of immunotherapies such as immune checkpoint inhibitors. For instance, metabolic competition-induced nutrient deprivation and acidosis not only reduce T cell expansion but also trigger T cell exhaustion, preventing effective tumor clearance by the immune response [67,68] (Fig. 2). Consequently, tumor cells optimize nutrient uptake through phospholipid metabolic reprogramming (e.g., enhanced phospholipid synthesis and uptake) and engage in intense nutrient competition with immune cells, such as $CD8^+$ T cells, within the TME. This competition induces microenvironmental nutrient deprivation, acidosis, and immunosuppression, impairing immune cell effector functions and thereby promoting tumor growth and immune evasion (Fig. 2). Understanding this process facilitates the development of therapeutic strategies targeting phospholipid metabolism, including modulation of phospholipid pathways, to mitigate nutrient competition and restore anti-tumor immunity.

3.4. Phospholipid-epigenetic crosstalk cements the aggressive tumor phenotype

The initiation and progression of cancer are closely linked to epigenetic modifications and metabolic reprogramming, with complex interactive networks between the two that jointly maintain the malignant phenotype of tumor cells. Epigenetic modifications, including DNA methylation, histone modifications, and RNA modifications, regulate gene expression without altering DNA sequences, thereby influencing cell proliferation, differentiation, and survival [69]. These modifications activate oncogenes or suppress tumor suppressor genes, perpetuating the malignant phenotype of tumor cells. Common epigenetic modifications in tumors include histone H3 lysine 36 trimethylation (H3K36me3) and DNA hydroxymethylation, which regulate genes involved in cell proliferation, differentiation, and survival. For example, abnormal DNA methylation and histone modifications are directly associated with tumor initiation and progression, leading to cellular dedifferentiation and metastasis [70–72]. Reprogramming of phospholipid metabolism plays a pivotal role in tumors, as its metabolites can directly influence the activity of epigenetic modification enzymes. For instance, *D*-2-hydroxyglutarate (D-2HG), a metabolite formed during lipid metabolism, inhibits histone demethylases (HDMs), leading to altered histone methylation patterns that promote cellular dedifferentiation, mesenchymal transition, and tumor growth (Fig. 2). This mechanism has been demonstrated in breast cancer oncogene alcohol dehydrogenase iron-containing 1 (ADHFE1)-mediated metabolic reprogramming, significantly enhancing the malignant phenotype of tumor cells [73]. Furthermore, lactate and lactylation can also regulate histone modifications, thereby influencing macrophage polarization and T cell function, ultimately promoting tumor progression and metastasis [74] (Fig. 2).

Epigenetic modifications exert direct regulatory effects on the expression of genes related to lipid metabolism. The histone H3K36me3 transferase SET domain containing 2 (Setd2) serves as a prime example. Setd2 catalyzes H3K36me3 modification in the promoter region of the *Lpcat4* gene in T cells, thereby upregulating *Lpcat4* transcription. LPCAT4-mediated synthesis of PC(16:0,18:2) alleviates endoplasmic reticulum stress and oxidative stress, thereby reducing HIF-1α transcriptional activity. This regulatory cascade ultimately suppresses T helper 17 cell (Th17) differentiation and promotes Treg development [75] (Fig. 2). Tregs exert immunosuppressive effects within the TME. Through phospholipid remodeling mechanisms, Setd2 functions as an epigenetic "brake" in T cell function regulation, thereby shaping an immunosuppressive microenvironment conducive to tumor growth. In summary, a positive feedback loop emerges between phospholipid metabolic reprogramming and epigenetic modifications that supports the malignant tumor phenotype. Phospholipid metabolism furnishes tumor cells with essential energy and molecular precursors, such as membrane phospholipids, thereby supporting their rapid proliferation and adaptation to the TME. Concurrently, epigenetic modifications consolidate malignant phenotypes—including enhanced invasiveness and drug resistance—by stabilizing gene expression patterns that favor tumorigenesis, such as the silencing of tumor suppressors or activation of oncogenes. This intricate interplay not only illuminates core mechanisms of tumorigenesis but also unveils novel therapeutic strategies. Combining drugs targeting lipid metabolic pathways with epigenetic modulators holds promise for improving cancer patient outcomes [76,77].

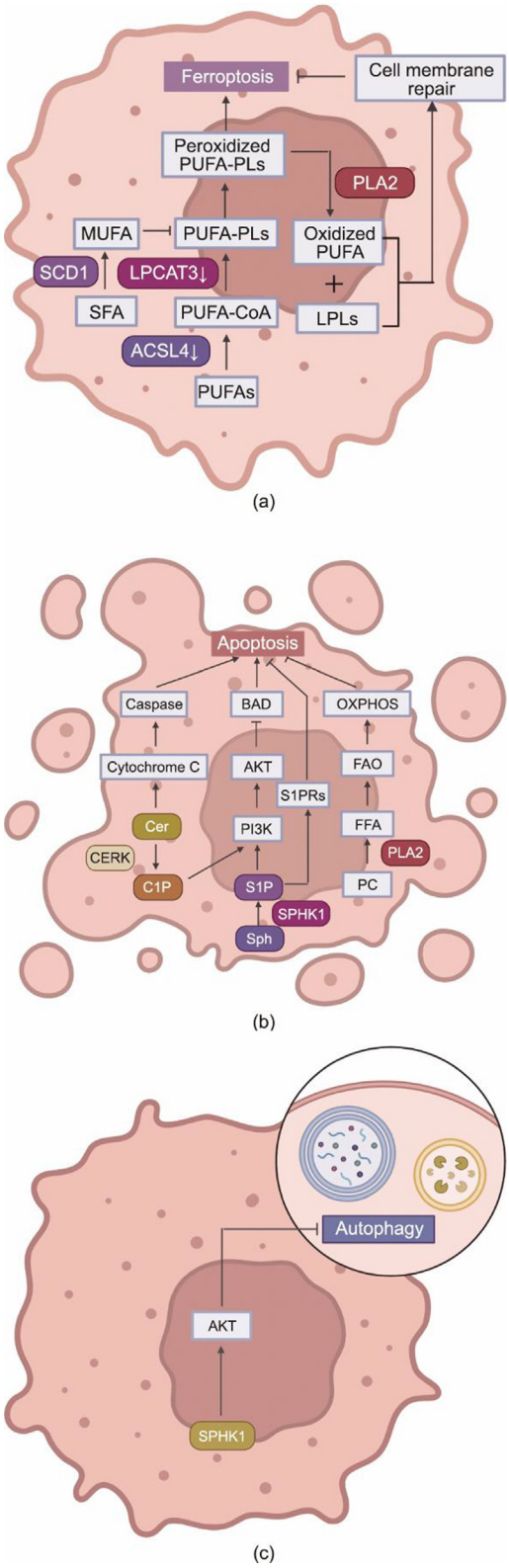
The extensive remodeling of the TME by phospholipid metabolic reprogramming does not merely create a permissive soil for tumor growth; it actively fortifies the tumor against therapeutic attack (Fig. 2). The immunosuppressive niche, sustained oxidative stress, nutrient-deprived conditions, and stabilized aggressive phenotype collectively establish a formidable defensive barrier. Within this self-reinforcing pathological ecosystem, tumor cells leverage the same phospholipid-driven mechanisms to evade various cell death pathways and develop resistance to chemo-, targeted, and immunotherapies. The following section will detail how phospholipid metabolism mediates these key resistance mechanisms, completing the chain from initiation and progression to ultimate therapeutic resilience.

4. Fortifying cellular defenses via phospholipid metabolism-mediated resistance

4.1. Lipid peroxidation-related phospholipid metabolism confers ferroptosis resistance

Lung cancer cells acquire ferroptosis resistance primarily through phospholipid metabolic reprogramming that modulates the content of polyunsaturated fatty acid phospholipids (PUFA-PLs)—the key substrates for lipid peroxidation, which is a core driver of ferroptosis [78,79] (Fig. 3). Two well-supported mechanistic chains underlie this resistance: First, SCD1-mediated fatty acid remodeling reduces membrane PUFA-PL content. SCD1 catalyzes the conversion of saturated fatty acids (SFAs) to monounsaturated fatty acids (MUFAs), which then replace PUFA-PLs in cell membranes. This replacement lowers the substrate pool for lipid peroxidation, thereby directly reducing cellular sensitivity to ferroptosis [80,81] (Fig. 3). Second, downregulation of LPCAT3 suppresses PUFA-PL synthesis. acyl-CoA synthetase long-chain family member 4 (ACSL4) first catalyzes free PUFAs into PUFA-CoAs, and LPCAT3 further mediates the acylation of PUFA-CoAs to generate PUFA-PLs. Downregulation of LPCAT3 directly reduces PUFA-PL production, decreasing lipid peroxidation levels and enhancing ferroptosis resistance [82,83] (Fig. 3). Additionally, PLA2 contributes to ferroptosis resistance by repairing peroxidized membranes. PLA2 specifically hydrolyzes peroxidation-damaged PUFA-PLs, releasing oxidized PUFAs and lysophospholipids (LPLs), which avoids the amplification of lipid peroxidation signals and maintains membrane integrity [84,85] (Fig. 3). These findings are supported by

in vivo studies showing that PLA2 inhibition combined with glutathione peroxidase 4 (GPX4) inhibitors (ferroptosis inducers) significantly enhances antitumor efficacy in lung cancer xenografts [85], confirming the critical role of phospholipid metabolism in regulating ferroptosis resistance.



4.2. Sphingolipid imbalance and PI3K/AKT pathway mediate apoptosis evasion

Phospholipid metabolic reprogramming drives apoptosis resistance in lung cancer mainly through sphingolipid imbalance and abnormal activation of the PI3K/AKT signaling pathway, both of which have sufficient experimental evidence [86,87]. The dynamic equilibrium between Cer and S1P is a core regulatory node of apoptosis (Fig. 3). Chemotherapeutic agents induce apoptosis by promoting Cer accumulation, which disrupts mitochondrial membrane integrity, facilitates cytochrome c release, and activates the caspase cascade [87] (Fig. 3). In contrast, lung cancer cells upregulate SPHK1 to enhance S1P production. S1P binds to its receptors (S1PRs) on the cell membrane, activating the PI3K/AKT signaling pathway to inhibit death receptor-mediated apoptosis [87] (Fig. 3). Ceramidase kinase (CERK)-mediated conversion of Cer to ceramide-1-phosphate (C1P) also activates the PI3K/AKT pathway, further reinforcing apoptosis resistance [87] (Fig. 3). The PI3K/AKT pathway exerts anti-apoptotic effects by suppressing pro-apoptotic proteins. Activated PI3K converts phosphatidylinositol (4,5)-bisphosphate (PIP2) to phosphatidylinositol (3,4,5)-trisphosphate (PIP3), which sustains AKT activation. Activated AKT directly inhibits the activity of BCL2-associated agonist of cell death (BAD) (a pro-apoptotic member of the BCL-2 family), blocking the apoptotic process and conferring significant survival advantages to lung cancer cells [86,88,89] (Fig. 3). Clinically relevant evidence shows that this pathway is frequently activated in inflammation-associated lung cancer, promoting the ITC transition by evading apoptosis [90].

4.3. Phospholipid metabolic reprogramming assists autophagy escape

Phospholipid metabolic reprogramming aids lung cancer autophagy escape mainly via SPHK1-mediated AKT activation, membrane lipid composition alteration, and coordinated autophagy-energy metabolism regulation, with sufficient experimental support [91–97]. Autophagy maintains cellular homeostasis under stress, while lung cancer cells enhance autophagy for metabolic demands; autophagy escape is a key tumor survival strategy [94]. SPHK1, a core phospholipid metabolic enzyme, is upregulated in NSCLC patients and A549 cells. Studies show elevated SPHK1 activates AKT, enhancing NSCLC invasion and migration [96]. As AKT negatively regulates autophagy, its activation suppresses autophagy and promotes survival, forming a key mechanistic chain for autophagy escape (Fig. 3). Notably, direct validation of SPHK1–

Fig. 3. Schematic of phospholipid metabolic reprogramming mediating tumor cell resistance to ferroptosis/apoptosis and autophagy escape. (a) Ferroptosis resistance: Tumor cells limit ferroptosis by reducing membrane PUFA-PLs—key substrates for lipid peroxidation. Two mechanisms: ① SCD1 converts SFA to MUFA, displacing PUFA-PLs to lower their content; ② downregulation of LPCAT3 suppresses PUFA-PL synthesis from PUFA-CoA (generated by ACSL4). Additionally, PLA2 hydrolyzes peroxidized PUFA-PLs to release oxidized PUFAs and LPLs, promoting membrane repair and further inhibiting ferroptosis. (b) Apoptosis resistance: Sphingolipid imbalance drives resistance. Cer induces apoptosis by promoting mitochondrial cytochrome C release and activating the caspase cascade. In contrast, S1P activates the PI3K/AKT pathway via its receptors (S1PRs), inhibiting the pro-apoptotic protein BAD to block apoptosis. PLA2 mobilizes PC to release free fatty acids (FFAs), sustaining FAO and OXPHOS to support tumor cell survival and suppress apoptosis. CERK converts Cer to C1P, which also activates the PI3K/AKT pathway to enhance apoptosis resistance. (c) Autophagy escape: Increased expression of SPHK1 activates the AKT signaling pathway, suppressing autophagy. This blockage enables autophagy escape, promoting tumor cell invasion and migration. Created in BioRender.

AKT on NSCLC autophagy is lacking, as the foundational study focused on invasion/migration [96].

Phospholipid metabolic reprogramming-altered membrane lipid composition directly affects autophagy key steps (autophagosome formation and lysosome fusion) [93]. This disruption of autophagic flux enables tumor cells to escape autophagic degradation. It also cooperates with autophagy to regulate energy metabolism in Kirsten rat sarcoma viral oncogene homolog (KRAS)-driven, liver kinase B1 (LKB1)-deficient lung cancer [91,92]. Autophagy maintains metabolic flexibility via lipid metabolism (critical for tumorigenesis) [91], and LKB1-deficient cells rely heavily on autophagy for metabolic homeostasis [92]. Autophagy deficiency induces energy crisis and cell death via enhanced FAO, but specific phospholipid mediators in this loop remain unclear. Indirectly, it may shape the TME: NSCLC cells secrete insulin-like growth factor 2 to induce fibroblast autophagy, converting them to CAFs that enhance tumor progression [97]. However, phospholipid metabolism's role in regulating such autophagy-inducing factor secretion is unclear.

4.4. Phospholipid metabolism links cell death resistance to therapeutic resistance

Phospholipid metabolic reprogramming drives therapeutic resistance in lung cancer by reinforcing cell death resistance mechanisms (ferroptosis, apoptosis, and autophagy escape) (Fig. 3). For cisplatin resistance in NSCLC, resistant cells exhibit enhanced mitochondrial function (increased proliferator-activated receptor gamma coactivator 1α (PGC-1α) expression) and reduced glycolysis, which is mediated by reactive oxygen species (ROS)-induced phospholipid metabolic remodeling [98]. Inhibiting peroxisome PGC-1α reverses this metabolic shift, restores cisplatin-induced ferroptosis/apoptosis, and enhances drug sensitivity [98].

In EGFR–TKI-resistant NSCLC cells, the mTOR complex 2 (mTORC2) is activated and contributes to metabolic reprogramming [99]. Knockdown of rapamycin-insensitive companion of mTOR (*Rictor*) enhances the spare respiratory capacity and rescues the growth rate of erlotinib-resistant cells during glucose deprivation [99]. Among NSCLCs with activating *EGFR* mutations, gene sets involved in glucose metabolism were enriched in patients with high expression of phosphorylated N-myc downstream regulated gene 1 (*p-NDRG1*; a readout of mTORC2 activity), and overall survival was negatively correlated with *p-NDRG1* levels, confirming the clinical relevance of this mTORC2-mediated metabolic resistance mechanism [99]. Additionally, recent evidence has further expanded the understanding of EGFR–TKI resistance mechanisms: A 2025 study highlights the critical role of LPA-mediated signaling and metabolic reprogramming in resistance to third-generation EGFR–TKIs [100]. Patients who did not respond to treatment exhibited elevated levels of glycerophospholipids and dysregulated LPL metabolism. Metabolomic profiling further revealed increased accumulation of LPLs, including LPA, during the development of resistance. Functional experiments confirmed that LPA promotes cancer cell migration and invasion while attenuating the efficacy of third-generation EGFR–TKIs. Disrupting the LPA–LPA receptor signaling axis reversed LPA-mediated drug resistance. These findings suggest that targeting LPA production or its downstream pathways may offer a novel therapeutic strategy to overcome resistance in *EGFR*-mutant lung cancer.

4.5. Unresolved questions and future directions

Despite significant progress in understanding phospholipid metabolism-mediated cell death resistance, several critical questions remain unresolved: ① Lung cancer subtype-specific regulatory mechanisms are unclear. For example, whether squamous cell carcinoma and adenocarcinoma exhibit distinct phospholipid metabolic patterns in regulating ferroptosis/apoptosis requires further investigation with subtype-specific clinical samples. ② The crosstalk between phospholipid metabolism and multiple cell death modalities is not fully elucidated. How phospholipid metabolic reprogramming coordinately regulates ferroptosis and apoptosis (e.g., whether S1P simultaneously modulates both pathways) lacks systematic studies. ③ Direct clinical evidence is insufficient. Most studies rely on *in vitro* and animal models, and the correlation between phospholipid metabolic markers (e.g., LPCAT3 and SPHK1) and cell death resistance in lung cancer patients needs large-cohort validation. ④ Therapeutic translation challenges persist. Although targeting phospholipid metabolism shows promise, off-target effects of lipid metabolic inhibitors (e.g., PLA2 inhibitors) and their combination strategies with existing therapies require further optimization.

4.6. Core regulatory nodes of phospholipid metabolism across the initiation–progression–resistance axis

A principal thesis of our review is that phospholipid metabolic reprogramming is not a stage-specific event but a continuous, driving force throughout lung cancer pathogenesis, from chronic inflammation to therapy-refractory disease. A critical corollary is the identification of specific enzymes, metabolites, and pathways that function as common regulatory nodes, integrating protumorigenic signals and executing core functions across the initiation, progression, and therapeutic resistance phases. Elucidating these pivotal hubs is essential for comprehending the interconnected "full-chain" regulatory network and for devising coherent therapeutic strategies. Herein, we summarize the common regulatory nodes of phospholipid metabolism in the "full-chain" to help readers better understand the complete regulatory network.

4.6.1. The SPHK1/S1P axis

The SPHK1/S1P axis serves as a paradigm of a pleiotropic lipid signaling module [42–44]. In initiation and progression, SPHK1 overexpression elevates intracellular and extracellular S1P, which drives tumor cell proliferation and survival via activation of PI3K/AKT, STAT3, and Ras/ERK pathways, while simultaneously fueling inflammatory signaling through NF-κB activation [42,44]. During microenvironment remodeling, S1P acts as a potent chemotactic and instructional lipid mediator, promoting angiogenesis, recruiting immune cells, and contributing to an immunosuppressive niche [33,34]. In therapeutic resistance, elevated SPHK1/S1P is clinically correlated with resistance to EGFR–TKIs and chemotherapy [45,46]. Mechanistically, it confers resistance to apoptosis and may facilitate autophagy dysregulation [87,96], while its inhibition can synergize with immune checkpoint blockade [46].

4.6.2. The PI3K/AKT/mTOR signaling network

This central signaling hub constitutes a common conduit for diverse phospholipid-derived signals and a master regulator of lipid metabolism [45,86]. During initiation/progression, it is activated by phospholipid-coupled receptors (e.g., S1PR and LPAR), promoting growth and survival, and inhibiting apoptosis [42,43]. In the context of microenvironment remodeling, this network modulates immune cell function and metabolic competition [64,65]. For therapeutic resistance, the mTORC2 emerges as particularly critical, driving the metabolic reprogramming that underlies EGFR–TKI resistance [99]. Sustained AKT activation downstream of PI3K is a central mechanism of apoptosis evasion and broad-spectrum drug resistance [86,88,89].

4.6.3. SCD1

SCD1, a key enzyme in fatty acid desaturation, governs membrane phospholipid composition and fluidity [45,80]. Its role in initiation/progression involves converting SFAs to MUFAs, a shift that supports membrane biosynthesis for rapid proliferation [45,80]. In therapeutic resistance, SCD1 activity critically influences cell fate by modulating susceptibility to ferroptosis. By increasing the MUFA/SFA ratio in membrane phospholipids, SCD1 reduces the incorporation of PUFAs, thereby limiting substrates for lipid peroxidation and enhancing cellular defense against this form of iron-dependent cell death [80,81].

4.6.4. PLA2 family

PLA2 enzymes initiate the cascade of bioactive lipid mediator generation by hydrolyzing membrane phospholipids [35,36]. In initiation/progression, PLA2-mediated release of AA provides the substrate for synthesizing pro-inflammatory and immunosuppressive eicosanoids (e.g., PGE2 and LTB4), which fuel chronic inflammation and early immune evasion [36,37]. These mediators are direct agents of microenvironment remodeling, shaping the immune landscape by regulating DC, T cell, and neutrophil function [37,38]. In therapeutic resistance, PLA2 plays a dual role: it can repair peroxidized membrane phospholipids to limit ferroptosis propagation [84,85], and its signaling derivatives contribute to apoptosis evasion pathways [101].

4.6.5. The epigenetic–lipid metabolism interface

A bidirectional crosstalk exists between phospholipid metabolism and epigenetic regulation [73–75]. During initiation/progression, oncometabolites derived from altered cellular metabolism, including lipid metabolic pathways (e.g., D-2HG), can directly inhibit epigenetic modifiers, altering histone methylation landscapes to promote a malignant phenotype [73]. Conversely, epigenetic regulators control the expression of key phospholipid metabolic enzymes [75]. This interface is pivotal for microenvironment remodeling and resistance, as exemplified by the histone methyltransferase Setd2 regulating LPCAT4 expression in T cells to promote an immunosuppressive Treg phenotype, thereby cementing a pro-tumorigenic microenvironment [75].

Notably, the functional implementation of these core regulatory nodes is driven by key phospholipid metabolic enzymes. To systematically integrate the core biological functions of these key enzymes, their specific roles in the lung cancer initiation–progression–resistance axis, as well as the reported representative inhibitors (including evidence levels), and intuitively present the core value of enzyme-level regulation and its clinical transformation potential, we present an integrated table below (Table 1 [35–38,41,43,45,46,55,80,81,84–87,101–111]).

Collectively, the above sections (Sections 2–4) have elaborated on the critical roles of phospholipid metabolism in lung cancer initiation, progression, and cellular defense reinforcement, which are predominantly mediated by three core metabolic pathways. To systematically clarify the key links (synthesis, remodeling, degradation, and signaling output) of each pathway and their synergistic mechanism in supporting the proposed "phospholipid metabolic switch," the following integrated comparative table is supplemented (Table 2 [42,43,55,60–62,80–85,87–89,96,98,99]). As summarized in Table 2, the sphingolipid balance pathway, PLA2-related pathway, and PUFA-PL metabolic pathway synergistically support the "phospholipid metabolic switch" through complementary metabolic links and non-overlapping functional outputs (apoptosis/autophagy escape, immunosuppression, ferroptosis resistance, and therapy resistance), forming a core regulatory network driving lung cancer progression.

In summary, the pathogenesis of lung cancer, from inflammatory inception to therapy-refractory progression, is orchestrated by a dynamic and reinforcing network of core phospholipid metabolic nodes. Key hubs include the SPHK1/S1P axis, the PI3K/AKT/mTOR network (with distinct roles for mTORC2), SCD1, the PLA2 family, and the epigenetic–lipid interface. These nodes collectively transduce inflammatory and oncogenic signals into sustained proliferative, survival, and adaptive advantages. They empower tumor cells to autonomously proliferate, instruct and reshape their microenvironment, and ultimately deploy robust defenses against therapeutic assault. Consequently, these regulatory hubs represent promising targets for strategic intervention. Their interconnectedness suggests that combination therapies co-targeting these nodes may be particularly effective in disrupting the resilient "initiation–progression–resistance" cascade in lung cancer.

5. Translating phospholipid metabolism into clinical strategies across cancers

5.1. Phospholipid metabolites as biomarkers

5.1.1. Diagnostic biomarkers

As the leading cause of cancer-related deaths worldwide, early diagnosis of lung cancer has long been a challenge [112]. Traditionally, lung cancer screening relies on LDCT screening, but it has drawbacks such as high false-positive rates, radiation exposure, and relatively high costs [113]. With the rapid development of high-throughput technologies in recent years, biomarkers based on phospholipid metabolism have attracted increasing attention in lung cancer screening, among which the glycerophospholipid metabolic pathway is particularly critical. For example, a study successfully identified nine lipid molecules with diagnostic potential from serum samples using liquid chromatography–mass spectrometry (LC–MS), including LPC, PC, and triglycerides. These lipids have been confirmed as key features for early cancer detection. The LC–MS-based targeted detection method developed based on these lipid signatures achieved 100% specificity in an independent validation cohort, and demonstrated high diagnostic sensitivity and specificity in both hospital-based lung cancer screening cohorts and prospective clinical cohorts [114] (Fig. 4). This non-invasive, high-precision, and specific detection method is expected to optimize existing lung cancer screening strategies, especially for large-scale screening of high-risk populations.

5.1.2. Prognostic biomarkers

Specific phospholipid metabolic patterns are closely associated with the prognosis of lung cancer patients. High expression of ACSL3 and low expression of acyl-CoA cholesterol acyltransferase 1 (ACAT1) have been validated as independent prognostic factors for lung adenocarcinoma [115] (Fig. 4). Mechanistically, this signature correlates with TME remodeling, DNA methylation status, and ferroptosis sensitivity, which collectively influence tumor progression and therapeutic response [115]. Therefore, strategies targeting the regulation of ACAT1 and ACSL3 may bring new breakthroughs in immunotherapy for lung adenocarcinoma [115]. These biomarkers enable risk stratification of patients and provide a basis for personalized treatment decision-making.

5.2. Early intervention to block the ITC pathway in precancerous lesions

5.2.1. Intervention by targeting key enzymes

Phospholipid metabolism intervention has emerged as a key strategy for preventing the progression of precancerous lesions to malignant tumors in lung cancer and pan-cancers. Its core

Table 1
Key phospholipid metabolic enzymes, core roles, and representative inhibitors.

Key enzyme	Core roles	Representative inhibitors: evidence level
Choline kinase α (ChoKα)	A key rate-limiting enzyme in PC biosynthesis; promotes tumor cell proliferation, invasion, and drug resistance; synergizes with PLD1 to regulate the choline–phospholipid metabolic cycle [102,103]	TCD-717 (also known as RSM-932A): *in vitro*, *in vivo*, patient data [104,105]
PLD1	Catalyzes the conversion of PC to phosphatidic acid (PA); regulates oncogenic signaling pathways such as Wingless-related integration site (Wnt)/β-catenin and NF-κB; participates in inflammatory microenvironment remodeling and ITC transition [103,106,107]	VU0155069: *in vitro*, *in vivo* [106,107]
Glycerophosphodiester phosphodiesterase 5/6 (GDPD5/6)	Regulates choline–phospholipid metabolism; promotes tumor cell migration and invasion [108,109]	None, validated by gene silencing (small interfering RNA) [108]
SPHK1	Catalyzes the conversion of sphingosine to S1P; regulates the "Cer (pro-apoptotic)–S1P (pro-survival)" balance; promotes tumor proliferation, immune microenvironment remodeling, and EGFR–TKI resistance [43,46,86,87]	PF543: *in vitro*, *in vivo* [86]
SMase	Hydrolyzes SM to generate pro-apoptotic Cer; activates the mitochondrial apoptotic pathway (BCL2/BAX), thereby inhibiting tumor survival and regulating sphingolipid metabolic balance [41,110]	None (research focuses on activators/mimetics) [41,110]
Acid ceramidase	Degrades Cer to attenuate apoptotic signaling; maintains tumor cell survival and drug resistance [110]	B13, LCL385: *in vitro*, *in vivo* [110]
Neutral/alkaline ceramidase	Degrades Cer to promote tumor cell survival; participates in sphingolipid metabolic reprogramming and therapeutic resistance [110]	DeMAPP: *in vitro* [110]
LPCAT2	Catalyzes the biosynthesis of PAF; belongs to the "phospholipid metabolic switch" inflammation–immune remodeling axis; promotes immunosuppressive TME by regulating PAF production; a potential target for reversing tumor immunosuppression [55,111]	*N*-phenylmaleimide derivatives: *in vitro*, *in vivo* [111]
SCD1	Catalyzes the conversion of SFAs to MUFAs; regulates membrane phospholipid composition and mediates tumor cell ferroptosis resistance and proliferation [45,80,81]	A939572: *in vitro*, *in vivo*; CVT-11127: *in vitro*; g-PPT: *in vitro*, *in vivo* [45,81]
PLA2 family	Hydrolyzes membrane phospholipids to release AA; promotes the production of pro-inflammatory lipid mediators such as PGE2 and LTB4; participates in ITC transition, immune microenvironment remodeling, and ferroptosis resistance [35–38,84,85,101]	Varespladib (LY315920): *in vitro*, *in vivo*, patient data [35]; Darapladib: *in vitro*, *in vivo*, patient data [85]

Evidence level definitions: *in vitro* = experiments using cell lines or biochemical assays; *in vivo* = experiments using animal models (xenografts, spontaneous tumor models, etc.); patient data = clinical evidence including enzyme expression patterns, correlation with prognosis, or pathological features in human tumor samples.

principle lies in effectively blocking the central pathway of "inflammation-driven progression of precancerous lesions" by targeting key enzymes and regulating lipid balance [116]. Studies have shown that PLD is a critical intersection of phospholipid metabolism and inflammatory signaling. PLD activity is significantly elevated in precancerous lesions such as lung epithelial dysplasia and colorectal adenoma. By catalyzing the conversion of PC to phosphatidic acid (PA), PLD activates downstream key inflammatory signaling pathways including NF-κB and HIF-1α. This process promotes the infiltration of TAMs and neutrophils, while increasing the secretion of inflammatory cytokines such as IL-1β and TNF-α, thereby establishing a positive feedback loop of "persistent inflammatory activation → abnormal proliferation of precancerous cells → malignant progression" [117,118]. Therefore, PLD is regarded as a highly promising intervention target. For example, the PLD inhibitor 5-fluoro-2-indolyl deschlorohalopemide (FIPI) can inhibit PLD-mediated cytoskeletal reorganization and neutrophil chemotaxis, effectively reducing inflammatory cell infiltration in precancerous lesion models, thus verifying its intervention efficacy [119] (Fig. 4). Additionally, PLD1 inhibitors such as VU0155069 suppress Wingless-related integration site (Wnt)/β-catenin signaling in cancer-initiating cells, attenuating intestinal tumorigenesis and holding potential for extrapolation to lung cancer precancerous intervention [106,107].

5.2.2. Regulation of lipid balance

Lipid metabolism imbalance constitutes the metabolic basis of the ITC pathway. The core of intervention lies in restoring the pro-inflammatory–anti-inflammatory lipid homeostasis, among which the sphingosine metabolic pathway is a key regulatory node. Inducing apoptosis of precancerous cells and reducing the secretion of inflammatory cytokines can be achieved by increasing the production of pro-apoptotic Cer or inhibiting the synthesis of pro-survival S1P (e.g., by inhibiting SPHK1) (Fig. 4). For example, in preclinical xenograft models of NSCLC, PF-543 targeting SPHK1 significantly inhibited cell cycle progression and tumor growth [86].

5.2.3. Dietary intervention

Dietary lipid components also directly affect phospholipid metabolism in the body, making dietary intervention an important strategy for regulating the progression of inflammation to cancer. Studies have revealed that dietary SFAs (such as palmitic acid and stearic acid) significantly promote macrophage and neutrophil-mediated pulmonary inflammatory responses by activating signaling pathways including the NLRP3 inflammasome, NF-κB, and TLR4, thereby creating a microenvironment conducive to the progression of precancerous lesions [120–122] (Fig. 4). Animal models have confirmed that diets rich in SFAs increase the incidence of hepatocellular carcinoma and promote the expression of hepatic inflammatory mediators, such as TNF and IL-1 [109]. Therefore, modifying dietary composition to reduce the intake of pro-inflammatory lipids is crucial for regulating metabolic pathways at the source and inhibiting precancerous lesions.

5.3. Inhibitors targeting key enzymes in phospholipid metabolic reprogramming

5.3.1. Inhibitors of key enzymes in the choline–phospholipid axis

The development of inhibitors targeting key phospholipid metabolic enzymes has emerged as a crucial strategy for targeted therapy, particularly in oncology and inflammatory diseases. In cancer research, multiple phospholipid metabolic enzymes have been validated as potential therapeutic targets due to their dysregulation in malignant progression. For instance, choline kinase α (ChoKα) is a key enzyme in phospholipid metabolism that plays

Table 2
Integrated comparative table of core pathways supporting the "phospholipid metabolic switch."

Core pathway	Synthesis	Remodeling	Degradation	Signaling output/function
Sphingolipid balance pathway	SPHK1 catalyzes Sph to S1P [87]; CERK catalyzes Cer to C1P [87]	No obvious remodeling; the core is the dynamic balance regulation between pro-apoptotic molecules (Cer) and pro-tumor molecules (S1P/C1P) [87]	A-/N-/B-SMase hydrolyze SM to generate Cer [87]	Cer activates the mitochondrial apoptosis pathway: destroys membrane integrity, releases cytochrome C, and activates the caspase cascade [87]; S1P binds to S1PR1–5 to activate Ras/ERK, PI3K/AKT, and NF-κB/STAT3 pathways [42,43,87]; S1P/C1P activate the PI3K/AKT pathway to inhibit the pro-apoptotic protein BAD [87–89]; the SPHK1–AKT–mTOR pathway mediates autophagy escape [96]
PLA2-related pathway	No direct phospholipid synthesis process; relies on membrane phospholipids (e.g., PC) as core substrates [55,84]	Hydrolyzes membrane phospholipids to generate LPLs (e.g., LPC) and FFAs (e.g., AA), remodeling the lipid composition of the cell membrane [55,84]	Hydrolyzes peroxidized PUFA-PLs to release oxidized PUFAs [84,85]; mobilizes PC to release FFAs [55]; generates LPC from membrane phospholipids [55]; releases PAF from PtdCho [55]	AA is metabolized by COX-2 to generate PGE2 (induces DCs to secrete IL-10, promotes Treg differentiation to achieve immunosuppression) and by 5-/12-LOX to generate LTB4 (enhances neutrophil infiltration, amplifies inflammation, and mediates chemoresistance) [55]; LPC is converted to LPA by ATX, activates the Rho–ROCK pathway to upregulate MMP2/9, and promotes EMT and invasion [55]; FFAs support tumor cell FAO/OXPHOS energy metabolism [55]; hydrolyzes peroxidized PUFA-PLs to repair membrane damage and enhance ferroptosis resistance [84,85]; enhances cell death resistance to drive cisplatin and EGFR–TKI resistance [98,99]
PUFA-PL metabolic pathway	ACSL4 catalyzes free PUFAs to generate PUFA-CoA [82]; LPCAT3 mediates the acylation of PUFA-CoA to generate PUFA-PLs; downregulation of LPCAT3 can directly inhibit PUFA-PL synthesis [82,83]	SCD1 catalyzes SFAs to MUFAs, which replace PUFA-PLs on the cell membrane and remodel the membrane fatty acid composition [80,81]	PLA2 hydrolyzes peroxidized PUFA-PLs (clearing damaged phospholipids) [84,85]; PUFA-PLs undergo peroxidation to generate peroxidation products such as 4-HNE and MDA [55,60–62]	PLA2 hydrolyzes peroxidized PUFA-PLs (clearing damaged phospholipids) [84,85]; PUFA-PLs undergo peroxidation to generate peroxidation products such as 4-HNE and MDA [55,60–62]

This table is summarized based on the core pathways in Sections 2–4 of the manuscript, aiming to clarify the key links of "synthesis–remodeling–degradation–signaling output" of each pathway and their synergistic role in supporting the "phospholipid metabolic switch" (directional transformation from physiological phospholipid metabolism to pathological reprogramming).

a central role in PC biosynthesis. ChoKα is overexpressed in various human cancers, and its activity is significantly associated with malignant phenotypes, drug resistance, metastatic potential, as well as tumor progression and metastasis [102,123]. Elevated ChoKα expression has been detected in cancers such as breast cancer, lung cancer, colorectal cancer, prostate cancer, ovarian cancer, and liver cancer [105]. ChoKα inhibitors exert anti-proliferative effects on cancer cells by downregulating phosphocholine (PCho) levels. Specifically, the ChoKα inhibitor TCD-717 (also known as RSM-932A) has demonstrated potent anti-tumor activity in both *in vitro* and *in vivo* studies. This inhibitor significantly reduces intracellular PCho and PC levels in tumor cells, thereby altering the phospholipid composition of cell membranes, inducing apoptosis, and ultimately inhibiting tumor cell proliferation [104,105] (Fig. 4). PLD1 is another critical enzyme in phospholipid metabolism that catalyzes the conversion of PC to PA—a key secondary messenger in multiple cellular signaling pathways [103]. Studies on breast cancer have revealed that PLD1 and ChoKα exhibit functional synergy in the choline–phospholipid metabolic pathway, jointly regulating the PC synthesis and catabolism cycle in tumor cells, which indicates that PLD1 may also serve as a potential therapeutic target for cancer treatment. The selective PLD1 inhibitor VU0155069 blocks PLD1-mediated PA production, thereby inhibiting oncogenic signaling pathways such as Wnt/β-catenin and NF-κB [106] (Fig. 4). In adenomatous polyposis coli multiple intestinal neoplasia heterozygous mice ($Apc^{Min/+}$) and azoxymethane/dextran sulfate sodium (AOM/DSS) mouse models, this inhibitor exhibited efficacy in suppressing intestinal tumorigenesis, with mechanisms closely related to regulating phospholipid metabolism, inhibiting inflammatory signaling, and remodeling the immune microenvironment [107]. Members of the glycerophosphodiester phosphodiesterase (GDPD) family, such as GDPD5 and GDPD6, play key roles in choline–phospholipid metabolism. In breast cancer cells, silencing the *GDPD5* or *GDPD6* gene increases glycerophosphocholine (GPC) levels, thereby inhibiting cell migration and invasion. Notably, *GDPD5* silencing exhibits a particularly significant inhibitory effect on cell proliferation and invasion, indicating that GDPD5 and GDPD6 may serve as novel molecular targets for breast cancer therapy [108] (Fig. 4).

5.3.2. Inhibitors of key enzymes in sphingolipid metabolism

Sphingolipid metabolic homeostasis is tightly regulated by a cascade of key enzymes, and dysregulation of this pathway is not only a core feature of lung cancer progression [41–43] but also a critical mechanism underlying therapeutic resistance (e.g., resistance to EGFR–TKIs) [45,46]. Pharmacological modulation of sphingolipid metabolism via specific inhibitors can impact key

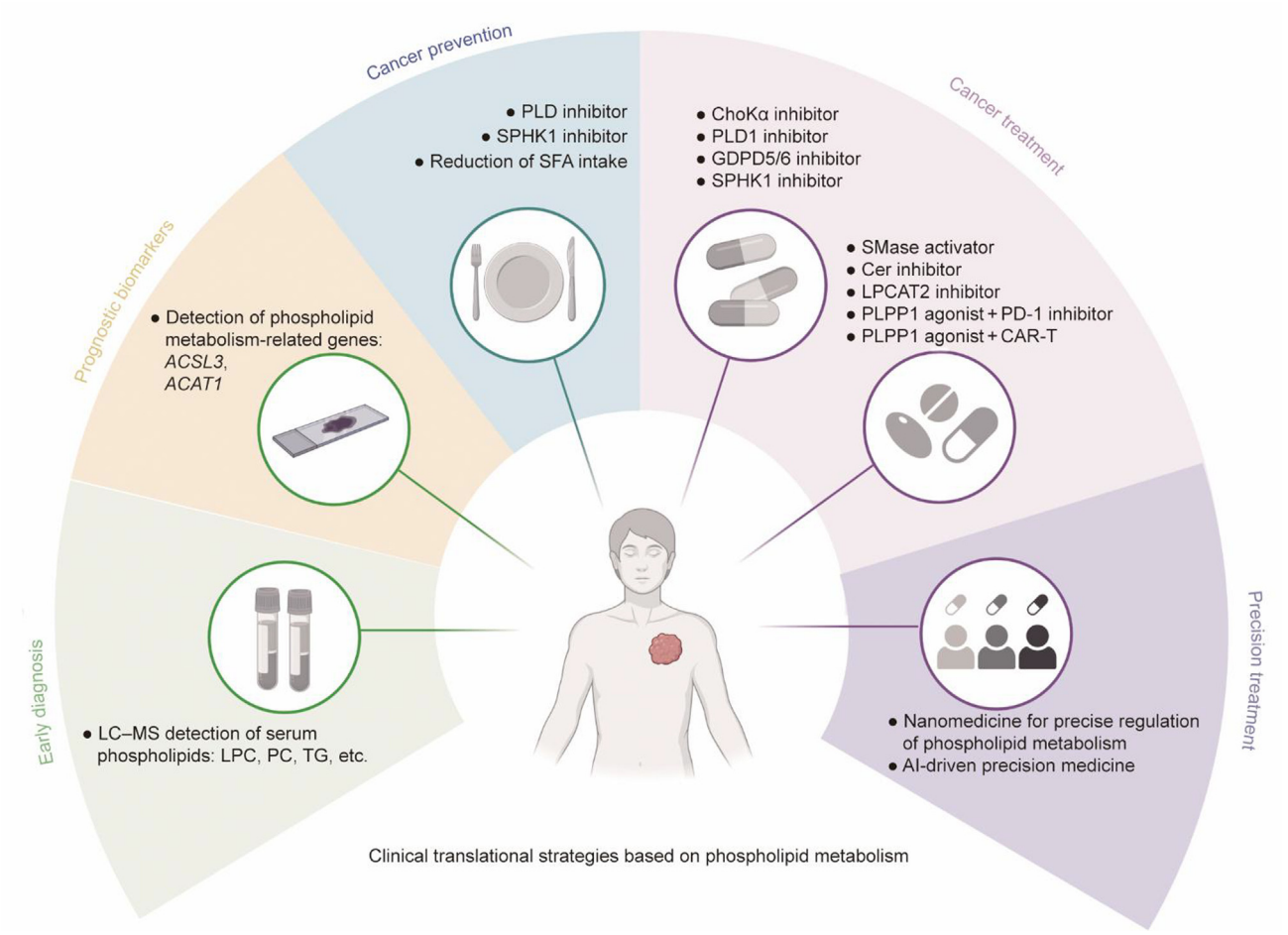


Fig. 4. Schematic of phospholipid metabolism-based clinical translational strategies for cancer. This schematic highlights the core role of phospholipid metabolism in cancer pathogenesis and its translational potential across early detection, prevention, targeted therapies, and precision regimens. Early diagnosis: Non-invasive detection of serum phospholipids (e.g., LPC, PC, and triacylglycerol (TG)) via targeted LC–MS, enabling high-specificity screening for early-stage cancer. Prognostic biomarkers: Identification of phospholipid metabolism-related genes (e.g., *ACSL3* and *ACAT1*) in tumor tissues. These genes act as independent prognostic indicators (e.g., in lung adenocarcinoma), correlating with TME remodeling, DNA methylation status, and ferroptosis sensitivity to guide patient risk stratification. Cancer prevention: Two strategies block the ITC cascade: ① reduction of SFA intake to mitigate pro-inflammatory lipid-driven signaling; ② targeting key enzymes (e.g., PLD inhibitors and SPHK1 inhibitors) to suppress pro-tumor lipid mediator production (e.g., PLD-mediated PA synthesis and SPHK1-driven S1P generation), thereby inhibiting inflammation-fueled premalignant progression. Cancer treatment: ① Inhibitors targeting core phospholipid metabolic enzymes (e.g., ChoKα inhibitor TCD-717, PLD1 inhibitor VU0155069, GDPD5/6 inhibitors, SPHK1 inhibitors, Cer inhibitors, and LPCAT2 inhibitors) disrupt membrane phospholipid homeostasis and downstream oncogenic pathways (e.g., Wnt/β-catenin and NF-κB); ② combination therapies: PLPP1 agonists paired with PD-1 inhibitors or chimeric antigen receptor T (CAR-T) therapy to restore T cell metabolic fitness. Precision treatment: Personalized interventions leverage ① nanomedicine for precise regulation of phospholipid metabolism to target tumor-specific metabolic vulnerabilities; ② artificial intelligence (AI)-driven precision medicine to tailor regimens based on individual phospholipid metabolic profiles, optimizing therapeutic efficacy. Created in BioRender.

pathological processes in tumor cells, including growth, death, and autophagy [110]. Therefore, targeting core enzymes in sphingolipid metabolism has emerged as a rational and highly promising therapeutic strategy.

SPHK1, which catalyzes the conversion of sphingosine to S1P, is frequently overexpressed in NSCLC and correlates with poor prognosis [43,46]. Targeting SPHK1 (e.g., with the inhibitor PF-543) exerts anti-tumor effects by disrupting the balance between pro-survival S1P and pro-apoptotic Cer (Fig. 4). The mechanism involves primarily reducing the production of the pro-survival signaling lipid S1P, and concomitantly, by alleviating S1P-mediated suppression of apoptotic signaling, facilitating the restoration of the mitochondrial apoptosis pathway mediated by Cer [86,87]. Specifically, in NSCLC cell lines and xenograft models, PF-543 treatment downregulates the activity of core pathways driving tumor proliferation and invasion—including Ras/ERK and PI3K/AKT—while enhancing cancer cell sensitivity to chemotherapy [86]. Beyond lung cancer, targeting SPHK1 has shown efficacy in acute myeloid leukemia by inducing myeloid cell leukemia 1 (MCL1)-dependent cell death [124], further supporting the translational potential of SPHK1-targeted strategies across cancer types (Fig. 4).

In addition to directly targeting upstream nodes of S1P synthesis, intervening in downstream components of Cer metabolism to disrupt the "Cer (pro-apoptotic)–S1P (pro-survival)" balance axis also serves as a crucial strategy for impairing sphingolipid homeostasis in tumor cells [110,125]. SMase, which hydrolyzes SM to generate pro-apoptotic Cer, is a potential therapeutic target [41]. SMase activators or mimetics designed to restore intracellular Cer levels and reactivate apoptotic pathways in tumor cells represent an ongoing exploratory strategy [41,110] (Fig. 4). On the other hand, ceramidases attenuate apoptotic signaling by degrading Cer; their inhibitors, such as acid ceramidase inhibitors B13 and LCL385, and neutral/alkaline ceramidase inhibitor D-e-MAPP, have demonstrated synergistic potential with SPHK1 inhibitors in preclinical studies [110]. These strategies target distinct nodes of the sphingolipid pathway and are expected to maximize therapeutic efficacy.

5.3.3. Inhibitors of PAF biosynthetic enzymes

In addition to targeting core nodes of choline–phospholipid metabolism to disrupt the basic metabolism of tumor cells, intervening in specific pro-inflammatory lipid mediators produced downstream—such as PAF—represents another complementary strategy for regulating the tumor inflammatory microenvironment. The development of specific inhibitors against PAF biosynthetic enzymes (e.g., LPCAT2), including *N*-phenylmaleimide derivatives, has opened new therapeutic avenues for treating various life-threatening inflammatory diseases driven by PAF, such as anaphylaxis, sepsis, acute respiratory distress syndrome, and bronchial asthma [111]. Notably, as a lipid mediator secreted by tumor cells, PAF broadly inhibits anti-tumor immunity by binding to receptors on immune cells [55]. Therefore, extending strategies targeting PAF synthesis (e.g., LPCAT2 inhibitors) to reverse the tumor immunosuppressive microenvironment represents an emerging research direction with substantial translational potential (Fig. 4).

5.3.4. Targeting phospholipid phosphatase 1 (PLPP1): A novel link between phospholipid metabolism and immunotherapy

In addition to the aforementioned enzymes, recent studies have identified PLPP1—a key enzyme regulating phospholipid metabolism in immune cells—as a novel target linking phospholipid metabolism to immunotherapy response [64]. Specifically, $CD8^+$ T cells within the TME of lung cancer exhibit reduced levels of PC and PE compared to their circulating counterparts, which is associated with decreased PLPP1 expression (PLPP1 catalyzes the synthesis of PC and PE in T cells). T cell-specific deletion of *PLPP1* compromises anti-tumor immunity by promoting ferroptosis and cell death in $CD8^+$ T cells; moreover, unsaturated fatty acids abundant in the TME can selectively induce ferroptosis in PLPP1-deficient $CD8^+$ T cells. Mechanistically, PD-1 signaling in $CD8^+$ T cells recruits the transcription factor GATA binding protein 1 (GATA1) to the *PLPP1* promoter, leading to transcriptional repression of *PLPP1*. While PD-1 blockade upregulates PLPP1 expression and restores anti-tumor function in $CD8^+$ T cells, it fails to rescue the dysfunction of PLPP1-deficient populations. These findings highlight that PD-1-mediated regulation of phospholipid metabolism (via PLPP1) in $CD8^+$ T cells plays a critical role in shaping T cell fitness and response to immunotherapy, suggesting that targeting PLPP1 or its downstream phospholipid metabolic pathways may synergize with immune checkpoint inhibitors to enhance anti-tumor efficacy (Fig. 4).

6. Future horizons: From spatial decoding to precision intervention

Phospholipid metabolic serves as a pivotal "metabolic switch" linking chronic inflammation to lung cancer progression, but its spatial heterogeneity and dynamic evolution during the inflammation-cancer transition remain poorly understood—these unresolved questions hinder the translation of mechanistic insights into clinical applications. To address this, future research needs to rely on technological innovation, advanced model systems, and translational breakthroughs. This section focuses on three core directions, forming a coherent narrative from "decoding mechanisms" to "validating functions" to "clinical intervention." The core future research directions of phospholipid metabolism in lung cancer, including technological innovation, advanced model systems, and translational therapeutic breakthroughs, are systematically summarized in Fig. 5.

6.1. Technological advances: Decoding spatial and functional heterogeneity

A fundamental challenge in current research on phospholipid metabolism in lung cancer lies in deciphering its heterogeneity—specifically, unveiling the spatial organizational principles of different phospholipid molecules within the tumor ecosystem and tracking their dynamic evolution throughout the continuum from chronic inflammation to malignant transformation. Traditional lipidomics methods based on tissue homogenization struggle to capture metabolic differences at this microregional scale, constituting a major bottleneck for in-depth mechanistic understanding. In recent years, breakthroughs in spatial resolution technologies, particularly the rise of spatial lipidomics and multimodal imaging, are fundamentally changing this landscape. These technologies enable the visualization and quantitative analysis of the spatial distribution and chemical states of phospholipid metabolism within tumors and TME at near-cellular to subcellular resolution, providing unprecedented powerful tools to directly address the aforementioned core questions. Below is a detailed analysis of their characteristics:

6.1.1. Spatial lipidomics

With continuous technological advancements, spatial lipidomics, as an emerging technique, offers unprecedented avenues for investigating micro-regional metabolic heterogeneity in phospholipid metabolism during lung cancer. Unlike traditional lipidomics based on tissue homogenization, which obscures spatial information, techniques such as mass spectrometry imaging (MSI) and laser microdissection-coupled platforms enable the direct mapping of lipid distributions within tissue architectures [126,127] (Fig. 5). This capability (its core advantage) has revealed striking compartmentalization; for instance, polyunsaturated PE (18:0/22:6) is enriched in airways while saturated phosphatidylglycerol (PG(16:0/16:0)) dominates alveolar regions in lung tissues [128]. Furthermore, integration with transcriptomics and proteomics via multi-omics platforms can correlate spatial lipid patterns with molecular phenotypes, providing a systems-level understanding of TME heterogeneity [126,129].

However, the translation of spatial lipidomics into routine research and clinical application is constrained by several significant technical challenges. First, detection sensitivity for low-abundance, yet biologically critical lipid mediators remains a hurdle. For example, key signaling phospholipids like S1P and LPA often exist at low concentrations in tissues. In lung studies, detecting these molecules via techniques like matrix-assisted laser desorption/ionization (MALDI)-MSI without advanced signal amplification (e.g., artificial intelligence (AI)-assisted methods) can be difficult [128] (Fig. 5). While novel approaches like tissue-expansion mass-spectrometry imaging (TEMI) promise enhanced sensitivity, they are not yet widely adopted [129]. Second, standardization of sample processing is a major source of variability. The choice of tissue preservation method critically impacts lipid recovery. A quantitative study demonstrated that PC recovery from formalin-fixed, paraffin-embedded (FFPE) lung cancer tissues was 42% lower compared to fresh-frozen samples [126]. Furthermore, inconsistencies in matrix application for MSI can lead to coefficient of variation values as high as 28% in phospholipid signals [130]. Third, there is a fundamental trade-off between spatial resolution and analytical coverage. Achieving high resolution (e.g., 5 μm) to resolve cellular heterogeneity comes at the cost of prolonged acquisition times and limited field-of-view. Analyzing a 1 cm^2 lung tumor section at such resolution can exceed 20 h and may cover only 60% of the region of interest, potentially missing critical areas like micro-metastatic niches [127]. This limits its feasibility for large-scale clinical assessments, such as comprehensive preoperative staging [131]. Finally, data analysis presents considerable complexity. The integration of spatial lipidomic data with other omics layers (e.g., transcriptomics) requires sophisticated, often custom bioinformatics pipelines and can take expert teams weeks to complete for robust association analysis [132]. The compatibility

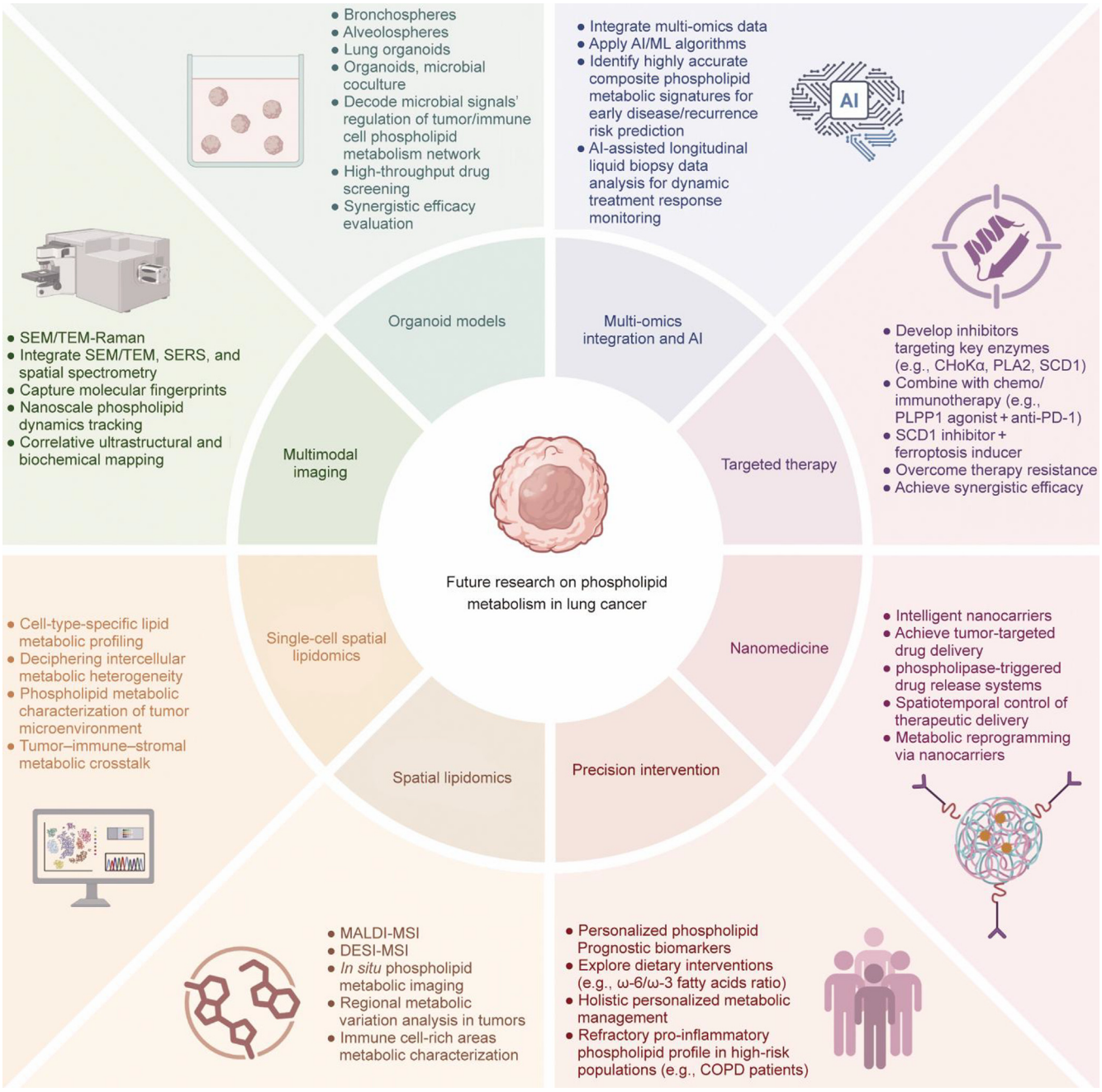


Fig. 5. Schematic framework of future research priorities in phospholipid metabolism of lung cancer, centered on an integrated approach from molecular dissection to clinical application. The diagram encapsulates eight interrelated themes surrounding the core topic of phospholipid metabolic reprogramming in lung cancer. Spatial lipidomics: Employs MALDI-MSI and desorption electrospray ionization (DESI)-MSI to map regional phospholipid heterogeneity in tumors, enabling characterization of metabolic variations in immune-rich microenvironments and tumor subregions, and further supports exploration of phospholipid in situ metabolic variation within the tumor ecosystem. Single-cell spatial lipidomics: Dissects cell-type-specific lipid metabolic profiles (tumor, immune, and stromal cells), deciphers intercellular phospholipid metabolic crosstalk, reveals the role of phospholipids in tumor–immune–stromal interactions, and strengthens characterization of TME and tumor–immune–stromal metabolic crosstalk. Multimodal imaging: Integrates high-resolution microscopy (SEM/TEM) with Raman spectroscopy, further incorporates SERS and spatial spectrometry for multi-technique integration, to correlate ultrastructural changes (e.g., organelle morphology and membrane dynamics) with biochemical signatures of phospholipid metabolism, capture molecular fingerprints of phospholipid metabolism, and facilitate dynamic tracking of inflammation–cancer transformation. Organoid models: Uses patient-derived organoids (bronchospheres and alveolospheres) and microbe–organoid co-cultures to simulate metabolic heterogeneity in TME, supports high-throughput drug screening, validation of phospholipid metabolic targets, decoding of microbial signals' regulation of tumor/immune cell phospholipid metabolism, and evaluation of synergistic efficacy of therapeutic strategies. Multi-omics integration and AI: Combines genome, transcriptome, proteome, metabolome, and microbiome data with spatial mapping (MSI, spatial transcriptomics) to construct system-level metabolic networks. AI/ML algorithms mine these datasets to identify highly accurate composite metabolic signatures for early disease/recurrence risk prediction, conduct AI-assisted longitudinal liquid biopsy data analysis for dynamic treatment response monitoring, model metabolic fluxes, and stratify patients for personalized therapy. Targeted therapy: Develops inhibitors against key phospholipid metabolic enzymes (e.g., ChoKα, LPCAT1, and SCD1) and combines them with chemo/immunotherapy (e.g., PLPP1 agonist + anti-PD-1) to reverse TME immune suppression, enhance therapeutic efficacy, and specifically address the need to overcome therapy-induced metabolic resistance. Nanomedicine: Designs intelligent nanocarriers for targeted drug delivery, adopts PL-triggered drug release systems to enable spatiotemporal control of therapeutic agents, and realizes metabolic reprogramming of TME cells (e.g., CAFs and TAMs) via nanocarriers. Precision intervention: Translates mechanistic insights into clinical practice, including application of personalized phospholipid prognostic biomarkers, exploration of personalized metabolic intervention strategies, implementation of holistic personal metabolic management, rectification of proinflammatory phospholipid profiles in high-risk populations (e.g., COPD patients), and dynamic metabolic monitoring (e.g., magnetic resonance spectroscopy) to modulate phospholipid metabolism. Created in BioRender.

with common clinical archives is also limited. As most retrospective clinical samples are FFPE tissues, the associated lipid degradation poses a problem; estimates suggest 20%–30% of metabolites may be undetectable in such material, complicating biomarker validation studies [133,134]. Addressing these challenges through technological innovation, protocol standardization, and advanced computational tools is imperative for spatial lipidomics to fully realize its transformative potential in lung cancer research.

6.1.2. Multimodal imaging (scanning electron microscopy (SEM)/transmission electron microscopy (TEM)-Raman)

Multimodal imaging approaches that correlate molecular vibrational signatures with ultrastructural context offer a powerful strategy for studying metabolic reprogramming *in situ* (Fig. 5). Raman spectroscopy, especially when integrated with confocal microscopy, provides a non-invasive, label-free method to probe the biochemical fingerprint of cells and tissues based on molecular vibrations (its core advantage). It has demonstrated utility in lung cancer research for detecting metabolic shifts associated with malignancy, such as decreased lipid unsaturation (a hallmark of phospholipid oxidation) [135]. Its strength lies in providing live-cell compatible, chemically specific information, and it has shown promise in early diagnosis via exosome analysis [136–138]. Conversely, electron microscopy (EM), including SEM and TEM, offers unmatched nanoscale resolution of cellular and organelle morphology, crucial for observing structural hallmarks of processes like EMT and autophagy [139] (another core advantage of the multimodal system). Furthermore, integrating machine learning (ML) algorithms into the analysis of such multimodal data enables the automated and high–accuracy identification of complex metabolic phenotypes, thereby providing a powerful computational tool for tracing the dynamic evolution of metabolism along the inflammatory–to–cancer continuum [130,140,141] (Fig. 5).

However, Raman spectroscopy is fundamentally constrained by its inherently weak scattering efficiency (~10–8), necessitating acquisition times of several hours even for microscale specimens. This temporal limitation fundamentally precludes its application to dynamic live-cell imaging and high-throughput screening modalities [142]. This limited sensitivity poses significant challenges for trace metabolite analysis, as conventional Raman detection of lipid mediators often requires concentrations exceeding 10 μg·mL^{-1}. While surface-enhanced Raman scattering (SERS) leverages plasmonic nanostructures to lower detection limits to pg·mL^{-1}–ng·mL^{-1} ranges, this enhancement comes at the cost of biological fidelity. Gold nanoparticle substrates are internalized via receptor-mediated, temperature-dependent endocytosis, leading to asymmetric cellular uptake and inhomogeneous distribution [143]. Critically, this process perturbs native metabolism through ROS generation and transcriptional stress, as demonstrated by three-dimensional (3D) SERS mapping showing nanoparticle-induced spectral variations in otherwise healthy cells. Consequently, studies of minor metabolic subpopulations remain constrained by a fundamental trade-off between sensitivity and physiological relevance [144].

Turning to EM, a major drawback is the requirement for vacuum conditions and extensive sample preparation, which involves steps such as glutaraldehyde fixation, graded ethanol dehydration, osmium tetroxide post-fixation, and heavy-metal staining [145]. These procedures frequently introduce structural artifacts such as specimen shrinkage of up to 50%, cracking due to incomplete dehydration, and extraction of cytoplasmic elements during fixation, ultimately eliminating the possibility of observing dynamic, native-state biological processes [145]. Moreover, the resolution benefits of EM are offset by non-physiological conditions required for imaging, as all water must be removed to prevent boiling under vacuum, significantly altering native ultrastructure [146]. The ultimate promise of multimodal imaging lies in correlative analysis, but challenges persist: aligning nanoscale EM features with chemical maps from other modalities requires sophisticated registration approaches. Current workflows remain low-throughput due to the need for dedicated sample preparation protocols and specialized instrumentation, limiting routine application in many research settings [147].

Therefore, while the SEM/TEM-Raman correlative paradigm holds immense conceptual promise for providing a comprehensive spatiotemporal view of phospholipid metabolic changes during lung cancer progression, current implementations are technically demanding. Future advancements aimed at improving Raman sensitivity (e.g., via coherent Raman techniques), developing gentler EM preparation methods, and creating more streamlined, high-fidelity correlative workflows will be crucial to unlock the full potential of this multimodal approach for mechanistic discovery [148].

In summary, spatial lipidomics and multimodal imaging form complementary technological systems that collectively address the fundamental question of "how phospholipid metabolic heterogeneity is organized and evolves." By elucidating the spatial patterns of phospholipid metabolism and their structure-function correlations while acknowledging and prospectively addressing their current limitations, these technologies lay a solid mechanistic foundation for subsequent functional validation and translational research.

6.2. Advanced model systems: Emulating the complex tumor ecosystem

A deep understanding of the functional significance of phospholipid metabolic heterogeneity in lung cancer requires experimental models that move beyond simplified studies of single cell types to recapitulate the multidimensional complexity of the human tumor ecosystem. Traditional two-dimensional (2D) cultures lack the critical 3D architecture and cell–cell signaling of the TME, while animal models are limited by inherent species differences in metabolism and host–microbiome interactions compared to humans.

Organoid models, an emerging 3D cell culture technology capable of mimicking the structure and function of human organs, show great potential in recreating the heterogeneous phospholipid metabolic microenvironment of lung cancer (Fig. 5). By introducing lung cancer cells along with relevant stromal cells (such as CAFs and immune cells) into organoid models, it is possible to construct lung cancer microenvironment models that more closely resemble the *in vivo* environment [149]. Taking a liver cancer organoid model as an example, research utilizing decellularized human amniotic membrane as a biomimetic scaffold constructed a liver cancer organoid containing the Huh-7 cell line, bone marrow-derived mesenchymal stromal cells, and human umbilical vein endothelial cell-conditioned medium. This model maintained viability for up to 21 d and exhibited metabolic characteristics similar to the liver cancer microenvironment [133]. This 3D architecture enables the direct investigation of how tumor-derived lipid mediators (e.g., PGE2 and LPA) reprogram the metabolism and function of neighboring cells. Furthermore, organoid models have been employed for the screening and evaluation of potential therapeutic agents for lung cancer [150,151], allowing for the assessment of phospholipid metabolism inhibitors within a context that better predicts *in vivo* efficacy and TME-driven resistance.

Tumor evolution is not confined to local cellular interactions but is profoundly regulated by systemic factors, among which the microbiome plays a central role. Substantial evidence indicates that the gut microbiota is a key regulator of host lipid metabolism and systemic immunity. Its dysregulation is closely associated with

cancer development and therapy response, influencing the TME and treatment sensitivity through immune modulation [152–154]. Therefore, simulating only tumor cells and their immediate adjacent environment is insufficient; this critical systems biology variable must be incorporated.

Consequently, the research frontier is shifting towards building integrated organoid–microbiome systems, developing combined models such as organoids co-cultured with specific microbial communities or their bioactive metabolites (e.g., short-chain fatty acids) (Fig. 5). Such synthetic ecosystems would combine the fidelity of organoids to tumors and the TME with the systemic metabolic-immune regulatory capacity of the microbiome. First, they can be used for mechanistic dissection, precisely revealing how specific microbial signals regulate phospholipid metabolic networks within tumor and immune cells, ultimately determining the immune phenotype of the TME. Second, they can drive therapeutic discovery, enabling high-throughput drug screening within the complete pathological context that includes the microbial ecology, and systematically evaluating the synergistic efficacy of metabolic inhibitors, immunotherapies, and microbiome-modulating strategies (e.g., prebiotics and postbiotics) (Fig. 5).

6.3. Translational and therapeutic innovation: Towards mechanism-targeted precision medicine

The ultimate goal of decoding phospholipid metabolic heterogeneity and validating its function is to translate these mechanistic insights into mechanism-targeted precision medicine strategies. Achieving this translation faces two major core challenges: first, how to precisely deliver therapeutic agents to specific cells and metabolic targets within the TME; and second, how to address the vast heterogeneity among patients to match the optimal therapy for each individual. To this end, nanomedicine and AI-driven precision medicine have emerged as key and complementary technological pillars, propelling lung cancer treatment towards a deeply personalized mode targeting metabolic mechanisms. Notably, the intricate role of phospholipid metabolism in lung cancer pathogenesis presents a dual landscape of immense therapeutic promise and significant translational challenges [18,90]. Moving beyond correlative observations to actionable interventions necessitates shifting the focus from describing associations to addressing specific research gaps via well-defined implementation paths [116,155], which are elaborated in detail below as the core of translational innovation. These primary translational bottlenecks (research gaps) and their corresponding strategic implementation paths can be synthesized into four interconnected areas closely aligned with the overarching goal of advancing mechanism-targeted precision medicine, and they are elaborated as follows (Fig. 5).

First and foremost, the inadequate precision of phospholipid-based biomarkers constitutes a key translational barrier. Current phospholipid signatures, while altered in lung cancer, lack the specificity required for robust clinical decision-making, with tumor heterogeneity, subtype-specific variations, and the absence of validated multi-metabolite panels limiting their utility compared to established standards like PD-L1 expression or imaging [156,157]. To bridge this gap, leveraging AI and ML to integrate spatial lipidomics data with matched multi-omics profiles from large cohorts is crucial [131,158], as this integrated approach holds the potential to identify and validate composite phospholipid metabolic signatures capable of predicting early-stage disease, molecular subtypes, and recurrence risk with high accuracy [32,114] (Fig. 5). Concurrently, developing longitudinal liquid biopsy platforms using high-throughput targeted MS to dynamically track specific phospholipid mediators (e.g., S1P and LPA) in patient serum is essential, as this strategy would elucidate real-time metabolic adaptation and serve as a predictive tool for treatment response and the emergence of resistance [29,159].

Another critical translational bottleneck is the lack of tumor-selective therapeutic targeting. Key phospholipid-metabolizing enzymes (e.g., SPHK1 and PLA2) are ubiquitously active, raising concerns about on-target toxicity, while existing inhibitors often lack precise delivery to the tumor site [160]. The development of smart, PL-responsive nanomedicine offers a promising solution in this regard: designing nanoparticle systems that remain inert in circulation but are specifically activated by tumor-overexpressed PLs (e.g., secreted PLA2 (sPLA2)) within the TME enables a "triggered-release" strategy, which can concentrate the delivery of encapsulated metabolic inhibitors or chemotherapeutics to maximize efficacy while minimizing systemic exposure [77,161] (Fig. 5). Furthermore, exploiting context-specific metabolic vulnerabilities is key—identifying genetic or phenotypic contexts (e.g., concurrent *KRAS* mutation) that confer synthetic lethality with the inhibition of specific phospholipid pathways will allow for the design of biomarker-selective clinical trials, focusing interventions on the patient populations most likely to benefit [99,162] (Fig. 5).

A third major research gap that hinders clinical translation is overcoming therapy-induced metabolic adaptation and resistance. Tumor cells can rapidly rewire their lipid metabolism to evade targeted inhibitors, a process driven by poorly characterized compensatory pathways that lead to acquired resistance [134,155]. Addressing this challenge requires the systematic functional mapping of resistance metabolomes, and utilizing tools like functional genomics (e.g., clustered regularly interspaced short palindromic repeats (CRISPR) screens) coupled with longitudinal metabolomics in patient-derived organoids treated with phospholipid-targeting agents can systematically uncover these metabolic bypass mechanisms [150,162]. The knowledge gained from such studies is foundational for designing rational combination therapy blueprints; for instance, logical strategies include co-targeting a phospholipid synthesis enzyme (e.g., SCD1) with a dependent cell death pathway (e.g., ferroptosis inducers), or combining a phospholipid metabolism modulator with immunotherapy to counteract metabolite-driven immunosuppression [46,77,85] (Fig. 5).

Beyond therapeutic interventions, another under-explored frontier lies in preventive strategies and sustainable modulation of the TME. Current research heavily focuses on cytotoxic approaches, leaving premalignant intervention and long-term microenvironment normalization as open frontiers. Conducting dietary-pharmacologic interception trials represents a viable prevention strategy, and controlled studies are needed to evaluate whether dietary regimens (e.g., modulating the omega-6/omega-3 ratio) or specific nutraceuticals can reverse pro-inflammatory phospholipid profiles in high-risk individuals, such as those with COPD [120,163,164] (Fig. 5). Additionally, metabolic reprogramming of stromal cells via advanced delivery systems is a promising avenue—employing nanocarriers or engineered exosomes to deliver lipid-modulating agents specifically to CAFs or TAMs can disrupt their tumor-supportive functions [77,165], aiming to restore an immune-permissive microenvironment and potentially sensitize tumors to immunotherapy [64,166] (Fig. 5).

The aforementioned implementation paths are strongly supported by the two core technological pillars (nanomedicine and AI-driven precision medicine) highlighted earlier. Specifically, nanomedicine serves as a key enabler for addressing the bottlenecks of "lack of tumor-selective therapeutic targeting" and "under-explored microenvironment-modulating strategies." As a promising future strategy in lung cancer therapy, its core value lies in precise regulation of lipid metabolic pathways, targeted modulation of the TME, and overcoming drug delivery barriers. For instance, integrating nanotechnology can enhance the efficacy of

chemotherapy, immunotherapy, and photodynamic therapy by precisely modulating lipid metabolic pathways [77]; it can also improve therapeutic outcomes by targeting non-tumor cells (e.g., CAFs and immune cells) within the TME to regulate their lipid metabolism [77] (Fig. 5). Critically, nanomedicine drug delivery systems (NDDSs) offer a direct solution to the clinical challenge of effective tumor delivery of phospholipid metabolism inhibitors—for example, nanoparticles sized between 100 and 200 nm can accumulate in tumors via the enhanced permeability and retention effect [165], which directly aligns with the PL-responsive nanomedicine strategy proposed earlier for tumor-selective targeting.

In parallel, AI and ML play an indispensable role in addressing the gap of "inadequate precision of phospholipid-based biomarkers." As core tools for multi-omics data integration and precise patient stratification, they enable the integration of spatial lipidomics data with matched genomics, proteomics, and other omics profiles from large cohorts [131,158]—a pivotal approach for identifying and validating composite phospholipid metabolic signatures with high accuracy for predicting early-stage disease, molecular subtypes, and recurrence risk, thereby directly addressing the specificity and precision bottlenecks of current phospholipid biomarkers (Fig. 5). Additionally, AI-driven analysis can facilitate the interpretation of longitudinal liquid biopsy data, aiding in real-time tracking of phospholipid mediator dynamics and prediction of treatment response and resistance [29,159] (Fig. 5).

The most promising direction lies in the deep integration of nanomedicine and AI, which would form a "design–deliver–monitor–optimize" closed-loop precision medicine system. Within this framework, AI informs the design of nanocarriers by identifying the optimal targeting motifs or combination therapies for a patient's specific tumor profile (Fig. 5). In turn, nanocarriers can serve as diagnostic tools, delivering imaging probes to provide real-time, spatially resolved feedback on drug distribution and early treatment response. This data stream can then be fed back into AI models for dynamic adjustment of the treatment plan.

In conclusion, translating the mechanistic understanding of phospholipid metabolism into clinical impact necessitates a paradigm shift from descriptive biology to solution-oriented, interdisciplinary engineering. By focusing on the four core research gaps outlined above and diligently pursuing the corresponding implementation paths—with robust support from the synergistic development of nanomedicine and AI-driven precision medicine—the field is poised to develop the next generation of precise diagnostics, effective and tolerable therapies, and novel prevention paradigms. The deep integration of nanomedicine and AI forms a "design–deliver–monitor–optimize" closed-loop precision medicine system, which translates fundamental phospholipid metabolism research findings into clinically implementable, dynamically adaptive personalized treatment strategies. Coupled with the continuous advancement of technological tools (spatial lipidomics and multimodal imaging) and the refinement of experimental models (organoid–microbiome systems), this will open a promising new path for ultimately improving the prognosis of lung cancer patients and disrupting the vicious cycle of inflammation and metabolic dysregulation that fuels this disease (Fig. 5).

7. Discussion, limitations, and conclusion

7.1. Discussion

This review systematically elaborates on phospholipid metabolic reprogramming as the core "metabolic switch" connecting chronic inflammation to malignant transformation in lung cancer, providing a detailed chain of evidence from driving tumorigenesis and remodeling the immune microenvironment to mediating various forms of therapy resistance. This chapter aims to integrate and elevate the aforementioned mechanistic findings, critically examine the limitations and contradictions within current understanding, clarify translational bottlenecks, and systematically outline key targets, thereby delineating a clear pathway and future direction from basic biology to clinical practice.

7.1.1. An integrated network perspective: The phospholipid metabolic switch as a cooperative system

Phospholipid metabolic reprogramming is not a collection of isolated pathways but a highly integrated network that transforms chronic inflammatory and oncogenic signals into a sustained malignant phenotype. This network operates through three functionally defined and synergistic axes, collectively constituting the "phospholipid metabolic switch."

The first axis focuses on inflammation and immune remodeling, centered on the release of AA by PLA2 and its downstream metabolism. It acts as a communication hub between tumor cells and the TME. It converts inflammatory stimuli into a continuous stream of lipid mediators (e.g., PGE2 and LTB4). These mediators not only directly promote tumor cell proliferation but also systematically shape an immunosuppressive TME by inducing Treg differentiation and recruiting pro-tumor neutrophils, thereby paving the way for tumor development [23,25,37,38].

The second axis concerns cell fate decisions, involving sphingolipid metabolic balance and fatty acid modification. Overexpression of SPHK1 leads to the accumulation of S1P, which in turn activates key pro-survival pathways such as PI3K/AKT and STAT3, and is closely associated with resistance to EGFR–TKIs [44–46]. Concurrently, enzymes such as SCD1 enhance cellular resilience under stress by altering the fatty acid saturation of membrane phospholipids to help cells resist ferroptosis [80,81]. This axis endows tumor cells with a powerful intrinsic survival toolkit.

The third axis constructs a self-reinforcing feedback loop, enabling bidirectional crosstalk and epigenetic consolidation. On one hand, tumor-derived lipid signals (e.g., LPA) and nutrient competition suppress anti-tumor immunity [55,63,64]; on the other hand, the resulting harsh microenvironmental conditions such as hypoxia and oxidative stress further upregulate the expression of metabolic enzymes like PLD [53]. Crucially, metabolites such as D-2HG can directly interfere with epigenetic modifications like histone demethylation, thereby stabilizing gene programs promoting processes like EMT and "locking in" the malignant phenotype [73,74].

In summary, inflammatory signals initiate this network; the immune remodeling axis modifies the external ecology; the cell fate axis strengthens internal resilience; and the bidirectional crosstalk axis ensures the dynamic stability and continuous evolution of the entire system. This integrated perspective reveals phospholipid metabolic reprogramming as an active, organizing core mechanism in the progression of lung cancer.

7.1.2. Critical appraisal: Contradictory findings and context-dependency

Despite the increasingly complete chain of evidence, in-depth scrutiny reveals that the role of phospholipid metabolism in lung cancer exhibits significant context-dependency, and current understanding still contains contradictions and limitations, which impose higher demands for precise intervention.

First, core lipid signaling molecules often exhibit a "double-edged sword" nature. S1P is a typical example. Although its tumor-promoting role has been well-documented in lung cancer models [42,43], its physiological function in lymphocyte trafficking implies that systemic blockade may lead to immunosuppressive side effects [33]. This suggests that targeting the S1P pathway may require subtype-selective inhibitors or localized delivery

strategies. Similarly, the lipid peroxidation end-product 4-hydroxynonenal (4-HNE) is generally cytotoxic but can also activate protective pathways such as Nrf2 under specific conditions, making its impact on tumors complex and highly context-dependent [59,60,62].

Second, the importance of specific metabolic enzymes can vary dramatically depending on genetic background, tumor subtype, and microenvironmental pressures. For instance, while SCD1-mediated MUFA production is a key ferroptosis resistance mechanism [80], its critical role may be most pronounced in cells already possessing high levels of PUFA-PLs (a cellular state determined by enzymes like ACSL4 and LPCAT3) [82,83,167]. Furthermore, the functions of broad enzyme families like PLs (PLA2 and PLD) are often attributed to the entire family, despite different isoforms potentially playing distinct or even opposing roles (e.g., in inflammation versus resolution, or in tumor cells versus immune cells), which may lead to overgeneralization in the literature [36,52,53].

Finally, the gap between correlation and causality remains a major challenge. Lipidomics studies have clearly established associations between specific phospholipid profiles and disease states [26,114], yet it remains difficult to definitively assert whether these changes are drivers or bystander phenomena. To bridge this gap, future research designs based on inducible genetic manipulations or temporal pharmacological interventions are needed to clarify causal chains.

7.1.3. Unresolved questions and translational bottlenecks

Translating the significant biological discovery of phospholipid metabolism into clinically accessible therapeutic benefits still faces numerous unresolved mechanistic puzzles and practical translational barriers.

At the mechanistic level, several core scientific gaps persist. These include the lack of systematic elucidation of the temporal dynamics of the phospholipid metabolic network from precancerous lesions through metastasis and acquired therapy resistance. The association between dynamic changes in metabolic enzyme expression, phospholipid species composition, and signaling pathway activation and clinicopathological tumor characteristics requires deeper exploration. The distribution pattern of phospholipid metabolic reprogramming within lung cancer cell populations remains unclear—whether it is a universal feature of tumor cells or is enriched only in stem-like or persistent subpopulations. Answering this question relies on the deep application of emerging single-cell lipidomics and spatial lipidomics technologies, which have been proven to reveal metabolic heterogeneity [126,129]. The molecular mechanisms of the gut–lung axis regulating lung cancer phospholipid metabolism need further clarification. How the gut microbiota systemically modulates pulmonary tumor phospholipid metabolism through yet-to-be-defined specific metabolites and downstream signaling pathways, and the precise identification of key molecular nodes involved, remains an open question [152].

Beyond these mechanistic unknowns, the clinical translation of phospholipid metabolism-targeting strategies faces multiple practical obstacles. Phospholipid metabolism is significantly influenced by systemic metabolic factors such as diet, obesity, and cardiovascular diseases. Refining tumor-specific phospholipid signatures (e.g., specific phospholipid species and metabolic enzyme expression patterns) from this complex background noise to develop robust, clinically validated diagnostic or prognostic biomarkers remains a core technical challenge [32,114]. As phospholipid metabolism is a core pathway essential for the basic functions of all cells, targeted intervention risks off-target toxicity. Therefore, designing inhibitors that selectively target metabolic addictions specific to tumor cells or particular TME components (e.g., CAFs and immune cells), or leveraging delivery systems like nanomedicine to enhance tumor targeting [165], becomes crucial for ensuring treatment safety while exerting therapeutic effects [77,160]. Tumor cells possess remarkable metabolic plasticity, making single-pathway inhibition prone to compensatory resistance. For example, inhibiting SPHK1 may trigger tumor cells to upregulate alternative lipid synthesis or salvage pathways to maintain viability [92,101]. This necessitates the upfront planning of rational combination therapies, such as pairing phospholipid metabolism inhibitors with immune checkpoint inhibitors [64] or simultaneously targeting parallel and non-redundant metabolic nodes, to effectively overcome adaptive resistance.

These unresolved mechanistic questions and translational challenges must be progressively addressed through multidisciplinary collaboration and technological innovation to lay a solid foundation for the clinical application of phospholipid metabolism-targeted therapies.

7.2. Limitations

While this review synthesizes extensive evidence supporting the pivotal role of phospholipid metabolism in lung cancer, several limitations in the current body of research must be acknowledged. First, many of the mechanistic insights discussed are derived from preclinical models, including cultured cell lines and genetically engineered mouse models. Although invaluable, these systems cannot fully replicate the complexity of human tumor ecosystems, including the full spectrum of immune cell interactions and the dynamics of the human TME. Second, the phospholipid and sphingolipid metabolic networks are characterized by remarkable redundancy and compensatory pathways. This inherent adaptability suggests that targeting a single enzyme or metabolite may lead to limited efficacy or the rapid emergence of resistance, underscoring the need for combination approaches. Third, several promising diagnostic and therapeutic strategies highlighted here, such as specific plasma lipid signatures or spatial lipidomics-guided interventions, are still in early developmental or validation phases. Their clinical utility and robustness require confirmation in large-scale, prospective cohorts. Finally, significant metabolic heterogeneity exists between different lung cancer subtypes and among patients, as well as spatially within individual tumors. This heterogeneity poses a substantial challenge for designing universally effective, phospholipid metabolism-targeted therapies and emphasizes the imperative for personalized metabolic profiling.

7.3. Conclusion

In conclusion, this review consolidates the compelling evidence that phospholipid metabolic reprogramming is not merely a bystander but a central driver and “phospholipid metabolic switch” in the ITC transition of lung cancer. This review systematically delineates its multi-dimensional regulatory mechanisms: at the cell-autonomous level, it drives malignant transformation through the modulation of bioactive lipid mediators (e.g., S1P, PGE2, and LPA) and the crosstalk between phospholipid and sphingolipid metabolic networks; in the TME, it reshapes the pathogenic niche by fostering immunosuppression, perpetuating phospholipid peroxidation-induced inflammation-oxidative stress cycles, intensifying nutrient competition between tumor and immune cells, and mediating phospholipid–epigenetic interactions; furthermore, it endows tumor cells with robust survival advantages by conferring resistance to ferroptosis, apoptosis, and autophagy, while diminishing the efficacy of clinical therapies such as EGFR–TKIs and chemotherapy.

Notably, targeting phospholipid metabolic reprogramming harbors substantial translational potential in clinical practice. Phospholipid metabolites (e.g., LPC and PC) have emerged as reliable diagnostic and prognostic biomarkers, enabling non-invasive early

screening and risk stratification of lung cancer. Key metabolic enzymes including SPHK1, PLD1, and LPCATs represent validated therapeutic targets, with their inhibitors demonstrating promising antitumor activity in preclinical models. Moreover, combinatorial strategies—such as the combination of metabolic enzyme inhibitors with immunotherapy or chemotherapy—have exhibited synergistic efficacy, addressing the limitations of monotherapies.

Despite these advances, several overarching challenges persist in translating these findings into clinical benefits: achieving precise target selectivity to minimize off-target toxicity, developing efficient tumor-targeted drug delivery systems for enhanced bioavailability, and overcoming metabolic adaptability-driven therapeutic resistance. Looking forward, integrating spatial multi-omics technologies, advanced preclinical models (e.g., patient-derived organoids), and AI-aided analysis will be instrumental in deciphering metabolic heterogeneity, identifying patient-specific vulnerabilities, and advancing personalized lipid metabolism-targeted therapies for lung cancer.

CRediT authorship contribution statement

Wei-Qian Bao: Writing – original draft, Visualization, Conceptualization. **Tian-Tian Xu:** Writing – original draft, Conceptualization. **Bi-Qing Huang:** Writing – original draft, Conceptualization. **Shu-Qin Li:** Writing – review & editing, Data curation. **Meng-Lin Jiang:** Writing – review & editing, Data curation. **Gang-Yuan Ma:** Writing – review & editing. **Cui-Fen Zhang:** Data curation. **Li-Qing Chen:** Data curation. **De-Zhi Li:** Data curation. **Nan-Jie Zhou:** Resources. **Tu-Liang Liang:** Writing – review & editing. **Lu Gan:** Data curation. **Xiao-Ting Peng:** Data curation. **Yuan-Yuan Song:** Resources. **Jun Zheng:** Writing – review & editing. **Yujuan Zhan:** Writing – review & editing. **Hu-Dan Pan:** Supervision. **Quan Liu:** Writing – review & editing. **Yicheng Zhao:** Writing – original draft, Conceptualization. **Liang Liu:** Writing – original draft, Supervision, Resources, Conceptualization. **Run-Ze Li:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Declaration of generative AI in scientific writing

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