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Decoding protein-phospholipid interaction networks in cancer: the role of acyl-chain remodeling

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Lipids, particularly phosphoinositides, are increasingly recognized as important markers and causal regulators in cancer progression. Less appreciated, however, are the functional consequences of changes in phospholipid acyl chain length and saturation. These alterations reshape membrane biophysics and rewire membrane-associated signaling complexes, suggesting that acyl-chain remodeling represents an emerging regulatory layer in cancer biology. Distinct tumor types or their models exhibit characteristic acyl chain profiles, often shifting toward shorter, more saturated chains that alter physical and functional interactions. Stress conditions and the tumor microenvironment further diversify these profiles, linking acyl chain composition to cellular plasticity, invasiveness, and metastatic potential. In this review, we summarize the molecular factors and enzymatic pathways that govern phospholipid acyl chain remodeling in cancer and examine their relevance to dynamic protein interaction networks. We describe how dysregulated lipid metabolism at the fatty acid level intersects with oncogenic signaling and highlight emerging chemical biology and multi-omics approaches that enable interrogation of protein-phospholipid interaction networks in physiological contexts. Together, these developments position acyl chain-resolved lipid analysis as a central challenge in chemical biology, requiring new probe design and integrative data frameworks to decode lipid–protein interaction networks in cancer. Finally, we discuss how emerging tools for acyl chain-resolved lipid analysis and targeted modulation reveal how membrane remodeling rewires signaling pathways and reshapes the tumor lipid–protein interactome, opening new opportunities for cancer diagnosis and therapeutic intervention.

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Introduction

Metabolic reprogramming is a hallmark of cancer.[1] Beyond proteins and nucleic acids, lipids are increasingly recognized as active regulators of tumor progression.[2] Changes in the fatty acid (FA) composition of lipid species alter membrane biophysics,[3] influencing oxidative stress sensitivity and drug resistance, and can promote invasion and metastasis.[4] However, while lipid–protein interactions are traditionally considered in terms of headgroup chemistry or lipid oxidation,[5,6] the role of acyl chain composition and molecular interactions along the carbon backbone has been largely overlooked. From a chemical biology perspective, this represents a major blind spot as acyl chains encode physicochemical information that is largely invisible to most existing assays, yet fundamentally shapes how signaling complexes assemble and function in tumor cells.

Alterations in phospholipid acyl chain length and saturation can influence the lipid–protein interaction network through three distinct but interconnected mechanisms (Fig. 1). Changes in bulk lipid composition can indirectly affect membrane fluidity and thereby influence accessibility, assembly, localization, and activity of membrane-associated protein complexes.[3,7,8] Differences in lipid acyl chain composition may directly modulate lipid–protein interactions by altering binding strength, specificity, and membrane partitioning. Although studies suggest that acyl chain structure influences membrane biophysics and protein association, the mechanism by which acyl chain variation influences binding affinities is insufficiently understood.[3,7–9] Acyl chain modifications also shape the signaling role of FAs. Distinct species can activate different receptors or signaling pathways and serve as precursors for several lipid mediators, including eicosanoids.[10] In this framework, acyl-chain composition functions as a context-dependent regulator of signaling networks, rather than a static property of membrane lipids. These interconnected mechanisms are summarized schematically in Fig. 1, which integrates acyl chain remodeling with lipid–protein interaction networks and downstream signaling consequences.

Recent studies have reported altered phospholipid acyl chain compositions in cancer,[11–15] although most observations remain correlative and derived from *in vitro* systems, and only one has examined changes in phosphoinositides specifically.[13] These alterations vary across cancer types and correlate with invasiveness. For example, a comparison of human colon, cervix, and pancreatic cancer cell lines revealed an increase in phosphatidylinositol (PI) 36:1 and 36:2, with each cell line displaying a distinct PI acyl chain signature.[11] In general, tumor cells in culture exhibit a shift towards shorter, more saturated phospholipids, with individual tumors maintaining a characteristic PI acyl chain fingerprints.[11] Mechanistic links between specific acyl chain alterations and defined signaling outcomes remain limited, highlighting a key gap in the field.

Environmental stress further reshapes cancer lipid profiles. Elevated temperature or UVA exposure induces distinct phospholipid signatures in melanoma cells, including increased saturation and reciprocal changes in phosphatidylcholine (PC) and PI levels.[12] Low extracellular pH, associated with highly invasive behavior, correlates with longer, more unsaturated acyl chains, particularly species containing seven to ten double bonds.[12] Across multiple breast cancer cell lines and primary tumors, PI acyl chains seem to be generally shorter and more saturated than in healthy controls,[13,14] with substantial subtype-specific variation. The tumor microenvironment contributes to this heterogeneity: tumor-associated stroma in breast cancer is enriched in PI 38:4, whereas this species is reduced in adjacent cancer cells.[13,14] Correlations have also been reported between acyl chain composition and invasiveness, with indolent lesions enriched in saturated or monounsaturated PI species and

Carsten Schultz

Carsten Schultz, PhD, studied chemistry at the University of Bremen, Germany. After his PhD, he joined Nobel Laureate Roger Tsien in 1990. He started his own lab in Bremen in 1993 and moved to the MPI for Molecular Physiology in Dortmund in 2000. From 2001 to 2019, he served as a group leader and later a tenured senior scientist at EMBL Heidelberg. In 2016, Carsten was appointed Chair of Chemical Physiology and Biochemistry at OHSU in Portland, OR. His research focuses on the role of lipids in disease, applying chemical biology to study their functional translation to the protein world.

Andrew Emili

Andrew Emili, PhD, is a pioneer of functional proteomics who has transformed how protein-interaction networks are measured and understood. Over two decades, he has developed mass spectrometry and computational approaches to map cellular and tissue protein interaction networks at scale. His research established that phenotypic states are governed by modular protein associations rather than linear pathways. By integrating functional proteomics, structural analysis, and network modeling, his lab has generated maps of macromolecular complexes in disease, revealing how their remodeling drives cell state transitions across cancer and other disorders. He has published over 320 papers and trained more than 150 scientists.

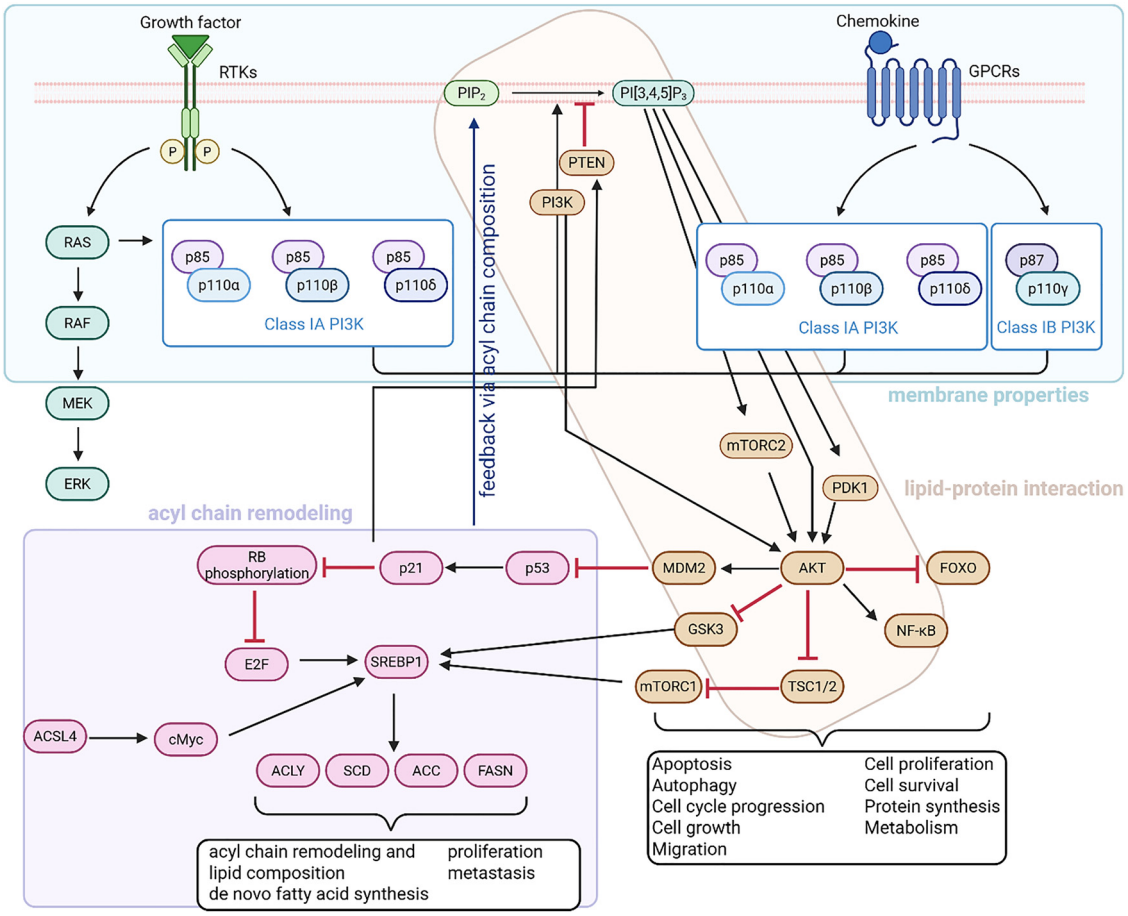

Fig. 1 Schematic overview of acyl chain-dependent regulation of oncogenic signaling networks in cancer.[30,43,44,69] This schematic illustrates how acyl-chain remodeling interfaces with oncogenic signaling networks, acting through three interconnected mechanisms: modulation of membrane biophysical properties, direct effects on lipid–protein interactions, and generation of bioactive lipid species. In this context, lipid metabolic enzymes function as chemical control points that couple phospholipid remodeling to signaling specificity and downstream cellular outcomes. The figure is anchored on the PI3K/AKT/mTOR and PIP_2/$PI[3,4,5]P_3$ signaling networks, which represent central regulators of cell proliferation, survival, metabolism, and cancer progression. These pathways are initiated by growth factor stimulation of receptor tyrosine kinases (RTKs) and by signaling through G-protein coupled receptors (GPCRs). RTK activation leads to RAS-mediated phosphorylation of RAF, MEK, and ERK, thereby promoting cell proliferation, migration, and survival. RTKs also activate class IA PI3K complexes, while GPCRs activate both class IA and IB PI3K complexes, which catalyze the conversion of phosphatidylinositol bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-trisphosphate ($PI[3,4,5]P_3$), a process negatively regulated by PTEN. $PI[3,4,5]P_3$ recruits PDK1 and AKT to the plasma membrane, where AKT is activated by PDK1 and mTORC2. Activated AKT phosphorylates multiple downstream effectors, including MDM2, GSK3, FOXO, TSC1/2, and NF-κB, thereby regulating apoptosis, autophagy, cell-cycle progression, cell growth, migration, proliferation, survival, protein synthesis, and metabolism. AKT signaling further converges on cell-cycle control through regulators such as the p21/Rb/E2F axis and intersects with p53-dependent pathways, as well as on lipid-metabolic control through SREBP1 and key enzymes including ACLY, SCD, ACC, and FASN, linking PI3K/AKT pathway activation to *de novo* fatty acid synthesis, proliferative capacity, and metastatic potential. **Additional abbreviations**: ACC, acetyl-CoA carboxylase alpha; ACLY, ATP citrate lyase; ACSL4, Long-chain-fatty-acid-CoA ligase 4; AKT, AKT serine/threonine kinase; cMyc, MYC proto-oncogene; E2F, E2F transcription factor family; ERK, extracellular signal-regulated kinase; FASN, fatty acid synthase; FOXO, forkhead box O transcription factor; GSK3, glycogen synthase kinase 3, MEK, mitogen-activated protein kinase kinase (MAP2K); MDM2, mouse double minute 2 homolog; mTORC1, mechanistic target of rapamycin complex 1; mTORC2, mechanistic target of rapamycin complex 2; p21, cyclin-dependent kinase inhibitor 1A (CDKN1A); p53, tumor protein p53; p85, PI3K regulatory subunit; p110α, PI3K catalytic subunit alpha; p110β, PI3K catalytic subunit beta; p110δ, PI3K catalytic subunit delta; p110γ, PI3K catalytic subunit gamma; p87, PI3K regulatory subunit (class IB); PDK1, 3-phosphoinositide-dependent protein kinase 1; PI3K, phosphoinositide 3-kinase; PIP_2, phosphatidylinositol bisphosphate; PIP_3, phosphatidylinositol trisphosphate; PTEN; phosphatase and tensin homolog; RAF, rapidly accelerated fibrosarcoma kinase; RAS, rat sarcoma GTPase; RB, retinoblastoma protein; SCD, stearoyl-CoA desaturase; SHIP1, Src homology 2 (SH2) domain containing inositol polyphosphate 5-phosphatase 1 or inositol-polyphosphate 5-phosphatase domain (INPP5D); SREBP1, sterol regulatory element-binding protein 1; TSC1/2, tuberous sclerosis complex 1 and 2.

aggressive lesions enriched in polyunsaturated PI, implicating PI-polyunsaturated fatty acids (PI-PUFAs) for stromal invasion and metastasis.[14,15] Most of the discussed findings derive from *in vitro* experiments using various cancer cell lines. Only two studies[14,15] have examined human tissue samples, and just one publication[11] included an *in vivo* mouse study on pancreatic cancer, underscoring how challenging it remains to investigate these mechanisms in human cancer biology.

PIs, together with other phospholipids, serve as central organizers of signaling pathways and lipid–protein interaction

networks that govern oncogenic processes.[16,17] Yet, despite growing recognition of lipid remodeling in cancer, acyl chain variation in phosphoinositides remains poorly characterized, largely because their low abundance and high number of negative charges pose persistent challenges for sensitive mass spectrometric detection.[18] In this review, we summarize current understanding of phospholipid acyl chain remodeling in cancer, with a particular focus on phosphatidylinositol and its phosphorylated derivatives. We outline the multi-enzyme machinery that establishes and reshapes acyl chain profiles, examine how dysregulated lipid metabolism intersects with oncogenic signaling networks, and highlight emerging chemical biology strategies, including activity-based probes, advanced lipidomics, and proximity-labeling approaches, that enable mechanistic dissection of protein-phospholipid interactions in native contexts. Finally, we discuss how acyl chain-resolved lipid analysis can open new avenues for molecular diagnostics and targeted therapeutic intervention.

1. Multi-protein machinery of acyl chain remodeling

The acyl chain composition of phosphoinositides is controlled by three pathways (Fig. 2): the *de novo* PI synthesis, the PI recycling cycle, and the Lands Cycle. PI synthesized through the *de novo* pathway accumulates saturated and monounsaturated acyl chains, whereas the Lands Cycle enriches the abundant 38:4 acyl chain composition. In contrast, synthesis through the PI recycling cycle primarily maintains the canonical 38:4 composition and has little

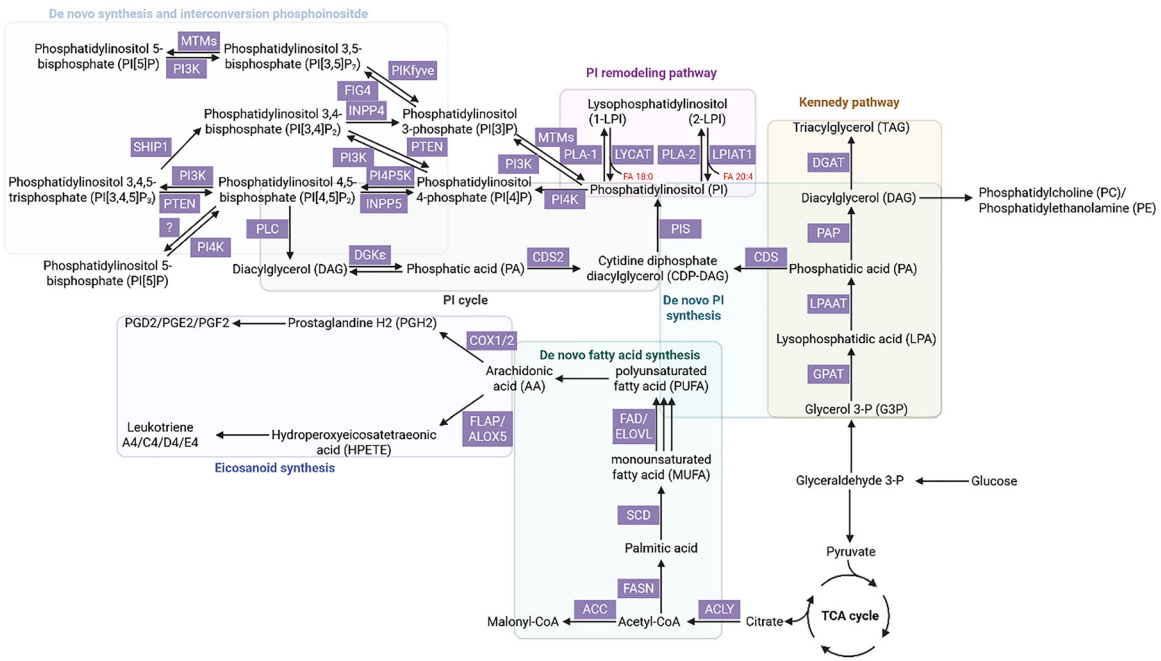

Fig. 2 Schematic overview of the pathways involved in the synthesis and metabolism of fatty acids (FA), eicosanoids, phosphatidylinositol (PI) and phosphoinositides.[13,16,21,27,70] Glucose-derived citrate is converted to acetyl-CoA by ATP citrate lyase (ACLY) and further carboxylated to malonyl-CoA by acetyl-CoA carboxylase (ACC). Repeated condensation of acetyl-CoA and malonyl-CoA by fatty acid synthase (FASN) generates palmitic acid, a fully saturated C16 FA. Introduction of a double bond at the Δ9 position by stearoyl-CoA desaturase (SCD) produces monounsaturated FAs (MUFA), which can subsequently undergo elongation and further desaturation to yield FAs with diverse chain lengths and saturation states. Some essential FAs need to be provided from dietary sources and cannot be synthesized by human cells. Arachidonic acid (AA) is converted into prostaglandins and leukotrienes through prostaglandin-endoperoxide synthase (COX) and arachidonate lipoxygenase (ALOX) pathways, respectively. Differentially saturated FAs are incorporated into glycerol 3-phosphate (G3P) *via* the Kennedy pathway, where sequential acylation by G3P acyltransferase (GPAT) and lysophosphatic acid acyltransferase (LPAAT/AGPAT) generates lysophosphatidic acid (LPA) and phosphatidic acid (PA). PA can be further converted to diacylglycerol (DAG) by phosphatic acid phosphatase (PAP) and to triacylglycerol (TAG) by diacylglycerol *O*-acyltransferase (DGAT). *De novo* synthesis of phosphatidylinositol (PI) proceeds through conversion of PA to cytidine diphosphate DAG (CDP-DAG) by CDP-DAG synthases (CDS1/2), followed by addition of *myo*-inositol by PI synthase (PIS). In the Lands cycle, PI is deacylated to lysophosphatidylinositol (LPI) by members of the phospholipase A (PLA) family, with PLA1 hydrolyzing the *sn*-1 position and PLA2 the *sn*-2 position. Acetylation of LPI is mediated by lysophosphatidylinositol acyl transferase (LPIAT1/MBOAT7), which preferentially incorporates arachidonic acid at the *sn*-2 position, and by lysocardiolipin acyltransferase 1 (LYCAT1/LCLAT1), which transfers 18 : 0 to the *sn*-1 position. The *de novo* synthesis and interconversion of phosphoinositides is described in detail by Barneda *et al.*,[21] Tolias *et al.*,[70] and Posor *et al.*[16] The most relevant step in the context of this review is the PIP_2/PI[3,4,5]P_3 interconversion by phosphoinositide 3-kinase (PI3K), phosphatase and tensin homolog (PTEN), Src homology 2 (SH2) domain containing inositol polyphosphate 5-phosphatase 1 (SHIP1) that is influencing AKT activity in cancer. **Additional abbreviations**: AGPAT, 1-acylglycerol 3-phosphate *O*-acyltransferase; COX1/2, cyclooxygenase 1/2; DGAT, diacylglycerol *O*-acyltransferase; DGKε, diacylglycerin kinase ε; ELOVL, fatty acid elongase; FADS, fatty acid desaturase; FIG4, FIG4 phosphoinositide 5-phosphatase; FLAP, lipoxygenase activating protein; INPP4, inositol-polyphosphate 4-phosphatase; INPP5, inositol-polyphosphate 5-phosphatase; MBOAT7, membrane-bound *O*-acyltransferase domain-containing protein 7; MTM, myotubularin; PI4K, phosphoinositide 4-kinase; PI4P5K, phosphatidylinositol 4-phosphate 5-kinase; PLC, phospholipase C.

impact on overall acyl chain diversity. Although both the *de novo* and recycling pathways use phosphatidic acid (PA) as a key intermediate, only the *de novo* pathway drives a net increase in PI abundance. The Lands cycle, by comparison, regulates acyl chain composition through iterative deacylation and acylation reactions, enabling selective maintenance and enrichment of specific FA species. Together, these pathways define the lipid chemical context in which oncogenic signaling complexes assemble, linking acyl chain remodeling directly to the regulation of cancer-relevant signaling networks.[13,19–21]

1.1 *De novo* PI synthesis and the PI cycle

In the *de novo* pathway, PI is synthesized through sequential acylation steps beginning with glycerol 3-phosphate (G3P).[19,20] Glycerol 3-phosphate acyl transferases (GPAT) catalyze the first acylation at the *sn*-1 position to form lysophosphatidic acid (LPA), followed by a second acylation at the *sn*-2 position mediated by lysophosphatidic acid acyltransferases (LPAAT). Of the four mammalian LPAAT isoforms, only LPAAT3/γ/AGPAT3 seems to have specificity for polyunsaturated FAs (PUFAs). Phosphatic acid (PA) is then converted to cytidine diphosphate diacylglycerol (CDP-DAG) by CDP-DAG synthase (CDS), of which two isoforms exist in mammals (CDS1 and CDS2).[19,20] Notably, CDS2 appears to be selective for the 38:4 acyl chain composition *in vitro*,[22] suggesting a potential role in enriching this species of phosphoinositides. In the final step, *myo*-inositol is transferred by PI synthase (PIS) to generate PI.

Newly synthesized PI enters the PI cycle, in which successive phosphorylation and dephosphorylation reactions generate phosphoinositide species while regenerating PI with a marked enrichment/maintenance of the 38:4 acyl chain composition. A central signaling intermediate outside the PI cycle is phosphatidylinositol 3,4,5-trisphosphate (PI[3,4,5]P_3), produced by phosphorylation of phosphatidylinositol 4,5-bisphosphate (PI[4,5]P_2) by multiple phosphatidylinositol 3-kinase (PI3K) isoforms. PI[3,4,5]P_3 is hydrolyzed PI[4,5]P_2 by phosphatase and tensin homolog (PTEN) or to phosphatidylinositol 3,4-bisphosphate (PI[3,4]P_2) by Src homology 2 (SH2) domain containing inositol polyphosphate 5-phosphatase 1 (SHIP1/INPP5D). Despite central roles in oncogenic signaling, acyl chain selectivity has not been systematically described for any of these enzymes.[19,20]

PI[4,5]P_2 itself is generated by phosphorylation of phosphatidyl 4-phosphate (PI[4]P) by phosphatidylinositol 4-phosphate 5-kinase (PI4P5K) and can be hydrolyzed by phospholipase C (PLC) to produce DAG.[19,20] These DAG species enter the PI cycle to regenerate PI. Notably, both PI4P5K activity and PLC recruitment appear to be sensitive to the phosphoinositide acyl chain composition, suggesting either preferential kinase substrate recognition or altered membrane engagement relative to polyunsaturated species.[23] It could be speculated that the level of unsaturation determines the exposure of the lipid headgroup, which in turn influences kinase kinetics.

Together, these acyl chain-dependent steps define a lipid-encoded layer of regulation within the PI signaling axis, with direct implications for how oncogenic pathways are tuned in cancer. In the following, we refer to the three phosphatidylinositol bisphosphate isomers as PIP_2 and the three phosphatidylinositol phosphate isomers as PIP, unless further specified.

1.2 Lands cycle and remodeling enzymes

In the Lands cycle, PI is deacylated by members of the phospholipase A (PLA) family. Positional specificity within the PLA family, PLA1 at the *sn*-1 position and PLA2 at the *sn*-2 position, confers functional consequences for inflammatory and oncogenic pathways. While PLA DDHD domain containing 1 (DDHD1) is a PLA1 isoform with preference for releasing 18:0, cytosolic PLA2α (cPLA2α) shows preference for the release of arachidonic acid (AA) from the *sn*-2 position, fueling eicosanoid production and protumorigenic inflammation. Acylation further reinforces disease-linked lipid programs,[19] as lysophosphatidylinositol acyltransferase 1 (LPIAT1/MBOAT7) selectively incorporates AA into lysophosphatidylinositol (LPI), preserving the canonical 38:4 PI; loss of this enzyme disrupts this balance, driving accumulation of alternative PI species (34:1, 36:4, 40:6) associated with altered membrane properties and aberrant signal transduction. Complementarily, lysocardiolipin acyltransferase 1 (LYCAT1/LCLAT1) enforces 18:0 enrichment at the *sn*-1 position, and its deficiency shifts PI composition toward shorter and more unsaturated chains (16:0, 18:1, 18:2), a remodeling pattern increasingly linked to metabolic reprogramming, inflammation, and cancer progression.[19,20,24]

This remodeling axis establishes a lipid-encoded regulatory layer that fine-tunes phosphoinositide signaling strength and duration, with direct consequences for oncogenic pathway activation and disease progression.

1.3 *De novo* fatty acid synthesis

De novo fatty acid synthesis plays a central role in shaping the acyl chain landscape of phospholipids with direct consequences for metabolic disease, inflammation, and cancer. This pathway begins with ATP citrate lyase (ACLY)-mediated conversion of citrate to acetyl-CoA, followed by acetyl-CoA carboxylase (ACC)-driven formation of malonyl-CoA and fatty acid synthase (FASN)-dependent elongation to generate palmitic acid, the pivotal saturated intermediate in lipid anabolism.[25–27] From this node, palmitic acid can be desaturated by stearoyl-CoA desaturase (SCD) to produce Δ9-monounsaturated FAs (MUFAs) or elongated by elongation of very long chain fatty acids protein (ELOVL) to yield longer chain species, both of which are preferentially incorporated into phospholipids through the Lands cycle.[25–27] In oncogenic and metabolic contexts, upregulation of ACLY, ACC, FASN, and SCD potentially reprograms membrane composition toward more saturated and monounsaturated lipids, enhancing membrane rigidity, growth factor receptor signaling, and resistance to oxidative stress.[2,25–28] Conversely, generation of polyunsaturated fatty acids (PUFAs) depends on sequential desaturation by fatty acid desaturases (FADs) before phospholipid incorporation, as direct enzymatic desaturation of acyl chains does not occur at the phospholipid level in mammals. This constraint places PUFA biosynthesis at a critical intersection in cancer between membrane remodeling and inflammatory signaling, linking *de novo* lipogenesis directly to eicosanoid production and disease progression.[25,26]

Viewed through a chemical biology lens, *de novo* fatty acid synthesis acts as a molecular control layer that connects lipid composition to signaling output and cancer progression.

Together, the outlined pathways illustrate how cells maintain and remodel phosphoinositides and FAs. However, when these processes become impaired, particularly during cancer progression, lipid–protein interaction networks can become profoundly altered.

- Acyl chain remodeling of phosphoinositides is mainly regulated by *de novo* PI synthesis and the Lands cycle.
- The Lands cycle regulates acyl chain composition through deacylation and acylation.
- FAs synthesized through the *de novo* FA synthesis are incorporated into phospholipids through the Lands cycle.

2. Dysregulated protein interaction networks in cancer

2.1 Fatty acid metabolism as a driver of membrane interaction landscape

The reprogramming of fatty acid synthesis and metabolism is a hallmark of cancer and has profound implications for protein-phospholipid interaction networks. Cancer cells rely on elevated FA synthesis and uptake to support proliferation and energy demands,[25] but these pathways also determine the saturation state, chain length, and distribution of acyl chains in phospholipids. Changes in the balance of saturated FAs (SFAs), MUFAs, and PUFAs in bulk phospholipids alter membrane fluidity, stiffness, and lateral organization,[29] thereby modulating the dynamics of membrane-associated protein complexes. These biophysical changes in membrane architecture are therefore likely to exert major effects on the binding, clustering, and activity of membrane-associated protein complexes.[25,26] Notably, increased rigidity in highly saturated membranes can reduce drug permeability and stabilize oncogenic signaling, whereas polyunsaturated lipids promote more fluid membranes associated with enhanced invasiveness.[25,26]

Desaturases such as SCD and FADs are frequently upregulated in cancers, driving increased mono- or polyunsaturation in FAs and, consequently, in phospholipids.[28,30–33] SCD1 is overexpressed in many tumor types, including melanoma, colorectal cancer, and clear-cell renal carcinoma, and elevated SCD1 levels correlate with poor outcomes in colorectal, lung, liver, thyroid, prostate, pancreatic, kidney, skin, and breast cancers.[34] Five isoforms of the elongating proteins ELOVL are reported in mammals, each potentially displaying distinct substrate specificity:[25] ELOVL 1, 3, and 6 preferentially elongate SFAs and MUFAs; ELOVL5 elongates MUFAs and PUFAs; and ELOVL7 acts on SFAs and PUFAs. Although the involvement of ELOVLs and cancer development is well established, individual tumor types exhibit distinct expression patterns and prognostic associations of these isoforms.[25]

These observations highlight the need for chemical tools that can resolve how acyl chain composition alters protein binding and complex assembly, rather than inferring function from bulk lipid profiles. At the level of physical interaction networks, reprogrammed FA metabolism likely acts as a high-order regulator, reshaping the physical landscape in which signaling proteins operate. For example, by tuning the saturation level of bulk lipid species such as PC and phosphatidyl ethanolamine (PE), cancer cells indirectly but pervasively rewire lipid–protein interaction networks, modifying signaling behavior without requiring changes in protein sequence or expression. However, direct causal links between specific acyl chain changes and defined protein interaction networks remain largely unresolved.

2.2 Stromal-tumor lipid crosstalk and eicosanoid signaling

Besides their effects on membrane fluidity, PUFAs, particularly AA, serve as central precursors for eicosanoid biosynthesis. AA is converted to prostaglandin H_2 (PGH_2) or leukotrienes by cyclooxygenases (COX1 and COX2) or leukotriene synthases, respectively (Fig. 2), and PGH_2 is subsequently processed into additional prostaglandins.[27] Proinflammatory eicosanoid levels are frequently elevated in cancer, where these lipids promote proliferation and migration but can also influence differentiation and apoptosis in a context-dependent manner. Increasing evidence points to the tumor stroma as a major source of eicosanoids, positioning stromal-epithelial lipid exchange as a key regulatory axis in the tumor microenvironment.[35–37]

Eicosanoids are now recognized as potent immunomodulators, mediating crosstalk between epithelial tumor cells and surrounding stromal and immune compartments. Among these, prostaglandin E_2 (PGE_2) is particularly well characterized for its role in tumor immunosuppression: it downregulates anti-tumor T helper 1 (T_H1) responses while promoting immunosuppressive T_H2 cytokine profiles, inhibits CD8+T cell proliferation and effector function, impairs dendritic cell differentiation and antigen-presenting capacity, and suppresses natural killer cell-mediated cytotoxicity.[35–37] Through these coordinated effects, dysregulated PUFA metabolism embeds lipid signaling directly into the circuitry of immune evasion in cancer.

Dissecting these lipid-mediated immune circuits will therefore require proximity-resolved and acyl chain-sensitive chemical biology approaches that can map signaling lipids and their interacting proteins directly within the tumor microenvironment.

2.3 Cytidine diphosphate diacylglycerol synthase (CDS) enzymes as network hubs

While global FA metabolism establishes the membrane context of oncogenic signaling, specific enzymatic nodes determine how individual phospholipid classes are routed into signaling-competent species. CDS occupies a central position in this network (Fig. 3) by converting PA into CDP-DAG, thereby controlling both PI abundance and its acyl chain composition. Downregulation of CDS activity leads to increased levels of PA enriched in 38:4 acyl chains, selective DAG and triacylglycerol (TAG) species, and an enrichment of shorter, more saturated PI species impacting both PLC- and PI3K-dependent signaling pathways.[22,38]

In cancer cell lines, PI synthesis has been shown to support cell survival independent of canonical PI3K signaling, with this dependence mapping to CDS1 or CDS2. CDS1 expression is

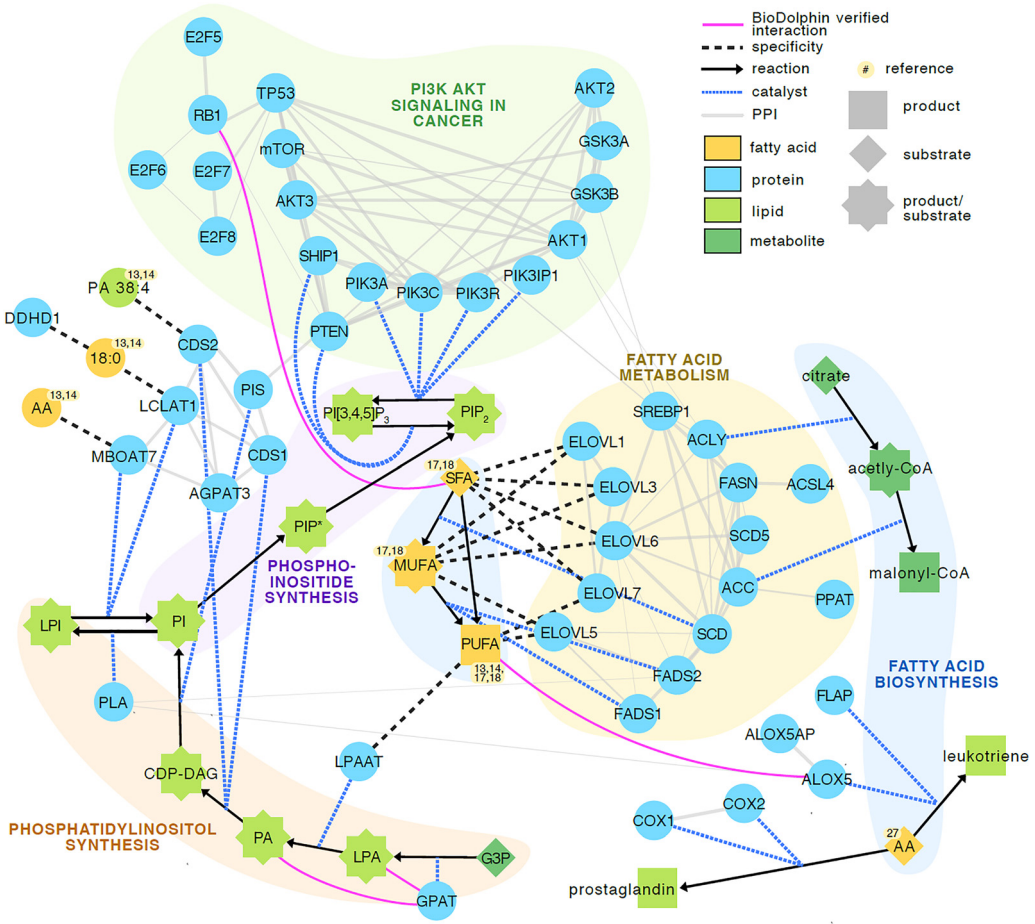

Fig. 3 Integrated network of PI3K/AKT signaling and lipid metabolism in cancer. The biochemical network illustrates the interplay between PI3K/Akt signaling and lipid metabolic pathways in cancer. Protein–protein interactions (PPIs) are obtained from the STRING database and are shown as grey solid lines, including only interactions with a combined score ≥ 0.7. Synthetic reactions of metabolites, fatty acids (FAs), and lipids curated from the literature are depicted as black arrows.[13,21,27] Enzymes catalyzing specific reactions are indicated by blue dotted lines, while literature reported FA or lipid specificities are highlighted with bold black dashed lines.[19,20,24,25,27] BioDolphin-verified lipid–protein interactions are shown as pink lines.[63] FAs are highlighted (yellow), as are proteins (blue), lipids (light green), and metabolites (dark green). The network is organized into five color-coded functional modules: PI3K/Akt signaling in cancer (green), phosphoinositide synthesis (purple), phosphatidylinositol synthesis (orange), fatty acid metabolism (yellow), and fatty acid biosynthesis (blue). The PI3K/AKT signaling module highlights key oncogenes and tumor suppressors, including TP53, PTEN, MTOR, AKT isoforms, GSK3A/B, and multiple PI3K subunits. The phosphoinositide synthesis module highlights enzymes involved in the conversion of phosphatidylinositol (PI) into phosphoinositides These metabolites serve as key signaling lipids. The PI synthesis module highlights enzymes involved in the biosynthesis and remodeling of PI. The FA metabolism module highlights enzymes involved in elongation and desaturation of saturated FAs (SFA), contributing to membrane biophysics and signaling lipid pools, whereas the FA biosynthesis module highlights enzymes involved in the *de novo* synthesis of FAs. In addition, the network includes the eicosanoid biosynthetic pathways, illustrating the conversion of arachidonic acid (AA) into prostaglandins and leukotrienes. This network highlights how lipid chemistry intersects with signaling topology, providing a framework for chemical biology-driven interrogation of membrane-associated interaction networks. *Phosphoinositide synthesis scheme is simplified for clarity; additional detail is provided in Fig. 2. **Protein abbreviations**: ACACA, acetyl-CoA carboxylase alpha (ACC); ACLY, ATP citrate lyase; ACSL4, Long-chain-fatty-acid-CoA ligase 4; AGPAT3, 1-acylglycerol-3-phosphate *O*-acyltransferase 3; AKT1/2/3, AKT serine/threonine kinase 1/2/3; ALOX5, arachidonate 5-lipoxygenase; CDS, cytidine diphosphate diacylglycerol synthase; COX1/2, cyclooxygenase 1/2; DDHD1, PLA DDHD domain containing 1; ELOVL1/3/5/6/7, elongation of very long chain fatty acids protein 1/5/6/7; FADS1/2, fatty acid desaturase 1/2; FASN, fatty acid synthase; FLAP, lipoxygenase activating protein; GPAT, glycerol 3-phosphate acyltransferase; GSK3A/B, glycogen synthase kinase 3 alpha/beta, LCLAT, lysocardiolipin acyltransferase; LPAAT, lysophosphatidic acid acyltransferase; MBOAT7, membrane-bound *O*-acyltransferase domain-containing protein 7; MTOR, mechanistic target of rapamycin; PIK3A/C/R/IP1, phosphoinositide 3-kinase alpha/gamma/regulatory subunit/interacting protein 1; PIS, phosphatidylinositol synthase; PLA, phospholipase A; PPAT, phosphoribosyl pyrophosphate amidotransferase; PTEN; phosphatase and tensin homolog; RB1, retinoblastoma protein; SCD, stearoyl-CoA desaturase; SHIP1, Src homology 2 (SH2) domain containing inositol polyphosphate 5-phosphatase 1 or inositol-polyphosphate 5-phosphatase domain (INPP5D); SREBF1, sterol regulatory element-binding transcription factor 1; TP53, tumor protein p53. **Lipid and metabolite abbreviations**: AA, arachidonic acid; CDP-DAG, cytidine diphosphate diacylglycerol; FA, fatty acid; G3P, glycerol 3-phosphate; LPI, lysophosphatidylinositol; LPA, lysophosphatidic acid; MUFA, monounsaturated FA; PA, phosphatidic acid; PI, phosphatidylinositol; PIP, phosphatidylinositol monophosphate; PIP_2, phosphatidylinositol bisphosphate; PIP_3, phosphatidylinositol trisphosphate; PUFA, polyunsaturated FA; SFA, saturated FA.

frequently reduced in tumors and is associated with poor survival, whereas CDS2 proves essential in many cancer contexts, consistent with the synthetic lethal interaction described between CDS1 and CDS2.[19,22,38–40]

From a network perspective (Fig. 3), CDS therefore functions as a hub that integrates PA-generating pathways, acyl chain-selective remodeling, and phosphoinositide turnover, positioning it as a key regulator of lipid-driven signaling architecture in cancer. From a chemical biology standpoint, CDS emerges not only as a metabolic node but as a strategic control point for probing how acyl chain changes propagate through phosphoinositide signaling networks.

2.4 The p53-SCD-SREBP-PI3K/AKT lipid signaling circuit

A well-characterized example of a lipid signaling interaction network is the circuit connecting p53, SCD, sterol regulatory element-binding protein (SREBP), and PI3K/AKT signaling (Fig. 1 and 3). In this network, mutations in p53 drive SREBP-dependent changes in FA desaturation and phospholipid acyl chain composition, which feed into altered phosphoinositide levels, AKT activation, and further stimulation of FA synthesis, creating a positive feedback loop that tightly couples lipid metabolism to oncogenic signaling.

p53 mutations are the most common genetic alterations in human cancers, occurring in approximately 50% of tumors.[41] A shift of PI acyl chain composition from 38-carbon to 34- and 36-carbon species has been observed in association with p53 mutations. In non-transformed cells, p53 suppresses SCD expression, thereby limiting monounsaturation, and remodels phospholipid profiles through repression of SREBP1 and the p21/Rb/E2F pathway (Fig. 1).[30] In cancer, loss of p53 function leads to upregulation of SCD and increased levels of monounsaturated phospholipids.[30] This remodeling is associated with altered PIP_2 abundance and may influence $PI[3,4,5]P_3$ levels – key regulators of AKT signaling. Enhanced conversion of monounsaturated PI precursors may accelerate phosphoinositide synthesis, while altered membrane fluidity reshapes AKT and upstream signaling assemblies.[11,30,42]

In nascent tumors, p53 mutations likely further disrupt the PTEN-mediated suppression of AKT by reducing $PI[3,4,5]P_3$ hydrolysis to PIP_2, thereby amplifying AKT phosphorylation and signaling (Fig. 1).[11,30,42] Activation of SREBP1 downstream promotes *de novo* FA synthesis, closing the feedback loop that links oncogenic signaling to sustain lipid supply. Multiple mechanisms contribute to SREBP1 activation, including c-Myc/SREBP1-dependent upregulation of ACLY, ACC, FASN, and SCD *via* ACSL4, and AKT/mTOR-driven inhibition of glycogen synthase kinase 3 (GSK3), which stabilizes SREBP1 by limiting its phosphorylation, ubiquitination, and proteasomal degradation.[43–45]

Viewed as an interaction network, as illustrated in Fig. 3, this circuit demonstrates that changes in phospholipid acyl chain composition are not merely downstream consequences of metabolic reprogramming but active determinants in signaling behavior. Dissecting this network at the lipid–protein level will therefore require tools (Fig. 4) capable of resolving acyl chain-specific lipid changes, their spatial organization, and the composition of co-localized signaling complexes. Approaches that couple lipid chemistry with proximity mapping will be essential for directly interrogating how altered acyl-chain landscapes reshape oncogenic signaling networks.

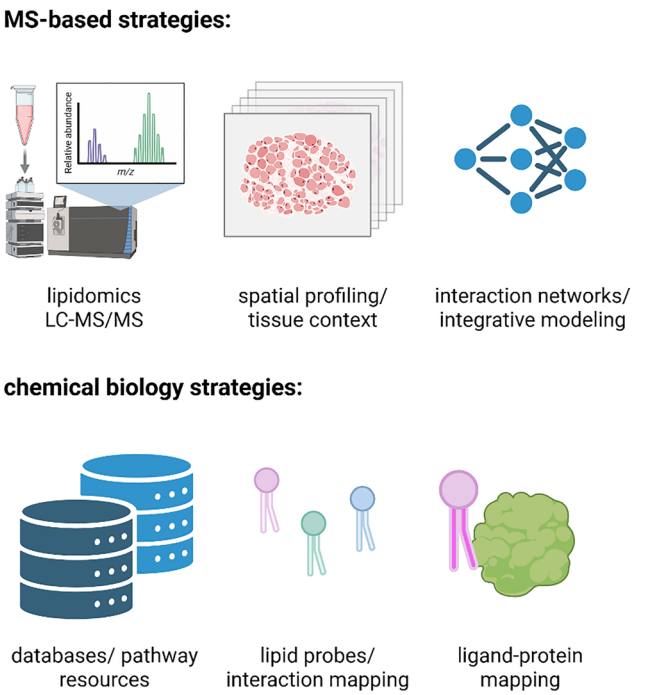

Fig. 4 Chemical biology and multi-scale approaches to study lipid–protein interaction networks. Schematic overview of key methodological approaches used to interrogate lipid–protein interactions and acyl chain-dependent signaling. These include analytical lipidomics and mass spectrometry for resolving lipid composition, chemical biology strategies such as multifunctional probes and proximity-based approaches for mapping lipid–protein interactions, and spatial and multi-omic frameworks that integrate lipid, protein, and tissue context. Together, these complementary methods enable interrogation of lipid–protein interaction networks across molecular, cellular, and tissue scales, while highlighting current limitations in sensitivity, acyl-chain resolution, and *in situ* applicability.

- Cancer cells rely on increased FA synthesis, impacting acyl chain compositions of phospholipids, membrane biophysics, protein binding, and signaling.
- PUFAs act as precursors for eicosanoids, important inflammatory lipid mediators impacting proliferation, migration, differentiation, and apoptosis.
- The p53-SCD-SREBP-PI3K/AKT network creates a positive feedback loop coupling lipid metabolism and oncogenic signaling.

3. Methods that reveal the lipid–protein interaction basis of lipid remodeling

3.1 Mass spectrometry-based approaches for phosphoinositides

Analyzing phosphoinositides, particularly $PI[3,4,5]P_3$, remains technically demanding due to their low abundance (phosphoinositides represent $<15\%$ of total phospholipid content found

in eucaryotic cells)[46] and highly charged chemical structures, which makes conventional extraction approaches inadequate.[18,47] Acidified extraction protocols combined with an initial neutral extraction have improved recovery by mitigating charge-related losses and reducing interference from abundant neutral lipids.[18,47,48] High-pressure liquid chromatography (HPLC) coupled to mass spectrometry (MS) has become the standard analytical platform, providing detailed structural information, and recent improvements in instrumentation and methods have significantly enhanced the detection. Targeted MS strategies further increase sensitivity and specificity by resolving PI[3,4,5]P_3 that co-elutes with more abundant lipids.[18,47] Additional progress has come from derivatization methods such as methylation, which neutralize negative charges and thereby improve both stability and detection limits.[18] Despite these advances, commonly used workflows still cannot resolve individual acyl chain compositions of each phosphoinositide species. To overcome this limitation and distinguish headgroup isomers, chromatographic separation with chiral columns can be employed, enabling relative quantification of distinct phosphoinositide species together with their acyl chain profiles.[49]

3.2 Chemical biology strategies for lipid–protein interactomics

Current methods for studying lipid–protein interactions are often constrained by the low binding affinities characteristic of many such interactions, which frequently fall in the lower micromolar range. As a result, much of the mechanistic insight has so far been derived from simulation studies and molecular dynamics calculations, while experimentally tractable chemoproteomic approaches are only beginning to emerge.[50] Structural methods like X-ray crystallography or cryo-EM have provided detailed views of specific ligand binding pockets and interaction interfaces, particularly for membrane proteins, and nanodiscs have enabled protein structural studies in defined lipid environments. However, the role of acyl chain remodeling in shaping these interactions has remained largely unexplored.[51]

Recent knockout and inhibitor studies combined with heavy atom label-based lipidomics have begun to reveal protein involvement in acyl chain remodeling, but major advances are expected from the development of multifunctional lipid derivatives that enable chemoproteomic interrogation of lipid–protein interactions in an acyl chain-resolved manner.[13,21,38,51] By enabling direct, chemically precise mapping of lipid–protein interfaces, these approaches have the potential to transform our understanding of how membrane composition regulates signaling networks in cancer and other diseases.

3.2.1 Multifunctional lipid probes. Multifunctional lipid probes exemplify how chemical design, rather than biological manipulation, can define the molecular interaction space in living systems, positioning probe chemistry as a primary driver of discovery in lipid–protein interactomics. These derivatives typically contain a photo-crosslinkable moiety that enables covalent capture of proteins in close proximity upon 365 nm light exposure, together with a bioorthogonal clickable affinity handle for downstream enrichment and pulldown. After isolation, protein complexes are proteolytically digested and analyzed by proteomics, allowing identification of interaction partners for specific lipids. Such probes have been developed and applied by several groups studying lipid–protein interactions,[52–57] yet their systematic application in disease contexts remains to be developed. Although many of these lipids have been tested in cancer cell lines such as HeLa cells, essential controls needed to interpret disease-related changes are still lacking. Related efforts include the use of alkyne- and azide-modified sphingosines in infection models, as well as the application of a trifunctional sphingosine probe in a study of Niemann–Pick Disease Type C.[58–60] However, none of these mentioned probes have yet been employed for systemic mapping of lipid–protein interactions in cancer. Adjusting the acyl chain compositions of these derivatives represents a powerful strategy to directly probe how lipid remodeling alters protein interaction landscapes in pathological settings, but has not yet been reported in a lipid–protein interaction network manner

Looking ahead, the continued evolution of these chemistries – toward greater residue selectivity, tunable reactivity, and *in situ* compatibility – promises to establish multifunctional lipid probes as foundational tools for decoding cancer-specific lipid–protein interaction networks.

3.2.2 Databases and resources. For a system-level understanding of lipid–protein interactions, comprehensive curated databases are essential. Several public resources are available, yet they remain incomplete, particularly with respect to phosphoinositides and acyl chain specificity. The DBLiPro database compiles lipid-associated proteins and metabolites from the literature and major repositories such as UniProt, KEGG, LMPD, Lipid Raft, and NCBI, providing metabolic pathway associations but limited information on structural interactions.[61] The MemProtMD database focuses on membrane lipid–protein interactions derived from molecular dynamics simulations.[62] The BioDolphin database offers a broad catalog of lipid–protein interactions across organisms but lacks coverage of key lipids, including phosphoinositides.[63] Notably, acyl chain resolved phospholipid interactions remain under-studied. We highlight reported lipid–protein interactions from BioDolphin in our network representation (Fig. 3), underscoring how many critical features of these interactions remain unsolved. The Lipid Interactome Repository compiles interactions identified using multifunctional lipid derivatives and currently contains proteomic data from selected glycerophospholipids, sphingolipids, and fatty acids from cell line studies.[64] However, disease models are not yet represented.

Moving forward, comparative analysis of lipidomes and lipid interactomes in cancer *versus* healthy models will be essential for defining tumor-specific interaction networks and for identifying context-dependent vulnerabilities in lipid-mediated signaling.

3.3 Multi-omics integration – current methods and challenges

3.3.1 Integration of lipidomics and multi-omics frameworks. Multi-omics approaches provide a powerful scheme for identifying key regulators of signaling and network interactions in complex diseases such as cancer. While integration of transcriptomics and proteomics has become routine, incorporation of metabolomics and lipidomics data remains challenging,

with data analysis and harmonization representing major bottlenecks. One strategy to improve consistency is the use of simultaneous extraction workflows, which enable the isolation of protein, lipid, and metabolites from the same sample and their processing through established omics pipelines. Reliable identification and quantification of lipids and metabolites, however, continues to lag behind that of proteins and nucleic acids, in part due to limited annotation depth. Lipids can be mapped using resources such as KEGG and Reactome, but typically only at the class level, leaving critical molecular detail unresolved. Although mass spectrometry-based lipidomics can provide rich information on acyl chain length and saturation, integration of these features into multi-omic analyses has remained difficult. Many disease-associated alterations in signaling lipids are subtle and manifest primarily at the level of acyl chain composition rather than total abundance, and are therefore frequently overlooked in conventional integrative workflows.[65,66] Addressing this gap will transform lipidomics from a descriptive layer into a mechanistic component of multi-omics analyses, with direct implications for understanding and targeting dysregulated signaling networks in cancer

3.3.2 Spatial omics and chemical biology in tissue context. Combining spatial resolved omics datasets offers new opportunities to interrogate lipid–protein interactions with their native tissue context. Among available techniques, matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) provides a powerful and moderately high-throughput approach for mapping biomolecular distributions and obtaining semi-quantitative information on relative abundance across defined regions. Its ability to detect both lipids and proteins *in situ* makes it particularly valuable for pre-clinical and clinical investigations. Although early MALDI-MSI workflows struggled to detect phosphoinositides because of their low abundance and chemical instability, recent methodological advances have substantially improved sensitivity and coverage.[65–68]

Looking ahead, computational integration of spatial multi-omics data with multi-modal tissue profiling in diseases such as cancer will be instrumental in resolving how lipid remodeling shapes protein interaction networks within specific microenvironments and in identifying spatially constrained signaling mechanisms that drive early disease progression.

- The low abundance and chemical nature of phosphoinositides demand more instrument and method optimization for studying these lipids compared to bulk lipids.
- The development of multifunctional lipid probes has great potential to study lipid–protein interactions, but has yet to be implemented in disease models. The variation of acyl chains in these probes would help in understanding the impacts of the remodeling.
- Current databases are lacking acyl chain resolved phospholipid interactions.
- Integration of lipidomics into the multi-omics workflow could be a powerful tool, but is yet difficult due to limitations in lipidomics annotations.
- New advances in MALDI-MSI workflows overcome earlier limitations on analyzing phosphoinositides with this method, potentially opening new pathways of studying lipid–protein interactions.

4. Conclusion and perspective

Acyl chain remodeling in phospholipids is increasingly recognized as a critical determinant of cancer progression. As we have described throughout this review, alterations in fatty acid composition reshape membrane biophysics and, in turn, modulate the binding, organization, and activity of membrane-associated protein complexes that govern key oncogenic signaling pathways. Yet, despite the centrality of these processes, acyl chain specificity has been defined for only a limited subset of enzymes within the phospholipid biosynthetic and remodeling pathways. By synthesizing evidence across lipid metabolism, phosphoinositide signaling, and protein interaction networks, we have emphasized that acyl chain composition functions not merely as a downstream consequence of metabolic reprogramming but as an active determinant of signaling behavior. This additional regulatory layer fundamentally reshapes how signaling networks must be conceptualized and interpreted in cancer.

We further noted that only a small fraction of lipid–protein interactions has been characterized in tumor cells, and that many annotated examples lack critical information on phosphoinositides and acyl chain-resolved binding. This gap represents a major barrier to the effective integration of lipidomics with proteomics and system-level network analysis. As a result, fundamental questions remain about how lipid remodeling influences pathway selectivity, signaling amplitude, and cellular plasticity in oncogenic contexts. Addressing these challenges will require not only deeper analytical resolution but also conceptual frameworks that treat lipids as dynamic regulators of protein function rather than static membrane components. It should be mentioned that many lipids and lipid alterations have not been mentioned in this review, for instance, the unexplored roles of lyso-glycerol lipids and the effects of lipids carrying dicarboxylic acids.

Finally, we have highlighted how recent advances in chemical biology – ranging from acyl chain-resolved lipidomics and generation of multifunctional probes to proximity labeling and integrative spatial multi-omics – are beginning to provide precisely the tools needed to overcome these limitations. By enabling direct interrogation of lipid–protein interfaces in their native cancer cell and tumor microenvironment, these approaches position chemical biology at the center of efforts to decode how membrane composition encodes signaling logic. In this light, acyl chain remodeling emerges not merely as a metabolic feature of cancer but as a chemical logic layer that links membrane structure to network behavior and opens new opportunities for mechanistic discovery, diagnostic innovation, and targeted therapeutic development.

Conflicts of interest

B. B. is a co-founder of Molecular Tools, Inc., USA. C. S. is a co-founder and shareholder of SiChem GmbH, Germany and Molecular Tools, Inc., USA.

Data availability

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

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