Lp-PLA2 in the cancer landscape: From molecular mechanisms to therapeutic potential (Review)

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Abstract. Lipoprotein-associated phospholipase A2 (Lp-PLA2), an important member of the phospholipase A2 superfamily, was originally investigated for its proinflammatory role in cardiovascular diseases. Recent studies have revealed its significant role in tumorigenesis: It can act as either a tumor promoter or a tumor suppressor depending on the context. The present review systematically outlined the dual mechanisms by which Lp-PLA2 contributes to cancer pathogenesis. As a tumor promoter, it promotes cancer progression via the induction of epithelial-mesenchymal transition, glutathione peroxidase 4-mediated resistance to ferroptosis, and vascular endothelial growth factor-dependent angiogenesis; conversely, as a tumor suppressor, it inhibits tumor growth by suppressing the Wnt/β-catenin pathway in breast cancer gene 1-mutated cancers or by promoting apoptosis. Mechanistic investigations clarify the interactions between Lp-PLA2 and critical oncogenic pathways, such as the Notch and HIF1α pathways, while emphasizing the functional dichotomy that is influenced by the microenvironment. Current evidence supports the development of microenvironment-guided targeting strategies and the potential value of Lp-PLA2 as a prognostic biomarker and therapeutic target. These findings contribute to a theoretical framework for comprehending the context-dependent roles of Lp-PLA2 and may guide the development of innovative therapeutic approaches.

Contents

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Abbreviations: AA, arachidonic acid; ALDH, aldehyde dehydrogenase; BRCA1, breast cancer gene 1; CPT1A, carnitine palmitoyltransferase 1a; CSCs, cancer stem cells; DLBCL, large b-cell lymphoma; EMT, epithelial-mesenchymal transition; FASN, fatty acid synthase; GPX4, glutathione peroxidase 4; HCC, hepatocellular carcinoma; 12-HETE-PPARγ, 12-Hydroxyeicosatetraenoic Acid-Peroxisome Proliferator-Activated Receptor Gamma; LDL, low-density lipoprotein; Lp-PLA2, lipoprotein-associated phospholipase a2; LPC, lysophosphatidylcholine; ox-FFA, oxidized free fatty acids; PAF, platelet-activating factor; PAF-AH, platelet-activating factor acetylhydrolase; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; PEs, phosphatidylethanolamines; PLA2, phospholipase a2; PLA2G7, phospholipase a2 group vii; TAMS, tumor-associated macrophages; TCGA, The Cancer Genome Atlas; TME, tumor microenvironment; VEGF, vascular endothelial growth factor; VLDL, very-low-density lipoprotein

Key words: lipoprotein-associated phospholipase a2, cancer, molecular mechanism, biomarker, ferroptosis, tumor microenvironment, therapeutic target

1. Introduction

Lp-PLA2, also referred to as platelet-activating factor acetylhydrolase (PAF-AH), is an inflammation-related hydrolase encoded by the phospholipase A2 group VII (PLA2G7) gene and is a member of group VII of the phospholipase A2 (PLA2) superfamily (1,2). The α/β hydrolase domain of the enzyme utilizes a catalytic triad consisting of Ser273, Asp356 and His376 to selectively hydrolyze the sn-2 acyl chain of oxidized phospholipids, resulting in the production of proinflammatory mediators such as lysophosphatidylcholine (LPC) and oxidized free fatty acids (oxFFAs) (3-5) (Fig. 1). Under normal physiological conditions, Lp-PLA2 is predominantly secreted by hematopoietic cells, including monocytes and macrophages, as well as by hepatocytes, such as Kupffer cells. It plays a crucial role in regulating lipid metabolism and inflammatory responses through its interaction with low-density lipoprotein (LDL) (6-9).

While the proatherogenic function of Lp-PLA2 in the context of cardiovascular diseases has been extensively documented, particularly its role in promoting plaque progression via LPC and oxFFAs (10-12), its role in cancer remains controversial. Advances in the study of tumor metabolic reprogramming have led to an increased focus on the regulatory role of Lp-PLA2 in oncogenesis (13-15). Emerging evidence indicates that the expression and function of Lp-PLA2 are markedly dependent on tumor type. For example, in hepatocellular carcinoma (HCC), Lp-PLA2 has been shown to promote tumor cell proliferation by activating the PI3K/AKT signaling pathway (16), whereas in triple-negative breast cancer, its downregulation has been associated with the acceleration of EMT (17) (Fig. 2). These divergent findings indicate that Lp-PLA2 may contribute to tumorigenesis through mechanisms that are specific to particular tissues.

Currently, there are three primary challenges in research on Lp-PLA2 in the context of oncology: i) The dual role of Lp-PLA2 as either a protumorigenic or antitumorigenic factor has yet to be fully clarified; ii) its regulatory network within the tumor microenvironment (TME), including aspects such as immune suppression and ferroptosis resistance, has not been systematically explored; and iii) the clinical applicability of Lp-PLA2, including its potential as a liquid biopsy biomarker or target for therapy, has not been validated in multicenter studies (18-23). The present review synthesized recent advances in the field, emphasizing the tumor type-dependent mechanisms of Lp-PLA2, its role in remodeling the TME, and its translational potential, with the aim of providing novel strategies for precision cancer therapy.

2. The role of Lp-PLA2 in tumorigenesis mechanisms

Tumorigenesis is a multifaceted and sequential process characterized by genetic mutations, epigenetic modifications and alterations in the TME (24-26). Increasing evidence suggests that dysregulation of lipid metabolism and chronic inflammation are critical contributors to cancer development (27-29). Lp-PLA2, a pivotal enzyme in lipid metabolism, is markedly upregulated in various malignancies, including HCC and prostate cancer. It facilitates tumorigenesis by hydrolyzing oxidized phospholipids, thereby producing protumor metabolites such as LPC (30,31). Notably, missense mutations, which are the most common type of mutation in the PLA2G7 gene, may influence the differential expression of PLA2G7 across different cancers and its potential link to tumorigenesis (32).

Epigenetic regulation: Methylation and expression aberrations of the PLA2G7 gene. DNA methylation, a significant epigenetic modification, plays a crucial role in regulating gene expression and is implicated in tumorigenesis (33,34). Research has revealed that hypermethylation of the PLA2G7 promoter leads to the suppression of gene expression, a mechanism observed in various cancers. In the cell line 293 and the human colon adenocarcinoma cell line SW480, hypermethylation of the PLA2G7 promoter was negatively associated with transcriptional activity, confirming that DNA methylation silences PLA2G7 expression (35). Furthermore, pancancer analysis of data from The Cancer Genome Atlas (TCGA) revealed a positive correlation between PLA2G7 methylation levels and the expression of DNA methyltransferases (DNMT1/3A). In cervical and renal cancers, the PLA2G7 methylation level exhibited a significant inverse association with the PLA2G7 mRNA expression level, suggesting that DNMT-mediated methylation serves as a key regulatory mechanism (32).

Clinically, patients with HCC exhibiting high levels of PLA2G7 methylation have markedly lower 5-year survival rates than those with low PLA2G7 methylation, indicating its potential as a prognostic biomarker. These findings collectively underscore the role of PLA2G7 epigenetic silencing in the early stages of tumorigenesis and provide a theoretical foundation for methylation-targeted therapeutic interventions.

Lipid metabolic reprogramming: Lp-PLA2-mediated energy supply in tumors. Metabolic reprogramming is a hallmark of cancer cells and is characterized by the remodeling of lipid metabolism to supply components for biomembranes and energy molecules (36). To accommodate the demands of rapid proliferation, tumor cells adopt distinct lipid metabolic patterns, including enhanced *de novo* lipogenesis and alterations in oxidative phosphorylation (37). Lp-PLA2 serves as a critical regulator in this context. By hydrolyzing the sn-2 ester bond of phospholipids, it produces LPC and free fatty acids [such as arachidonic acid (AA)], which activate at least three oncogenic pathways (38,39).

In the initial stages of tumorigenesis, Lp-PLA2 expression is markedly increased, which facilitates the breakdown of oxidized phospholipids. Its metabolites promote tumor cell proliferation through three mechanisms: LPC increases membrane fluidity by 37±5% via lipid raft formation; AA and its derivatives activate inflammation-related pathways; and β-oxidation increases ATP production by 1.5-fold (30) (Fig. 3).

In HCC and cholangiocarcinoma, Lp-PLA2 was found to be highly expressed (31). Its catalytic products activate the Gαi-ERK1/2 pathway through the LPC-GPCR axis. Moreover, AA metabolism promotes tumor progression via both the COX-2/PGE2 pathway and the 12-hydroxyeicosatetraenoic acid/peroxisome proliferator-activated receptor γ (12-HETE-PPARγ) pathway (Fig. 3). Organoid experiments

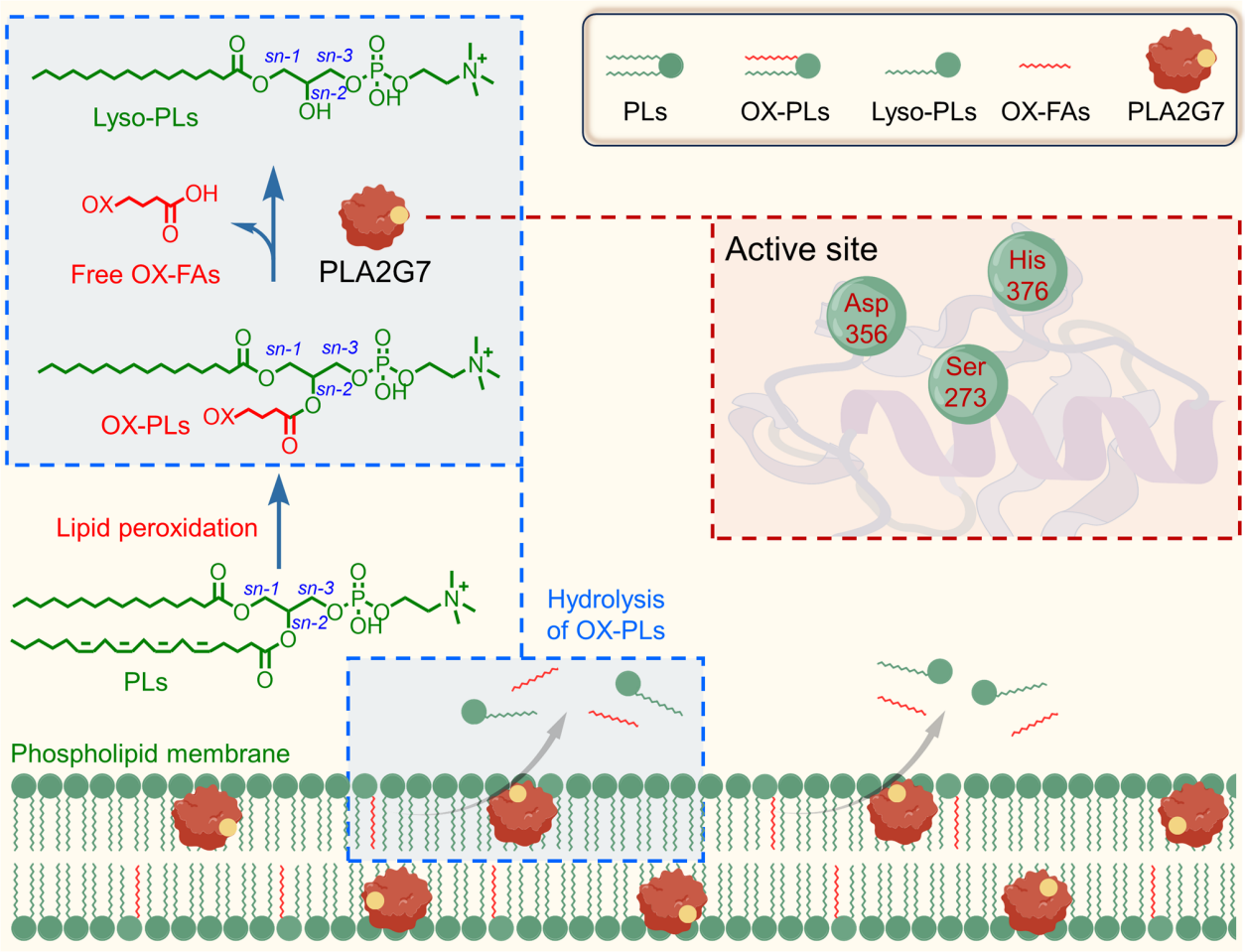

Figure 1. A brief illustration of the catalytic active site of Lp-PLA2 and its catalytic mechanism. PLs typically feature a saturated fatty acid at the sn-1 position of glycerol, while the fatty acid at the sn-2 position may vary, being either saturated, monounsaturated, or polyunsaturated. Notably, polyunsaturated fatty acids at the sn-2 position are susceptible to oxidation under conditions of oxidative stress, leading to the formation of ox-PLs through a process referred to as lipid peroxidation. Lp-PLA2 is a hydrolase enzyme characterized by a catalytic triad active site (Ser273-Asp356-His376) that effectively catalyzes the hydrolysis of the oxidized fatty acid at the sn-2 position, resulting in the release of ox-FFAs and lyso-PLs (5). Lp-PLA2, lipoprotein-associated phospholipase a2; PLs, Phospholipids, ox-PLs, oxidized phospholipids, ox-FFAs, oxidized free fatty acids, lyso-PLs, lysophospholipids.

demonstrated that the specific inhibitor darapladib exerted dose-dependent inhibitory effects in HCC models, reducing tumor formation by 60%. This inhibition was partially reversed by exogenous AA, confirming the central role of AA in tumorigenesis (Table I).

In prostate cancer, Lp-PLA2 contributes to lipid metabolism dysregulation by increasing fatty acid synthase (FASN) and carnitine palmitoyltransferase 1A (CPT1A) activity (40). Following Lp-PLA2 silencing, significant alterations in key migration-related genes were observed: Rac1 decreased by 45±6%, impairing pseudopod formation; CDC42 decreased by 38±5%, disrupting cell polarity, and STAT3 decreased by 52±7%, affecting migration-related gene expression. Mechanistically, Lp-PLA2 upregulates FASN via mTORC1 while promoting CPT1A-mediated β-oxidation (ATP increased by 60%) and increasing mitochondrial membrane potential (the JC-1 ratio increased by 1.4-fold), establishing a 'metabolism-motility coupling' mechanism (41,42). These findings highlight potential therapeutic targets, although further investigation is warranted regarding the roles of Lp-PLA2 isoforms (such as Lp-PLA2-α/β) and microenvironmental regulation.

Regulation of signaling pathways: activation of the PI3K/AKT and JAK/STAT pathways. As a crucial regulator of lipid metabolism, Lp-PLA2 in HCC activates two significant oncogenic pathways; the PI3K/AKT pathway and the JAK/STAT pathway, through its metabolites LPC and oxFFA (43-45). In HepG2 and Huh-7 HCC cell models, the overexpression of PLA2G7 promotes malignant phenotypes via the LysoPC-PI3K/AKT axis (43). Specifically, PI3K, in conjunction with PDK1, converts PIP2 to PIP3, which subsequently activates AKT. Phosphorylated AKT inhibits the proapoptotic protein Bad while activating the antiapoptotic protein Bcl-2, thereby suppressing apoptosis. Additionally, AKT accelerates cell cycle progression by modulating CDK/Cyclin complexes (43,46).

Importantly, the study by Guo and Yang (46) first revealed that PLA2G7 promotes tumor immune evasion via the JAK/STAT1/PD-L1 axis. PLA2G7 silencing resulted in a 2.3±0.4-fold reduction in p-STAT1 levels and a 58±6% decrease in PD-L1 expression. Gene set enrichment analysis confirmed the enrichment of PLA2G7 in the Programmed death-ligand 1/Programmed cell death protein 1 (PD-L1/PD-1) checkpoint pathway. Mechanistically, PLA2G7 promotes STAT1 phosphorylation, increasing phosphorylated (p-)STAT1 binding

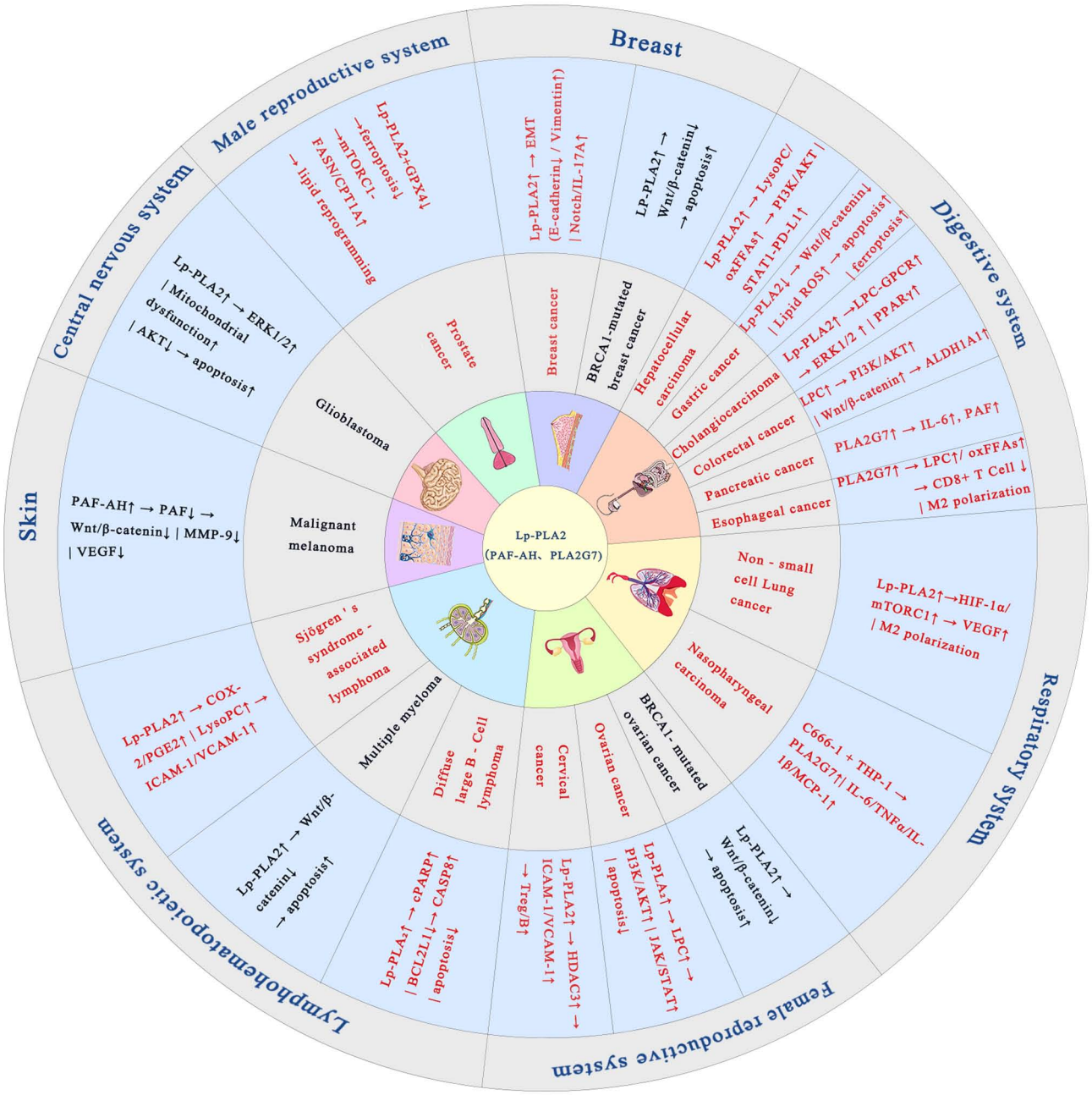

Figure 2. Opposing roles of Lp-PLA2 in different cancers: promoting or suppressing tumour progression. The circular diagram presented illustrates the diverse roles of Lp-PLA2, which is encoded by the PLA2G7 gene, in the process of carcinogenesis. The diagram is segmented into various colored sections that represent the oncogenic (red), anticarcinogenic (black), and regulatory (indicated by arrows) functions of Lp-PLA2. Each section provides detailed information regarding specific cancer types, relevant cell lines (such as THP-1 for PMA-differentiated macrophages and C666-1 for nasopharyngeal carcinoma), as well as the molecular mechanisms or alterations in gene expression that are modulated by Lp-PLA2. For example, in the context of breast cancer, Lp-PLA2 influences tumorigenesis by affecting the mutation status of BRCA1, whereas in hepatocellular carcinoma, it plays a role in the regulation of STAT3/STAT1 signaling pathways. Additionally, the diagram indicates variations in Lp-PLA2 expression levels (with upward arrows denoting increases and downward arrows indicating decreases) and outcomes from co-culture experiments (denoted by a plus sign). This visualization emphasizes the intricate interactions of Lp-PLA2 within tumour biology, highlighting its functional plasticity that is dependent on the specific context of various TMEs. AKT, protein kinase B; ALDH1A1, aldehyde dehydrogenase 1 family member A1; BRCA1, breast cancer gene 1; CD8, cluster of differentiation 8; ERK1/2, extracellular signal-regulated kinases 1 and 2; GPX4, glutathione peroxidase 4; HDAC3, histone deacetylase 3; HIF-1α, hypoxia-inducible factor-1 alpha; ICAM-1, intercellular adhesion molecule-1; IL-1β, interleukin-1 beta; IL-6, interleukin-6; JAK, Janus kinase; LPC, lysophosphatidylcholine; LP, lysophospholipid/lipid peroxidation; Lp-PLA2, lipoprotein-associated phospholipase a2; .MCP-1, monocyte chemoattractant protein-1; MMP-9, matrix metalloproteinase-9; mTORC1, mechanistic target of rapamycin complex 1; oxFFA, oxidized free fatty acid; PAF, platelet-activating factor; PAF-AH, platelet-activating factor acetylhydrolase; PI3K, phosphoinositide 3-kinase; PLA2G7, phospholipase A2 group VII; PGE2, prostaglandin E2; STAT, signal transducer and activator of transcription; THP-1, human monocytic leukemia cell line; TNF-α, tumor necrosis factor-alpha; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; Wnt/β-catenin, wingless-type MMTV integration site family/β-catenin signaling pathway.

to the PD-L1 promoter and increasing PD-L1 transcription. The application of an exogenous STAT1 activator (2NP) fully reversed this phenotype, validating the existence of the PLA2G7-JAK/STAT1-PD-L1 axis (46).

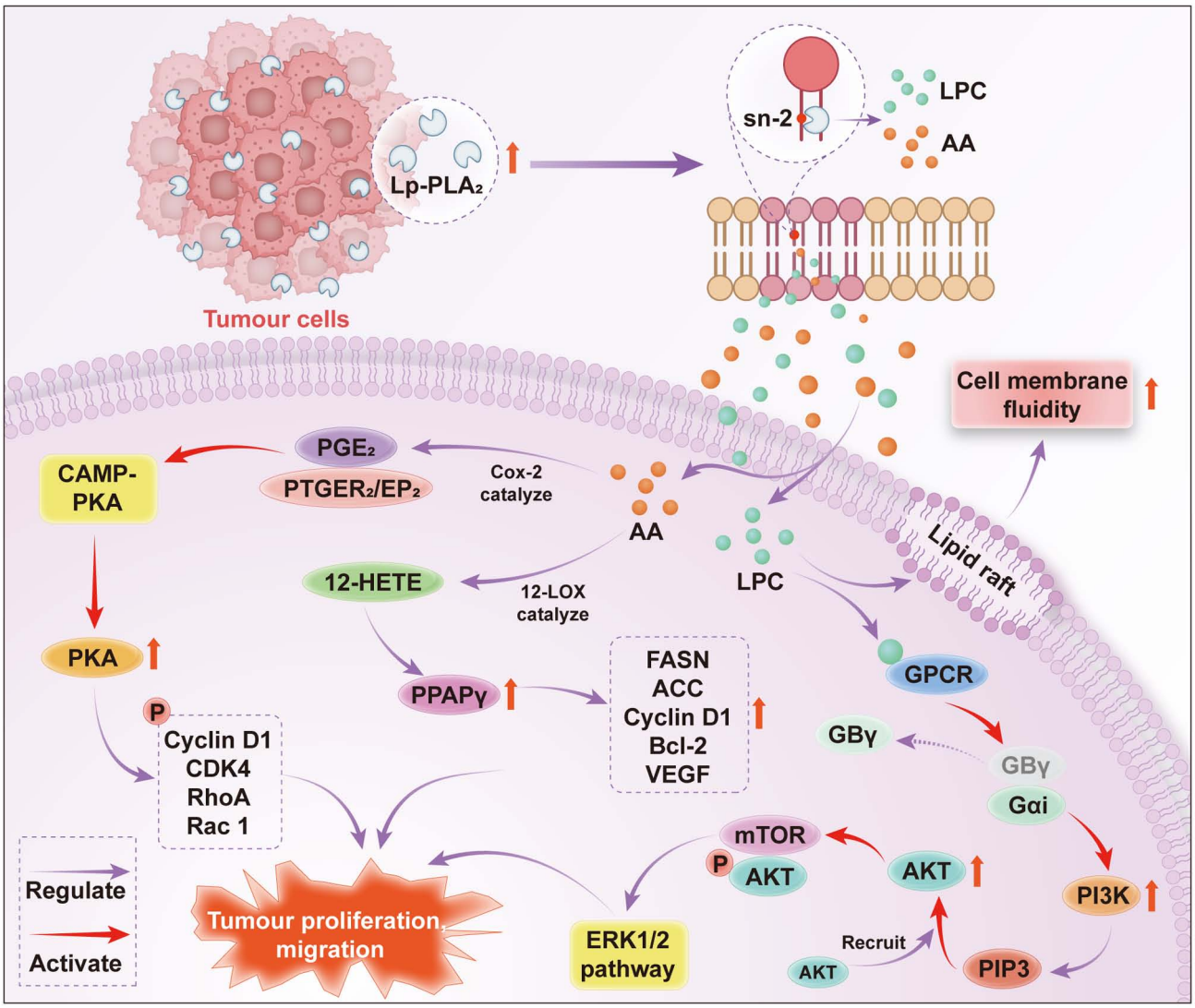

Figure 3. The role of Lp-PLA2 in lipid metabolic reprogramming and the associated downstream signaling pathways in cancer. Lp-PLA2 is notably upregulated in cancer. Its enzymatic product, LPC, serves dual oncogenic roles: i) Facilitating the assembly of lipid rafts to improve membrane fluidity and (ii) activating Gαi-ERK1/2 signaling through the LPC-GPCR pathway. Additionally, metabolites of AA derived from Lp-PLA2 contribute to tumor progression through two interrelated pathways: the established COX-2/PGE2 signaling cascade and the recently discovered 12-HETE-PPARγ pathway. Collectively, these mechanisms play a significant role in driving cancer pathogenesis. AA, arachidonic acid; ACC, acetyl-CoA carboxylase; AKT, protein kinase B; cAMP, cyclic adenosine monophosphate; CDK4, cyclin-dependent kinase 4; COX-2, cyclooxygenase-2; EP2, prostaglandin E2 receptor 2; ERK1/2, extracellular signal-regulated kinases 1 and 2; FASN, fatty acid synthase; GBY, G-protein βγ subunit; Gai, inhibitory G-protein α subunit; GPCR, G-protein-coupled receptor; 12-HETE-PPARγ, 12-hydroxyeicosatetraenoic acid-peroxisome proliferator-activated receptor γ; 12-LOX, 12-lipoxygenase; LPC, lysophosphatidylcholine; Lp-PLA2, lipoprotein-associated phospholipase a2; mTOR, Mechanistic target of rapamycin; PC, phosphatidylcholine; PI3K, phosphoinositide 3-kinase; PIP3, phosphatidylinositol-trisphosphate; PKA, protein kinase A; PPARγ, peroxisome proliferator-activated receptor γ; PGE2, prostaglandin E2; PTGER2, prostaglandin E2 receptor 2; Rac1, Ras-related C3 botulinum toxin substrate 1; RhoA, Ras homolog family member A; VEGF, vascular endothelial growth factor.

Further investigations revealed cross-talk between the PI3K/AKT and JAK/STAT pathways, which reshapes the tumor microenvironment (TME). Owing to the heterogeneity of the microenvironment, the interaction patterns of these pathways vary markedly, which influences tumor progression, immune evasion, and treatment responses (Table II).

Maintenance of cancer stem cell properties: Regulation of aldehyde dehydrogenase (ALDH) activity. ALDH1A1, a key regulator of cancer stem cell (CSC) self-renewal and drug resistance, is tightly regulated by multiple pathways, including the PI3K/AKT and Wnt/β-catenin pathways, which are associated with Lp-PLA2 (38,47,48). The PI3K/AKT/mTOR pathway directly activates ALDH1A1 via β-catenin/TCF4, whereas the PLA2G7-LPC-Wnt axis indirectly upregulates its expression, particularly in prostate cancer (38). The Notch and Hippo/YAP pathways regulate ALDH1A1 promoter activity through the NICD-HEY1 and YAP-TEAD pathways, respectively (49,50).

ALDH1A1, recognized as a CSC marker, is involved in aldehyde detoxification and tumor initiation (51,52). In prostate cancer models, the silencing of PLA2G7 leads to a reduction in ALDH1A1 expression, thereby suppressing tumor initiation and metastasis (38). Additionally, ALDH1A1 sustains CSC stemness through the retinoic acid-RAR/RXR feedback loop, and its expression modulated by hypoxia 1α/NF-κB) and inflammation (TGF-β/Smad).

Table I. Functions of lipid metabolites mediated by LP-PLA2 in neoplastic tissues and results of experimental validation.

Metabolite	Generation pathway	Direct effect	Downstream pathway	Tumour phenotype	Experimental validation
LPC	Hydrolysis by LP-PLA2	Increases membrane fluidity	Gαi-ERK1/2 phosphorylation	Increased migration and invasion capacity	Migration was suppressed in organoid models
AA	Released by LP-PLA2	Serves as a precursor for inflammatory mediators	COX-2/PGE_2	Increased immune evasion and angiogenesis	Tumour formation was restored by exogenous AA
12-HETE	Derived from AA metabolism	Activates PPARγ	Transcription of PPARγ target genes	Enhancement of cell survival and drug resistance	Apoptosis was increased after inhibitor treatment

AA, arachidonic acid; COX-2, cyclooxygenase-2; ERK1/2, extracellular signal-regulated kinases 1 and 2; Gαi, inhibitory G-protein α subunit; 12-HETE, 12-hydroxyeicosatetraenoic acid; LPC, lysophosphatidylcholine; Lp-PLA2, lipoprotein-associated phospholipase a2; PGE2, prostaglandin E2; PPARγ, peroxisome proliferator-activated receptor γ.

Table II. PI3K/AKT-JAK/STAT crosstalk and therapy in TMEs (Lp-PLA2).

Molecular marker/ microenvironment type	Dominant pathway crosstalk mechanism	Key features	Targeted strategy
PLA2G7 (HCC)	PI3K/AKT-STAT1→PD-L1↑ and anti-apoptosis	MDSCs↑, PD-L1↑	PI3K inhibitor + JAK inhibitor
ALDH1A1 (Breast cancer)	PI3K/AKT-STAT3→inflammation↑ and MDSC expansion	M2 macrophage↑, neutrophil infiltration	JAK2 inhibitor + PI3Kδ inhibitor
Hypoxic tumour	HIF-1α-STAT3-AKT positive loop feedback	Angiogenesis↑, glycolysis↑	HIF-1α inhibitor + AKT inhibitor
Virus-associated tumour	Viral protein→PI3K/AKT and STAT5 antagonism	T-cell exhaustion	Antiviral therapy + immune checkpoint inhibitor
ALDH1B1/L1 (HCC)	PI3K/AKT inhibition + STAT1 quiescence	Low inflammation level	ALDH1B1/L1 activator

AKT, protein kinase B (PKB); ALDH1A1, aldehyde dehydrogenase 1 family member A1; ALDH1B1, aldehyde dehydrogenase 1 family member B1; HCC, hepatocellular carcinoma; HIF-1α, hypoxia-inducible factor-1 α; JAK, Janus kinase; Lp-PLA2, lipoprotein-associated phospholipase a2; MDSCs, Myeloid-derived suppressor cells; PD-L1, Programmed death-ligand 1; PI3K, Phosphoinositide 3-kinase; PLA2G7, Phospholipase A2 group VII; STAT1, signal transducer and activator of transcription 1; STAT3, signal transducer and activator of transcription 3; STAT5, signal transducer and activator of transcription 5; TME, tumor microenvironment.

Clinically, elevated ALDH1A1 expression is associated with poor prognosis across various cancers (53). Of prostate cancers, ~50% express PLA2G7, which is associated with high-grade tumors. Silencing of PLA2G7 reduces LPC levels, inducing apoptosis, whereas statins increase the anti-proliferative effects of this protein.

The aforementioned mechanisms are interrelated and collectively contribute to the complex role of Lp-PLA2 in tumor progression.

3. The dual role of Lp-PLA2 in tumor development

Lp-PLA2 has been identified as having a context-dependent dual role in tumor biology and its functional implications vary according to tumor type and the characteristics of the microenvironment (54). Unlike traditional pro-oncogenic factors such as VEGF and MYC, Lp-PLA2 influences tumor progression through various pathways. For example, it collaborates with glutathione peroxidase 4 (GPX4) to inhibit ferroptosis in prostate cancer while concurrently suppressing the Wnt/β-catenin signaling pathway in breast cancer gene 1 (BRCA1)-mutated breast cancer (17,55,56) (Table III). This seemingly contradictory behavior may be attributed to substrate selectivity (such as differential hydrolysis of oxidized phospholipids versus PAF) or the heterogeneity of the microenvironment (such as variations in reactive oxygen species levels and immune cell infiltration).

Lp-PLA2 and tumor progression. Lp-PLA2 may affect tumor progression via the regulation of various mechanisms,

Table III. Dual regulatory roles of Lp-PLA2 in tumours and associated mechanisms.

Function of Lp-PLA2	Key mechanism	Related tumours	Therapeutic implications
Pro-tumour effects	EMT induction (↓E-cadherin, ↑vimentin)	Breast cancer, prostate cancer	Targeting of Lp-PLA2 or combination with Notch inhibitors
	Synergistic inhibition of ferroptosis with GPX4	Prostate cancer	Combination with ferroptosis inducers (such as erastin)
	Promotion of tumor immune evasion via lipid mediator generation	HCC	PLA2G7 inhibition combined with PD-1 blockade
Antitumour effects	Suppression of Wnt/β-catenin pathway	BRCA1-mutated breast/ovarian cancer	Potential as a prognostic marker or therapeutic target

BRCA1, breast cancer gene 1; EMT, epithelial-mesenchymal transition; GPX4, glutathione peroxidase 4; HCC, hepatocellular carcinoma; Lp-PLA2, lipoprotein-associated phospholipase a2; PD-1, programmed cell death protein 1; PLA2G7, phospholipase A2 group VII.

including EMT, ferroptosis, angiogenesis, and apoptosis, with effects highly specific to the tumor type.

Promotion of EMT and tumor metastasis. EMT is a pivotal process in cancer metastasis and is characterized by the loss of epithelial characteristics and the acquisition of mesenchymal traits in epithelial cells (57). EMT not only facilitates metastasis but also contributes to the generation, functionality and drug resistance of cancer stem cells (58). Key features of EMT include the downregulation of the epithelial adhesion molecule E-cadherin and the upregulation of the mesenchymal marker vimentin (59,60). Elevated vimentin expression is associated with increased aggressiveness and a poor prognosis for metastatic tumors (61-63).

In breast cancer, a significant positive association is observed between Lp-PLA2 expression and vimentin expression. Silencing Lp-PLA2 results in a marked reduction in vimentin levels, thereby inhibiting EMT. Furthermore, the downregulation of E-cadherin, a hallmark of EMT, is reversed upon Lp-PLA2 silencing, reinforcing its role in promoting EMT. The functional impairment of Lp-PLA2 also influences the IL-17A, Notch and oncostatin M signaling pathways, underscoring its importance in regulating EMT, cell migration and invasion (17). The proinflammatory cytokine IL-17A is a crucial initiator of breast cancer metastasis, chemotherapy resistance, angiogenesis and cell proliferation (17). Concurrently, the Notch pathway is been closely associated with the activation of EMT in cancer cells (64-68). Notably, inhibition of the Notch pathway induces growth arrest in breast cancer stem cells and suppresses EMT (50). These findings elucidate the complex mechanisms through which Lp-PLA2 regulates tumor metastasis and EMT via multiple signaling pathways.

Synergistic inhibition of ferroptosis by Lp-PLA2 and GPX4. Ferroptosis, an iron-dependent form of programmed cell death, is distinct from apoptosis and necrosis. Its primary mechanism involves the depletion of glutathione, leading to the loss of GPX4 activity and the initiation of lipid peroxidation cascades mediated by lipoxygenases or cytochrome P450 oxidoreductase (69,70). Recent studies have increasingly clarified the role of ferroptosis in various pathological processes, particularly in cancer initiation, progression, and metastasis. Under conditions of oxidative stress, intracellular polyunsaturated fatty acids undergo oxidation, resulting in the accumulation of lipid peroxides, which disrupt membrane integrity and trigger ferroptosis (71-73). Under normal physiological conditions, the antioxidant system, in which GPX4 plays a central role, maintains redox homeostasis by reducing lipid peroxides, thereby inhibiting ferroptosis (74).

Prostate cancer cells exhibit resistance to ferroptosis through a unique dual-defense mechanism. Lp-PLA2 specifically hydrolyses oxidized phospholipids (such as oxidized phosphatidylethanolamine) in cell membranes, directly eliminating lipid peroxides, whereas GPX4 indirectly reduces peroxidation products through reduction reactions (55). These mechanisms are functionally complementary: GPX4 relies on antioxidant pathways to repair oxidative damage, whereas Lp-PLA2 mitigates the accumulation of oxidized phospholipids through hydrolysis. Structurally, Lp-PLA2 cleaves the sn-2 oxidized acyl ester bond (but not nonoxidized phospholipids) to directly remove PE-OOH, whereas GPX4 reduces free peroxides via its Sec46 residue (75,76). This substrate preference and catalytic division create spatial-metabolic complementarity (Table IV). Their synergistic action markedly promotes tumor cell survival in high-ROS environments induced by radiotherapy or chemotherapy (55,77).

Targeting key regulators of ferroptosis (such as GPX4 degradation or ALOX15 activation) has emerged as a novel strategy to increase the sensitivity of tumors to therapies (78). However, the role of Lp-PLA2 in maintaining membrane lipid homeostasis may diminish the efficacy of such treatments, suggesting the potential benefit of combining Lp-PLA2 inhibitors (such as darapladib) with ferroptosis inducers (55,79). Furthermore, ferroptosis resistance has been identified as a critical characteristic of tumor metastasis. During the metastatic process, tumor cells rely on endogenous defense mechanisms and microenvironmental resources for survival: early stages depend on the Lp-PLA2-GPX4 axis to maintain oxidative membrane stability, whereas distal colonization involves the uptake of antioxidant molecules (such as oleic acid) from the lymph or cerebrospinal fluid to further reinforce ferroptosis

Table IV. Compared molecular mechanisms of Lp-PLA2 and GPX4 in ferroptosis inhibition.

Feature	Lp-PLA2	GPX4
Mechanism	Hydrolysis of oxidized phospholipids (such as PE-OOH)	Reduction of lipid peroxides (GSH-dependent)
Substrate preference	Oxidized sn-2 acyl ester bonds	Free peroxides
Functional complementarity	Direct clearance of membrane oxidative damage	Oxidative damage repair
Therapeutic implications	Combined use of inhibitors with ferroptosis inducers	Targeted therapy via GPX4 degradation

GPX4, glutathione peroxidase 4; GSH, glutathione; Lp-PLA2, lipoprotein-associated phospholipase a2; PE-OOH, phosphatidylethanolamine hydroperoxide.

resistance (80). This discovery provides a theoretical foundation for combination therapies targeting metastatic tumors.

Promotion of tumor angiogenesis. VEGF is a key proangiogenic factor that activates the MAPK/ERK and PI3K/AKT pathways upon binding to VEGFR, thereby promoting tumor cell growth, proliferation, migration, and invasion (81,82). In the TME, VEGF is produced by tumor cells and regulated by immune cells (83). Immune cells have been shown to modulate local VEGF signaling by releasing VEGF and its soluble receptor VEGFR-1, potentially contributing to tumor immune evasion (84).

Further investigations revealed that Lp-PLA2 upregulates VEGF expression in human umbilical vein endothelial cells via the HIF1α and mTORC1 pathways, thereby promoting angiogenesis and cell migration. Additionally, hydrolysis products of Lp-PLA2 stimulate VEGF release from tumor cells and surrounding immune cells, further supporting tumor growth and angiogenesis (85). These findings underscore the dual role of Lp-PLA2 in facilitating tumor progression through VEGF signaling within the TME.

Activation of cell signaling pathways. Aberrant activation of cell signaling pathways is critical for tumor growth and progression (86). Lp-PLA2 has been shown to activate the Rho GTPase pathway, which regulates cytoskeletal dynamics and cell motility, thereby markedly promoting the migration and invasion of prostate cancer cells (87). Moreover, PAF-AH IB2 (the catalytic subunit of intracellular PAF-AH) is overexpressed in ovarian cancer cells, promoting proliferation and acting as a key mediator of oncogenic tyrosine kinase signaling. It synergizes with the tyrosine kinase-VEGFR pathway to regulate the abnormal proliferation of ovarian cancer cells (88).

Inhibition of tumor cell apoptosis. Apoptosis, a programmed cell death process, plays a pivotal role in cancer development, progression, and treatment. The acquisition of antiapoptotic traits is recognized as a hallmark of cancer cells, conferring survival advantages, promoting tumor evolution, and contributing to therapeutic resistance (89). Consequently, the inhibition of apoptosis is considered a critical factor in tumor progression (90).

In ERG-positive prostate cancer, silencing PLA2G7 markedly increased the mRNA expression of the proapoptotic gene CASP8, indicating activation of the extrinsic apoptotic pathway. Concurrently, the downregulation of the antiapoptotic gene BCL2L1 further promoted apoptosis. In another study, PLA2G7 silencing resulted in increased cleavage of cleaved poly ADP-ribose polymerase (cPARP), suggesting the activation of apoptosis through both intrinsic and extrinsic pathways (91). In diffuse large B-cell lymphoma (DLBCL), Lp-PLA2 knockdown markedly increased apoptosis rates and treatment with darapladib also induced apoptosis, confirming the antiapoptotic role of Lp-PLA2 in DLBCL (92).

Knockdown of PAF-AH IB2, the catalytic subunit of intracellular PAF-AH, markedly increased the percentage of apoptotic ovarian cancer cells. The mechanisms involved included i) G_2/M cell cycle arrest, with a significant increase in G_2/M-phase cells, which promotes inhibition of proliferation and induction of apoptosis; ii) increased phosphorylation of p53-Ser15 and reduced phosphorylation of p44/42 MAPK, which triggers apoptosis; iii) caspase activation, with the proportion of caspase-positive cells increasing from 17.6±2.5% to 35.2±3.1%; and iv) increased sensitivity to PAF (88). These results underscore the critical role of Lp-PLA2 and related enzymes in tumor cell apoptosis, suggesting their potential as therapeutic targets.

Tumor-suppressive function of Lp-PLA2. Lp-PLA2 (PAF-AH) has demonstrated considerable functional heterogeneity across various tumor types. This enzyme exerts distinct biological effects within different TMEs through its selective hydrolysis of the sn-2 acetyl group of platelet-activating factor (PAF). While Lp-PLA2 predominantly facilitates tumor progression, it has also been reported to exhibit inhibitory effects under specific conditions (93). The variability in its function is influenced by multiple factors, including substrate selectivity, interactions among signaling pathways, and the characteristics of the TME.

Protective role in BRCA1-mutated tumours. Lp-PLA2 expression levels are markedly higher in breast cancer samples with BRCA1 mutations than in wild-type samples. Functional analyses indicates that silencing Lp-PLA2 markedly improves the survival, proliferation and migratory

capabilities of HCC1937 cells, suggesting that its protective effects may be mediated through the negative regulation of the Wnt/β-catenin signaling pathway (56). Similarly, in BRCA1-mutated ovarian cancer, elevated Lp-PLA2 expression is associated with a favorable prognosis, which is also associated with modulation of the Wnt/β-catenin pathway (94). These observations indicate that Lp-PLA2 may function as a tumor suppressor in tumors with specific genetic backgrounds by regulating critical signaling pathways.

Multifaceted regulatory mechanisms. The dual role of Lp-PLA2 is governed by several regulatory mechanisms. First, substrate competition effects have been noted: Under oxidative stress conditions, Lp-PLA2 promotes tumor progression by hydrolyzing oxidized phospholipids (such as PE-OOH), whereas in PAF-rich microenvironments, it inhibits tumor progression through the degradation of PAF (54). Second, interactions among signaling pathways have been identified: In BRCA1-mutated tumors, Lp-PLA2 inhibits the Wnt/β-catenin pathway, whereas in prostate cancer, its metabolites (such as lysophosphatidic acid) activate the Notch-EMT axis (56,64,94). Third, regulation by the TME has been demonstrated: IL-10 secreted by tumor-associated macrophages (TAMs) can upregulate Lp-PLA2 expression, although the functional heterogeneity between M1- and M2-polarized TAM subsets remains unclear (95-97). These findings elucidate the intricate regulatory network of Lp-PLA2 within the TME.

Tissue-specific functional variations. The involvement of the Wnt/β-catenin pathway in tumorigenesis is highly tissue specific. Lp-PLA2 has been shown to exert protective effects on breast and ovarian cancers through the modulation of this pathway. Conversely, divergent functions have been observed in other tumor types. For example, in colorectal and pancreatic cancers, increased Lp-PLA2 expression is closely linked to cancer cachexia; however, neither genetic knockdown nor pharmacological inhibition markedly alleviate symptoms, suggesting that Lp-PLA2 may primarily serve as an inflammatory biomarker rather than a direct pathogenic factor. Similarly, in lung cancer models, increased Lp-PLA2 levels are associated with tissue wasting, probably reflecting systemic inflammatory responses akin to those observed in colorectal cancer. These functional discrepancies can be attributed to variations in lipid substrates (such as PAF versus oxidized phospholipids) and the composition of immune cells within the TME. For example, in microenvironments dominated by M1 macrophages, Lp-PLA2 is posited to promote inflammation, whereas under different conditions, it may exhibit anti-inflammatory properties (95). These complexities underscore Lp-PLA2 as a potential therapeutic target for specific tumor types, highlighting the necessity of considering both tumor classification and microenvironmental characteristics in clinical applications.

4. Lp-PLA2 and the TME

The TME, which includes stromal cells, immune cells, extracellular matrix components and soluble factors, constitutes a complex ecosystem that markedly influences tumor progression. The TME facilitates tumor immune evasion and metastasis through mechanisms related to immunosuppression and chronic inflammation (98). Lp-PLA2, a crucial regulatory molecule within the TME, plays dual roles in modulating inflammation and immune responses.

Immune evasion. Recent investigations have revealed that Lp-PLA2 (PLA2G7) contributes to tumor immune evasion via two primary mechanisms. First, it alters the immunosuppressive TME by inhibiting T lymphocyte proliferation and promoting the polarization of macrophages towards the M2 phenotype (99). Second, its hydrolytic products, namely, lyso-PC and ox-FFAs, have been shown to facilitate metabolic reprogramming and energy supply in M2 macrophages through the PPARγ/Arg-1 pathway and CPT1A-mediated fatty acid oxidation, respectively (100,101). Clinical studies have indicated that in HCC, macrophages with increased PLA2G7 expression display a pronounced M2-polarized phenotype, which is associated with poor patient outcomes and resistance to immunotherapy. Conversely, the inhibition of PLA2G7 has been shown to reverse immunosuppression and enhance the infiltration of CD8+ T cells (99). Mechanistic studies involving small interfering (si)RNA-mediated silencing of PLA2G7 (siPLA2G7) revealed significant suppression of HCC progression and downregulation of PD-L1 expression; notably, these effect may be mediated by the STAT1 signaling pathway (46). Furthermore, patients exhibiting high expression of both PLA2G7 and CD68 present decreased CD8+ T-cell infiltration, which is indicative of an immunosuppressive TME (99) (Fig. 4). Additionally, in cervical cancer and other malignancies, the level of PLA2G7 expression is associated with the degree of immune cell infiltration (102), suggesting a conserved role for Lp-PLA2 in immune evasion across various cancer types.

Interaction between inflammation and tumors. Research has indicated that Lp-PLA2 plays a significant role in tumor immune evasion through its immunomodulatory effects and its substantial impact on the TME by mediating inflammatory responses (103). Within this microenvironment, Lp-PLA2 has been shown to hydrolyze phospholipids, resulting in the production of inflammatory mediators such as arachidonic acid. This process recruits inflammatory cells and stimulates the secretion of protumorigenic factors, thereby increasing tumor cell proliferation, migration and invasion (87,104). For example, in the context of prostate cancer, inflammatory responses mediated by PLA2G7 markedly promote tumor progression (87). In cases of lymphoma associated with Sjögren's syndrome, LPC generated by Lp-PLA2 is observed to upregulate the expression of adhesion molecules, such as ICAM-1 and VCAM-1, which promote interactions between tumor cells and endothelial cells, thereby facilitating metastasis (105). Additionally, oxidized fatty acids and LPC derived from Lp-PLA2 induce the migration and proliferation of smooth muscle cells, further promoting tumor angiogenesis. Collectively, these findings position Lp-PLA2 as a pivotal element linking tumor immunity and inflammatory responses (Table V).

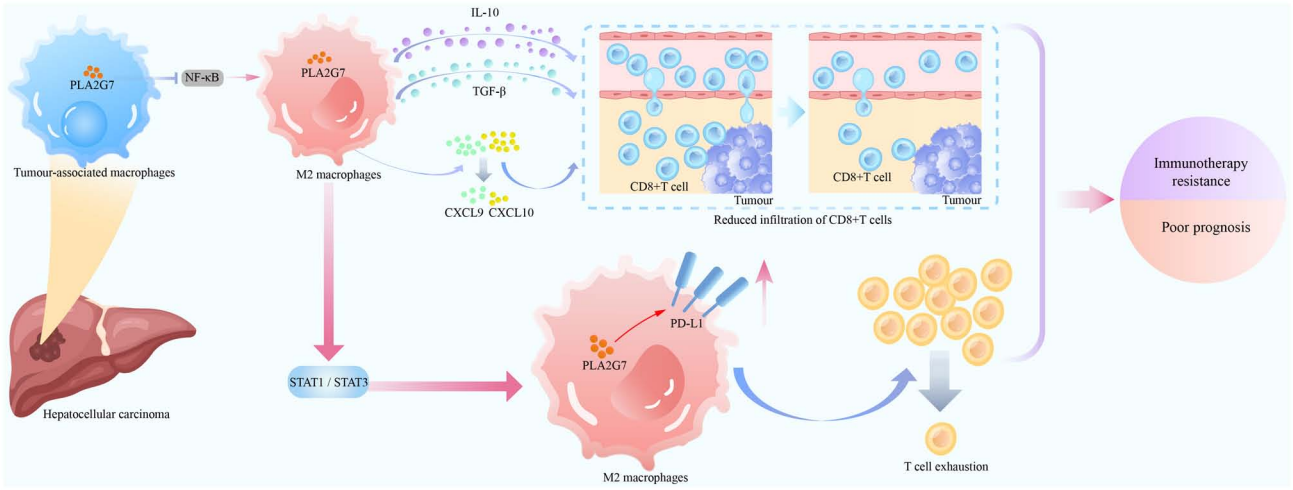

Figure 4. Lp-PLA2-Driven immunosuppression in the TME. PLA2G7 orchestrates tumor immune evasion through two integrated mechanisms: (i) cell-intrinsic suppression of T lymphocyte proliferation to cripple antitumor immunity, and (ii) cell-extrinsic polarization of macrophages toward the M2 phenotype that establishes an immunosuppressive niche. These coordinated actions culminate in adverse clinical outcomes and acquired immunotherapy resistance. CD8, cluster of differentiation 8; CXCL9, C-X-C motif chemokine ligand 9; CXCL10, C-X-C motif chemokine ligand 10; HNF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL-10, interleukin-10; Lp-PLA2, lipoprotein-associated phospholipase a2; PD-L1, programmed death-ligand 1; PLA2G7, phospholipase A2 group VII; STAT1, signal transducer and activator of transcription 1; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor β; TME, tumor microenvironment.

Despite advances in understanding the mechanisms by which Lp-PLA2 operates within the TME, several areas remain to be clarified, including its tissue-specific regulatory mechanisms, potential synergistic interactions with other immune checkpoints, and translational potential in clinical settings.

5. Lp-PLA2 as a tumor biomarker

Diagnostic value of Lp-PLA2. Studies have highlighted the considerable diagnostic ability of Lp-PLA2 across various malignancies. In the context of lung cancer, serum levels of Lp-PLA2 are positively associated with CA199 and pleural effusion Lp-PLA2 but negatively associated with AFP and LDH. These associations can be assessed to effectively differentiate malignant pulmonary conditions from benign pulmonary conditions (20). The underlying mechanism suggests that Lp-PLA2 may modulate CA199 expression by hydrolyzing ox-LDL, thereby activating inflammatory pathways and influencing LDH and AFP levels through metabolic reprogramming. In terms of diagnostic efficacy, Lp-PLA2 exhibits superior sensitivity and specificity compared with traditional biomarkers such as CEA and CA125. Additionally, variations in Lp-PLA2 concentrations are indicative of pathological subtypes; specifically, increased levels are predictive of adenocarcinoma and reduced levels are predictive of squamous cell carcinoma. In other malignancies, Lp-PLA2 has also shown diagnostic relevance: Its activity is associated with PSA levels and inversely associated with PON1 activity in prostate cancer (106); increased Lp-PLA2 levels are noted in early-stage cachexia associated with colorectal and pancreatic cancers (116) and Lp-PLA2 gene methylation levels are closely associated with clinical outcomes in specific cancer types (32). Collectively, these findings position Lp-PLA2 as a significant pancancer diagnostic biomarker.

Prognostic evaluation value of Lp-PLA2. Numerous studies have confirmed the prognostic relevance of Lp-PLA2 across various malignancies. In hematological cancers, increased PLA2G7 expression in patients with DLBCL is markedly associated with adverse prognostic indicators, including increased monocyte infiltration, heightened macrophage differentiation, increased serum β2-microglobulin levels, decreased albumin levels and increased CD10 positivity. These associations may be mediated by IL-34 secretion, which promotes tumor progression (92,117). In solid tumors, Lp-PLA2 expression levels are strongly associated with disease progression in prostate cancer and melanoma (20,118). Notably, increased expression of other members of the PLA2 family, such as PLA2G2A, markedly delays disease recurrence in small-cell lung cancer (119), further emphasizing the prognostic importance of PLA2 proteins. These findings underscore the importance of Lp-PLA2 and its family members as critical molecular markers for cancer prognosis.

Despite these promising findings, current research is limited by sample heterogeneity and a lack of multicenter validation. Future investigations should prioritize the standardization of detection protocols and the elucidation of the molecular mechanisms underlying Lp-PLA2 across various cancers to fully harness its potential as a pancancer biomarker in clinical settings.

6. Therapeutic strategies targeting Lp-PLA2 in tumors

Current investigations into Lp-PLA2-targeted tumor therapies have focused predominantly on the formulation of small-molecule inhibitors, the assessment of combination therapies, and the validation of the role of Lp-PLA2 in modulating the TME (120-122) (Fig. 5). Nevertheless, its potential applications in targeting cancer stem cells, regulating premetastatic niches, and therapeutic interventions involving interactions with epigenetic modifications remain inadequately explored.

Table V. Tumour-specific effects of Lp-PLA2/PLA2G7 on the immune microenvironment and clinical correlations.

First author/s, year	Tumour type	Major immune alterations	Key inflammatory mediators	Signalling pathways	Clinical correlations	(Refs.)
Guo, 2024; Zhang, 2024	HCC	Decreased CD8+ T-cell infiltration; increased M2 macrophage infiltration	Elevated IL-10 and TGF-β	STAT1/STAT3 pathway	Associated with advanced stage	(46,99)
Alinezhad, 2016; Benli, 2017	Prostate cancer	Enhanced Treg recruitment; reduced NK cell activity	Increased arachidonic acid metabolites; elevated COX-2/PGE2	PPARγ activation	Associated with Gleason score	(87,106)
Wu, 2024; De, 2024	Non-small cell lung cancer	Increased PD-L1+ macrophage infiltration; impaired DC maturation	Elevated IL-6 and IL-8	NF-κB activation	Predictive of-immunotherapy response	(107,108)
Cha, 2020; Yang, 2015	Breast cancer	Increased MDSC and TAM infiltration	Elevated lysophosphati-dylcholine and VEGF	CSF1/CSF1R axis	Associated with metastasis risk	(109,110)
Zhang, 2024; Oliveira, 2021; Schol, 2024; Song, 2024	Melanoma	Impaired CD8+ T-cell function; increased N2 neutrophil infiltration	Elevated PGE2 and ROS	TLR4/MyD88 pathway	Darapladib enhanced PD-1 efficacy	(99,111-113)
Chu, 2023; Wang, 2021; Pang, 2025	Cervical cancer	Increased B Cell infiltration and Tregs	Elevated ICAM-1/VCAM-1	HDAC3 activation	Associated with persistent HPV infection	(102,114-115)

CD8, cluster of differentiation 8; COX-2, cyclooxygenase-2; CSF1, colony-stimulating factor 1; DC, dendritic cell; HDAC3, histone deacetylase 3; HCC, hepatocellular carcinoma; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; Lp-PLA2, lipoprotein-associated phospholipase a2; MDSC, myeloid-derived suppressor cell; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; nK, Natural killer cell; N2, neutrophil type 2; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PGE2, prostaglandin E2; PLA2G7, phospholipase A2 group VII; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; STAT1, signal transducer and activator of transcription 1; STAT3, signal transducer and activator of transcription 3; TAM, tumor-associated macrophage; TGF-β, transforming growth factor β; TLR4, Toll-like receptor 4; Treg, regulatory T cell; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

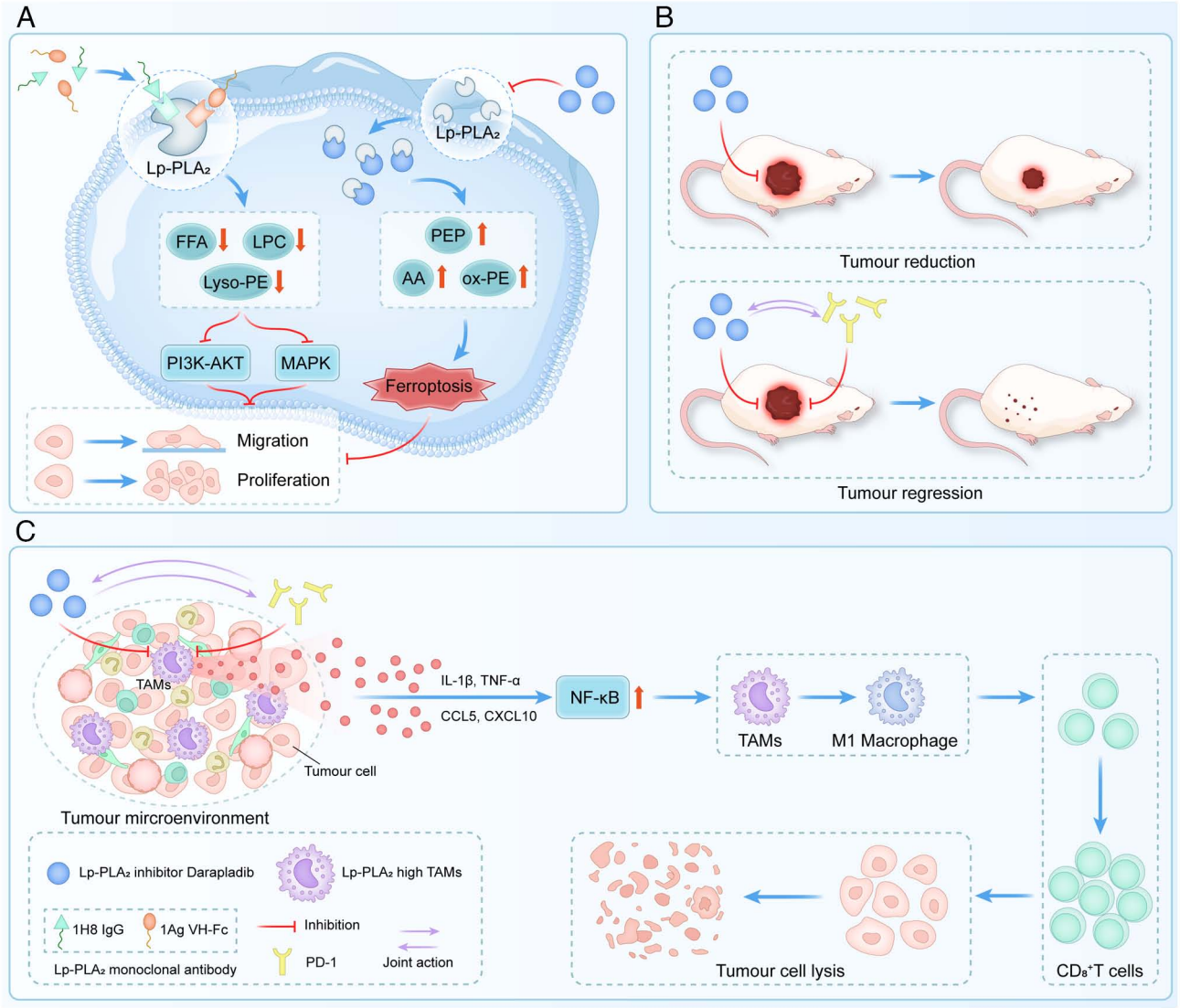

Figure 5. Therapeutic strategies targeting Lp-PLA2 in tumor treatment. (A) Therapeutic strategies aimed at targeting Lp-PLA2 in the context of tumour treatment. Three distinct methodologies are presented: i) The small-molecule inhibitor darapladib, which enhances lipid metabolism, thereby increasing the susceptibility of cancer cells to ferroptosis. ii) Monoclonal antibodies (1H8 IgG and 1Ag VH-Fc) that selectively bind to specific epitopes of Lp-PLA2, effectively inhibiting the proliferation and migration of tumor cells. B and C the synergistic antitumor effects observed when darapladib is combined with PD-1 blockade. *In vitro* and *in vivo* studies both indicate that the combination of darapladib with a PD-1 inhibitor results in a significant reduction in tumor growth compared to the effects of monotherapy. AA, arachidonic acid; CCL5, C-C motif chemokine ligand 5; CD8, cluster of differentiation 8; CXCL10, C-X-C motif chemokine ligand 10; FFA, free fatty acid; IL-1β, interleukin-1 β; LPC, lysophosphatidylcholine; Lp-PLA2, lipoprotein-associated phospholipase a2; Lyso-PE, lysophosphatidylethanolamine; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; Ox-PE, oxidized phosphatidylethanolamine; PD-1, programmed cell death protein 1; PEP, phosphatidylethanolamine plasmalogen; PI3K-AKT, phosphoinositide 3-kinase-protein kinase B pathway; TAMs, tumour-associated macrophages; TNF-α, tumor necrosis factor-α.

Small-molecule inhibitors and ferroptosis induction. Small-molecule inhibitors present distinct advantages in tumor therapy because of their capacity to selectively bind and modulate the activity of target proteins (123). Ferroptosis, an iron-dependent form of cell death, is pivotal in various diseases (80,124-127) and holds particular significance in cancer treatment (128-130). Inducers of ferroptosis tend to increase the treatment sensitivity of chemotherapy-resistant or refractory cancer cells, thereby offering a novel approach to anticancer therapy.

Research has indicated that the Lp-PLA2 inhibitor darapladib can increase the sensitivity of cancer cells to ferroptosis by remodeling lipid metabolism. Preclinical studies have shown that darapladib promotes the polarization of tumor-associated macrophages towards an immunostimulatory phenotype, markedly inhibiting the growth of HCC. In murine models of HCC, monotherapy with Darapladib resulted in a 45.2±4.8% reduction in tumor volume, whereas its combination with anti-PD-1 antibodies led to a 68.7±6.3% reduction. Mechanistically, Lp-PLA2 has been shown to inhibit ferroptosis by decreasing the levels of polyunsaturated fatty acid-containing phosphatidylethanolamines (PEs) and cleaving oxidized Pes (30). Consequently, the inhibition of Lp-PLA2 has emerged as a promising strategy for inducing ferroptosis in cancer therapy.

Darapladib (SB-480848), a highly selective benzoxazinone-class Lp-PLA2 inhibitor, features a 4-chlorobenzenesulfonamide group that specifically

interacts with the hydrophobic pocket (S1' site) of the Lp-PLA2 active center. Its diethylaminoethyl side chain engages in charge interactions with the catalytic triad (Ser273/His351/Asp319), achieving an inhibition constant of 0.25 nM and demonstrating selectivity exceeding 1,000-fold over other phospholipase A2 subtypes. Structure-activity relationship studies have indicated that the chlorine atom at the 4-position of the benzene ring is essential for maintaining inhibitory activity, as its removal results in a potency reduction of ~100-fold (19,30).

Development of antibody-based therapeutics. In addition to small-molecule inhibitors, antibody-based therapeutics present significant potential for targeting Lp-PLA2. Two fully human anti-PLA2G7 monoclonal antibodies (1H8 IgG and 1A9 VH-Fc) have been successfully developed; these antibodies bind distinct epitopes of PLA2G7 with high specificity without competing with its catalytic triad. 1H8 IgG effectively inhibits PLA2G7 enzymatic activity, whereas the bispecific antibody 1H8 IgG-1A9 further enhances this inhibition. *In vitro* experiments confirm that these antibodies markedly suppress PLA2G7-mediated tumor cell migration, thereby offering a novel strategy for PLA2G7-targeted therapy (131).

Compared with small-molecule inhibitors, antibody drugs exhibit extended half-lives and heightened target specificity, thereby minimizing off-target effects and facilitating sustained therapeutic outcomes. The design of bispecific antibodies illustrates the potential for enhanced efficacy through simultaneous binding to multiple epitopes, providing new insights for the development of more potent Lp-PLA2-targeted agents.

Combination therapy and clinical potential. Darapladib has demonstrated extensive therapeutic potential across various tumor models. In HCC models, it not only markedly inhibits tumor growth but also enhances the infiltration of macrophages and CD8+ T cells, thereby improving the efficacy of anti-PD-1 immunotherapy (99). However, in C26 tumor-bearing mice, darapladib does not delay the progression of colon cancer despite a marked reduction in circulating Lp-PLA2 activity, indicating its limited potential as a monotherapy (116). Consequently, future investigations should explore its combination with other therapies, such as antibody drugs or immune checkpoint inhibitors, to address the limitations of single-agent approaches and further elucidate its therapeutic potential.

Compared with other ferroptosis inducers (such as elastin), darapladib, a specific Lp-PLA2 inhibitor, offers superior target selectivity, reduced off-target effects, and immunomodulatory effects by reshaping the TME to increase CD8+ T-cell activity. Furthermore, its pharmacological properties are well characterized, and its safety has been validated in clinical trials, underscoring its translational potential. Its synergistic effects with immune checkpoint inhibitors may also aid in overcoming drug resistance (116).

Several gaps in knowledge remain: The role of Lp-PLA2 metabolites in the TME remains inadequately understood, the interplay between PLA2G7 inhibition and ferroptosis pathways necessitates further investigation and the failure of Lp-PLA2 inhibitor in certain cancer models may be attributed to metabolic compensation, microenvironmental adaptation, or genetic background. Future research should prioritize multiomics analyses to elucidate the functional heterogeneity of PLA2G7 and identify predictive biomarkers of the treatment response. Additionally, innovative combination strategies that integrate the strengths of antibody drugs and small-molecule inhibitors may pave the way for novel Lp-PLA2-targeted therapies.

7. Conclusions and future perspectives

Lp-PLA2 has a multifaceted and context-dependent role in tumor biology. It may promote tumor progression through mechanisms such as induction of EMT, suppression of ferroptosis and activation of angiogenesis. Conversely, in certain contexts, particularly in cancers with BRCA1 mutations, Lp-PLA2 may function as a tumor suppressor by inhibiting the Wnt/β-catenin signaling pathway. This functional dichotomy is closely linked to its hydrolytic activity, by which it produces bioactive lipids, including LPC and oxFFAs. These metabolites are known to influence critical signaling pathways, such as the PI3K/AKT and JAK/STAT pathways, and to modulate the immunosuppressive TME. Preclinical investigations have indicated that small-molecule inhibitors targeting Lp-PLA2, such as darapladib, as well as antibody-based therapies, exhibit potential therapeutic efficacy; however, their effectiveness varies markedly across different tumor types, underscoring the necessity for precision medicine approaches in patient stratification and the design of combination therapies.

Future research should prioritize addressing three principal issues. First, a deeper understanding of the determinants of the functional polarity of Lp-PLA2, including substrate selectivity, epigenetic regulation and the characteristics of the TME, is needed. Second, therapeutic strategies should be refined by investigating the synergistic potential of Lp-PLA2 inhibitors in conjunction with ferroptosis inducers or immunotherapies, as well as by developing innovative targeted delivery systems. Third, the establishment of a reliable biomarker system through multiomics approaches is essential for identifying patient populations that are likely to benefit from Lp-PLA2-targeted therapies. Furthermore, exploring the noncanonical functions of Lp-PLA2, such as its role in regulating tumor stemness and stromal remodeling, is expected to reveal new opportunities for clinical applications.

In conclusion, Lp-PLA2 serves as a pivotal link between lipid metabolism, inflammation, and tumor progression. While its dual mechanisms present challenges for research, they also offer unique opportunities for the development of novel anticancer therapies. By integrating fundamental research with clinical translation, precision intervention strategies targeting Lp-PLA2 are expected to represent a significant advancement in oncology, particularly for cancers characterized by metabolic dysregulation or immunosuppressive microenvironments. Future endeavors should focus on elucidating the spatiotemporal specificity of Lp-PLA2's molecular mechanisms and clinically validating potential biomarker-guided individualized treatment regimens.

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Authors' contributions

XY and YT contributed equally to this work. XY conceived the review topic and wrote the manuscript. YT conducted literature analysis and created the figures and tables. NL, LL and JZ critically revised the manuscript. JX and CL revised and reviewed the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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