

Doi:10.32604/biocell.2025.060045

REVIEW





Phospholipid Metabolism Reprogramming of Cancer Stem Cells and Its Impacts on Stemness

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ABSTRACT: Cancer Stem Cells (CSCs) are cancer cells with self-renewal and tumorigenesis abilities. CSCs in tumor tissues are the leading cause of tumor progression, recurrence, and drug resistance. CSCs have distinct metabolic features that contribute to maintaining their self-renewal and stemness. Phospholipids are essential components of cell membranes and play fundamental roles in cellular activities. CSCs have abnormal phospholipid metabolism, which affects their self-renewal, differentiation, invasion, and drug resistance. Compared with non-CSCs, the phospholipid metabolism of CSCs mainly focused on significantly increased fatty acid (FAs) and phospholipid synthesis, phospholipid unsaturation, and lipolysis-fatty acid oxidation (FAO). In brief, FA and phospholipid metabolism in the anabolic and catabolic pathways are strictly regulated in CSCs to maintain self-renewal and stemness activity. In this review, we summarize the alterations in phospholipid metabolism in CSCs and their impacts on the stemness of CSCs, and we put forward the potential applications of targeting phospholipid metabolism for CSCs, to provide directions for the development of drugs targeting the phospholipid metabolism.

KEYWORDS: Neoplastic stem cells; cancer stem cells; phospholipids; phosphatides; metabolism

Highlights

- 1- Increased phospholipid synthesis, desaturation, and FAO in CSCs.
- 2- Effect of phospholipid metabolizing enzymes on the characteristics of CSCs.
- 3- Effect of phospholipid regulated signaling pathway on the characteristics of CSCs.

1 Introduction

Since the discovery of CSCs in acute myeloid leukemia, researchers have identified CSC-like cells in a variety of solid tumors, including lung, breast, and pancreatic cancer [1–4]. These CSCs represent a distinct subset of tumor cells with the ability to self-renew, playing a crucial role in tumor initiation and progression, and significantly influencing the prognosis of cancer patients [5]. CSCs exhibit several important biological characteristics (Fig. 1). First, like normal stem cells, CSCs possess the ability to self-renew and can generate more CSCs through division, thereby maintaining tumor growth and expansion. This ability enables CSCs to survive treatments and plays a crucial role in tumor recurrence. Second, CSCs have differentiation potential.



Although they can self-renew, they can also differentiate into various tumor cell types. This contributes to tumor heterogeneity, which complicates treatment. Third, CSCs have strong tumor-forming capabilities. In a suitable microenvironment, they can give rise to new tumors, making them a source of tumor recurrence and metastasis. Fourth, CSCs generally exhibit high drug resistance. They can evade chemotherapy and radiotherapy through mechanisms such as the activation of anti-apoptotic pathways. This resistance is a key factor in the failure and recurrence of cancer treatments. These biological characteristics make CSCs a critical focus in tumor biology research and cancer treatment. Understanding these features is essential for developing new therapeutic strategies, particularly targeting CSCs. In, addition, a defining feature of CSCs is their ability to generate phenotypically and functionally diverse cell populations. Surface hallmarks, biomolecules highly expressed on the cell membrane of CSCs, play a crucial role in stem cell maintenance and tumorigenicity. Although these hallmarks vary across solid tumors and only a few common markers exist between them, they can be utilized for CSC isolation, characterization, and targeted therapy [6,7]. Ongoing research continues to uncover potential surface hallmarks of CSCs, Table 1 summarizes the biomarker molecules of CSCs.



Figure 1: Differentiation of CSCs. CSCs are a type of cell with self-renewal, differentiation potential, and tumorinitiating ability. On one hand, CSCs can differentiate into cancer progenitor cells, which then give rise to heterogeneous cancer cells, or into transit amplifying cells, ultimately leading to tumor formation. On the other hand, CSCs possess self-renewal capability, allowing them to maintain a subset of daughter cells with the same self-renewal potential while differentiating, thus preserving the stability of the CSC population

Surface marker	Cancer
CD34	Liver cancer [8], non-small cell lung cancer [9]
CD133	Lung cancer [10], ovarian cancer [11], prostate cancer [12], liver cancer [13], brain
	cancer [14]

Table 1: Types	of surface	markers in	the top	cancers
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(Continued)

Table I (continued)	
Surface marker	Cancer
CD44	Breast cancer [15], lung cancer [10], prostate cancer [12], liver cancer [13],
	pancreatic cancer [16]
CD24	Breast cancer [15], gastric cancer [17], liver cancer [18], pancreatic cancer [16]
CD166	Lung cancer [19], colorectal cancer [20], gastric cancer [21]

Table 1 (continued)

Phospholipids are crucial components of cell membranes, contributing to both structural diversity and energy storage, as well as supporting various metabolic processes. They play key roles in regulating cellular functions, including cell adhesion, migration, signal transduction, and apoptosis [22]. The metabolic intermediates and by-products of phospholipids are involved in numerous cellular activities, supplying energy and modulating signaling pathways that influence cell morphology and function [23]. Furthermore, enzymes responsible for phospholipid metabolism help regulate essential biological processes, such as the cell cycle and cell proliferation [24].

The metabolism of nutrients in the tumor microenvironment undergoes dynamic changes throughout tumor progression. Recent clinical and experimental evidence indicates that phospholipid metabolism plays a role in tumorigenesis, particularly in critical oncogenic signaling pathways [25,26]. Notably, phospholipid metabolism is reprogrammed in CSCs, and these alterations regulate the phenotype of CSCs to some extent, such as the expression and maintenance of stemness, invasion, and metastasis [27]. Studies have identified certain phospholipid metabolites and enzymes as potential metabolic markers for CSCs [28]. In brief, phospholipid metabolism maintains rapid tumor proliferation, invasion, and metastasis [29,30]. This review examines the metabolic changes in phospholipids in CSCs and their regulatory effects on CSC stemness.

2 Classification, Synthesis, and Metabolism of Phospholipids

Phospholipids are lipids that contain phosphoric acid and primarily include glycerophospholipids and sphingomyelin. As key components of cell membranes, phospholipids exhibit a diverse range of chemical structures and functions. Phospholipid metabolism encompasses a complex network of biochemical processes, regulated by various enzymes and transporters. These processes include the synthesis, transformation, and degradation of phospholipids, as well as the synthesis, uptake, transport, and breakdown of glycerol and FA (Fig. 2).

The basic structure of glycerophospholipids consists of a glycerol backbone, FAs, phosphoric acid, and a group attached to the phosphoric acid. Based on the nature of the attached group, glycerophospholipids are primarily classified into phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylinositol (PI), phosphatidic acid (PA), and cardiolipin (CL). Glycerophospholipids are synthesized in all tissue cells, primarily through the diglyceride and cytidine diphosphate (CDP)-diglyceride pathways. FAs are essential precursors in the synthesis of phospholipids. Citrate is converted to palmitate and Fas through a series of enzymatic reactions such as ATP citrate lyase (ACLY), acetyl CoA carboxylase (ACC), and fatty acid synthase (FASN). In the endoplasmic reticulum, palmitate can be converted to unsaturated FAs (UFAs) by stearoyl COA desaturase (SCD) or further extended by elongases of very long-chain fatty acids (ELOVL) to generate long-chain FAs (LCFA) [31–33]. During the *de novo* synthesis of phospholipids, FAs are taken up as primary precursors via fatty acid binding protein (FABP) and the fatty acid transporter CD36. FA is converted to fatty acyl-CoA under the action of fatty acyl-CoA synthetase (ACS) and reacts with glycerol-3-phosphate to generate PA. Glycerol-3-phosphate has two primary sources: it can be generated

from glycerol by the enzyme glycerol kinase, or from dihydroxyacetone phosphate (DHAP) by glycerol-3phosphate dehydrogenase. Additionally, studies have shown that FAs contribute to phospholipid synthesis by esterifying with glycerol-3-phosphate to form PA [34]. PA generates diglyceride (DAG) under the action of phosphatidic acid phosphatase (PAP), further generating PC, PE, and other phospholipids. Phospholipids can also undergo conversion via intermolecular head group exchange, such as when ethanolamine is substituted for serine. Additionally, due to the structural diversity of phospholipids, the composition of fatty acyl chains in mammalian cells is also regulated by deacylation and reactive acylation, a pathway referred to as the Land's cycle [35]. Sphingomyelin, commonly found in brain tissue, consists of sphingosine, FAs, and various head groups (including phosphocholine and phosphoethanolamine. Sphingomyelin synthesized from phosphocholine is the most common and essential component of various membrane structures of neural tissues [36].



Figure 2: Synthesis, decomposition, and transformation of Phospholipids. In *de novo* phospholipid synthesis, FAs are absorbed by FABP and CD36, converted into acyl-CoA by ACS, and then react with glycerol-3-phosphate to form PA. Glycerol-3-phosphate is generated either by glycerol kinase from glycerol or by glycerol-3-phosphate dehydrogenase from DHAP. FAs promote phospholipid synthesis by esterifying with glycerol-3-phosphate to form PA. FAs can be derived from glucose. Glucose enters the cell via GLUT transporters, is converted into pyruvate, and then into acetyl-CoA in the mitochondria, where it participates in the citric acid cycle. Citrate is enzymatically converted into palmitate and FAs by enzymes such as ACLY, ACC, and FASN. In the endoplasmic reticulum, palmitate can be converted into UFAs by SCD or elongated into LCFAs by ELOVL. Phospholipids can then be converted into various products, including glycerol, PA, diacylglycerol, and others, through the action of different enzymes

Phospholipases catalyze the breakdown of phospholipids, generating glycerol, FAs, and other bioactive substances such as lysophospholipids, ceramide, and sphingosine. Glycerol can be converted into glycerol-3phosphate, which is used for phospholipid synthesis, and gluconeogenesis to produce glucose, or converted into DHAP, an intermediate in glycolysis. DHAP can then enter the glycolytic pathway and the tricarboxylic acid (TCA) cycle. Fs can be reused for phospholipid synthesis or enter the final stage of fatty acid metabolism—FAO, also known as β -oxidation. First, long-chain acyl CoA synthetases (ACSLS) activate free FAs and convert them into fatty acyl-CoAs. The transfer of fatty acyl-CoAs through the mitochondrial membrane is a critical rate-limiting step. Acyl-CoAs are converted into fatty acylcarnitines by carnitine palmitoyltransferase 1 (CPT1) in the presence of carnitine, and the fatty acylcarnitines are then transported into mitochondria by carnitine acylcarnitine translocase (CACT). Fatty acylcarnitines are eventually reconverted to fatty acyl-CoA by CPT2. Fatty acyl-CoAs enter the mitochondrial matrix and undergo β-oxidation, catalyzed by the oxidase system. This process involves four sequential reactions: dehydrogenation, hydration, another dehydrogenation, and thiolysis. The result is the formation of acetyl-CoA and a shortened fatty acyl-CoA, which has two fewer carbon atoms than the original. Acetyl-CoA enters the TCA cycle. Phospholipid metabolism can also involve many bioactive substances. Sphingosine is converted to sphingosine 1 phosphate (S1P) under the action of sphingosine kinase (SPHK), with lysophosphatidic acid (LPA), ceramide, and other mediators acting as second messengers to regulate cellular activities, resulting in a variety of biological effects.

3 Phospholipid Metabolic Reprogramming in CSC

Due to the rapid proliferation of tumor cells and insufficient angiogenesis of tissues, tumors usually live in hypoxic, acidic, and nutrient-deprived microenvironments. Therefore, tumor cells must regulate their cellular bioenergetics effectively to cope with the adverse environment. This process is called metabolic reprogramming [37,38]. CSCs showed prominent metabolic characteristics. More and more studies have shown that metabolic reprogramming and CSC characteristics are two highly intertwined processes in tumor development [39]. In recent years, studies have shown that reprogramming of phospholipid metabolism is closely related to the occurrence, progression, and prognosis of tumors, especially CSCs, including ovarian CSCs, breast CSCs, endometrial CSCs, pancreatic cancer stem cells (PaCSCs) and glioma stem cells (GSCs), etc. Phospholipid metabolism has similar characteristics in CSCs or CSC-like cells of these different tissues and organs. For example, there are different degrees of increase in phospholipid content and FAO in breast CSCs and ovarian CSCs, and the degree of phospholipid unsaturation and FAO metabolism are significantly increased in gastric cancer stem cells (GCSCs) and GSCs.

3.1 Increased Phospholipid Synthesis

In tumor tissue, both endogenous and exogenous lipids contribute to a significant increase in FA and phospholipid content due to the high metabolic demand in CSCs, where the synthesis rate of these lipids accelerates [40]. CSCs are heterogeneous populations with different metabolic states associated with their potential for tumor initiation. Quiescent CSCs have low metabolic rate and slow cell division [41]. Enzymes involved in FA and phospholipid synthesis, including FASN, SCD, PAP, etc., are significantly upregulated in CSCs [42–45]. It has been demonstrated that phospholipid content increases with cell transformation and tumor progression, regulating various oncogenic processes, such as tumor growth, CSC formation, and metastasis. For example, lipid analysis of breast cancer tissue demonstrated a significant increase in phospholipid content. PA and its product, LPA, are increased in cancer cells and CSCs compared to nonmalignant cells. Seo et al. isolated spherical cells A2780-SP from A2780 epithelial ovarian cancers (EOCs) and determined their CSC-like properties by identifying their high sphere-forming ability, drug resistance

to chemotherapy such as paclitaxel or cisplatin, and expression of stem cell markers including SRY-box transcription factor 2 (SOX2) and aldehyde dehydrogenase 1 (ALDH1) [46]. Their results demonstrated that the ATX-LPA-LPARI signaling axis was involved in maintaining ovarian CSC stemness, and ovarian CSCs could enhance their stem cell properties when treated with LPA. This included inducing stem cell-related gene expression, enhancing microsphere formation, increasing chemotherapy resistance, and boosting tumorinitiating potential in mice. CSCs can also utilize the metabolic intermediates from the Warburg effect to synthesize phospholipids, further enhancing their self-renewal growth properties. Lysophosphatidylcholine acyltransferase (LPCAT), a vital enzyme of the Land's cycle, is involved in tumor progression through membrane phospholipid remodeling [47]. A recent study found that overexpression of LPCAT1 alters the contents of PC and PE, leading to increased stemness and metastasis of CSCs [48].

3.2 Phospholipid Desaturation

By comparing CSCs with non-stem cells, researchers found that CSCs contain more UFAs and phospholipids than non-stem cells, affecting the stemness of cancer cells and the formation of CSCs [49]. The metabonomic results of a colon cancer study also indicated that CSCs contained higher levels of unsaturated phospholipids, with similar effects on CSCs [50]. In GSCs, researchers found that the synthesis and utilization of polyunsaturated FAs (PUFAs) were significantly increased, thereby changing the composition and structure of membrane phospholipids [51]. Unsaturated lipid is considered a unique metabolic biomarker of ovarian CSCs [52]. ALDH and CD133 are described as characteristic markers of CSCs. The authors used hyperspectral stimulated Raman scattering (SRS) microscopy to chemically image ALDH+/CD133+ cells to identify and characterize the unsaturation of lipids in ovarian CSCs. It is known that the peak at 3002 cm is mainly from unsaturated lipids, while the lipid droplets in ALDH+/CD133+ cells have a stronger signal at 3002 cm, which means that ALDH+/CD133+ CSCs have a higher level of unsaturated lipids. Stearoyl-CoA desaturase 1 (SCD1) first attracted attention for its role in the pathway that produces monounsaturated fatty acids (MUFAs). Functionally, SCD1 is a rate-limiting enzyme that catalyzes the formation of MUFAs from saturated FAs. Most of the UFAs in the body are products of SCD1 catalysis. Moreover, SCD1 is highly expressed in liver, lung, breast, and other tumors and shows an increased proportion of unsaturated lipids. In recent years, studies have found that SCD1 is closely related to CSCs. Overexpression of SCD1 promotes the proliferation and migration of CSCs and inhibits cell death [53]. Blocking SCD1 reduces the expression of ovarian CSC markers and prevents tumorigenesis in vivo, which is consistent with the role of SCD1 in breast cancer [54]. Furthermore, SCD1 was overexpressed in primary GCSCs, and SCD1 inhibition reversed the epithelial-mesenchymal transformation (EMT) process and reduced the probability of gastric cancer metastasis in vitro and in vivo [55].

A new pathway of lipid desaturation remodeling has recently been identified and shown to regulate the final effects of SCD1 [56]. Sapienate and another fatty acid desaturase 2 (FADS2) were discovered. They also found that when SCD1 is inhibited, FADS2 compensates for the loss of SCD1 activity. Elevated FA unsaturation is positively correlated with SCD1 or FADS2 levels and the oncogenic capacity of ovarian cancer cells. Inhibition of SCD1/FADS2 retards tumor growth and reduces CSC formation and decreases drug resistance. Phospholipid desaturation in CSCs was further investigated, potentially opening new opportunities to target them.

3.3 Increased Lipolysis-FAO

The conversion and utilization of phospholipid metabolites such as FAs, glycerol, and choline by CSCs is increased in different tumors. Many types of tumors use FAO as their primary energy source [57]. Studies have shown that triple-negative breast cancer (TNBC) controls tumor growth via FAO and promotes

metastasis. FAO also activates Src oncoprotein in TNBC, associated with acquiring tumor cell stemness [58]. Inhibiting FAO decreases the self-renewal capacity and tumorigenicity of breast and liver CSCs while increasing their sensitivity to chemotherapy [59,60]. Therefore, increased FAO in CSCs is critical for CSC generation and survival in response to inflammatory signaling. FABP plays a vital role in FA uptake and transports FAs to different organelles to function after uptake. A recent study found that FABP promotes TNBC progression and breast CSCs activity. In vitro and in vivo studies have shown that knocking down FABP4 inhibits breast CSC activity, such as tumor-initiating ability. In vivo studies have also shown that knocking down FABP4 reduces metastatic ability and tumor progression in TNBC [61]. A recent study found that FAO activity increased in PaCSCs, with related metabolic genes also upregulated. Active metabolism may contribute to the metastasis of PaCSCs. In addition, exogenous supplementation of FAs significantly enhanced the self-renewal capacity and tumor formation abilities of CSCs. Inhibiting FAO metabolism has the opposite effect, reducing the self-renewal and tumor-forming abilities of CSCs, while enhancing their sensitivity to chemotherapeutic drugs [62] Leukemia stem cells (LSCs) increase free FAs by secreting proinflammatory factors and promoting lipolysis. These FAs enter LSCs via CD36 and are eventually utilized for energy production through FAO to support stem cell survival and evade chemotherapy [63]. CD36 expression is elevated in GSCs, and the uptake of oxidized phospholipids promotes GSC proliferation [64]. Furthermore, Singh et al. found that the coat protein complex I (COPI)-Arf1 complex regulates stem cell survival through the lipolysis FAO pathway. The knockdown of the associated genes blocks lipolysis and selectively kills stem cells. They also used an ARF1 inhibitor and found that CSC formation was significantly reduced in Drosophila but had a negligible effect on normal stem cells, which was somewhat sufficient to visualize the dependence of CSCs on the lipolysis-FAO [65].

In addition, FAO produces abundant antioxidants, such as NADPH, which can promote the survival of CSCs. FAO reduces the production of reactive oxygen species (ROS) that are detrimental to stem cells. However, studies have also shown that noncytotoxic doses of ROS can instead promote neoplastic transformation and stem cell features in renal epithelial cells, which may explain the increase in the content and utilization of unsaturated phospholipids and UFAs in CSCs, suggesting that an appropriate amount of ROS is required to maintain stemness [66].

4 Altered Enzymatic Activity in Phospholipid Reprogramming in CSCs

Enzymes involved in phospholipid metabolism have been evaluated in different cancers, and the results showed that they are involved in tumorigenesis and development, especially in cell carcinogenesis, tumor progression, and cancer cell properties (such as rapid proliferation, migration, and invasion) and have important regulatory roles. These enzymes include choline kinase α (CHK α), ethanolamine kinase (ETNK), phospholipase A (PLA), phospholipase D (PLD), phospholipase C (PLC), sphingomyelinase (SM), among others [67].

4.1 CHKa

CHKa is a critical enzyme in the CDP-choline pathway, involved in the first step of lecithin synthesis, and phosphorylates choline to phosphorylcholine to form phosphorylcholine, which is essential for cell membrane structures. Its encoding gene is an oncogene that promotes tumorigenesis and progression. In breast, ovarian, colorectal, and other cancers, gene overexpression and enzyme activity highly increased, resulting in higher levels of phosphorylated choline in tumor tissue [68–70]. CHKa can regulate cell proliferation and tumorigenesis in breast and prostate cancers [71]. CHKa can also induce lipid droplet degradation when energy is insufficient [72]. MN58b, a derivative of HC-3, a small molecule inhibitor

of CHKα, has been shown to inhibit CHKα activity. C/EBP homologous protein (CHOP), a major proapoptotic transcription factor induced by endoplasmic reticulum stress, is activated by CHKα inhibition, which exacerbates the stress response in cancer cells and triggers apoptosis through this pathway [73]. In addition, Koch et al. found that recurrence and metastasis of glioblastoma were mainly driven by EMT and brain CSCs. Inhibition of CHKα regulating choline metabolism can significantly reduce the expression of EMT-related genes in glioblastoma cells and invasiveness [74]. Lacal et al. found that the combination of traditional chemotherapeutic agents and choline kinase inhibitors improved survival and quality of life in patients with non-small cell lung cancer (NSCLC), suggesting that inhibition of CHKα may be the basis for the development of new treatments [75].

4.2 PLD

PLD is a hydrolase enzyme that acts on lecithin, producing PA and choline [76]. PA functions as a second messenger that binds directly to the mammalian target of Rapamycin (mTOR) and can also be converted into DAG via PAP or into LPA via PLA2. Studies have confirmed that PLD directly affects proliferation, invasion, metastasis, and drug resistance [77]. Elevated PLD activity or increased expression of PLD1 and PLD2 has been observed in various cancers and transformed cells. Activated PLD promotes the production of PA, which in turn activates Yes-associated protein (YAP) signaling, contributing to drug resistance in squamous cell carcinoma [78]. Muñoz-Galván et al. found that PLD2 is overexpressed in colon cancer, and its product, PA, induces senescence-associated secretory phenotype (SASP) that increases the stem cell properties. They also confirmed this link in a mouse experimental model, showing that high PLD2 expression increases stemness and tumorigenesis [79]. More recently, they reported that PLD2 is also overexpressed in ovarian cancer, contributing to chemoresistance. They found that hypoxia-inducible factor 1 (HIF-1) is required for maintaining CSCs, and hypoxia-induced ovarian cancer stemness depends on PLD2 expression. In summary, the HIF-1 α -PLD2 axis promotes the generation and maintenance of CSCs under hypoxic conditions [80] Upregulation of PLD has been linked to increased occurrence and invasion of breast tumors and bladder cancer [81,82]. A study found that PLD1 is elevated in GSCs, especially in recurrent glioblastoma, and this upregulation correlates with GSC resistance to temozolomide. Inhibition of PLD1 sensitizes GSCs to temozolomide and reduces the occurrence of glioblastoma [83]. Additionally, a recent study revealed that PLD1 regulates the self-renewal capacity of cancer-initiating cells through the E2F1-miR-4496- β -catenin axis. Importantly, PLD1 inhibition specifically targets GSCs, not neural progenitor cells, and reduces the self-renewal capacity of CSCs in colorectal cancer and gastric cancer. Therefore, PLD1 may serve as a novel therapeutic target for GSCs [84]. In addition, PLD has been positively associated with rapamycin resistance in human breast cancer cells [85].

PLD also links survival and migration signals of human cancer cells to stress responses. Interestingly, PLD does not always act independently within cells. PLD1 and CHK α interact. CHK α silencing increases PLD1 expression and *vice versa* [86]. Therefore, whether alone or in potential synergy, PLD is undoubtedly a promising therapeutic target for cancer treatment [87].

4.3 PLC

PLC cleaves the phosphate group from phospholipids, and it exists in two main types: phosphatidylcholine-specific and phosphatidylinositol-specific [67]. The former hydrolyzes PC to generate DAG and phosphorylcholine, while the latter hydrolyzes phosphatidylinositol-4,5-bisphosphate (PIP2) to produce DAG and IP3, both of which are the key second messengers in cells. PC is the most abundant in cells, while PI, especially PIP2, only exists in trace amounts. Based on this, phosphatidylcholine-specific PLC may produce more persistent DAG elevation than phosphatidylinositol-specific PLC [67]. DAG activates protein

kinase C and induces sustained mitotic signaling, possibly leading to cellular transformation. Correlative studies have demonstrated that phosphatidylcholine-specific PLC activity and DAG levels are elevated, and cell transformation and loss of contact inhibition occur in ovarian [88], breast [89], and squamous cell carcinomas [90]. Among them, ovarian cancer studies have shown that PLC is related to cancer cell transformation, proliferation, migration, and invasion. Squamous cell carcinomas showed differential stemness potential with up-regulated mRNA levels of stemness-related markers, which suggests that PLC is associated with transforming non-stem cells to stem cells in tumor tissues. Research by Schnoeder et al. found that Phospholipase C Gamma 1 (PLC γ 1) is highly expressed in hematopoietic stem cells and myeloid leukemia and concluded that PLC γ 1 is required for the maintenance of LSCs [91]. Furthermore, Okada et al. indicated that PLC ϵ plays a crucial role in maintaining the survival, stemness, and tumor-initiating ability of GSCs [92].

4.4 SM and SK

SM acts similarly to PLC by releasing phosphocholine or phosphoryl ethanolamine from sphingomyelin to generate ceramide. In addition, cancer cells can convert ceramide into sphingosine, which is subsequently phosphorylated by sphingosine kinasel (SK1) to produce S1P. S1P also belongs to lysophosphatide and is an essential bioactive mediator in the cellular process. Recent studies have shown that SM and SK1 are involved in biological processes such as cell cycle arrest, migration, and inflammation and the promotion of breast cancer development through regulation of CSCs apoptosis and proliferation [93]. SM exerts its anti-cancer effects by releasing ceramide and can be divided into three types based on its optimal pH: acidic sphingomyelinase (ASM), neutral sphingomyelinase (nSMase), and alkaline sphingomyelinase (alk-SM) [94,95]. Studies have shown that cells or mice deficient in ASM resist apoptosis induced by anti-tumor stimuli. Conversely, overexpression of ASM sensitizes cancer cells to chemotherapy and radiotherapy [96]. Drug-induced ASM-ceramide has been shown to improve microvascular function, making radiationresistant colorectal CSCs more responsive to radiotherapy [97]. Therefore, ASM is a potential target for anticancer therapy. nSMase inhibits tumor growth and promotes apoptosis. In the nSMase-2 deficient mice, the formation of liver tumors was increased, and the tumor tissue significantly expressed CD133 and EpCAM mRNA levels, which were markers of liver cancer CSCs [98]. CD133+ cells exhibited increased sphingomyelin and ceramide levels, suggesting that the absence of nSMase-2 supports the survival and proliferation of CSCs. Lw et al. showed that overexpression of SK1 can enhance the survival and proliferation of breast CSCs. They identified that signal transducer and activator of transcription 1 (STAT1) and Interferon (IFN) signal are the critical regulatory targets of SK1, with SK1 activation suppressing STAT1 signaling [99]. Moreover, SK1 overexpression enhances the stemness and self-renewal of ovarian cancer cells through SOX2-dependent mechanisms [100]. In addition, it has long been reported that SIP and its receptor SIPR play an essential role in promoting the proliferation and dry phenotype of CSCs [101]. SK1 promotes growth and inhibits apoptosis. SIP, produced by SK1, can be secreted through specific transporters, acting through autocrine or paracrine. Different SIP receptors are coupled with distinct G proteins to regulate various signaling pathways, including mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT), and PLC-mediated signaling pathways [102].

4.5 PLA2

In addition to the above enzymes, PLA2 has also been implicated in regulating CSCs and maintaining stemness [103]. PLA2 catalyzes the release of FAs from the second carbon group of glycerol. As an extracellular pattern of PLA2, secreted phospholipase A2 (sPLA2) is widely involved in different types of human cancers. Long non-coding RNA (LncRNA) plays a vital role in biological processes such as cell

metabolism and stemness maintenance [104]. Xu et al. found that sPLA2 overexpression promoted cell migration, invasion, and stemness [105]. Silencing LncRNA SLNCR1 downregulated sPLA2 expression, while sPLA2 overexpression can weaken the inhibitory effect of LncRNA SLNCR1 silencing on cell stemness. This indicates that LncRNA SLNCR1 may regulate the stemness in NSCLC by interacting with sPLA2. PLA2G16, is a member of the current PLA2 family. Liu et al. found a new LncRNA regulating phospholipid metabolism in BCSCs by bioinformatics analysis called LncROPM [106]. They discovered that in BCSCs LncROPM significantly promoted phospholipid metabolism and free FA production by increasing the stability of corresponding mRNA, especially arachidonic acid which activated signaling pathways such as PI3K/AKT and Hippo/YAP, which participated in the maintenance of BCSC stemness. Notably, the study found that LncROPM-PLA2G16 signaling significantly enhanced the chemoresistance of BCSCs, suggesting that targeting the LncROPM-PLA2G16 axis may be a new treatment strategy for breast cancer patients.

5 Phospholipids Affect CSCs by Modulating Signal Transduction

In addition to participating in energy metabolism and cell membrane formation, phospholipids also participate in signal transduction, where they help regulate various cellular functions [107]. In phospholipid metabolism, several messengers activate tumor-related signal pathways, such as PI3K/AKT, Ras/ERK, and MAPK pathways [108]. Phospholipid metabolism is closely linked to the carcinogenic signal pathway (Fig. 3). For example, it affects the cell membrane by changing phospholipid molecules' structure, composition, and content, thus regulating the clustering of membrane receptors and modulating downstream carcinogenic signaling [109]. Many studies have shown that phospholipids and their metabolites play a crucial role in maintaining the phenotype of cancers. They promote tumor proliferation, enhance drug resistance, and induce stemness-related gene expression, all of which are closely related to abnormal activation of signal pathways [110,111].

5.1 PI3K/AKT Pathway

PI3K/AKT pathway is an integral part of glycerophospholipid metabolism and is often sustainably activated in CSC. PI3K can phosphorylate PIP2 to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3), both of which are phospholipid components of the cell membrane. As the second messenger, PIP3 promotes the recruitment of phosphoinositol-dependent kinase-1 (PDK1), leading to the activation of AKT. Once activated, the PI3K/AKT signal will be transmitted to a series of downstream pathways, the most classic of which is the mTOR pathway. mTOR is a key regulator of growth and metabolism. Under normal circumstances, mTOR inhibits autophagy, but under adverse circumstances such as stress, mTOR activation may promote cell survival—this can be a mechanism by which cancer cells adapt to stress [112-114]. In many cancers, the PI3K/AKT pathway is highly activated and involved in cancer cell proliferation, migration, EMT, and CSC phenotypes [115–118]. Recently, a study on osteosarcoma found that the PI3K/AKT pathway was associated with CSCs phenotype [119]. High expression of human epidermal growth factor receptor 2 (HER2) associated with colorectal cancer is also associated with aberrant activation of the PI3K/AKT pathway, and targeting PI3K/AKT can kill liver disseminated colorectal CSCs [120]. Cancer cells often contain a large amount of PIP3 due to the increased activity of oncogenic proteins upstream of PI3K or the activation of PI3K mutation [121]. It is worth noting that the phosphatase and tensin homolog deleted on chromosome ten (PTEN) gene is a tumor suppressor gene and a negative regulator of PI3K, which can block the downstream pathway regulated by AKT [122]. Some cancers also showed down-regulation and even loss of PTEN function [123]. These lead to the dysregulation of the PTEN/PI3K/AKT pathway, which is essential for maintaining prostate and breast CSCs [124,125]. In addition, S1P is an active sphingolipid metabolite,

which can activate many tumor-related signal pathways, such as PI3K/AKT and RAS/ERK, by binding to the G protein-coupled S1P receptor (S1PR) [126].



Figure 3: Signal pathways involved in CSC regulation. In the phospholipid metabolism of CSCs, tumor-associated signaling pathways such as PI3K/AKT, RAS/ERK, and Hippo/YAP are often aberrantly activated. Phospholipid metabolism regulates the activity of these oncogenic signaling pathways to some extent. LPCAT1, a key enzyme involved in membrane phospholipid remodeling, when overexpressed, alters the lipid composition of the cell membrane, thereby promoting the activation of the MAPK/ERK signaling pathway, which enhances the stemness and metastatic potential of CSCs. Additionally, LPA and S1P activate YAP via G12/13-coupled receptors. S1P also activates the PI3K/AKT signaling pathway through binding to the G protein-coupled receptor S1PR. PA increases YAP activity by disrupting the formation of the LATS1-MOB1 complex and inhibiting the phosphorylation of LATS1/2. Inhibition of PA production via the PLD pathway can suppress the oncogenic activity of YAP

5.2 EGFR Pathway

The epidermal growth factor receptor (EGFR) is one of the most commonly amplified or mutated oncogenes in cancer. EGFR regulates cell proliferation and survival through downstream pathways, such as PI3K/AKT/mTOR and RAS/MAPK, and is related to stemness maintenance and drug resistance [127–129]. EGFR is a glycoprotein spanning the cell membrane and belongs to the tyrosine kinase receptor (TKR) family, including an extracellular ligand-binding region, a transmembrane (TM) domain, a jux-taposed membrane (JM) region containing tyrosine kinase, and C-terminal tail. The JM region plays a crucial role in the activation of EGFR. Research shows that PIP2 can regulate EGFR, and the JM region interacts with PIP2 [130]. The composition of membrane phospholipids can affect the EGFR signal by

controlling the membrane structure, and the EGFR signal can also change the membrane properties. EGFR is overexpressed or abnormally expressed in many tumors. Dysregulated EGFR signals are essential in maintaining stem cell-like properties and driving tumor progression [131,132]. In EGFRvIII positive cancer cells, a significant decrease in lysophosphatidylcholine (LPC), and a notable increase in saturated PC, which helps sustain EGFR signaling and promote tumor growth [133]. This result is achieved through LPCAT1. A recent study found that silencing LPCAT1 can inhibit the growth of endometrial carcinoma. Overexpression of LPCAT1 changes phospholipid components such as PC and PE, leading to increased cancer cell stemness and metastasis [48]. In addition, LPCAT1 is necessary for the proliferation of many cancer cells, and it has become a potential therapeutic target [134]. Additionally, the EGFR pathway is overexpressed in drug-resistant breast stem cells [135]. In preclinical Inflammatory breast cancer (IBC) models, EGFR inhibitor treatment can reverse EMT and inhibit tumor growth and metastasis progression [136].

5.3 Hippo/YAP Pathway

The Hippo pathway is evolutionarily conservative, including mammalian sterile 20-like kinase 1/2 (MST1/2), Salvador Family WW Domain Containing Protein 1 (SAV1), Large Tumor Suppressor Kinase 1/2 (LATS1/2), and Mps one Binder 1 (MOB1). MST1/2 phosphorylation activated LATS1/2, while LATS1/2 phosphorylation inhibited YAP and transcriptional coactivator with PDZ-binding motif (TAZ). YAP and TAZ are downstream effectors of the Hippo pathway, which are related to tumor cell proliferation, apoptosis, metastasis, and CSC properties [137]. The Hippo pathway restricts organ size by limiting cell growth and mediating stress-induced apoptosis, which are the keys to tumorigenesis. The Hippo/YAP pathway is aberrant in many solid tumors with enhanced YAP activity. For example, YAP is overexpressed in bladder cancer and is associated with cancer cell proliferation, migration, recurrence, and drug resistance [138]. The Hippo/YAP pathway is critical for maintaining the properties of CSCs, especially the downstream effector YAP. YAP is a crucial regulatory protein for CSC proliferation and carcinogenesis [139]. Studies have indicated that aberrant activation of YAP or TAZ maintains the survival, self-renewal, and multipotency of CSCs [140,141] and is highly associated with the EMT process. The Hippo pathway is abnormal in many cancers, and changes in the activity of its key components can lead to the occurrence and metastasis of tumors. It was found that LPA and S1P activated YAP through G 12/13 coupled receptors to regulate cell proliferation and tumorigenesis [142]. Han et al. found that PA also increases YAP activity by destroying the formation of the LATS1-MOB1 complex and inhibiting LATS1/2 phosphorylation. They also found that inhibition of PA production, specifically through the PLD pathway, can suppress the carcinogenic activity of YAP so that the PLD-PA-YAP axis may become a potential therapeutic target [143]. Phospholipase C Delta3 (PLCD3) is an oncogene related to the occurrence and progression of thyroid cancer and is related to the Hippo pathway. When PLCD3 was downregulated, the expression of YAP1/TAZ decreased significantly. PLCD3 silencing can also reverse EMT and induce apoptosis, but overexpression of YAP1 can compensate for this tumor inhibition [144]. Moreover, the Hippo pathway can also be regulated by sphingomyelin phosphate choline in a dual and reverse manner [145]. SCD1 has also been linked to YAP/TAZ expression in CSCs, adding another layer to the complex interplay between phospholipid metabolism and Hippo pathway signaling in cancer [146].

5.4 Ferroptosis

Ferroptosis is a new type of death driven by intracellular iron accumulation, membrane phospholipid peroxidation, and increased ROS. Many studies have shown that ferroptosis is related to various diseases, including cancers and ischemic diseases [147–149]. Ferroptosis is also closely related to the phenotype of

CSCs. For instance, CD44, a surface marker of CSC, is closely associated with the resistance of CSCs to ferroptosis. For example, the expression of variant subtype CD44v helps CSCs defend against ROS by promoting the synthesis of reduced glutathione (GSH) [150]. Similarly, studies have found that the overexpression of CD44 enhances the stability of Solute carrier family 7 member 11 (SLC7A11), a key component of the cystine/glutamate antiporter, and inhibits ferroptosis by promoting the interaction between SLC7A11 and ovarian tumor associated proteinase B1 (OTUB1), an ovarian tumor family member deubiquitinase [151]. The substrate of lipid peroxidation is PUFAs. Studies have shown that PE containing PUFA is the essential phospholipid for lipid peroxidation and ferroptosis [152]. The research indicates that LPCAT3 inhibitors reshape the content of membrane polyunsaturated phospholipids and partially prevent cell ferroptosis [109]. Simultaneously, some MUFAs also produce similar effects [30]. Furthermore, CSCs can actively regulate their differentiation status to avoid the adverse effects of ferroptosis. For example, YAP/TAZ is involved in cancer cells avoiding ferroptosis. The metabolism and utilization of iron in CSCs were significantly accelerated, and the iron concentration in CSCs was higher than in non-CSCs. When irons in cells increase, phospholipids containing PUFA are more likely to be peroxidized, resulting in the production of excessive ROS [153]. High levels of ROS can cause the loss of self-renewal and pluripotency of CSCs and enhance their radiosensitivity [154,155]. The intervention of ROS-regulating drugs on drug-resistant CSCs may have better therapeutic effects. Inhibition of ferritin expression can also impair the growth of GSCs [156]. In addition, many glutathione peroxidases (GPX) function in the proliferation, drug resistance, metastasis, and recurrence of CSCs. GSH is converted into oxidized glutathione (GSSG) by GPX4 and is used to consume intracellular peroxides. Therefore, inhibition of System X_c⁻ and GPX4 will accumulate lipid peroxides, leading to ferroptosis [157]. In addition, mesenchymal CSC populations associated with mesenchymal tumors are susceptible to ferroptosis [158].

6 Discussion

CSCs are a subset of cancer cells in the state of stem cells with stem cell characteristics. Studies have shown that CSCs widely exist in different types of tumors. Most tumor cells can be removed by radiotherapy and chemotherapy, but the critical oncogenic CSCs survive, enabling them to induce tumor recurrence and metastasis. The ultimate result of CSC research is to identify the pathways that selectively regulate CSCs and eradicate CSCs for these pathways. Studies have shown that the phospholipid metabolism pattern of CSCs is distinct from the others. Non-cancerous stem cells, such as those found in tissues like the bone marrow or brain, exhibit relatively stable and balanced metabolic profiles. Their phospholipid metabolism primarily supports the maintenance of cell pluripotency, differentiation potential, and tissue homeostasis. Compared to cancer cells, the overall metabolism of these stem cells is less dynamic. These stem cells primarily produce phospholipids required for stem cell maintenance and differentiation, rather than actively growing or surviving in hostile microenvironments. In contrast, CSCs often exhibit altered phospholipid metabolism as part of tumor heterogeneity. CSCs modulate their phospholipid metabolism to support rapid proliferation, survival, and resistance to therapy. To adapt to the tumor microenvironment, which may involve hypoxia, nutrient deprivation, and immune challenges, the metabolism of CSCs becomes more dynamic. This is mainly manifested in the upregulation of phospholipid synthesis, desaturation, and FAO. Therefore, the phospholipid metabolism of CSCs not only differs significantly from that of normal stem cells, but also provides key survival mechanisms that support their persistence, proliferation, and resistance to conventional cancer therapies. These unique metabolic characteristics make CSCs a promising target for the development of new and more effective cancer treatments. Therefore, a comprehensive and clear understanding of the biological characteristics and stem maintenance mechanism of CSCs is necessary to develop tumor therapy. This review introduces the types of CSCs and some surface markers, summarizes the unique phospholipid metabolism reprogramming of CSCs, and discusses the main ways to regulate the stemness characteristics of CSCs.

The rapid proliferation of tumor cells leads to excessive demand for energy supply and structural components, and significant changes have occurred in cellular metabolism. Phospholipid metabolic reprogramming is closely related to the characteristics of CSCs, which is mainly manifested in the upregulation of phospholipid synthesis, desaturation, and lipolysis-FAO. Targeting lipid metabolism has become a feasible strategy for therapeutic intervention. In addition, the combination of phospholipid metabolism-related inhibitors with chemotherapy drugs or immunotherapy can improve the anti-cancer effect. FASN is a major focus in targeting CSCs, and the development of novel FASN inhibitors is underway. The antitumor activity of FASN inhibitors has been confirmed in preclinical cancer models. For example, the novel FASN inhibitor AZ12756122, which targets FASN, represents a potential treatment option to overcome resistance to EGFR tyrosine kinase inhibitors [159]. Preclinical studies showed that combined with Osimertinib, it could synergistically reduce characteristics of the CSC in EGFR mutant NSCLC cells. This further highlights the importance and potential of FASN inhibitors in inhibiting CSCs and combating cancer. In addition, selective elimination of CSCs can be achieved by targeting SCD1. One study suggests that targeting SCD1 selectively eliminates colon CSCs by inhibiting Wnt and NOTCH signaling pathways [160]. SCD inhibitors, including A939572 and the novel compounds CVT-11127 or CVT-12012, have been studied for their effects on membrane lipid saturation and signal transduction, providing a new approach to fight against the chemotherapy resistance of cancer cells [161]. Additionally, the dependence of CSCs on FAO further justifies the rationale of targeting these cells with FAO inhibitors. Compounds like Etomoxir, which inhibit FAO, have shown potential in preclinical studies for slowing tumor growth, particularly in gliomas [162]. Furthermore, inhibition of PLD can suppress the carcinogenic activity of YAP, thereby regulating EMT and stemness. Therefore, PLD inhibitors are also a research hotspot. PLC is abnormally expressed in GSCs and LSCs, which may provide an opportunity to target specific signaling nodes for CSCs in leukemia and glioma. The research shows that combining clinical therapeutic drugs, such as cisplatin, with PLA2 inhibitors is expected to eliminate BCSCs and tumorigenesis effectively [163]. In the animal experimental model by Singh et al., using Arf1 inhibitors can reduce the formation of CSCs, and the impact on normal stem cells can be ignored [65]. Wang et al. also found that knocking down ARF1 could not only kill CSCs but also trigger tumor-specific immune responses. The dying CSCs were transformed into therapeutic vaccines to attract and activate immune cells to destroy large tumors and lead to lasting therapeutic effects [164]. These findings suggest that targeting lipid metabolism could provide a valuable therapeutic strategy for overcoming resistance and controlling tumor progression. Another strategy some researchers propose is building engineered fat cells to deliver anti-cancer drugs [165,166]. This approach allows for selective targeting and efficient elimination, enhancing the precision and effectiveness of cancer treatment.

Inhibition of the PI3K/AKT pathway has always been a research focus of targeted therapy. Tumors with abnormal PI3K/AKT pathway mutations may benefit from PI3K/AKT inhibitor-mediated molecular targeted therapy. Many small molecule inhibitors of the PI3K/AKT/mTOR signaling pathway have been studied in the preclinical stage. However, only a few PI3K and mTOR inhibitors have been approved for the treatment of human cancer in the clinic. Monotherapy is gradually changing to combination therapy, which has become a significant research direction [167]. At present, the regulatory role of S1P and DAG in the PI3K/AKT pathway may become potential research targets for cancer therapy. In recent years, new advances have been made in KRAS-targeted drugs, especially in KRAS-G12C inhibitors, such as AMG510 (Sotorasib) and MRTX849 (Adagrasib), both of which have been approved for clinical use [168]. Several RAF inhibitors have also demonstrated superior clinical efficacy in patients with RAF mutant cancers. The Hippo pathway is regulated by dual and reverse regulation of LPA, S1P, and phosphatidylcholine phosphate.

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Abnormal expression of SCD1 is also associated with YAP/TAZ in CSC, highlighting further potential targets for therapeutic intervention. Studies have found that the anti-tumor effect can be enhanced by inducing ferroptosis of tumor cells, and this anti-cancer strategy has broad prospects [169,170]. Disrupting the redox balance of CSCs through targeted use of ROS-regulating drugs will become the latest direction of cancer treatment research. Numerous studies have explored drugs and drug delivery systems designed to provide precise platforms for selectively targeting and killing tumor cells, offering significant potential for improving cancer treatment outcomes [171,172].

Phospholipid reprogramming is a key metabolic change that supports the rapid growth and survival of tumor cells. This process is closely related to the Warburg effect and glycolysis, both of which contribute to the altered metabolic patterns of cancer cells. Phospholipid reprogramming involves several key alterations: increased phospholipid synthesis, enhanced desaturation of phospholipids, and increased FA uptake and FAO. The Warburg effect is characterized by cancer cells preferentially using glycolysis to generate ATP, a shift that has significant implications for phospholipid metabolism. On one hand, the glycolytic pathway provides essential intermediates for phospholipid biosynthesis. For example, glycerol-3-phosphate is used to synthesize glycerophospholipids, including PC. Therefore, the upregulation of glycolysis in cancer cells directly contributes to increased phospholipid synthesis. On the other hand, the Warburg effect, by shifting cellular metabolism to glycolysis, also promotes the production of metabolic precursors. Acetyl-CoA, a precursor for fatty acid and phospholipid biosynthesis, is one such example. In cancer, glycolysis is often upregulated, leading to an increased production of acetyl-CoA, which further drives phospholipid synthesis.

In addition, there may be other compensation pathways in tumor tissues that can protect CSCs from energy deficiency and binding of signal intermediates. Therefore, we need more research on the heterogeneity of phospholipid metabolism in CSCs. In general, due to these metabolic changes' relative measurability and operability, some progress has been made in targeting phospholipid metabolism, inhibiting CSCs, reducing drug resistance, and other aspects in recent years. Further research on its regulatory mechanism is expected to develop targeted drugs to minimize drug resistance or new therapeutic strategies and synergistic combination therapies. An important concern related to this issue is the problem of cell models in in vitro studies, especially when it involves metabolism-related mechanisms. In the tumor microenvironment, factors such as hypoxia, abnormal vasculature, and competition among various cell types for limited nutrients contribute to the heterogeneity of tumor cells and are also factors that promote and maintain stemness in tumor cells. However, in in vitro studies, even when using nutrient-restricted media, there are still significant differences compared to the environment in which tumor cells exist in vivo. Even with the increasingly used organoid models, our experience shows that the tumor cells capable of forming tumor organoids are usually those with higher stemness, and the proportion of such cells is very high, which also differs from in vivo observations. Therefore, exploring new in vitro stem cell research models is a very important aspect of future research.

7 Conclusion

CSCs are a subgroup of cancer cells that have the characteristics of stem cells. CSCs are prevalent in various tumor types and can relapse and metastasize, unlike other tumor cells that are usually eliminated by radiation and chemotherapy. CSCs have a unique pattern of phospholipid metabolism that differs from that of other cancer cells: increased phospholipid synthesis, phospholipid desaturation, and lipolysis-FAO. Whether it is targeting phospholipid metabolites or related metabolic enzymes and the stemness signal axis of activation regulation, it opens the possibility for the development of targeted therapies aimed at these cells.

Acknowledgement: None.

Funding Statement: This work was supported by grants from National Natural Science Foundation of China (81902784, 81771086), by the Fund of Sichuan Provincial Department of science and technology (2024YFFK0393, 2022YFS0039), the Research and Develop Program, West China Hospital of Stomatology, Sichuan University (LCYJ2023-DL-2, RD-02-202002), the CAMS Innovation Fund for Medical Sciences (CIFMS, 2019-I2M-5-004). The funding agencies had no role in the study design, collection, analysis, or interpretation of data, writing of the report, or the decision to submit the article for publication.

Author Contributions: The authors confirm their contribution to the paper as follows: draft manuscript preparation: Qing Wang; review and editing: Yu Zhou, Yingqiang Shen; visualization: Luyao Cai, Shouyi Tang, Dan Pan, Zhen Wang; supervision: Qianming Chen, Yu Zhou, Yingqiang Shen. All authors reviewed the results and approved the final version of the manuscript.

Availability of Data and Materials: Not applicable.

Ethics Approval: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest to report regarding the present study.

Abbreviations

ACC	Acetyl CoA carboxylase
ACLY	ATP citrate lyase
ACS	Acyl CoA synthetase
ACSLS	Long-chain acyl CoA synthetases
AKT	Protein kinase B
ALDH1	Aldehyde dehydrogenase 1
ASM	Acid sphingomyelinase
BCAP	B-cell adaptor protein
BCR	B cell receptor
BCSCs	Brain cancer stem cells
CACT	Carnitine acylcarnitine translocase
CDP	Cytidine diphosphate
СНКа	Choline kinase a
СНОР	C/EBP homologous protein
CL	Cardiolipin
COPI	Coat protein complex I
CPT1	Carnitine palmitoyltransferase 1
CSCs	Cancer stem cells
DAG	Diglyceride
DHAP	Dihydroxyacetone phosphate
EGFR	Epidermal growth factor receptor
ELOVL	Extended by elongases of very long-chain fatty acids
EMT	Epithelial-mesenchymal transformation
EOCs	Epithelial ovarian cancers
ERK	Extracellular regulated protein kinases
ETNK	Ethanolamine kinase
FA	Fatty acid
FABP	Fatty acid binding protein
FADS2	Fatty acid desaturase 2
FAO	Fatty acid oxidation
FASN	Fatty acid synthase

FGFR	Fibroblast growth factor receptor
FRS2	FGF-receptor substrate 2
GAB1	GRB2-associated binder 1
GCSCs	Gastric cancer stem cells
GPCR	G Protein-Coupled Receptors
GPX	Glutathione peroxidases
GRB2	Growth factor receptor-bound protein 2
GSCs	Glioma stem cells
GSH	Reduced glutathione
GSSG	Oxidized glutathione
HER2	Human epidermal growth factor receptor 2
HIF-1	Hypoxia-inducible factor 1
IBC	Inflammatory breast cancer
IFN	Interferon
JM	Juxtaposed membrane
LATS1/2	Large Tumor Suppressor Kinase 1/2
LCFAs	Long-chain FAs
LncRNA	Long non-coding RNA
LPA	Lysophosphatidic acid
LPC	Lysophosphatidylcholine
LPCAT	Lysophosphatidylcholine acyltransferase
LSCs	Leukemia stem cells
MAPK	Mitogen-activated protein kinase
MARK4	Microtubule affinity regulating kinase 4
MEK	Mitogen-activated protein kinase kinase
MOB1	Mps one Binder 1
mTOR	Mammalian target of Rapamycin
MUFAs	Monounsaturated FAs
NSCLC	Non-small cell lung cancer
nSMase	Neutral sphingomyelinase
OTUB1	Ovarian tumor associated proteinase B1
PA	Phosphatidic acid
PaCSCs	Pancreatic cancer stem cells
PAP	Phosphatidic acid phosphatase
PC	Phosphatidylcholine
PDK1	Phosphoinositol-dependent kinase-1
PE	Phosphatidylethanolamine
PI	Phosphatidylinositol
PI3K	Phosphatidylinositol-3-kinase
PIP2	Phosphatidylinositol-45-bisphosphate
PIP3	Phosphatidylinositol 3,4,5-trisphosphate
PLA	Phospholipase A
PLC	Phospholipase C
PLCD3	Phospholipase C Delta3
PLCy1	Phospholipase C Gamma 1
PLD	Phospholipase D
PS	Phosphatidylserine
PTEN	Phosphatase and tensin homolog deleted on chromosome ten
PUFAs	Polyunsaturated FAs

Rheb	Ras homolog enriched in brain
ROS	Reactive oxygen species
RSK	Ribosomal S6 Kinase
S1P	Sphingosine 1 phosphate
S1PR	S1P receptor
SASP	Senescence-associated secretory phenotype
SAV1	Salvador Family WW Domain Containing Protein 1
SCD	Stearoyl COA desaturase
SHC	SH2-containing sequence
SK1	Sphingosine kinase 1
SLC7A11	Solute carrier family 7 member 11
SM	Sphingomyelinase
SOS	Son of Sevenless
SOX2	SRY-box transcription factor 2
SPHK	Sphingosine kinase
sPLA2	Secreted phospholipase A2
SRS	Stimulated Raman scattering
STAT1	Signal transducer and activator of transcription 1
TAZ	Transcriptional coactivator with PDZ-binding motif
TCA	Tricarboxylic acid
TCR	T cell receptor
TKR	Tyrosine kinase receptor
ТМ	Transmembrane
TNBC	Triple-negative breast cancer
TSC1/2	Tuberous sclerosis complex 1/2
UFAs	Unsaturated FAs
YAP	Yes-associated protein

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