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CONCISE REVIEW

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Aberrant lipid metabolism as an emerging therapeutic strategy to target cancer stem cells

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Abstract

Emerging evidence in cancer metabolomics has identified reprogrammed metabolic pathways to be a major hallmark of cancer, among which deregulated lipid metabolism is a prominent field receiving increasing attention. Cancer stem cells (CSCs) comprise <0.1% of the tumor bulk and possess high self-renewal, tumor-initiating properties, and are responsible for therapeutic resistance, disease recurrence, and tumor metastasis. Hence, it is imperative to understand the metabolic rewiring occurring in CSCs, especially their lipid metabolism, on which there have been recent reports. CSCs rely highly upon lipid metabolism for maintaining their stemness properties and fulfilling their biomass and energy demands, ultimately leading to cancer growth and invasion. Hence, in this review we will shed light on the aberrant lipid metabolism that CSCs exploit to boost their survival, which comprises upregulation in de novo lipogenesis, lipid droplet synthesis, lipid desaturation, and β-oxidation. Furthermore, the metabolic regulators involved in the process, such as key lipogenic enzymes, are also highlighted. Finally, we also summarize the therapeutic strategies targeting the key regulators involved in CSCs' lipid metabolism, which thereby demonstrates the potential to develop powerful and novel therapeutics against the CSC lipid metabolome.

KEYWORDS

cancer stem cells, fatty acid synthesis, lipid metabolism, metabolic rewiring, β-Oxidation

1 | LIPID DROPLETS—BIOSYNTHESIS, COMPOSITION, AND FUNCTION

Lipid droplets (LDs) are highly organized, spherical organelles that are cellular fat storage depots. LDs develop within the endoplasmic reticulum (ER) via a budding process and are then transported to the cytoplasm.[1] LDs consist of neutral lipids such as triacylglycerides (TAGs; which are the major form of energy storage within LDs), cholesteryl esters, and retinyl esters. The number and size of these droplets vary according to the cellular metabolic state. The multifaceted physiological functions of LDs include energy storage, biosynthesis of cellular membranes, and lipid metabolism. LDs exert a protective effect by sequestering the potentially toxic lipids within them, thereby preventing any unregulated lipolysis or lipid peroxidation and averting ferroptosis or any cytotoxic effect on the cells.[1,2] The surface of LDs harbors the required enzymes and proteins required for lipid metabolism and dynamically interacts with the mitochondria to enable efficient trafficking and distribution of fatty acids (FAs).[2] LDs also possess tightly regulated mechanisms for balancing lipid biogenesis and breakdown, thereby contributing to the homeostasis of the cell membrane and ER.

The function of LDs is twofold: one is to provide an alternative energy source when glycolysis is blocked; and second, to protect the FAs from the harmful effects of peroxidation. One of the protective effects of LDs in cancer cells may be facilitating a compensatory high antioxidant activity, which these cells exploit to combat any unfavorable effects due to heightened reactive oxygen species (ROS)

generation. The oxidative stress in cancer cells could also be overcome by cancer cells' increased oxidative stress tolerance. These events of ROS generation occur in the mitochondria, which are a harboring site for oxidative phosphorylation (OXPHOS) and β-oxidation, and contribute to cancer cell survival and growth. A study reported the effect of LDs in protecting breast cancer cells against ROS-mediated detrimental effects such as membrane lipid peroxidation.[3] However, the presence of elevated mitochondrial ROS levels can negatively impact polyunsaturated FAs by subjecting them to lipid peroxidation by ROS and incurring a deleterious effect on cellular functions.

2 | LIPID METABOLISM IN MAMMALIAN CELLS AND ITS METABOLIC SUBSTRATES

Having known the role of LDs, it is important to understand the pathways of lipid metabolism in mammalian cells, cancer cells, and cancer stem cells (CSCs) comprising small population of tumor-initiating cells possessing self-renewal and chemoresistant properties.[4] Lipid metabolism in mammalian cells can be broadly categorized into anabolic and catabolic arms. During anabolism, FAs are synthesized and stored as an energy reserve in LDs. In contrast, the catabolic arm of lipid metabolism breaks down the LDs to form free FAs, ultimately leading to energy production in mitochondria.[5] The major metabolic substrate that is required for anabolic FA synthesis is acetyl coenzyme A (acetyl-CoA), which is mostly derived from pyruvate via a glucose-dependent mechanism.[6] The acetyl-CoA then condenses with oxaloacetate to form citrate, which is then cleaved by cytosolic ATP citrate lyase (ACLY) and enters the FA synthesis pathway. The breakdown of lipids within LDs occurs through either lipophagy or lipolysis, the latter being commonly used to generate FAs for mitochondrial energy production and as signaling molecules.[5] The TAGs present within LDs usually undergo lipolysis via lipases such as adipose tissue triacylglycerol lipase (ATGL) and hormone-sensitive lipase (HSL) that hydrolyze the ester bond in TAGs, resulting in the generation of cytoplasmic free FA.[5,7] The free FA couples with CoA to form acyl CoA moieties that are then transferred to carnitine to generate acyl carnitine, which subsequently enters the mitochondrial matrix via the carnitine shuttle. Once inside the matrix, the acyl chains are recoupled to CoA and carnitine shuttles back from the matrix to the cytosol. The acyl CoA then undergoes β-oxidation inside the mitochondrial matrix to generate energy.[8]

3 | ROLE OF AUTOPHAGY IN CSC STEMNESS

Autophagy, which refers to the recycling of metabolic organelles,[9,10] generally aids in the survival of cancer cells by supporting their energy demands.[11] Another emerging mechanism of lipid mobilization that links autophagy with lipolysis is termed lipophagy.[12] Lipophagy is a macroautophagy process occurring in LDs, first described in mouse hepatocytes, and is the main mechanism of lipid catabolism in hepatocytes where ATGL and HSL are expressed at low levels.[13] Lipophagy is characterized by the engulfment of LDs by the autophagosome, followed by fusion of the latter with lysosomes containing lysosomal acid lipase and leading to LD degradation.[5,7,13] In fact, lipophagy is critical for the maintenance of lipid homeostasis whereas its inhibition can cause excessive LD accumulation, lipotoxicity, and may have implications in metabolic disorders.[13] It has been demonstrated that cancer cells perform lipophagy for enhanced lipid turnover in order to support metastasis and tumorigenesis.[14]

In general, autophagy enables CSCs to rapidly adapt to changes in their microenvironment, such as during cancer therapy,[15-17] and CSCs possess a heightened rate of autophagy compared to the non-CSC populations of the tumor bulk.[18] For instance, it has been shown that autophagy protects glioblastoma multiforme CSCs from the unfavorable conditions in the tumor microenvironment.[19] Also, autophagy has been observed to enhance the survival of pancreatic cancer cells by facilitating increased β-oxidation.[11] Furthermore, an augmented dependence of these pancreatic CSCs on autophagy and β-oxidation was observed, which was also confirmed by an increased sensitivity of CSCs to inhibition of these processes compared to non-CSCs.[11] The presence of autophagy markers in breast cancer stem-like cells, mammospheres, and in the ALDH-1$^+$ population of breast cancer cell lines, indicates that autophagy is critical for breast CSC maintenance.[20,21] In fact, inhibition of autophagy has been reported to impair CSC stemness and tumorigenesis properties.[22] Moreover, it was shown that autophagy could be a contributing factor for long-term persistence of colon CSCs after therapy.[23]

4 | REWIRING OF LIPID METABOLISM IN CANCER AND CSCS

In cancer cells, the most widely known metabolic reprogramming is the glycolytic switch, termed the Warburg effect.[24] Nevertheless, there are other metabolic changes among which aberrant lipid metabolism forms a major modification. Cancer cells depend on increased lipogenesis to sustain their rapid proliferation that demands a high level of anabolic lipid biogenesis for membrane synthesis.[25] Specific anticancer therapeutics that block glycolysis normally induce breakdown of LDs to release the free FA, which gets mobilized to mitochondria to sustain continued energy production through β-oxidation.[14,26,27] Hence, even

Significance statement

This review describes the significance of altered lipid metabolism present in cancer stem cells (CSCs) originating from various cancers. It discusses the critical metabolic modifications occurring in CSCs that enable advanced growth and tumorigenesis through enhanced dependence on fatty acid synthesis and β-oxidation to fulfill their heightened energy and biomass requirements. Furthermore, this review summarizes the various anticancer therapeutic strategies targeting CSC lipid metabolism.

during conditions of glucose withdrawal, where glucose-dependent lipid biosynthesis is impaired, β-oxidation continues and enables the tumor cells to sustain their energy demands. Supportive evidence on increased β-oxidation of FAs has been demonstrated to enhance pancreatic and breast cancer.[28,29] On the other hand, it has been reported that inhibition of β-oxidation induces apoptosis in leukemia cells.[30]

Similar to bulk cancer cells, CSCs also possess a complex network of modified metabolic pathways that enable them to exploit all the available metabolic intermediates to maximize their energy benefits. A study reported metabolic reprogramming of the processes starting from OXPHOS up to β-oxidation as the key event underlying the generation and stemness maintenance of Nanog positive CSCs in hepatocellular carcinomas (HCC). These CSCs showed an increased β-oxidation rate and inhibited OXPHOS, which was facilitated via the interaction of Nanog with peroxisome proliferator-activated receptor-δ.[29] It was found that silencing of Nanog downregulated β-oxidation, thereby chemosensitizing the CSCs to sorafenib, which resulted in glycolytic inhibition and increased OXPHOS.[31] A higher FA synthesis and activated mevalonate pathway were also observed in pancreatic CSCs as compared to the non-CSCs.[32] Recently, loss of histone variant macroH2A1 was demonstrated to induce a CSC-like phenotype in HCC observed by an increased expression of stemness-associated genes and upregulation of the nuclear factor-κB (NF-κB) pathway.[33] In addition to diverting cancer cells into a CSC-like phenotype, a reprogramming of metabolic pathways was also reported in the absence of macroH2A1. For instance, an increase in acetyl-CoA-dependent FA synthesis resulted in high intracellular lipid accumulation as well as a rewired carbohydrate metabolism leaning toward the pentose phosphate pathway, enabling the use of glycolytic intermediates for nucleotide synthesis in HCC cells.[34]

Since they are highly metabolically flexible, CSCs induce β-oxidation to support their survival during glucose limiting conditions. For instance, in the hypoxic niche where the CSCs reside, an increased uptake of FA and LD accumulation is observed. Furthermore, hypoxia-inducible factor-α and pyruvate dehydrogenase hinder entry of pyruvate into the tricarboxylic acid (TCA) cycle, thereby preventing glucose-induced FA synthesis. Hence, alternative carbon sources come into play such as glutamine, which undergoes reductive metabolism to form α-ketoglutarate, followed by generation of isocitrate and citrate, to enter FA synthesis.[35] Additionally, acetyl-CoA is synthesized from cytoplasmic acetate by acetyl-CoA synthase-2, which also helps to continue FA synthesis.[36] All the above factors in cancer cells result in an increased LD accumulation wherein the energy is conserved in the form of triglycerides. However, contrary to other cells in the hypoxic niche, the presence of CPT1 in cancer cells indicates the occurrence of β-oxidation to some extent, thereby

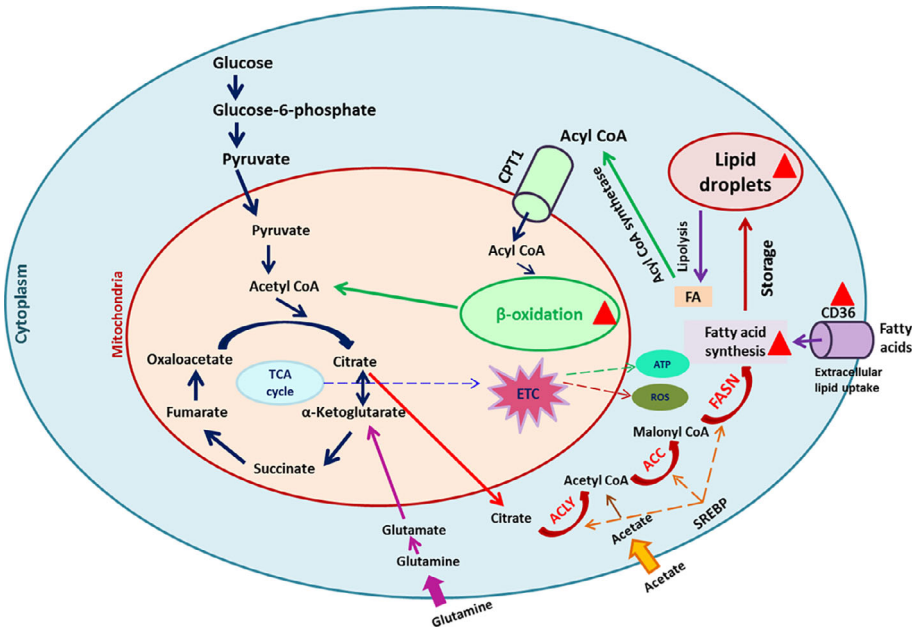

FIGURE 1 Lipid metabolism in cancer. Lipid metabolism is composed of both an anabolic arm (fatty acid synthesis) and catabolic arm (β-oxidation). Glycolysis converts glucose to pyruvate, which enters mitochondria to generate acetyl-CoA that combines with oxaloacetate to form citrate. During conditions of glucose withdrawal in the cancer environment, due to hypoxia or therapeutic blockade of glycolysis, citrate can be formed using alternative carbon sources such as glutamine or cytoplasmic acetate in order to sustain the biomass and energy requirements of cancer cells. Citrate is further cleaved by ACLY to acetyl-CoA, which is converted by ACC to malonyl CoA that is used to synthesize FAs by FASN. FAs are then stored in lipid droplets, which can be used to obtain FAs during lipolysis. FAs are additionally derived from extracellular lipid uptake. The FAs can undergo conversion to acyl CoA, which is then transported back into mitochondria using CPT1 to undergo β-oxidation that generates acetyl-CoA. Ultimately it enters the electron transport chain to generate ATP that fulfills the energy demands of cancer cells. In comparison to the bulk cancer cells, CSCs have been demonstrated to possess upregulated rates of FA synthesis, extracellular lipid uptake, intracellular lipid droplet accumulation, and β-oxidation, as indicated by red triangles in the figure. ACC, acetyl-CoA carboxylase; ACLY, ATP citrate lyase; ATP, adenosine triphosphate; CD36, cluster of differentiation 36; CPT1, carnitine palmitoyltransferase-1; ETC, electron transport chain; FASN, fatty acid synthase; ROS, reactive oxygen species; SREBP, sterol regulatory element-binding proteins; TCA, tricarboxylic acid cycle

indicating that a transformed lipid metabolic pathway exists in cancer cells as compared to normal cells in the same environment.[37] Furthermore, several studies described in the subsequent sections of this review have demonstrated a further increase in the rates of FA synthesis, lipid unsaturation, and LD content in the CSCs as compared to the non-CSC bulk cancer population. The metabolic pathways present in CSC lipid metabolism are depicted in Figure 1.

5 | HIGH LIPID CONTENT IN CANCER AND CSCS LINKING TO CANCER PROGRESSION AND CSC STEMNESS

Since LDs have obtained much attention on their cancer promoting role, they are even being considered as an additional hallmark of cancer with respect to their role in enhancing cancer aggressiveness and potential as a prognostic biomarker for detecting highly metastatic cancers. This section will provide insights into the association between lipid content, cancer progression, and CSC maintenance in cancers of different origins.

Lipid rafts, composed mainly of cholesterol, are major components of the cell membrane and facilitate signal transduction. However, excessive incorporation of FAs into the lipid rafts instils membrane phase separation and limits cell-cell contact, thereby promoting tissue invasion and contributing to cancer progression.[38] The higher lipid content in cancer cells reflects higher FA synthesis that sustains cancer cell growth and provides protection from chemotherapeutic stress, for example, LD-mediated protection from 5-fluorouracil and oxaliplatin in colorectal cancer.[39] High intracellular lipid accumulation, observed using Coherent anti-Stokes Raman scattering microscopy, was found in metastatic cancers.[38]

Moreover, a study on the abundance of LDs in various breast cancer cell lines showed a direct correlation of LDs to the cell lines' increasing degree of malignancy.[40] Cancer cells have been shown to exhibit a higher LD content than normal cells[41] in which 93% of TAGs are known to be acquired via de novo lipogenesis.[42] Furthermore, the number of LDs in colorectal CSCs was directly proportional to their tumorigenicity.[43] These studies corresponded to the clinical reports where breast cancer patients were shown to have high levels of total cholesterol, triglycerides, high-density lipoproteins, and low-density lipoproteins (LDLs).[44] Also, the link between high dietary intake of cholesterol and colorectal cancer prevalence has been reported.[45] Forty-one percent of colorectal cancer patients have been shown to possess higher LDL levels.[46] In fact, lowering of total cholesterol levels has resulted in reducing the risk for colorectal cancer.[47] Likewise, reduced levels of LDL and LDL receptor demonstrate good prognosis for patients with small cell lung cancer,[48] and intratumor cholesteryl ester accumulation has been suggested as a potential biomarker for breast cancer detection.[49]

Emerging evidence indicates the presence of higher lipid content within CSCs irrespective of cancer origin. One study demonstrated a higher level of lipids present in colorectal CSCs (CRCSCs) as compared to non-CSC cancer cell populations and normal epithelial colon cells, which was associated with LD^{high} CRCSCs' higher tumorigenic and clonogenic potential as compared to LD^{low} CRCSCs. The lipid content in CSCs also corresponded with high CD133 expression and upregulated Wnt pathway activation, which are known markers of CRCSCs.[43]

It was reported that a higher rate of de novo lipogenesis exists in glioma stem cells (GSCs) than in differentiated glioma cells, revealed by a marked incorporation of 14 [C]-glucose and 14 [C]-acetate into lipids.[50] In ovarian CSCs, measurement of intracellular lipid content and rates of unsaturation through single cell stimulated Raman scattering microscopy demonstrated that $ALDH^+/CD133^+$ CSCs have a higher amount of LDs within which a higher proportion of unsaturated lipids are present as compared to their non-CSC and monolayer counterparts.[51] Another study showed LD accumulation in glioblastoma cancer cells to be contributed by increased de novo lipogenesis as well as extracellular lipid uptake, which increased their sphere-forming and metastatic capabilities.[52]

Overall, the increased dependence of CSCs on de novo lipogenesis, evidenced by a higher intracellular lipid accumulation, has been well demonstrated by these studies. Furthermore, it suggests that further investigation is imperative to elucidate the mechanisms underlying these observations. These are most likely facilitated by modifications in the levels of key lipogenic regulators, which are described in the following section.

6 | PRO-TUMORIGENIC METABOLIC ALTERATIONS IN KEY LIPOGENIC ENZYMES AND THEIR THERAPEUTIC TARGETING TO COMBAT CANCER PROGRESSION

In addition to the metabolic alterations occurring in lipogenic enzymes that contribute to progression of cancer, this section also outlines the therapeutic strategies that target lipid metabolism in order to regulate cancer progression and CSCs.

6.1 | Sterol regulatory element-binding protein

Sterol regulatory element-binding proteins (SREBPs) are a family of transcription factors controlling the gene expression of various lipogenic enzymes such as fatty acid synthase (FASN), ACLY, and stearoyl CoA desaturase (SCD) by binding to sterol regulatory elements and E-box sequences of their gene promoters. A high expression of SREBP1 has been shown to be associated with shorter survival rates in pancreatic cancer patients.[30] An increased expression of the key lipogenic genes such as ACLY, acetyl-CoA carboxylase-1 (ACC), and FASN has been reported in CSCs as compared to the non-CSC population.[53] These genes are regulated by SREBP1, whose ectopic expression resulted in an increased expression of the above genes, corresponding to augmented lipogenesis and sphere formation in MCF10A breast stem-like cells.[53]

6.2 | Fatty acid synthase

An increased expression of FASN has been observed in several cancers such as breast, prostate, brain, colon, lung, bladder, gastric,

endometrial, ovary, kidney, skin, pancreatic, head and neck, tongue, and melanoma.[42,54-57] Overexpression of FASN has been shown to generate a cancer phenotype in non-cancerous epithelial cell lines such as breast MCF10A and HBL100 cell lines through activation of HER1/HER2 tyrosine kinase receptors.[58] In GSCs, an increased de novo lipogenesis facilitated by upregulation of FASN is observed to maintain the GSC stemness. Inhibition of FASN causes a reduction in stemness marker expression and inhibits the CSC functionalities such as proliferation and migration.[50] FASN has been shown to be upregulated via activation of the PI3K/AKT and the extracellular signal-regulated kinases (ERK) signaling pathways.[59]

Most of the therapeutic targeting against lipogenic enzymes has been directed against FASN. Pharmacological inhibition of FASN has been performed using cerulenin, a fungal metabolite, in GSCs, which resulted in a marked inhibition of their stemness properties including sphere formation, invasive abilities, and expression of stemness markers such as SOX2, nestin, CD133, and FABP7, accompanied by an increase in the levels of the differentiation marker glial fibrillary acid protein.[50] Another study demonstrated that the inhibition of FA and cholesterol synthesis by cerulenin and atorvastatin, respectively, highly inhibited pancreatic CSCs as compared to non-CSCs, indicating the noteworthy role of these pathways in CSC survival.[32] Another breast cancer study reported that resveratrol caused the inhibition of FASN, with a resultant increase in apoptosis and expression of pro-apoptotic genes DAPK2 and BNIP3. They also observed that the reduced FASN expression correlated with decreased intracellular lipid content, and number and size of MCF7 and MDA-MB-231 breast cancer cell line-derived CSC spheres. Furthermore, it was found that resveratrol administration in mice injected with CSCs from MDA-MB-231 breast cancer cells failed to initiate tumor growth by down-regulating FASN and causing suppression of lipogenesis.[60]

6.3 | ATP citrate lyase

By being the key enzyme regulating the rate-limiting step of citrate to acetyl-CoA conversion in the cytosol, ACLY tightly controls cancer metabolism and diverts the increased glycolytic flux into lipid biosynthesis. In addition to generating acetyl-CoA, which is directly used for lipid biosynthesis, the ACLY reaction also generates oxaloacetate, which, upon conversion to malate, subsequently enters the mitochondria and restabilizes the high NADH/NAD^+ ratio in the matrix. It helps to maintain a high mitochondrial membrane potential, thereby keeping the TCA cycle in the repressed state.[61] An upregulated ACLY expression is noted in breast CSCs compared to non-CSCs.[53]

A breast CSC study revealed $ERBB2^+$ breast cancer cells from the BT474 cell line to have an upregulated peroxisome proliferator-activated receptor-γ (PPARγ) expression, facilitating a high lipid content and protection from palmitate-induced lipotoxicity[62] Hence, treatment with the PPARγ antagonist GW9662 inhibited the CSCs' de novo lipogenesis pathway, as evidenced by the reduction in expression of lipogenic enzymes such as FASN, ACLY, MIG12, and NR1D1. This caused a reduction in the functionality of these CSCs by upregulating ROS production and resulting in a decrease in the number of breast CSCs along with diminished sphere formation and lowered expression of stemness genes (KLF4 and ALDH1).[63] Similarly, inhibition of ACC by soraphen downregulated $ALDH1^+$ CSC-like cells and their sphere formation potential in MCF7 breast cancer cells.[64]

6.4 | Stearoyl CoA desaturase

SCD is a desaturase enzyme present in the ER that converts stearic acid to oleic acid and palmitic acid to palmitoleic acid, all of which belong to the category of monounsaturated FAs (MUFA), which in turn form the building blocks of cellular membrane biosynthesis.[65,66] It has been reported that SCD is one of the important proteins required for cancer cell survival, which was found using RNA interference screening.[67] It was demonstrated that cancer cells depend on desaturation of saturated FAs by SCD1 for sustaining their proliferation.[68] SCD is one of the target enzymes of SREBP1 and a regulator of CSC stemness, and is highly expressed in various cancers such as colon, oesophageal, and prostate cancer, as well as in breast, ovarian, lung, and HCC CSCs.[69,70] In lung cancer, the CSCs are accompanied by an increased expression of their stemness genes such as CD133, CD44, CD24, and Sox2.[71]

Inhibition of SCD1 in ovarian cancer spheroids injected into mice reduced their tumor-initiating capability and proliferation, resulting in small tumor sizes.[72] Similarly, suppression of SCD1 reduced the number of $CD44^+$ $CD24^-$ cells and sphere-forming abilities in MCF10A breast cells.[69] Inhibition of SCD1 using betulinic acid was shown to induce apoptosis in colon CSCs[73] and chemosensitize lung CSCs to cisplatin.[71] In liver CSCs, SCD1 was shown to be critical for CSC generation regulated via Nanog.[31] However, contrary reports indicate that SCD1 plays a tumor suppressive role in chronic myeloid leukemia,[74] indicating its milieu-dependent role.

The effects of curcumin and berberine in exerting anti-tumorigenic effects in glioblastoma multiforme and breast cancer have been demonstrated to act via inhibiting LD accumulation.[75,76] In breast cancer, there was also an observed downregulation in expression of stemness genes such as ALDH1A3, CD49f, PROM1, and TP63, facilitated via the blockade of SCD1 by curcumin.[69]

It was demonstrated that SCD1 inhibitors CAY10566 and SC-26196 block conversion of saturated FAs to MUFA by inhibiting SCD1 and Δ6, respectively. It resulted in reduced ALDH1 marker expression, in vitro CSC sphere formation, and in vivo CSC tumor initiation capacity through suppression of the NF-κB pathway. This study postulated lipid desaturation as a key metabolic marker indicating disease progression.[51]

6.5 | CD36

CD36 is a FA transporter that transports free FA into mitochondria to enable β-oxidation. CD36 expression in $CD44^{bright}$ CSCs from oral squamous cell carcinoma permitted the uptake of palmitic acid and enhanced metastasis. Moreover, targeting of CD36 by neutralizing antibodies blocked β-oxidation, thereby completely abolishing metastasis in melanoma and breast cancer.[77] CD36 was also demonstrated to drive the proliferation of GSCs by facilitating the uptake of oxidized phospholipids, whereas its inhibition resulted in increased apoptosis

of GSCs.[78] With regard to nonsolid tumor CSCs, leukemic stem cells (LSCs) from gonadal adipose tissue were found to be CD36-enriched, conferring increased survival advantage and therapeutic evasion.[79,80]

6.6 | CPT1

The effect of etomoxir, which inhibits β-oxidation by blocking CPT1 and preventing FA entry into mitochondria for β-oxidation, has been studied on various CSCs. In one study, etomoxir chemosensitized leukemic cells, as evidenced by increased apoptosis, and decreased LSCs in primary human acute myeloid leukemia samples.[30,81] Blockade of CPT1A using avocatin-B (sourced from avocado fruit) also inhibited LSCs in acute myeloid leukemia, which was absent in LSCs lacking CPT1A.[82] Similarly, a study on HCC showed that the restoration of OXPHOS by Cox6a2/Cox15 overexpression or β-oxidation inhibition by etomoxir chemosensitized CSCs to sorafenib treatment.[31] Etomoxir generated decreased viability and sphere formation in breast CSCs derived from MDA-MB-468 and patient-derived cancer cells respectively. Examining this further, the role of CPT1B on β-oxidation facilitated via an activated JAK/STAT pathway was revealed in HCC1937 and MCF7 CSCs. Another inhibitor, AZD1480, resulted in reduced CSC viability and sphere formation via inhibiting the JAK/STAT pathway. Similar tumor-inhibitory effects were also observed when the silencing of STAT3 was performed in MDA-MB-468 breast CSCs, resulting in downregulation of β-oxidation of FAs.[83] The different methods of therapeutic targeting of lipid metabolism in CSCs described in this section are summarized in Figure 2.

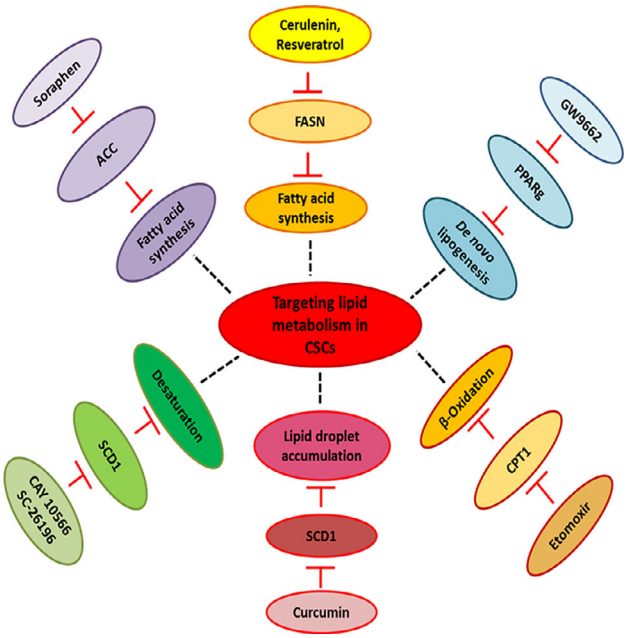

FIGURE 2 Targeting of lipid metabolism in CSCs. Various inhibitors directed against key regulators of lipid metabolism interfering with the processes of FA synthesis, lipid desaturation, or β-oxidation, which can specifically target CSCs, are summarized. CC, acetyl-CoA carboxylase; CPT1, carnitine palmitoyltransferase-1; CSCs, cancer stem cells; FASN, fatty acid synthase; PPARγ, peroxisome proliferator-activated receptor-γ; SCD1, stearoyl CoA desaturase-1

7 | CONCLUSION

Metabolic alterations represent a major approach by which cancer cells and CSCs evade the effects of an unfavorable environment. Among the reprogrammed metabolic pathways, lipid metabolism remains a key conduit on which the CSCs are highly dependent. In this review, we have described the reliance of CSCs on FA synthesis and β-oxidation to sustain their biomass and energy demands respectively, and the protective effect conferred by their high LD content that contributes to disease aggressiveness. Furthermore, we have summarized the key metabolic regulators that could be exploited for specific therapeutic approaches targeting CSC lipid metabolism. However, the complexity of other reprogrammed metabolic pathways such as glycolysis, mitochondrial respiration, glutamine metabolism, purine synthesis, and lysine catabolism that may be present in the CSCs needs to be considered. Nevertheless, this metabolic facet of CSCs remains relatively unexplored and offers several promising avenues that could be further delved into.

CONFLICT OF INTEREST

The authors indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

M.V.: conception and design, provision of study material, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript; S.W.: manuscript writing, final approval of manuscript; F.A.: conception and design, manuscript writing, final approval of manuscript; A.D.: conception and design, financial support, administrative support, manuscript writing, final approval of manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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