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REVIEW

Bioactive lipids in cancer stem cells

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Abstract

Tumours are known to be a heterogeneous group of cells, which is why they are difficult to eradicate. One possible cause for this is the existence of slow-cycling cancer stem cells (CSCs) endowed with stem cell-like properties of self-renewal, which are responsible for resistance to chemotherapy and radiotherapy. In recent years, the role of lipid metabolism has garnered increasing attention in cancer. Specifically, the key roles of enzymes such as stearoyl-CoA desaturase-1 and 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase in CSCs, have gained particular interest. However, despite accumulating evidence on the role of proteins in controlling lipid metabolism, very little is known about the specific role played by lipid products in CSCs. This review highlights recent findings on the role of lipid metabolism in CSCs, focusing on the specific mechanism by which bioactive lipids regulate the fate of CSCs and their involvement in signal transduction pathways.

Key words: Cancer stem cells; Lipid metabolism; Bioactive lipids; ABC transporters

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Core tip: Cancer stem cells (CSCs) are a minute portion of highly aggressive cells that survive conventional and targeted therapies and ultimately re-populate the tumour. Recent studies have elucidated that stearoyl-CoA desaturase-1 and 3-hydroxy-3-methyl-glutaryl-coenzyme A metabolic pathways involved in lipid metabolism are hyperactive in CSCs. However, the purpose of this enhanced activity is unclear. Here, we review the current literature and discuss the possible pathways and mechanisms that link the enhanced CSC lipid metabolism to bioactivity, specifically, with regard to structural lipids and active bio-molecules involved in cell signalling.

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INTRODUCTION

Cancer progression is characterised by a continuous changeable state generating a very complex and heterogeneous multitude of cells with different morphology, genotype, and phenotype. This heterogeneity is explained by two main models: The clonal evolution model and the cancer stem cell (CSC) model. According to the CSC model, cancers are a heterogeneous combination of genetically different subclones that are arranged in an organised hierarchy, with CSCs at the apex[1,2]. According to the stem cell theory for cancer, only a subset of cancer cells are accountable for tumour initiation and propagation[3]. The primary functional characteristics of CSCs are similar to those of normal stem cells, such as the capacity to self-renew and the ability to differentiate into different cell types. CSCs present an elevated tumorigenic potential and an increased resistance to conventional and targeted therapy[3-8]. Functional recognition of CSCs from the mass of the tumour population involves the demonstration that they are indeed able to self-renew and differentiate[9-13]. These cells must possess the ability to initiate a novel tumour, often in small numbers. There is much dispute on the specificity of markers to be used to identify CSCs. However, the most reliable are functional markers such as ABC transporter activity, namely ABCG2 and ABCB1, which are able to transport the fluorescent dyes Hoechst 33342 and rhodamine 123, respectively[14]. Aldehyde dehydrogenase activity and the ability to cycle slowly are among other characteristics commonly accepted as defining features of CSCs[5,15-18]. The concept that suggests CSCs rely on oxidative phosphorylation (OXPHOS) is becoming more accepted as the metabolic signature of CSCs, making metabolic targeting a rewarding opportunity within the CSC field[5,6,19-27]. Recent studies have highlighted the link between CSCs and enhanced activity in lipid metabolism, particularly for monounsaturated fatty acids and cholesterol. Recent reviews have brilliantly described the role of lipid metabolism alterations in CSCs[28-30]. However, the purpose behind this enhanced activity is not understood. In this review we discuss the latest advances in CSC lipid metabolism and describe how this enhanced lipid metabolism in CSCs can lead to the production of active biolipids as signalling molecules.

CSC metabolism

Similar to normal cells, CSCs use energy from mitochondrial OXPHOS, which produces more adenosine triphosphate (ATP) compared to glycolysis and produces tricarboxylic acid cycle intermediates utilised for macromolecule synthesis. CSC functions are regulated by a number of specific signalling pathways[31,32]. These pathways change in response to environmental stresses such as fluctuating oxygen and nutrient levels, pH, inflammation, and anticancer therapies[33]. While cancers rely on angiogenesis, the fast proliferation of cancer cells outstrips the blood supply, which is often leaky and lacks a normal hierarchical structure. Consequently, hypoxia and poor perfusion are common in tumours, so that there is a poor supply of nutrients and clearance of waste products. However, mitochondrial respiration is not impaired until the oxygen concentration drops below 1.0 μM[34]. Furthermore, it has been shown that even at oxygen levels of 0.5%, the electron transport chain is still capable of normal functioning[35]. It has also been reported that hypoxia is necessary for the preservation of embryonic stem cells in an undifferentiated state[36] and that it is accountable for the creation and maintenance of the stem cell niche[37-40,41,42]. These studies exemplify that hypoxia is a necessary condition for ensuring a balance between stem cell phenotypes and metabolism. In addition, it has been demonstrated that tumorigenesis is dependent on functioning mitochondria[5,43], since mitochondrial respiration results in the production of metabolites such as citrate, that can be utilised by ATP citrate lyase, to produce oxaloacetate and acetyl-CoA. In conditions where there are high levels of ATP, it has been shown that acetyl-CoA can be utilised for the regulation of protein acetylation and the synthesis of fatty acids[44]. These findings suggest a role for signalling molecules in the maintenance of the stem cell niche. A recent study demonstrated that glycosylation (specifically O-GlcNAc modification) of pluripotency markers sex-determining region Y-box 2 and octamer-binding transcription factor 4 takes place in undifferentiated mouse embryonic stem cells and

this is absent following differentiation[45]. Emerging evidence suggests that the metabolic phenotype of CSCs is dependent on their location, oxygen supply, and metastatic sites. There are studies suggesting that CSCs from lung, breast, glioblastoma, osteosarcoma, ovarian, nasopharyngeal, hepatocellular carcinoma, and colorectal cancers favour glycolysis compared to other differentiated cells *in vitro* and *in vivo*[46-52]. This variation may be due to differential location, availability of nutrients, oxygen, stage of lineage specification, tumour heterogeneity, and isolation techniques. It is possible to speculate that metabolic profiles of CSCs change as they migrate from the original site to the metastatic site and that this change is largely attributed to the tumour microenvironment in which they reside. While both glycolytic and mitochondrial metabolism are utilised by cancer cells, due to the heterogeneity among cancer cells within a tumour, some cells are reliant on glucose[53], while others have a strong dependence on aerobic glycolysis[54,55] due to an impaired TCA cycle or electron transport chain. However, due to the plasticity of cancer, some cells can alter their metabolic profile following therapeutic intervention by undertaking therapy-induced senescence[56]. Another impediment to cancer eradication is that slow-cycling CSCs demonstrate dependence on OXPHOS[5,7,57].

Aldehyde dehydrogenase metabolism

It was recently found that the prominent CSC marker aldehyde dehydrogenase (ALDH)1A1 modulates energy metabolism in adipocytes from several species[58]. In this study, retinoic acid deficiency in knock-out ALDH1A1 adipocytes inhibited adipogenesis and increased thermogenesis. Functional CSC markers such as ALDH1A1 activity are increasingly highlighted as a reliable marker in the literature. ALDH1A1 activity requires the involvement of metabolic and signalling pathways. Retinoids play an important role in energy metabolism, and their role in maintaining normal embryonic development is well understood. In retinoid metabolism, retinaldehyde can be oxidised to retinoic acid by ALDH1a1-3. Retinoic acid is a potent transcriptional regulator and controls more than 500 genes. The receptors for retinoic acid (RAR-α, RAR-β, and RAR-γ) are members of the nuclear hormone receptor superfamily, which includes receptors for steroid and thyroid hormones. Upon activation, these receptors initiate cell responses related to proliferation, apoptosis, and differentiation. There is also some evidence that retinoic acid can regulate signalling pathways inside the cell and that all-trans-retinoic acid can bind peroxisome proliferator-activated receptor beta-gamma (PPAR β-γ). The enzymes are involved in several biological functions and their functional role is likely related to cellular detoxification and maintenance of low reactive oxygen species[15].

Lipid metabolism

Lipid dysfunction has been observed as a trait of more aggressive cancers that have adverse survival outcomes. Research is highlighting the specific alterations occurring in pathways involving lipids and cholesterol. An emerging concept is that CSCs are highly dependent on enzymes associated with lipid metabolism, even though the precise reason for this reliance is not completely understood. Hyperactive metabolic routes that produce lipids and cholesterol, together with the increased uptake of exogenous lipids, are required by the tumour to enable proliferation. Lipids are not only substrates but can either provide structural scaffolds for proteins or be incorporated into the protein structure[59], which acts to stabilise signalling proteins to facilitate effective coupling between cellular receptors and signals[59,60]. Lipid metabolism may also be a crucial component in maintaining the cell membrane and protecting against peroxidation by chemotherapeutic agents or the hypoxic niche. It has been shown that the lipid bilayer leaflets have a non-symmetric distribution of lipids[61], and that this is dependent on several factors such as head group, chain length, and degree of saturation, all of which can affect the cell membrane's flexibility and construction[62,63]. Lipids such as steroid hormones or phosphoinositides can leave the cell and act as active signalling biomolecules in the tumour microenvironment. These molecules can act in an autocrine manner to initiate a signalling cascade that induces proliferation in neighbouring cancer cells[64,65].

De novo lipogenesis

Fatty acid synthesis and oxidation are indispensable components in the maintenance of the adult stem cell and CSC populations from various organs (Figure 1). Both anabolic and catabolic pathways are closely controlled in CSCs and are essential for self-renewal activity. Peroxisome proliferator-activated receptor (PPAR-δ) is crucial for lipid metabolism and is implicated in the control of energy homeostasis. The loss of PPAR-δ results in defects to haematopoietic stem cells but its agonist restores the defect. Similarly, inhibition of mitochondrial fatty acid oxidation generates the disappearance of haematopoietic stem cells[66]. These results suggest that the PPAR

fatty acid oxidation axis may be essential for stem cell conservation. Several investigations have linked lipogenesis to CSCs. *De novo* lipogenesis is more active in glioblastoma multiforme CSCs compared to the bulk tumour population and is needed for stem cell renewal in breast cancer[67,68]. Blockage of fatty acid synthase (FASN) has been shown to diminish breast CSC growth *in vivo* and maintain breast cancer cells through the PPARγpathway by upregulating *de novo* lipogenesis[69]. FASN is overexpressed in patient-derived glioblastoma stem cells, and its inhibition significantly reduces the expression of stemness markers SOX2, NESTIN, CD133, and FABP7, as well as reducing the CSCs' invasiveness and sphere forming ability[67]. Pancreatic CSCs also have higher *de novo* lipogenesis activity where FASN is overexpressed, and the CSCs are more sensitive to inhibition by FASN specific inhibitors[70]. Breast CSCs have shown elevated levels of lipogenic genes compared to non-CSCs, such as ATP citrate lyase, acetyl CoA carboxylase 1 (ACC1), and FASN. Furthermore, ectopic expression of master regulator of lipogenesis sterol-regulatory binding protein-1 upregulates downstream lipogenic genes (ATP citrate lyase, ACC1, and FASN), resulting in enhanced lipogenesis and mammosphere formation[68]. Inhibition of ACC notably impairs mammosphere forming ability and the number of $ALDH1A1^+$ cells in culture[71].

Lipid droplets

The co-culture of adipocytes with bone marrow-derived prostate cancer cells has demonstrated the ability of cancer cells to use lipids from adipocytes in their microenvironment in order to promote cancer growth[72]. When looking at stem cell components, both haematopoietic and leukemic-initiating cells depend on fatty acid oxidation. Elevated levels of lipid droplets have been observed in circulating tumour cells and are associated with more aggressive tumour types and poor survival outcomes. Increased extracellular lipid uptake contributes to lipid droplet accumulation and the tumour-initiating capacity in CSCs[73]. These lipid droplets can act as reservoirs inside the cell since they are filled with energy from various fatty acids, cholesterols, and triacylglycerol. An elevated content of lipid droplets is a distinctive feature of colorectal CSCs. There was a direct correlation between $CD133^+$ cells and lipid droplet amounts, and cells with an elevated level of lipid droplets have enhanced clonogenic potential *in vitro* and *in vivo*[74]. Lipophagy, a process that involves the fusion of lipid droplets with autophagosomes, confers resistance to pancreatic cancer cells through an increase in fatty acid β-oxidation[5]. The latest progresses in proteomics and metabolomics have highlighted the link between fatty acid oxidation and CSC fate[70,75,76]. For example, the homeobox protein NANOG stimulates hepatocellular carcinoma stem-like cells by reprogramming the metabolic state of cells from OXPHOS to fatty acid oxidation[52]. During lipophagy, free fatty acids are mobilised to the mitochondria, which confer survival to cancer cells when metabolic restrictions are induced[77,78]. Although lipid oxidation, lipid synthesis, and glucose metabolism are closely linked, the exact mechanisms underlying these interactions are not well understood. It is plausible to speculate that the lipid content of lipid droplets such as fatty acids, cholesterol, and triacylglycerol can be used to synthesise the cell membrane. These molecules can also be used to synthesise active signalling biomolecules or be exported out of the cell *via* exosomes to prepare the pre-metastatic niche.

Monounsaturated fatty acids/stearoyl-CoA desaturase 1 (SCD1)

Lipid desaturation is important in maintaining stemness, tumour formation, and metastasis in breast, colon, and prostate cancers[79,80]. SCD1 is an enzymatic node central to the conversion of saturated fatty acids to mono-unsaturated fatty acids[81]. Monounsaturated fatty acids are precursors to a number of fundamental plasma membrane lipids such as triglycerides, cholesterol esters, and diacylglycerols[82]. More importantly, they can have signalling properties and act as direct effectors of SCD1 activity. In particular, palmitoleic acid has been found to mediate several processes such as enhanced oxygen consumption, fatty acid oxidation, and ATP content in adipocytes. As previously mentioned, lipids act as essential components of the cell wall, which contributes to signal transduction, migration, and metastatic potential[83,84]. Overexpression of SCDs promotes cancer cell proliferation and inhibits cell death[79,80,85]. Lipid unsaturation has been recognised as a biomarker for ovarian CSCs, and its blockage decreases tumour-forming abilities *in vivo*[76,85]. The same has also been observed in breast CSCs[85]. SCD1 inhibition hindered sphere-forming ability, along with a reduction in markers ALDH1A1, NANOG, and OCT4, and reverted chemoresistance in lung CSCs, while more differentiated cells were unaffected[86]. The presence of carbon-to-carbon single or double bonds can have both physical and chemical properties that are essential in the constitution of cell membranes and signal transduction. As previously mentioned, monounsaturated fatty acids are used as

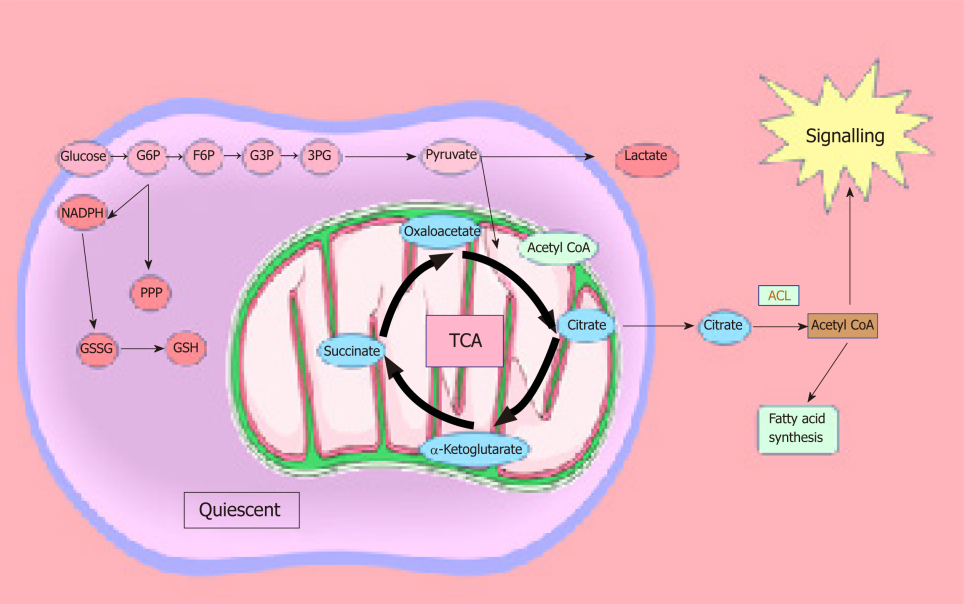

Figure 1 Cancer cells use glucose-derived metabolites for biosynthesis to support uncontrolled cell proliferation. Intermediates such as glucose-6-phosphate enter the pentose phosphate pathway and pyruvate is converted to lactate. Cancer stem cells are quiescent by contrast and use glucose-derived pyruvate for mitochondrial metabolism. The reason behind this metabolic shift is unclear. We propose that it is used for the synthesis of bioactive signalling molecules. TCA: Tricarboxylic acid cycle.

progenitors to a number of molecules, which can act as signalling molecules themselves or as substrates for other signalling molecules. For example, cholesterol esters can enter the mevalonate pathway to synthesise steroid hormones. Phosphoinositides can be converted into lysophosphoinositides. Both of these molecules are powerful bioactive lipids. Similarly, the cell membrane and all of its components such as lipid rafts, in which signalling receptors are embedded, cannot function properly without the proper distribution of triacylglycerides and diacylglycerides. Since CSCs are known for their metastatic potential and chemotherapy evasion, it is important to note that these lipid by-products can be involved in signal transduction for both migration and physical protection from peroxidation. These findings suggest that lipid desaturases may be the optimal targets for tumour prevention in a variety of cancers. Interestingly, recent data has shown that SCD-dependent fatty acid desaturation is not the only source of monoun-saturated fatty acids in cancer cells[87]. Indeed, it has identified a novel desaturation pathway, the sapienate biosynthesis, as an alternative source of monounsaturated fatty acids.

3-hydroxy-3-methyl-glutaryl-coenzyme A

The mevalonate pathway is the metabolic pathway responsible for the formation of steroid hormones and cholesterol. This is a highly conserved pathway that involves a series of reactions including the rate-limiting step, catalysed by 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, which converts HMG-CoA to mevalonate[88]. Mevalonate downstream products comprise cholesterol, geranylgeranyl pyrophosphate, farnesyl diphosphate synthase, and ubiquinone. The mevalonate metabolic route is important in protein prenylation, a post-translational modification that tethers the Ras and Rho family of GTPases to the membrane, which is required for the correct functioning of G protein-coupled receptors, and inhibition of the mevalonate pathway decreased sphere-forming ability in ALDH1A1$^+$ breast CSCs[89]. There is some controversy whether or not increased blood cholesterol is correlated with tumour incidence and mortality. The use of blood cholesterol-lowering statins is correlated with a reduced cancer incidence[90]. However, some reports have shown no correlation[91]. While pre-clinical and mechanistic studies generally support the use of statins for anticancer therapy, conflicting reports may be attributable to compensatory upregulation of HMG-CoA reductase by statins and the resulting dose-limiting toxicities[92]. Nevertheless, total cholesterol is a poor prognostic factor in several different cancers[93], and statin use is associated with reduced cancer-related mortality in cancer patients[94]. Recent studies have found that either blocking cholesterol synthesis or the HMG-CoA pathway exclusively eliminates stem cells of glioblastoma multiforme, colorectal, and lung cancers[95,96]. Further, a high-fat diet enhances *in vivo* tumour growth, which is supressed by statin treatment[97]. These

results strongly suggest that there exists an important and positive role of cholesterol in the biology of CSC functions. Pathways involved in both cholesterol biosynthesis and the synthesis of unsaturated fatty acids have been recently identified as the only selective druggable target in CSCs[98]. Interestingly, a recent study revealed that cholesterol biosynthesis is a key characteristic of breast CSCs and has a clear impact on patient outcome[99]. The findings of the latter study clearly identified the cholesterol biosynthesis pathway as crucial for CSC propagation and a therapeutic target. In addition, this study provides a mechanistic explanation for the beneficial therapeutic effect of the use of statins in breast cancer. Similarly, cholesterol biosynthesis has been found to be a crucial player in the tumorigenicity of human neuroblastoma cell lines and corresponding sphere-forming cells[100].

Lipid biomolecules in CSCs

The majority of studies on lipid metabolism in CSCs have elucidated the enzymes and metabolic pathways involved in lipid synthesis. However, the precise functional role played by the different lipid molecules in CSCs remains unclear. Lipids play a central role in the cell-cell signalling process by maintaining the integrity of the cell membrane and by making lipid rafts, which act as platforms for signal receptors[62,63,101,102]. We can speculate that the hyperactive metabolic activity is used to synthesise lipids, which not only have a structural function by making up the cell membrane, but also have a more active role as bioactive-lipid signalling molecules. These active biomolecules can be released into the extracellular space and activate downstream pathways involved in proliferation, migration/invasion, and differentiation in an autocrine and/or paracrine manner. The latest studies have shown that the metabolism required to produce ATP is tightly regulated in CSCs, and this metabolic profile differs in the bulk of the tumour population[27,103]. CSCs are plastic in nature and change their metabolism as they are migrating from their origin to the metastatic site. They seem to have a preference for OXPHOS and show reduced metabolic plasticity when stressed. As soon as ATP levels reach a certain level, ATP-citrate lyase catalyses the transformation of citrate and CoA to acetyl-CoA and oxaloacetate, respectively. Acetyl-CoA can be converted to malonyl-CoA, which can enter the fatty acid synthesis route. Malonyl-CoA is utilised by AMP-activated kinase in order to regulate the synthesis of fatty acids, which in turn are utilised for the production of phosphoinositides, eicosanoids, lysophospholipids, and sphingolipids[44] (Figure 2).

Lysophospholipids, such as lysophosphatidic acid and sphingosine 1-phosphate, have a key role in stem cell biology[104] and tumour progression[105]. The plasma membrane contains lipid rafts enriched with sphingolipids, which are important participants in signal transmission[106-114]. A recent study of the pancreas highlighted the role of sphingosine-1-phosphate in promoting the survival of progenitor cells and determining acinar and endocrine cell specification[107]. The bioactive lysophospholipid lysophosphatidylinositol can be secreted into the extracellular milieu, initiating a signalling cascade that stimulates the proliferation of surrounding cancer cells[65]. The conversion of acetyl-CoA into acetoacetyl-CoA allows its entry into the mevalonate pathway[44], which is integral for the production of cholesterol esters and steroid hormones that are crucial participants in prostate stem cell maintenance and lineage specification[107-108]. Haematopoietic cells are reliant on phospholipids and essential fatty acids during differentiation[109]. Arachidonic acid is involved in the synthesis of leukotriene, prostacyclin, and thromboxane from phospholipids[109]. Eicosanoids' primary physiological activity is related to inflammation and modulation of cardiovascular function and tone. Leukotrienes and prostaglandins can create a leaky vascular endothelium, which is a requirement for metastatic spread[110]. Interleukin 1B was found to maintain malignant melanoma initiating cells[111,112]. CSCs are known for their increased ABC transporter activity, which requires ATP for its function. We recently proposed that, apart from their role in chemoresistance, ABC transporter hyperactivity is possibly due to their exportation of signalling molecules, including lipids[113]. Several studies have shown that at least one-third of all 48 mammalian ABC transporters are involved in lipid transport[59,63]. Transporters such as ABCA1, ABCG1, ABCG4, ABCG5, and ABCG8 have been identified as sterol transporters[114]. ABC transporters of the C family transport bioactive lysophospholipids such as lysophosphatidylinositol and sphingosine 1-phosphate[64,115,116]. Of particular interest are ABCG2 and ABCB1, the most well studied members in CSCs. We hypothesise that they may play a specific role in CSCs to maintain stemness and sustain cell survival; specifically, by exporting bioactive-lipid signalling molecules such as steroid hormones, cholesterol, and metabolites, which are the result of enhanced lipid uptake and lipid metabolic pathways observed in CSCs[63,64,113,117,118]. Another emerging processthrough which CSCs can also signal is through the release of exosomes. Exosomes are lipid vesicles released from the cell,

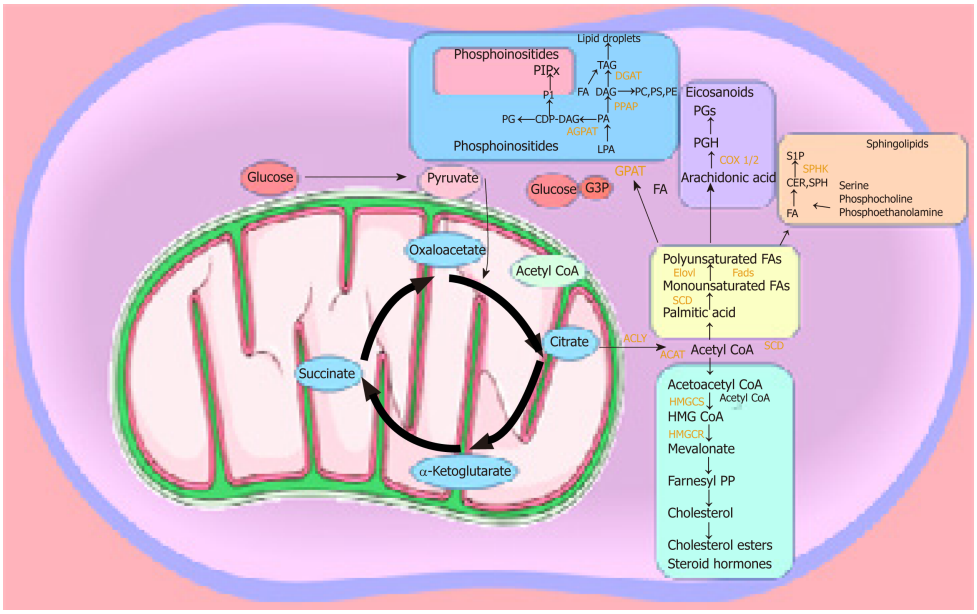

Figure 2 Citrate produced through mitochondrial metabolism can enter the fatty acid synthesis pathway. For example, citrate can enter the mevalonate pathway to produce steroid hormones and cholesterol esters, or it can go on to produce phosphoinositides and lysophospholipids. Both of these are powerful examples of signalling molecules. Therefore, the reason behind the enhanced metabolic activity, which was recently observed in cancer stem cells, must be understood.

which carry important messages including bioactive lipids or enzymes and are able to release signalling lipids. Exosomes are thought to be involved in specific cancer functions such as creating the pre-metastatic niche in the specific secondary site[119]. It is likely that enhanced lipid metabolism in CSCs is used to both synthesise exosomes and their content[120-122]. It would be interesting to analyse the lipidomic profile of CSC-derived exosomes to enhance our understanding of the specific role that exosomes play in cancer progression. Exploring these pathways could elucidate a vulnerability that might be beneficial in targeting these highly aggressive cells. However, first an understanding is needed of the mechanisms behind these metabolic pathways and what purpose they fulfil.

CONCLUSION

In conclusion, lipid metabolism is emerging as a viable target in CSCs. In particular, the enhanced pathways involved in lipid metabolism, such as SCD1 and HMG-CoA activity. However, some questions still need further investigation, such as the purpose for this enhanced activity. We propose that lipid signalling molecules are synthesised as a result of enhanced metabolic activity and that CSCs use those signals for their survival advantage. Lipid metabolism represents an intriguing target for cancer therapy and we further suggest that to target CSCs, these pathways must be understood. The identification of the deregulated pathways is a good starting point to eradicate CSCs. However, increased knowledge of the role played by bioactive lipids will provide a novel opportunity to eliminate these highly aggressive cells.

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