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Energy metabolism in cancer stem cells

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Abstract

Normal cells mainly rely on oxidative phosphorylation as an effective energy source in the presence of oxygen. In contrast, most cancer cells use less efficient glycolysis to produce ATP and essential biomolecules. Cancer cells gain the characteristics of metabolic adaptation by reprogramming their metabolic mechanisms to meet the needs of rapid tumor growth. A subset of cancer cells with stem characteristics and the ability to regenerate exist throughout the tumor and are therefore called cancer stem cells (CSCs). New evidence indicates that CSCs have different metabolic phenotypes compared with differentiated cancer cells. CSCs can dynamically transform their metabolic state to favor glycolysis or oxidative metabolism. The mechanism of the metabolic plasticity of CSCs has not been fully elucidated, and existing evidence indicates that the metabolic phenotype of cancer cells is closely related to the tumor microenvironment. Targeting CSC metabolism may provide new and effective methods for the treatment of tumors. In this review, we summarize the metabolic characteristics of cancer cells and CSCs and the mechanisms of the metabolic interplay between the tumor microenvironment and CSCs, and discuss the clinical implications of targeting CSC metabolism.

Key words: Cancer stem cells; Differentiated cancer cells; Metabolic characteristics;

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Core tip: Accumulating evidence indicates that the inadequacy of many treatments is due to their failure to target cancer stem cells (CSCs). Therefore, CSCs are a promising target for cancer treatment. Recently, it has been reported that CSCs exhibit a unique metabolic phenotype compared to normal cancer cells (non-CSCs), and CSCs can dynamically transform their metabolic state to favor glycolysis or oxidative metabolism. However, the mechanism of the metabolic plasticity of CSCs has not been fully elucidated, and existing evidence indicates that the metabolic phenotype of cancer cells is closely related to the tumor microenvironment (TME). In this article, we summarize the metabolic characteristics of non-CSCs and CSCs, highlight the mechanisms by which CSCs alter their energy metabolism *via* interactions with the surrounding TME, and discuss the potential therapeutic strategies to target energy metabolism in CSCs.

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INTRODUCTION

According to the World Health Organization statistics, cancer is still the most common cause of death, although multiple therapy strategies have significantly improved the overall survival rate of cancer patients. Accumulating evidence indicates that the inadequacy of many treatments is due to their failure to target cancer stem cells (CSCs). CSCs widely exist in different types of tumors and possess the ability to form tumors. Therefore, CSCs are a promising target for cancer treatment. Unfortunately, there are currently few therapeutic options for CSCs because CSCs are resistant to conventional therapies^[1].

Recently, it has been reported that CSCs exhibit a unique metabolic phenotype compared to normal cancer cells (non-CSCs). Non-CSCs metabolize glucose to produce lactate through glycolysis even in the presence of sufficient oxygen^[2], which is now known as the Warburg effect. Unlike non-CSCs, CSCs may be highly glycolytic or oxidative phosphorylation (OXPHOS)-dependent depending on the niches where the CSCs are located. Targeting the metabolism of CSCs would be a new strategy for CSC treatment.

In this review, we summarize the metabolic characteristics of non-CSCs and CSCs, highlight the mechanisms by which CSCs alter their energy metabolism *via* interactions with the surrounding tumor microenvironment (TME), and discuss the potential therapeutic strategies to target energy metabolism in CSCs (Figure 1).

CHARACTERISTICS OF ENERGY METABOLISM IN NON-CSCS

Somatic cells obtain energy or ATP mainly through the tricarboxylic acid (TCA) cycle and OXPHOS in a normoxic environment. Unlike normal cells, non-CSCs are highly proliferating and produce ATP mainly by glycolysis even in the presence of sufficient oxygen supply, which is called the Warburg effect or aerobic glycolysis^[3,4]. The reason is that ATP produced by glycolysis is 100 times faster than that produced by OXPHOS^[5]. Meanwhile, cancer cells upregulate the expression of glucose transporters (GLUTs) to gain more glucose. Increasing studies have demonstrated that various GLUTs are upregulated in different types of tumors^[6]. This abnormal energy metabolism is a hallmark of cancer cells and is believed to be the root of tumor formation and growth^[7]. Several common mechanisms have been reported to be involved in the regulation of glycolysis in cancer cells.

The typical glycolytic pathway includes several reversible enzyme reactions and three irreversible reactions, which are known as the committed steps. The first committed step is the phosphorylation of glucose to glucose-6-phosphate, a process

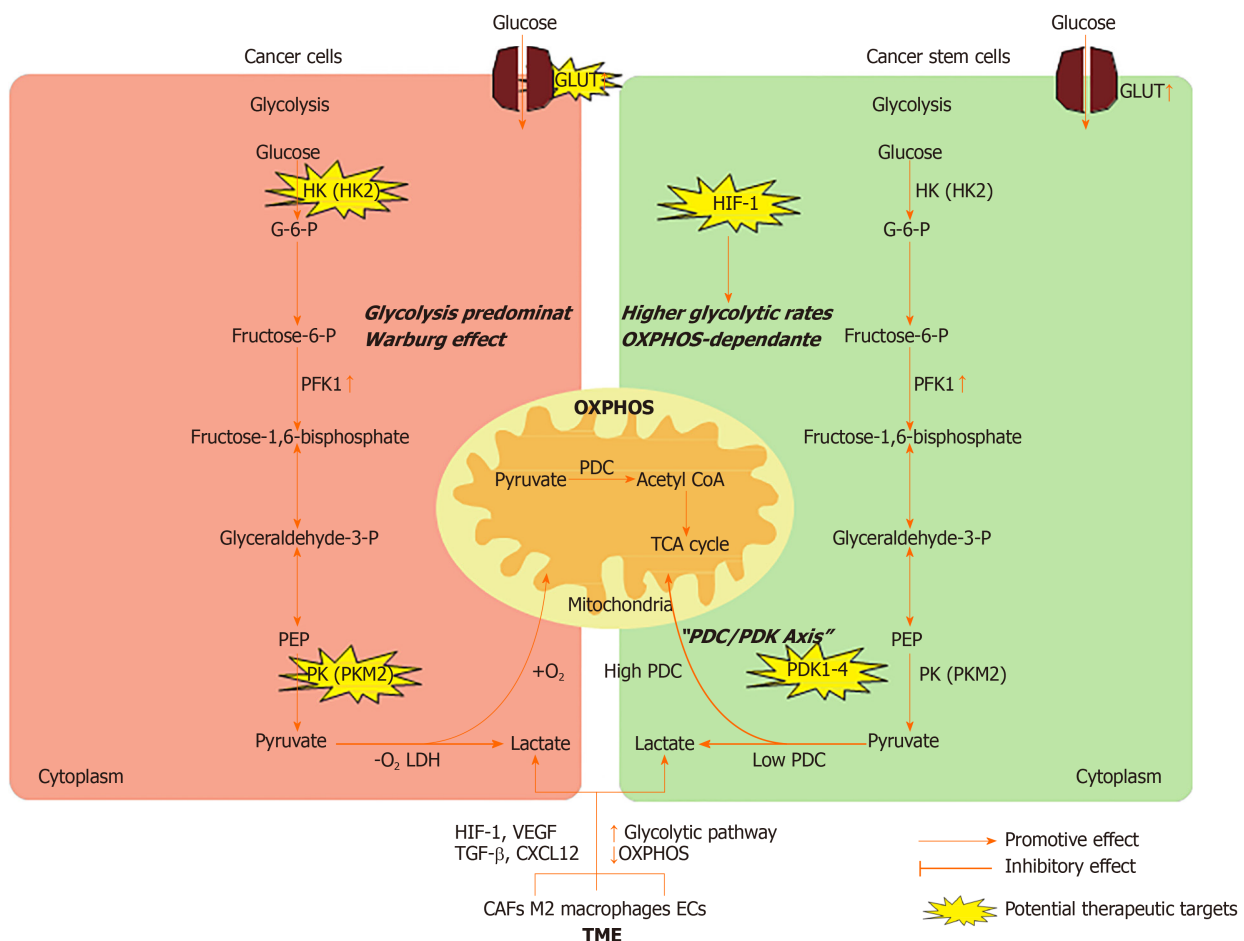


Figure 1 Energy metabolism in cancer cells and cancer stem cells. HK: Hexokinase; G-6-P: Glucose-6-phosphate; PFK1: 6-phosphofructo-1-kinase; PEP: Phosphoenolpyruvate; PK: Pyruvate kinases; PDC: Pyruvate dehydrogenase complex; LDH: Lactate dehydrogenase; OXPHOS: Oxidative phosphorylation; TCA: Tricarboxylic acid; CAFs: Cancer associated fibroblasts; ECs: Endothelial cells; PDGF: Platelet-derived growth factor; HIF: Hypoxia inducible factor; TME: Tumor microenvironment; OXPHOS: Oxidative phosphorylation.

catalyzed by hexokinase (HK). There are four known HK isoforms in mammalian cells, and HK2 is expressed at high levels in cancer cells^[8]. The high expression and activity of HK2 in cancer cells have been exploited to detect and image tumors by a method known as [18F]-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET). HK2 ablation reverses tumor formation *in vitro* and *in vivo* in non-small-cell lung cancer and breast cancer cells^[9]. Recently, HK2 was shown to be overexpressed in human colorectal cancer tissues and cell lines, and knockout of HK2 inhibited cell proliferation, colony formation, and xenograft tumor growth^[10]. The second committed step of glycolysis is catalyzed by 6-phosphofructo-1-kinase (PFK1), whereby fructose-6-phosphate (F6P) is converted to fructose-1,6-bisphosphate. Researchers have demonstrated that fructose-2,6-bisphosphate (F2,6BP) controls the rate of glycolysis by allosterically activating PFK1. F2,6BP is generated from F6P by the bifunctional 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFK2/F2,6BPase or PFKB) family, which contains four isoforms. Generally, the kinase activity of the PFKFB3 isoform is increased in cancer, thereby increasing the intracellular concentration of F2,6BP and the allosteric activation capacity for PFK1^[11]. PFK1 is also elevated in cancer cells and controls the most important steps of glycolysis^[12]. The last committed step of glycolysis is catalyzed by pyruvate kinases (PKs), which transform phosphoenolpyruvate into pyruvate. There are four PK isoforms, and PKM2 is expressed in rapidly proliferating cells, including cancer cells^[13]. It has been reported that PKM2 was overexpressed in various malignancies, including lung, breast, prostate, blood, cervical, kidney, bladder, and colon cancers^[14,15]. During the last step of glycolysis, PK mediates the production of pyruvate. At this point, the gatekeeper enzyme pyruvate dehydrogenase complex (PDC) determines whether glucose metabolism ends in glycolysis or progresses to the TCA cycle and OXPHOS in the mitochondria. When energy production ends in glycolysis, lactate dehydrogenases (LDHs) convert pyruvate to lactate. Because LDHs are reversible, cells secrete lactate through monocarboxylic acid transporters (MCTs)

to promote the reaction and prevent a highly acidic environment. Currently, the expression of LDHs and MCTs has been observed in many tumors, and the effects of LDH and MCT inhibition in cancer cells are under investigation^[16]. When pyruvate enters mitochondria for OXPHOS, it is irreversibly converted to acetyl-CoA by PDC decarboxylation. Phosphorylation mediated by pyruvate dehydrogenase kinase enzymes inhibits PDC activity and is involved in the pathophysiology of many metabolically integrated diseases, including cancer^[17]. Several studies have shown that both the decrease in PDK activity and the enhancement of PDC activity through drug suppression or reduced expression are associated with reduced tumor growth *in vivo*^[18]. In gastric cancer, compared with that in normal tissue, the expression of PDC is lower in tumor tissue, which predicts a poor prognosis^[19].

Hypoxia and activation of oncogenes have been reported to be involved in the upregulation of glycolytic flux^[20]. Irregular perfusion and subsequent tissue hypoxia are common features of solid tumors. Under hypoxic conditions, overexpression of hypoxia-inducible factor-1 (HIF-1) upregulates and activates glycolytic proteins, such as GLUTs and glycolytic enzymes, to increase glucose absorption and phosphorylation^[21]. Meanwhile, a number of oncogenes, including *RAS*, *SRC*, and *Myc*, and activated AKT have been known to promote glycolysis by increasing the expression of GLUTs and glycolytic enzymes^[22-24]. In addition, mutations in tumor suppressors (*e.g.*, PTEN, p53, and VHL) are related to the acceleration of glycolytic flux in cancer cells^[25]. In prostate cancer, mutation of PTEN increases the translation of *HK2* mRNA by activating the AKT-mTORC1-4EBP1 axis, and deletion of P53 enhances the stability of *HK2* mRNA by inhibiting miR143 biogenesis^[26].

METABOLIC CHARACTERISTICS OF CSCS

The metabolic characteristics of CSCs have been the focus of attention. Numerous studies have shown that the metabolic characteristics of CSCs are highly heterogeneous. Unlike non-CSCs, which mainly utilize glycolysis, CSCs exhibit a glycolytic or OXPHOS-dependent metabolic phenotype^[27,28].

Evidence that glycolytic rate is higher in CSCs than in non-CSCs

Normal stem cells mainly use glycolysis to generate energy^[29]. Therefore, CSCs were hypothesized to mainly rely on glycolysis, similar to normal stem cells^[30]. Indeed, a series of studies in osteosarcoma, glioblastoma, breast cancer, lung cancer, ovarian cancer, and colon cancer have proven that CSCs are more glycolytic than non-CSCs, both *in vitro* and *in vivo*^[31-33]. Moreover, it has been observed that the glucose uptake, glycolytic enzyme expression, lactate production, and ATP content of CSCs are significantly increased compared with those of non-CSCs^[34]. Many genes, including *PFKFB4*, *PDK1*, and *PKM2*, are upregulated in brain CSCs^[35]. Inhibition of glycolysis or glucose deprivation can lead to the death of CSCs^[36,37].

The glycolytic switch in CSCs plays a key role in stemness rather than being a consequence of achieving pluripotency^[38]. Studies have demonstrated that inducing the metabolic transition from OXPHOS to glycolysis can increase CSC-like property of CD44⁺CD24^{low}EPCAM⁺ cells in basal-like breast cancer^[39]. Interestingly, HIF-1 has been identified as a central driver of the cascade of events that initiates CSC metabolic reprogramming from OXPHOS to glycolysis^[40]. Furthermore, the role of HIF-1 in tumors is related to stem cell characteristics, including self-renewal, pluripotency, tumorigenicity, and therapy resistance, as demonstrated in breast, hematologic, prostate, bladder, and central nervous system malignancies^[36,41,42]. In CSCs, HIF-1 alters glucose uptake and metabolism through upregulating GLUT expression, HK2 and PK activity during glycolysis, and LDHA levels at the end of glycolysis and downregulating pyruvate dehydrogenase (PDH) levels^[40]. Moreover, HIF-1 reduces mitochondrial reactive oxygen species (ROS) production by increasing the glycolytic pathway and decreasing the TCA cycle. Dynamic maintenance of ROS homeostasis is necessary to induce breast cancer stem cell phenotypes in response to hypoxia or cytotoxic chemotherapy^[43].

Evidence that CSCs obtain energy mainly from OXPHOS

On the other hand, some studies have shown that CSCs from multiple tumor types (*e.g.*, acute myeloid leukemia, glioblastoma, melanoma, and pancreatic cancer) rely on OXPHOS and have low glycolytic reserves^[44-47]. According to these studies, CSCs consume less glucose, produce less lactate, maintain higher ATP levels, and are more inclined to mitochondrial OXPHOS than their differentiated offspring. It is not ideal to study the metabolism of CSCs in an experimental environment lacking a relevant microenvironment. In the absence of better models that preserve the physiological state of CSCs, to keep the metabolic characteristics of CSCs intact, the best

experimental strategy is to isolate them directly from patients and analyze them immediately or in the first step of *in vitro* culture. In glioblastoma specimens, low-passage, patient-derived CSCs are more dependent on OXPHOS than their differentiated offspring^[48].

Although OXPHOS produces energy at a much lower rate than glycolysis, it is a much more efficient energy source. Moreover, CSCs also increase the utilization of extracellular metabolites, such as pyruvate, lactate, glutamine, glutamic acid, alanine, and ketone bodies, to adapt to OXPHOS metabolism^[49-51]. Similarly, OXPHOS-dependent CSCs may gain selective advantages in specific tumor microenvironments^[4]. In addition, studies have shown that elevated OXPHOS levels in CSCs can promote chemotherapeutic resistance. It has been demonstrated that Myc and MCL1 synergistically promote chemotherapy-resistant CSCs by increasing mitochondrial OXPHOS^[52]. Additionally, compared with non-CSCs, CSCs have higher mitochondrial mass and mitochondrial membrane potential ($\Delta\psi_m$), which reflects that CSCs are more prone to mitochondrial metabolism^[53-55]. Although the specific settings leading to the OXPHOS phenotype in all tumor types mentioned above have not been fully characterized, studies have shown that the mitochondrial biogenesis regulator and transcription coactivator peroxisome proliferator-activator 1 alpha (PGC1 α) may play an important role in maintaining stemness characteristics^[56]. In breast cancer, the inhibition of PGC1 α prevents mammosphere formation and CSC marker expression^[57]. In addition, in pancreatic CD133⁺ CSCs, PGC1 α is essential for OXPHOS function, self-renewal ability, and tumorigenesis^[54]. Growing evidence indicates that mitochondrial function is the basis for maintaining CSCs and can be a target for cancer treatment.

METABOLIC INTERPLAY BETWEEN THE TME AND CSCS

Tumor cells are located in the niche and constantly interact with the surrounding microenvironment. The TME is composed of extracellular matrix (ECM), cancer-associated fibroblasts (CAFs), macrophages, endothelial cells (ECs), immune cells, and a complex network of signaling molecules. It is well acknowledged that the metabolic phenotype of CSCs is regulated by the changing TME, and CSCs also remodel the metabolism of cells in the TME^[58].

Metabolic interplay between CAFs and CSCs

Recently, it was reported that CAFs could significantly promote the formation and growth of tumor spheres, which indicates an increased tumor formation potential^[59]. In addition, in pancreatic cancers, CAFs have been shown to induce epigenetic and metabolic changes in cancer cells and CSCs, thereby promoting tumor progression^[60]. CAFs also have metabolic adaptations, and these metabolic adaptations are considered to support glycolysis and play a key role in the use of nutrition by cancer cells and CSCs. Drivers of metabolic changes in CAF activation may include transforming growth factor- β (TGF- β), platelet-derived growth factor (PDGF), hypoxia, HIF-1 α , and ROS-mediated caveolin 1 inhibition^[61], which induce CAFs to switch from OXPHOS to aerobic glycolysis. After metabolic reprogramming, CAFs show enhanced catabolism and produce metabolites (lactate, glutamine, and ketones), which are used by cancer cells and CSCs to promote the production of oxidative energy and are associated with their potential for tumorigenicity and resistance to treatment^[62]. The metabolic interaction between cancer cells and CAFs in the TME is called the reverse Warburg effect^[63]. In the TME, cancer cells, CSCs, and CAFs express different types of lactate MCTs. Previous studies have suggested that epithelial cancer cells with a stem-like phenotype express MCT-1, while CAFs and other differentiated cancer cells express MCT-4^[64]. MCT-4-expressing CAFs and differentiated cancer cells secrete lactate through glycolysis, which is absorbed by epithelial CSCs that express MCT-1 and subsequently serves as a substrate for the TCA cycle^[63].

Moreover, the autocrine and paracrine effects of CAFs on cancer cells have now been fully studied^[65]. Compared with normal fibroblasts, CAFs have the ability to enhance the production of ECM components and secrete unique cytokines, including stromal cell-derived factor-1 (SDF-1)/C-X-C-motif chemokine 12 (CXCL12), vascular endothelial growth factor, PDGF, and hepatocyte growth factor^[66,67]. In breast cancer, CAFs promote the growth of breast cancer cells by secreting SDF-1^[67]. In addition, CAFs can secrete TGF- β and induce epithelial-mesenchymal transition (EMT) and eventually develop drug resistance^[66]. The induction of EMT is involved in the acquisition of stemness, leading to reduced mitochondrial metabolism and increased glycolytic flux^[68]. Many EMT regulators, such as TGF- β , Wnt, Snail, and distal-less homeobox-2 (Dlx-2), are involved in the metabolic reprogramming of cancer cells^[69].

Metabolic interplay between macrophages and CSCs

Tissue inflammation is an important part of the TME, and inflammatory cells and soluble mediators of inflammation, such as cytokines and chemokines, are abundant in the TME. Evidence suggests that inflammation has a dual role in tumor development^[70].

Macrophages are one of the most abundant components of the TME and play an active role in tumorigenesis. CSCs can attract macrophages into tumors by producing proinflammatory cytokines and chemokines^[71]. Once entering the tumor, macrophages are activated by factors such as IL-4 and transformed into tumor-associated macrophages (TAMs), which need to be metabolically adapted to survive the harsh tumor environment. The M1 polarization of macrophages is induced by endotoxin, interferon- γ , and interleukin (IL)-1 α , with a pro-inflammatory role while the M2 phenotype, induced by IL-4, IL-10, IL-13, TGF- β , and glucocorticoids, has anti-inflammatory effects and is involved in the resolution of inflammation^[72]. In the TME, TAMs are forced to undergo metabolic reprogramming to compete with cancer cells for nutrition. In solid tumors, hypoxia is one of the important factors determining the vascular structure of tumors. It was found that under hypoxic conditions, TAMs strongly upregulated the expression of the negative regulator of mTOR-DNA damage response 1 (REDD1)^[73]. REDD1-mediated mTOR inhibition can block glycolysis in TAMs and reduce their excessive angiogenic response, thereby forming abnormal blood vessels. Moreover, lactate secreted by tumor cells can stabilize HIF-1 α and induce the expression of vascular endothelial growth factor (VEGF) and M2 polarization of TAMs^[74]. Importantly, the metabolic effects of cancer cells on TAMs are not unidirectional. TAMs exposed to hypoxia or lactate secrete a variety of metabolic cytokines, including IL-6, tumor necrosis factor- α (TNF α), and CC-motif chemokine ligand 5^[75-77]. Polarized M2 TAMs secrete IL-6 to enhance 3-phosphoinositide-dependent protein kinase 1-mediated phosphoglycerate kinase 1 threonine (T) 243 phosphorylation, which promotes protein kinase 1-mediated phosphoglycerate kinase 1-catalyzed glycolysis^[77]. TAMs secrete TNF α to promote tumor cell glycolysis, with increased GLUT-1 and HK-2 protein expression^[75]. M2 TAMs stimulate CC-motif chemokine ligand 5 secretion, which increases cell migration, induces EMT in cancer cells, and promotes aerobic glycolysis in breast cancer cells *via* AMPK signaling^[76]. CSCs induce the M2 phenotype in TAMs, which secrete IL-6, IL-10, TGF- β , and EGF and drive CSC self-renewal by activating the STAT3/NF- κ B signaling pathway^[78].

Metabolic interplay between ECs and CSCs

Tumor cell growth and culture require multiple strategies to meet oxygen and metabolic needs, which involve the formation of new blood vessels. The angiogenesis process during tumor progression requires the recruitment of endothelial progenitor cells in the TME, during which endothelial progenitor cells differentiate into blood vessels^[79]. Angiogenesis is considered a key process for tumor progression and metastasis, and the TME and CSCs are considered to be important promoters of this phenomenon. Elevated lactate concentrations in the TME were found to affect EC signaling by enhancing IL-8/CXCL8 signaling, thereby promoting angiogenesis^[80]. In addition, CSCs can induce angiogenesis by secreting HIF-1, VEGFA, CXCL12, and other factors^[81]. Moreover, in recent studies, CSCs have been shown to differentiate into ECs in a process known as "vascular mimicry" and generate their own vascular system *via* a VEGF-dependent pathway^[81]. Recently, in a study of gliomas, researchers found that the injection of CSCs into the right frontal lobe of nude mice induced stronger angiogenesis and more hemorrhagic tumors than injection of non-CSC control cells. Meanwhile, the angiogenic advantage of the CSC counterpart may be supported by the 10-20-fold increase in VEGF secretion^[82]. Importantly, VEGF supports the angiogenic switch mainly by stimulating the glycolytic pathway. Studies have shown that when the glycolytic pathway is inhibited by the rate-limiting enzyme PFKFB3 in endothelial cells, the efficiency of angiogenesis is reduced^[83]. Other studies have found that under different environmental states such as hypoxia or altered glucose metabolism, CSCs can differentiate into functional ECs^[84].

The formation of new blood vessels and tumor angiogenesis are necessary conditions for tumor progression. Tumor blood vessels provide nutrition and oxygen for tumors and provide a pathway for tumor metastasis. Recent studies have shown that "vascular endothelial factors" released by ECs promote tumor progression^[85]. In brain tumors, endothelial cells interact directly with tumor cells and secrete factors that maintain these cells in a stem cell-like state^[86]. In head and neck squamous cell carcinoma, it is reported that 80% of CSCs are located near blood vessels. In addition, ECs secrete a variety of growth factors, including EGF, induce EMT through the PI3K/Akt signaling pathway, and promote the maintenance of CSC characteristics in head and neck squamous cell carcinoma^[87]. In breast cancer, ECs secrete TNF α ,

activate the NF- κ B signaling pathway in CSCs, and eventually develop chemical resistance to doxorubicin and cyclophosphamide^[88]. In colorectal cancer cells, ECs activate the NANOGP8 pathway associated with CSCs in a paracrine manner^[89].

CLINICAL IMPLICATIONS

Since CSCs have distinct metabolic phenotypes, which are a response to tumor progression and recurrence. On the other hand, the metabolic phenotype of CSCs is highly flexible between OXPHOS and glycolytic phenotype due to regulation of the TME. Traditional anticancer treatments aim to suppress rapidly proliferating cancer cells and fail to eradicate CSCs. Therefore, it is necessary to develop strategies to target metabolism of CSCs based on finding of the mechanisms involved in maintaining metabolic phenotype of CSCs. Recently, a large number of studies have been designed to selectively target the metabolism of CSCs.

Targeting glycolysis

Most CSCs satisfy their energy demands through glycolysis, which is subject to complex regulation. Therefore, various glycolytic enzymes or transporters can be targeted, such as GLUT1-4, HK, PDK1, and PKM2. A direct antiglycolytic strategy was proposed to block the glucose uptake *via* GLUTs, resulting in a complete disruption of energy metabolism. Previous studies have reported that several agents, such as phloretin, fasentin, and WZB117, have excellent anticancer effects through glucose uptake inhibition and energy deprivation in preclinical models^[90-93]. Phloretin is an antagonist of GLUT2^[90,91], which suppresses colorectal cancer cell growth by inducing cell cycle arrest and apoptosis *via* p53-mediated signaling^[90]. In addition, phloretin significantly inhibits the migration of cancer cells through paxillin/FAK, Src, alpha smooth muscle actin (α -SMA), and E-cadherin signaling^[91]. Fasentin is a GLUT1 inhibitor, which causes glucose deprivation and G₀-G₁ cell cycle arrest^[92]. As a selective GLUT1 inhibitor, WZB117 effectively inhibits glucose uptake, reduces the amount of intracellular ATP, and causes cell cycle arrest^[93]. Since GLUTs are widely expressed in normal cells, specific inhibition of glucose uptake in CSCs is challenging.

HK enzymes are responsible for glucose phosphorylation. Several HK inhibitors including 2-deoxy-D-glucose (2-DG), lonidamine (LN), genistein-27 (GEN-27), and benserazide, have been exploited for cancer treatment^[94-97]. 2-DG is a well-studied antiglycolytic agent, which competitively inhibits glucose transport^[98]. Several clinical trials of 2-DG activity have been designed in cancer patients^[96,99,100]. However, the anticancer efficacy and safety of 2-DG are still inconclusive. Currently, 2-DG is widely used in combination with other agents like cisplatin or docetaxel^[100,101]. Another HK inhibitor LN has completed preclinical studies and several clinical trials have explored its effects for cancer treatment^[102]. Unfortunately, no significant survival benefit of LN has been studied in several cancer types, such as lung, breast, and ovarian cancers^[97,103,104].

Pyruvate in the cytosol is converted into mitochondrial acetyl-CoA, which can enter the Krebs cycle *via* PDH enzymes. PDH is negatively regulated by the PDK enzyme, leading to a shift from OXPHOS to glycolytic metabolism. Thus, targeting PDK may be another attractive approach to inhibit cellular proliferation and cancer growth by inducing cancer cell or CSC metabolic reprogramming. Dichloroacetate (DCA) can activate mitochondrial PDH by inhibiting its regulator, PDK, and then enhance reprogramming of metabolism from glycolysis towards mitochondrial OXPHOS^[105]. Several clinical trials are ongoing for testing DCA efficacy as an anticancer agent^[106,107]. DCA is known to be relatively well tolerated with few significant side effects, and tumor response assessed by FDG-PET revealed stable disease in eight patients but no response in others^[107]. Overall, the current results of DCA for cancer therapy are preliminary, supporting a favorable toxicity profile but limited anticancer efficacy.

PK converts phosphoenolpyruvate into pyruvate by dephosphorylation to generate ATP. Kefas *et al.*^[108] demonstrated that PKM2 was expressed in glioma stem cells. Furthermore, PKM2 knockdown in glioma stem cells led to decreased cell proliferation and impaired metabolism accompanied by a reduced ATP level, which indicated that inhibition of PKM2 was a potential target in glioma stem cells^[108].

Moreover, CD44 was previously reported to interact with PKM2 and thereby enhance the glycolytic phenotype, suggesting that it could also become a preferential target. Tamada *et al.*^[109] reported that ablation of CD44 led to inhibition of glycolysis, with an increase in ROS, and enhanced the chemotherapeutic drug effect in glioma, colorectal cancer, or lung cancer cells. As a surface marker of CSCs, it can also be utilized for effective cytotoxic drug delivery^[110].

On the other hand, CSCs can rapidly transition their metabolic phenotype under

heterogeneous environmental conditions (such as hypoxia and glucose deprivation); thus, targeting adaptive mechanisms is also an optional strategy. As mentioned above, HIF-1 α is one of the principle factors that reprograms cells to undergo glycolysis instead of OXPHOS^[21,111] and is also involved in angiogenesis, metastasis, and cell survival^[112]. Hence, targeting HIF-1 α is a potential therapy for cancer treatment as well.

Targeting mitochondrial OXPHOS

Previously discussed evidence for OXPHOS in CSCs indicated mitochondrial metabolism to be a potential therapeutic target for eliminating CSCs. Inhibition of the OXPHOS pathway inhibits sphere formation and tumorigenesis, manifesting the vulnerability of CSCs to mitochondria-targeted drugs^[47,113]. Several pharmacological agents targeting OXPHOS are currently being explored in preclinical studies and clinical trials for cancer treatment.

The anti-diabetic agent metformin has emerged as a promising candidate for targeting oxidative metabolism in pancreatic CSCs^[54]. Several clinical results suggested that cancer patients with diabetes treated with metformin had a better prognosis than those treated with other antidiabetic regimens, which aroused researchers' interest in the mechanisms^[114,115]. Wheaton's study on metformin found that its antitumor activity involved the impairment of OXPHOS through direct inhibition of mitochondrial electron transport chain complex I^[116]. Nevertheless, the use of metformin for cancer therapy remains controversial. The first clinical trial testing the effect of metformin in pancreatic ductal adenocarcinoma patients did not report a positive outcome^[117]. The MYME trial failed to provide evidence in support of the efficacy of metformin in treating metastatic breast cancer patients^[118], while another study on non-small-cell lung cancer showed a significant change in outcome with the addition of metformin to standard chemotherapy^[119]. Phenformin, another biguanide formerly used in diabetes, can be delivered to mitochondria more efficiently than metformin^[4]. This agent also induces cancer cell death by inhibiting complex I and promotes apoptosis, offering promising preclinical results in certain cancer types^[120], but its clinical application remains to be studied.

Previous studies that were developed to screen compounds that selectively eliminate CSCs eventually discovered several drugs that inhibit mitochondrial activity. For example, the antibiotic salinomycin was identified and found to inhibit OXPHOS^[121]. The study showed that salinomycin treatment could result in reduced expression of breast CSC genes and thus inhibit mammary tumor growth *in vivo*. Another antibiotic, tigecycline, was also identified in a screen using OXPHOS-dependent leukemia cells^[122]. This agent was found to suppress OXPHOS by inhibiting mitochondrial translation associated with mitochondrial ribosomes. However, the clinical utility of these two drugs has not been fully elucidated.

As mentioned before, CSCs relying on OXPHOS show an elevated $\Delta\psi_m$, which can also be exploited for selectively increasing drug delivery to the mitochondria. Triphenylphosphonium, as a delocalized lipophilic cation, accumulates in the mitochondrial matrix and can be conjugated to small compounds for selective drug delivery to mitochondria^[123]. A recent study showed that conjugation of triphenylphosphonium to doxorubicin, a DNA topoisomerase II inhibitor, directed its activity towards mitochondrial DNA, promoting drug selectivity for cancer cells with reduced mitochondrial DNA integrity and preventing the acquisition of resistance by drug efflux^[124].

Due to the metabolic plasticity of CSCs, dual inhibition of the glycolytic and OXPHOS energy pathways may be the best approach against tumor growth. One study using such a strategy elegantly demonstrated that sarcoma cells are more sensitive than normal cells to synergistic effects of inhibiting glycolysis with 2-DG and OXPHOS with oligomycin or metformin^[125]. These results suggest that the dual inhibition of glycolytic and mitochondrial respiration may represent a better approach to eradicating CSCs and cancer treatment^[126,127]. Despite limited clinical evidence, targeting CSCs by blocking their metabolic components still holds great potential in improving cancer treatments. In practice, combinational treatments involving both a standard cytotoxic therapy and a CSC-targeted therapy will probably enhance the antitumor effect.

CONCLUSION

CSCs are thought to be the source of cancer cell production, resistant to treatment, and responsible for metastasis, and eliminating them could lead to a permanent cure for patients. Increasing evidence indicates that CSCs have distinct metabolic

phenotypes compared to most differentiated tumor cells. Therefore, the metabolic phenotype of CSCs has attracted great interest. CSCs have a unique metabolic phenotype and exhibit metabolic plasticity between high levels of glycolysis and OXPHOS, which may be related to the TME. However, the mechanisms of CSC metabolic plasticity still need to be clarified. Targeting CSC metabolism is considered a new treatment to eliminate cancer recurrence or metastasis. Combining CSC-targeted drugs with traditional anticancer treatments may be a more effective strategy for treating cancer. It is hypothesized that tumor stem cells may be derived from genetic changes in normal stem cells. It is necessary to accurately distinguish these two similar cell types to eliminate the damage that targeting CSCs may cause to normal stem cells.

A large number of studies have provided evidence that metabolic plasticity of CSCs exists in different malignancy, but the mechanisms involved in this process still need to be explored in the future. The role of metabolic reprogramming in CSCs in tumorigenesis, metastasis, drug resistance, and tumor relapse needs more evidence. Targeting the metabolism of CSCs is a promising approach in cancer treatment. However, it is necessary to identify specific targets to selectively inhibit the metabolism of CSCs without causing damage to normal stem cells. We expect that more preclinical and clinical studies will be carried out to find effective new anticancer agents.

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