Original Article

Conflicting metabolic alterations in cancer stem cells and regulation by the stromal niche

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ABSTRACT

Recent studies have revealed that cancer stem cells (CSCs) undergo metabolic alterations that differentiate them from non-CSCs. Inhibition of specific metabolic pathways in CSCs has been conducted to eliminate the CSC population in many types of cancer. However, there is conflicting evidence about whether CSCs depend on glycolysis or mitochondrial oxidative phosphorylation (OXPHOS) to maintain their stem cell properties. This review summarizes the latest knowledge regarding CSC-specific metabolic alterations and offers recent evidence that the surrounding microenvironments may play an important role in the maintenance of CSC properties.

1. Introduction

Tumor cells produce energy to ensure their survival by a different strategy than normal cells [1]. Tumor cells metabolize glucose via glycolysis to produce energy in the form of adenosine triphosphate (ATP) despite the presence of abundant oxygen. This phenomenon was revealed by Otto Warburg in Germany in the 1920s and was named the Warburg effect [2]. This discovery was the beginning of cancer metabolism research. In the 21st century, with the development of sequencing technology, some cancer-specific metabolic pathways have been revealed, and it turns out that the Warburg effect is only one aspect of cancer metabolic mechanisms [3—6].

On the other hand, it is well known that cancer tissues are composed of a hierarchical structure of differentiated cells derived from cancer stem cells (CSCs); therefore, cancer consists of a diverse and heterogeneous cell population [7—9]. The existence of CSCs may play a crucial role in therapeutic resistance and recurrence. Recent studies have revealed that CSCs undergo various metabolic alterations that differentiate them from non-CSCs, and these studies show the possibility of developing curative therapy for CSCs by inhibiting specific metabolic pathways [10,11]. To achieve this objective, many researchers have investigated the metabolic phenotypes of CSCs derived from various cancers. However, there are conflicting hypotheses about whether CSCs depend on glycolysis or mitochondrial oxidative phosphorylation (OXPHOS) to maintain their stem cell properties. Interestingly, recent evidence demonstrates that the surrounding microenvironments may affect specific metabolism in CSCs. This review discusses the current knowledge of the regulation of CSC metabolism.

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2. Aerobic glycolysis in cancer (stem) cell

One of the most common forms of metabolic reprogramming in cancer cells is aerobic glycolysis, also known as the Warburg effect. Cancer cells are able to increase the rate of glucose uptake and produce energy in the presence of oxygen, allowing ATP production comparable to mitochondrial OXPHOS [12]. Although it is inefficient in terms of ATP production, cancer cells prefer glycolysis rather than mitochondrial OXPHOS because the intermediates of glycolysis can be used for cell proliferation. One of the intermediates of glycolysis, glucose-6-phosphate (G6P), is used in the pentose phosphate pathway (PPP) to generate NADPH, which is involved in the rapid proliferation of tumor cells. Other intermediates are also used in the anabolic reactions of glycogen or lipid synthesis [13]. Glycolysis can also reduce reactive oxygen species (ROS) production compared to mitochondrial OXPHOS. In addition, increasing the metabolic flux to the PPP upregulates the level of the antioxidant glutathione and suppresses ROS levels [14,15]. Thus, cancer cells avoid the accumulation of ROS and create a more appropriate environment for their survival.

For instance, stem-like glioblastoma cells have a characteristic energy metabolism, which is low mitochondrial OXPHOS and high glycolysis for ATP generation to maintain their stemness and tumor-forming capacity [16]. This study suggests that glycolytic metabolism may play an important role in CSC maintenance. Indeed, some types of CSCs are known to prefer glycolysis rather than mitochondrial OXPHOS for acquiring their stem cell properties. Differential proteomics analysis indicates a shift toward glycolytic metabolism and the promotion of highly tumorigenic activities in breast CSC spheres. This study also revealed that treatment with 2-deoxyglucose, a well-known inhibitor of glycolysis, inhibits breast CSC proliferation [17]. Similarly, glycolysis is more active in CSCs in lung cancer than in the bulk of cancer cells. Glucose is an essential nutrient, especially for lung CSCs, and the levels of glucose in the tumor microenvironment significantly affect lung CSC expansion. Glucose starvation causes a rapid depletion of lung CSCs. However, a high amount of glucose upregulates glycolysis and consequently increases the lung CSC population through ATP-mediated suppression of AMPK and activation of the Akt pathway [18]. In addition, some CSCs are known to overexpress glycolysis-related factors, such as pyruvate dehydrogenase kinase 1 (PDK1) and glucose transporter 1 (GLUT1) [19,20]. PDK1 promotes the metabolic switch to glycolysis from mitochondrial OXPHOS. PDK1 expression in breast CSCs is induced by hypoxia inducible factor 1a (HIF1a) under hypoxia and maintains the properties of breast CSCs by activating glycolysis. Liver metastases from primary breast cancer relies on a HIF1a/PDK1-dependent axis for intrinsic metabolic reprogramming [21]. Moreover, screening of hypoxia-related long noncoding RNAs (lncRNAs) revealed that lncRNA H19 is responsible for PDK1 induction and breast CSC maintenance [22]. The upregulation of GLUT1 plays an important role in the maintenance of uterine endometrial CSCs through activation of the glycolytic pathway. Uterine endometrial CSCs express high amounts of aldehyde dehydrogenase (ALDH), and a high level of ALDH elevates the levels of GLUT1 and promotes glucose uptake; consequently, uterine endometrial CSCs depend on glycolysis [23].

It is widely known that there is a direct link between epithelial−mesenchymal transition (EMT) and the induction of CSC properties. The induction of EMT promotes the generation of CSCs, and CSCs isolated from mouse or human breast cancers express EMT markers [24]. The Snail-G9a-Dnmt1 complex, which is critical for EMT activity, represses fructose-1,6-biphosphatase 1 (FBP1), and the loss of FBP1 induces high glucose uptake, followed by enhanced aerobic glycolysis in breast CSCs [25]. These results suggest that EMT enhances glycolysis and confers tumor cells with CSC-like characteristics. Moreover, comprehensive analysis reveals that the downregulation of mitochondrial genes is correlated with the expression of EMT gene signatures in 20 different cancer types. In accordance with this study, these cancers display upregulated expression of glycolysis [26]. The findings of these studies suggest that the glycolytic metabolic profile in EMT-induced cancer cells enhances the properties and tumorigenicity of CSCs.

Taken together, glycolysis is considered an essential metabolic pathway not only for non-CSCs but also for several CSCs, suggesting that the metabolic switch to glycolysis is responsible for the maintenance of the characteristics os CSCs, such as EMT.

3. Mitochondrial OXPHOS metabolism in CSCs

Mitochondria are cellular organelles of eukaryotic cells and have their own mitochondrial DNA to divide and multiply [27,28]. Mitochondria perform many important metabolic reactions, such as fatty acid oxidation (FAO), glutaminolysis and reductive carboxylation in mitochondria-damaged cells [29]. Among these metabolic functions, one of the most significant for eukaryotic cells is the synthesis of ATP by aerobic respiration using the tricarboxylic acid (TCA) cycle. The main fuel of the TCA cycle is acetyl-CoA, which is derived from glucose.

Although glycolytic metabolic reprogramming is common in cancer cells, several types of CSCs have been reported to prefer mitochondrial OXPHOS for energy production. A unique imaging system revealed that glioma CSCs consumed less glucose and produced less lactate while maintaining higher ATP levels than their differentiated glioma cells [30]. Similarly, in glioblastoma CSCs, gliomaspheres depend on OXPHOS for energy production and survival. Moreover, insulin-like growth factor 2 (IMP2) has been identified as a key regulator of mitochondrial OXPHOS in primary gliomaspheres [31]. A subpopulation of dormant pancreatic cancer cells, which have the features of CSCs, is also mainly dependent on mitochondrial OXPHOS. Transcriptomic and metabolic analyses of this subpopulation reveal prominent expression of genes governing mitochondrial function, autophagy, and lysosome activity, as well as a strong reliance on mitochondrial respiration and decreased dependence on glycolysis for cellular energetics [32]. Furthermore, it has been revealed that the metabolism of pancreatic CSCs is regulated by the balance between MYC and PGC-1a. Mechanistically, suppression of MYC and subsequent increase in PGC-1a were identified as the key determinants of the OXPHOS dependency of pancreatic CSCs [33]. MYC is known to be related to stemness in many types of cancer. In hepatocellular carcinoma, MYC activation leads to enhanced CSC properties. However, when exceeding a threshold level, MYC induces a proapoptotic program and the loss of CSC potential both in vitro and in vivo, which suggest that proper expression levels and balance are important for CSC survival [34]. PGC-1a is known to be the active regulator of mitochondrial biogenesis. PGC-1a-positive melanoma cells exhibit an increased mitochondrial energy metabolism, and conversely, PGC-1a-negative cells are more glycolytic. Suppression of PGC-1a in melanoma cells reduces the expression of ROS detoxification genes, such as superoxide dismutase 2 (SOD2) and GpX1, and increases ROS levels, leading to apoptosis [35]. In addition, invasive breast cancer cells exhibit a shift toward mitochondrial OXPHOS via a PGC-1a-dependent pathway. Silencing of PGC-1α in breast cancer cells attenuates proliferation, metastatic ability and EMT [36]. These findings suggest that PGC-1a expression may play a critical role in mitochondrial OXPHOS to maintain the properties of CSCs.

CSCs in an abundant oxygen environment utilize ROS induced by mitochondrial OXPHOS for their proliferation. For instance, MYC and MCL1 cooperate to upregulate mitochondrial OXPHOS followed by ROS production. HIF-1a expression induced by ROS

accumulation enhances CSC enrichment and mammosphere formation. MYC and MCL1 are frequently coamplified in chemotherapy-resistant triple-negative breast cancer tissues [37]. Moreover, NOX1 is preferentially expressed in LGR5-positive colon CSCs. ROS production by NOX1 mediates mammalian target of rapamycin complex 1 (mTORC1) activation in colon cancer spheroids, and the activation of mTORC1 is essential for the proliferation of spheroids and colon CSCs [38]. Taken together, OXPHOS and stemness are closely related, which is one of the reasons why some types of CSCs prefer mitochondrial OXPHOS to glycolysis.

Intriguingly, increasing evidence reveals that stromal and immune cells affect the characteristics of CSCs in the tumor microenvironment [39–42]. Stromal cells, known as the stromal niche, play an important role in CSC metabolism by secreting the metabolites that are used for the TCA cycle [43]. Cancer-associated fibroblasts (CAFs) among stromal cells enhance the Warburg effect by interacting with cancer cells and producing lactate. CSCs can take advantage of lactate as a fuel for mitochondrial OXPHOS. This concept is widely known as the reverse Warburg effect [44,45]. Interestingly, the full mitochondrial genome can be identified in circulating extracellular vesicles (EVs) from patients with metastatic breast cancer. A precise functional study demonstrated that CAF-derived EVs transfer their mtDNA to breast CSCs, leading to the activation of mitochondrial metabolic activities, and mitochondrial OXPHOS-deficient breast CSCs restore metabolic activities by transferring mtDNA-laden EVs [46]. This mechanism suggests that metabolic interactions between CSCs and their niche cells are important, especially for the maintenance of CSC mitochondrial OXPHOS. Consistently, a recent study revealed that pancreatic cancer cells are forced to utilize mitochondrial OXPHOS, increase expression of CSC biomarkers and pluripotency genes, and upregulate immune evasion properties through the accumulation of protumor immune cells [47]. Given these findings, it is possible that elucidation of the relationship between CSCs and their stromal niche will lead to the development of more effective therapies targeting CSC-specific metabolism in combination with conventional therapies, including immunotherapy.

4. Redox state in CSCs

Mitochondrial OXPHOS, while enabling efficient energy formation, increases ROS production and changes the cellular redox status [48,49]. As mentioned above, increasing evidence suggests that some CSCs utilize ROS production as active mediators of proliferation. However, high levels of ROS are life-threatening, even for cancer cells, because ROS damages various cellular components, such as DNA, proteins, and lipids, and eventually induces cellular senescence or death. Therefore, cancer cells have acquired the
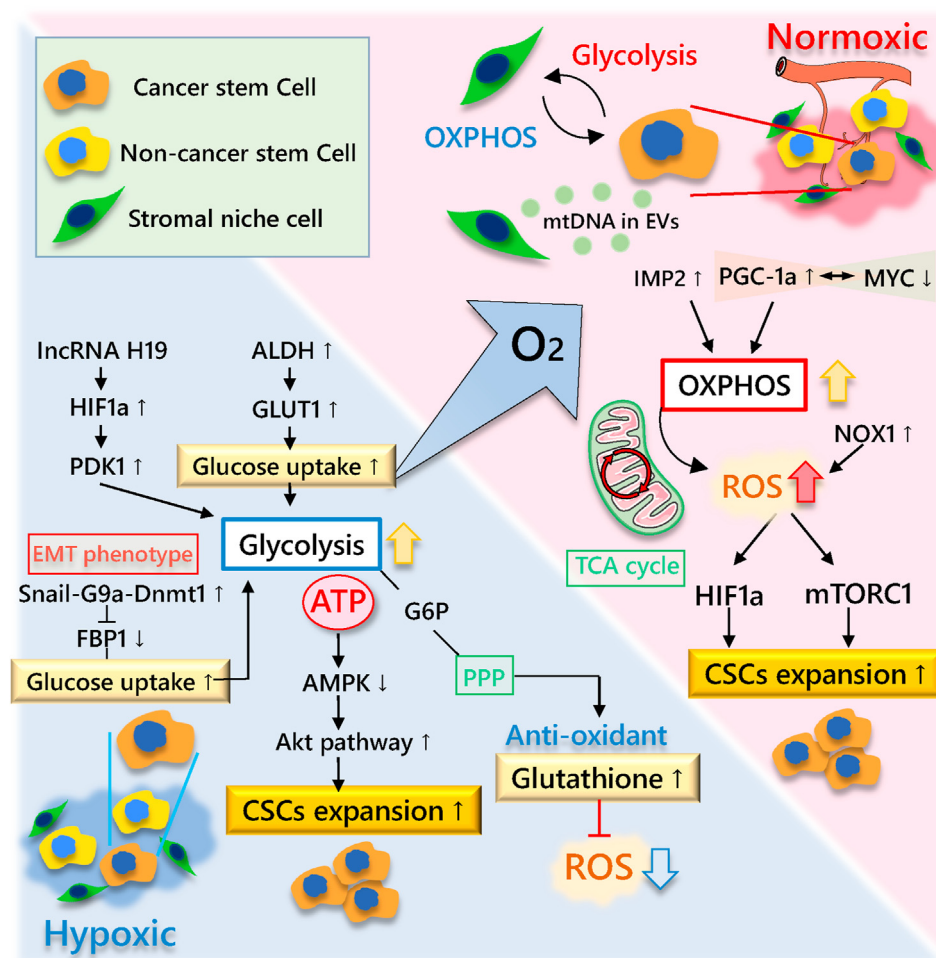

Fig. 1. The conflicting metabolic alterations in CSCs. In a hypoxic environment (blue), CSCs promote glycolysis through the HIF1a/PDK1-dependent axis, GLUT1 elevation, and EMT phenotype and proliferate by activating the Akt pathway. Moreover, CSCs upregulate the level of the antioxidant glutathione using PPP. On the other hand, in a normoxic environment (red), CSCs enhance mitochondrial OXPHOS by increasing IMP2 or PGC-1a. ROS produced by OXPHOS promotes CSC proliferation by activating HIF1a or mTORC1. Moreover, the interaction with stromal niche cells enhances OXPHOS in CSCs.

ability to adjust their intracellular ROS levels by developing their antioxidant system through a specific metabolic network [50].

Several stem cell markers are involved in the regulation of the redox state in the CSC population. CSCs generally maintain low ROS levels, exhibiting redox patterns to survive and maintain their stemness [51]. The CSC marker CD44, in particular the variant isoform (CD44v), interacts with and stabilizes xCT, a subunit of a glutamate-cystine transporter, to control the intracellular level of glutathione and protect against high levels of ROS in gastrointestinal CSCs [52,53]. Moreover, another significant pathway that inhibits high levels of ROS at the established tumor stage has been identified in breast CSCs. Although the glutathione antioxidant pathway is required for cancer initiation, CD44v and xCT upregulate the thioredoxin antioxidant pathway after cancer initiation. Indeed, combined inhibition of the antioxidant glutathione and thioredoxin antioxidant pathways leads to synergistic cancer cell death in vitro and in vivo [54]. The majority of leukemia stem cells (LSCs) are characterized by relatively low levels of ROS, and LSCs with low ROS aberrantly overexpress BCL-2. Inhibition of BCL-2 reduces mitochondrial OXPHOS [55]. The stem cell marker NANOG also contributes to hepatocellular carcinoma (HCC) progression by suppressing mitochondrial OXPHOS and activating FAO metabolism in tumor-initiating stem-like cells (TICs) in HCC. This study also revealed that the restoration of mitochondrial OXPHOS activity and inhibition of FAO alter the susceptibility of TICs to a standard care chemotherapy drug that is used to treat HCC [56]. Nuclear factor erythroid 2—related factor 2 (NRF2), also known as a redox regulator in CSCs, redirects glucose and glutamine into the glycolytic pathway under the sustained activation of PI3K-Akt signaling and prompts the switch from mitochondrial OXPHOX to glycolysis [57]. Moreover, NRF2 inhibits the conversion of pyruvate into acetyl-CoA by directly activating PDK1, leading to inhibition of the TCA cycle for head and neck cancer initiation [58]. Elucidation of the ROS reduction mechanism in CSCs, especially depending on mitochondrial OXPHOS for energy formation, may lead to the development of treatment strategies targeting CSCs.

5. Conclusion

CSCs have two conflicting metabolic phenotypes and flexibly switch the metabolic pathway to maintain CSC properties or redox homeostasis. In a hypoxic environment, CSCs produce energy through specific signaling by glycolysis-related factors and enhance CSC capacity by inducting EMT. However, in an abundant oxygen environment, CSCs proliferate while adjusting the ROS level produced by mitochondrial OXPHOS. Moreover, stromal niche cells have a vital impact on the complicated metabolic regulation in CSCs. Further investigations aimed at deciphering the mechanism of the interaction between CSCs and the stromal niche should pave the way to the development of novel therapies targeting CSC-specific metabolism (Fig. 1).

Declaration of competing interest

The authors disclose no conflicts.

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