frontiers | Frontiers in Epigenetics and Epigenomics

TYPE Review
PUBLISHED 11 September 2024
DOI 10.3389/freae.2024.1424163

OPEN ACCESS

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RECEIVED 27 April 2024
ACCEPTED 30 August 2024
PUBLISHED 11 September 2024

CITATION
Choi J-E and Baek I (2024) Interplay between epigenetics and metabolism controls cancer stem cell plasticity.
Front. Epigenet. Epigenom. 2:1424163.
doi: 10.3389/freae.2024.1424163

Interplay between epigenetics and metabolism controls cancer stem cell plasticity

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Tumors consist of cancer cells with different genetic, epigenetic, and phenotypic properties. Cancer stem cells are an important subpopulation of heterogeneous cancer cells and are capable of initiating and propagating tumors. The term cancer stem cells has become broader in efforts to understand their phenotypic plasticity to switch fates between self-renewal and differentiation. Cancer stem cell plasticity is significantly associated with the initiation of metastasis, resistance to therapy, and tumor recurrence. With our broadened knowledge of epigenetic regulation and metabolic reprogramming as key elements enabling such capabilities, an expansive body of literature has demonstrated the functional importance of each element in contributing to cancer stem cell characteristics. Recently, the direct interplay between epigenetic regulation and metabolic reprogramming has begun to be appreciated in the context of cancer stem cells with growing interest. In this review, we discuss the mechanisms by which cancer stem cells orchestrate the reciprocal regulation of cellular metabolism and epigenetic alterations. In the discussion, compelling, unanswered questions on this topic have been elaborated for the interest of the research community and how recent technological developments help tackle such research ideas. A comprehensive understanding of cancer stem cell attributes that are largely governed by epigenetic and metabolic reprogramming would enable the advancement of precise therapeutic options and the prediction of better responses to drugs, holding great promise in cancer treatment and cure.

KEYWORDS

epigenetics, cancer stem cell (CSC), cancer metabolism, oncogenic reprogramming, cellular plasticity, intratumor heterogeneity

1 Introduction

Tumor heterogeneity arises from multiple dimensions, including genetic and non-genetic levels with spatial and temporal differences. Our increasing understanding of tumor heterogeneity sheds light on cancer stem cells (CSCs), a subpopulation of cancer cells that demonstrate a higher capacity for tumor initiation, progression, metastasis, epithelial-mesenchymal plasticity, and drug resistance (Kreso and Dick, 2014; Nassar and Blanpain, 2016; Oskarsson et al., 2014). In addition to genetic heterogeneity within the tumor mass (Dagogo-Jack and Shaw, 2018), different non-genetic events can play functional roles in such capabilities in CSCs (Easwaran et al., 2014; Kim and DeBerardinis, 2019). Metabolic and epigenetic states are the two key non-genetic elements that contribute to CSC characteristics.

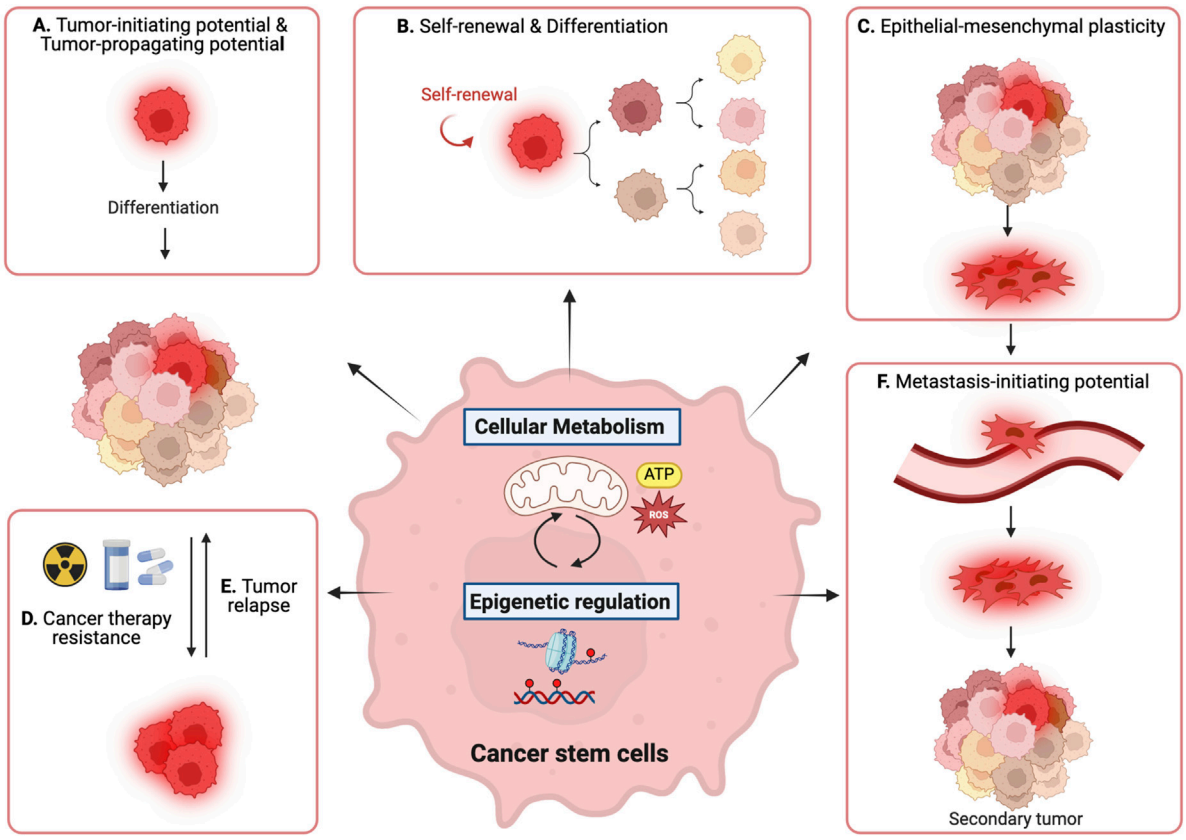

FIGURE 1
Reciprocal interaction between metabolic pathways and epigenetic regulation governs cancer stem cell (CSC) properties. **(A)** tumor-initiating and -propagating potential, **(B)** self-renewal and differentiation, **(C)** epithelial-mesenchymal plasticity, **(D)** cancer therapy resistance, **(E)** tumor relapse, and **(F)** metastasis-initiating potential.

The interplay between metabolism and epigenetics in a pool of cancer cells has been extensively studied over the past decade at the population-averaged level (Izzo et al., 2021). In this review, we focus on the direct interplay between metabolic and epigenetic regulations in CSCs, which is a growing area of interest. Potential future research questions that are yet to be answered will be discussed to highlight the significance of this research area, which directly affects the therapeutic response and recurrence rate of patients with cancer.

2 CSCs: a minor but functionally critical subpopulation of cancer cells

Tumors are heterogeneous, as they continuously evolve at multiple layers, including genetic and epigenetic alterations and metabolic reprogramming (Meacham and Morrison, 2013). Cell-intrinsic and cell-extrinsic models to explain intratumor heterogeneity strongly suggest the presence of a tumor subpopulation with a unique ability to initiate and propagate tumors, metastasize with epithelial-mesenchymal plasticity, relapse post-therapy, and develop insensitivity to anti-cancer drugs, now known as CSCs (Kreso and Dick, 2014; Nassar and Blanpain, 2016; Oskarsson et al., 2014) (Figure 1). They are termed as such because of their functional resemblance to normal stem cells, which are characterized by self-renewal and differentiation potentials. Notably, CSCs were first identified in human acute myeloid leukemia (AML) by Bonnet and Dick based on their ability to propagate primary tumors and recreate phenotypic heterogeneity (Bonnet and Dick, 1997; Lapidot et al., 1994). Since pioneering studies, an increasing body of evidence has supported the existence of CSCs in various cancer types, such as breast cancer (Al-Hajj et al., 2003; Ginestier et al., 2007), colorectal cancer (O'Brien et al., 2007; Ricci-Vitiani et al., 2007), and glioblastoma (Singh et al., 2004).

Furthermore, CSCs are critical targets for anti-cancer therapeutics because of their distinctive roles in metastasis, therapy resistance, and tumor relapse. These abilities are mainly attributed to their phenotypic plasticity, including dedifferentiation and transdifferentiation (Pérez-González et al., 2023). In addition to cell-autonomous dysregulation of cell fate, CSCs can change their fate in response to environmental cues, similar to normal tissue stem cells (Batlle and Clevers, 2017). This dynamic cell fate transition involves the reprogramming of metabolic and epigenetic processes, which have been recognized as cancer hallmarks (Hanahan, 2022). This metabolic transition is thought to be partially achieved through epigenetic regulation. Conversely, metabolic alterations can affect epigenetic states. Metabolism and epigenetic regulation are not distinct but rather intricately connected as important reciprocal regulators of CSC plasticity, orchestrating CSC identity and characteristics. A comprehensive understanding of these two

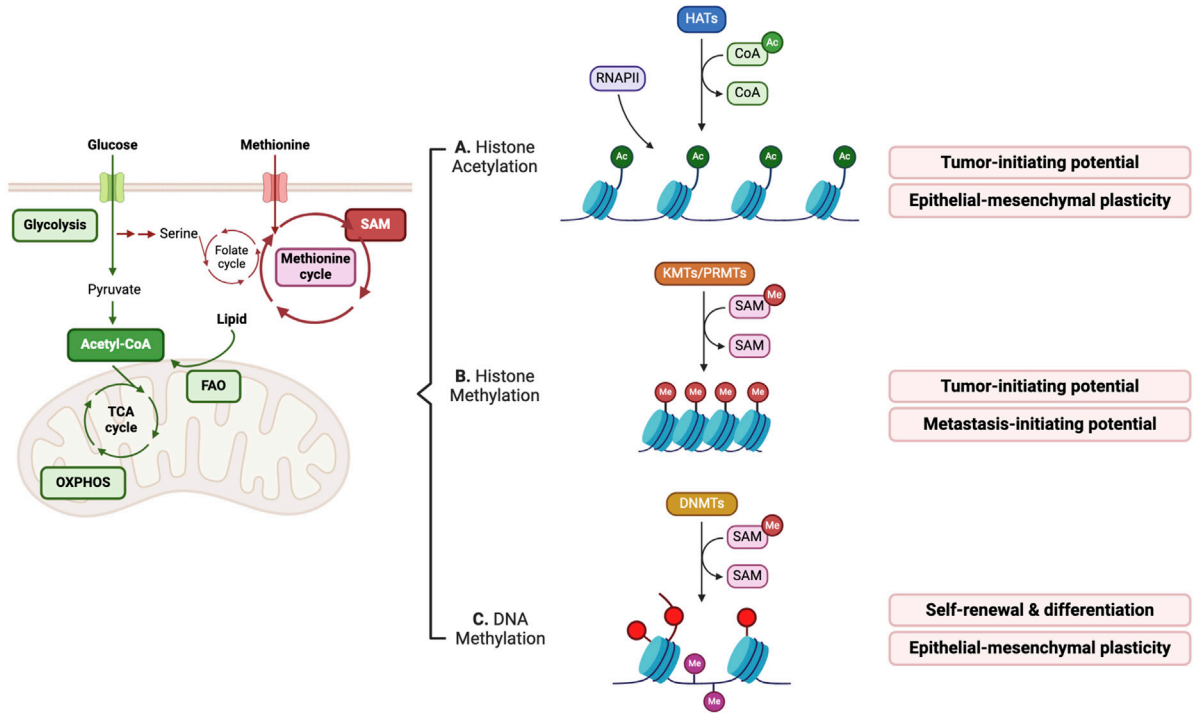

FIGURE 2
Metabolites serve as key substrates in producing epigenetic marks, thus affecting CSC properties. **(A)** Intracellular acetyl-CoA metabolism affects histone acetylation levels, in general promoting gene transcription associated with epithelial-mesenchymal transition (EMT) and enhancing tumor-initiating potential. **(B,C)** Intracellular S-Adenosyl methionine (SAM) abundance controls histone and DNA methylation states, which influences CSC features. RNAPII; RNA polymerase II.

regulatory circuits in CSCs would enable the eradication of aggressive tumor cells and enhance tumor-free survival.

3 Metabolism controls epigenetics in CSCs

Metabolic rewiring is a well-known adaptation of cancer cells that provides survival and growth advantages in response to a tumor microenvironment with limited nutrients and oxygen and with stress (Faubert et al., 2020). Metabolic reprogramming during carcinogenesis and metastasis has been studied extensively over the last two decades (Pavlova and Thompson, 2016). Recently, metabolic heterogeneity has begun to be appreciated within the cancer cell population, along with the discovery of different cell surface markers and the development of metabolite measurement technologies for cellular resolution (Demicco et al., 2024). Remarkably, the metabolic phenotypes of CSCs differ from those of non-CSCs, raising exciting research questions regarding the functional roles of distinct metabolic pathways in CSCs.

Metabolic intermediates can serve as direct substrates or cofactors for the modifications of epigenetic marks (Wellen et al., 2009; Shyh-Chang et al., 2013; Carey et al., 2015). As epigenetic marks can be dynamically regulated during embryonic stem cell (ESC) differentiation, partly under the influence of metabolic changes, the metabolic state is a crucial determinant of cell lineage and identity (Ryall et al., 2015; Moussaieff et al., 2015; Sperber et al., 2015; Etchegaray and Mostoslavsky, 2016). During carcinogenesis, cell fate changes, partly through chromatin rearrangements and DNA/RNA modifications, favoring oncogenic reprogramming. As direct substrates or cofactors of enzymes responsible for epigenetic modifications, metabolites can regulate such phenotypes via epigenetic alterations, affecting the tumor-initiating, tumor-propagating, or metastatic potential. In this section, the key metabolites are discussed individually, focusing on their roles in writing and erasing epigenetic marks in CSCs.

3.1 Metabolites that generate epigenetic marks in CSC regulation

Acetyl-CoA and S-adenosyl methionine (SAM) are the most well-studied substrates for donating acetyl and methyl groups, respectively, to create new epigenetic modifications (Figure 2) (Boon et al., 2020). Acetyl-CoA is mainly produced during glucose metabolism and fatty acid oxidation (FAO). An increase in glycolysis and FAO results in abundant acetyl-CoA, which augments levels of global histone acetylation (Sivanand et al., 2018). Conversely, a decrease in the glycolysis-mediated generation of acetyl-CoA leads to a reduction in histone acetylation and thus affects the differentiation of ESCs, which emphasizes that the levels of intracellular metabolites feeding into epigenetic modifications can govern the cell differentiation state (Moussaieff et al., 2015). Hypoxia-induced upregulation of genes

involved in glucose metabolism, such as glucose transporter 1 (GLUT1), pyruvate kinase isozyme M2, and pyruvate dehydrogenase A, enhances glucose influx and pyruvate production in breast cancer (Yang D. et al., 2020). This results in acetyl-CoA accumulation, an increase in histone H4 acetylation, and subsequent gene upregulation associated with cancer stemness, affecting the tumor-initiating capacity (Yang D. et al., 2020). An FAO-mediated increase in acetyl-CoA can epigenetically regulate epithelial-mesenchymal transition (EMT) gene expression, thus affecting EMT-driven metastasis in breast cancer (Loo et al., 2021). The balance between FAO and fatty acid storage regulates intracellular acetyl-CoA availability, a critical epigenetic module affecting epithelial-mesenchymal plasticity. These results suggest that the cell metabolic state can affect gene expression by providing surplus materials for writing epigenetic marks, thereby promoting the CSC potential of cellular plasticity, such as epithelial and mesenchymal states. Moreover, dietary palmitic acid can establish a stable epigenetic memory, particularly mediated by Set1A-dependent H3K4me3 deposition, critical for metastasis initiation and development of the pro-metastatic niche (Pascual et al., 2021). In addition to histone modifications, post-translational acetylation of non-histone proteins, such as signaling proteins and transcription factors (TFs) can also regulate the metastatic potential of breast cancer cells. For example, the exogenous supply of saturated fatty acid, palmitate, a rich source of acetyl-CoA, acetylates nuclear factor-kappaB p65 subunit, leading to the promotion of metastasis-initiating potential of breast cancer to lung and liver (Altea-Manzano et al., 2023).

As a methyl donor, SAM is involved in the creation of methylation marks on histone proteins, DNA and RNA. Aberrant regulations of glucose, glutamine, and serine/glycine metabolic pathways, and folate and methionine cycles have indirect and direct effects on the availability of intracellular SAM, thereby affecting the epigenetic modification of methyl group acceptors (Figure 2) (Mentch et al., 2015). Threonine and methionine, which are SAM-producing amino acids, can modulate histone methylation, thereby influencing ESC differentiation ability (Shyh-Chang et al., 2013; Shiraki et al., 2014). Histone methylation of lysine and arginine residues is mediated by lysine methyltransferases (KMTs) and protein arginine methyltransferases (PRMTs), respectively, which provide docking sites for epigenetic regulators (Stallcup, 2001). The number of covalent methyl groups in histones generates mono-, di-, and tri-methylation states and functions as regulatory signals that affect gene activation or repression, depending on the histone modifications at specific loci. In non-small cell lung cancer (NSCLC), tumor-initiating cells exhibit a unique metabolic dependence on methionine because of their demands for SAM. The key methionine cycle enzyme, methionine adenosyltransferase II alpha (MAT2A), plays a critical role in providing SAM for global increases in histone H3 methylation, such as H3K4me3, H3K9me3, H3K27me3, and H3K36me2/3, suggesting that the upregulation of histone methylation, regardless of active or repressive marks, can positively influence the tumor-initiating potential of NSCLC (Wang et al., 2019). In triple-negative breast cancer, restriction of SAM availability by MAT2A inhibition causes failure to maintain active H3K4me3 marks on the SOX9 gene locus, which is associated with CSC enrichment and tumor- and metastasis-initiating potential (Strekalova et al., 2019). In basal-like breast cancer, nicotinamide N-methyltransferase (NNMT), which negatively regulates SAM availability, can decrease H3K9me3 repressive marks and DNA methylation of the pro-metastatic genes, such as PR/SET domain-5, promoting basal-type cancer plasticity and metastasis-initiating potential by regulating H3K9me3 and DNA methylation (Couto et al., 2023).

DNA methylation occuring mainly at cytosine (5-methylcytosine [5-mC]) in cytosine-guanine (CpG) dinucleotides, is mediated by DNA methyltransferases (DNMTs), and regulates gene activation or repression by hypo or hypermethylation, respectively (Lyko, 2018). In glioblastoma stem cells (GSCs), increased NNMT expression depletes intracellular SAM levels, resulting in global DNA hypomethylation with a mesenchymal phenotype and the self-renewal of GSCs (Jung et al., 2017). The dependence of leukemia stem cells (LSCs) on oxidative phosphorylation (OXPHOS) in mitochondria links intracellular SAM availability to DNA methylation (Singh et al., 2020). An increase in mitochondrial copper under the inhibition of the mitochondria copper chaperone COX17 inhibits the enzymatic activity of S-adenosylhomocysteine hydrolase, thereby decreasing intracellular SAM levels (Singh et al., 2020). This specifically downregulates global DNA methylation but not histone methylation, which is essential for LSC viability and differentiation.

3.2 Metabolites that remove or regulate the removal of epigenetic marks in CSC regulation

Mitochondrial intermediates such as α-ketoglutarate (α-KG), succinate, and fumarate function as direct cofactors or inhibitory molecules in removing epigenetic marks (Xiao et al., 2012; Killian et al., 2013; Letouzé et al., 2013). These metabolites center on regulating α-KG-mediated dioxygenase reactions, mainly removing methyl group(s) from histone, DNA, or RNA, thus affecting cancer initiation, progression, and plasticity (Figure 3) (Losman et al., 2020). Moreover, 2-hydroxyglutarate (2-HG), an oncometabolite produced by isocitrate dehydrogenase (IDH) gain-of-function mutations can also directly inhibit epigenetic enzymes such as histone and DNA demethylases utilizing α-KG as a cofactor (Figure 3) (Dang et al., 2009; Losman et al., 2013; Xu et al., 2011; Chowdhury et al., 2011).

Lysine demethylases (KDMs) catalyze the removal of methyl groups from histone lysine residues. Except for KDM1 (lysine-specific demethylase 1 [LSD1]), which utilizes flavin adenine dinucleotide (FAD) as a cofactor, the other KDMs (KDM2–7, JmjC domain-containing histone demethylases) are α-KG-dependent lysine demethylases targeting H3K4, H3K9, H3K27, and H3K36 (Kooistra and Helin, 2012; Klose et al., 2006). Local nutrient availability in the microenvironment can modulate histone demethylase activity by affecting α-KG levels. In melanoma, limited glutamine availability in tumor core regions led to decreased α-KG levels, resulting in histone H3K27 hypermethylation through insufficient ability to activate the H3K27-specific demethylase KDM6B (Pan et al., 2016). This H3K27 hypermethylation results in a dedifferentiation phenotype and therapeutic resistance to BRAF inhibitors, which are key characteristics of CSCs. In squamous cell

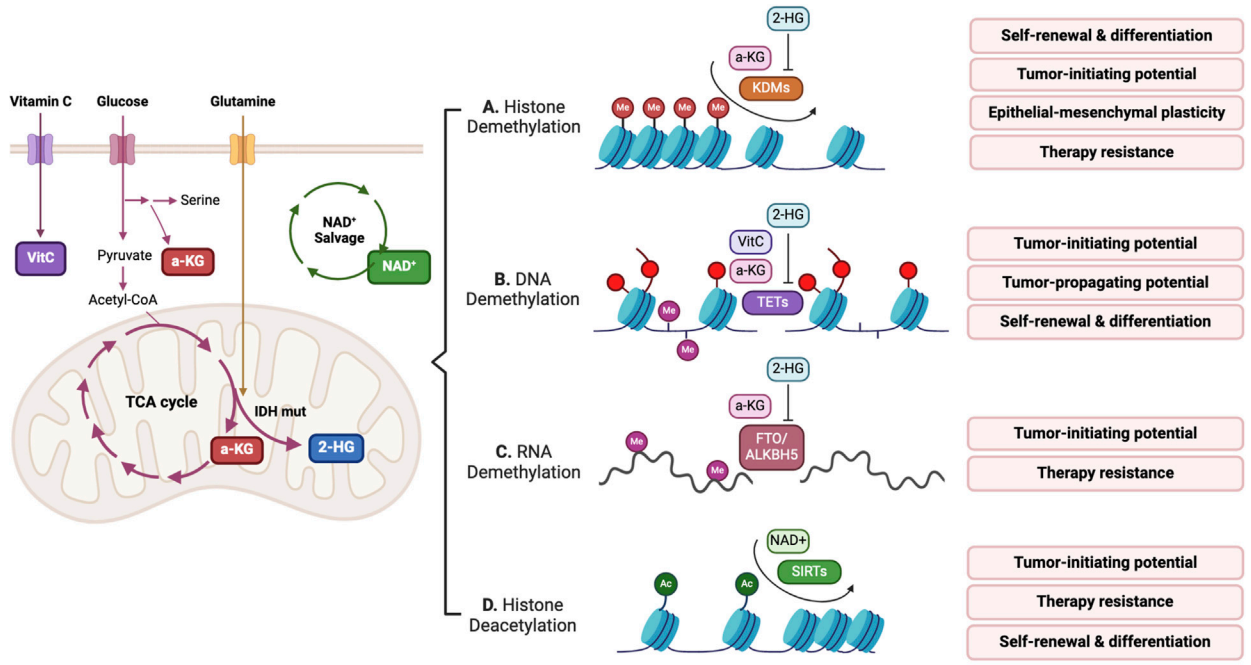

FIGURE 3
Metabolites take part in erasing epigenetic marks, which regulates CSC potential. **(A–C)** α-ketoglutarate (α-KG)-dependent demethylation reactions of histone, DNA, and RNA are largely governed by intracellular levels of α-KG and 2-hydroxyglutarate (2-HG), an oncometabolite. Dynamic regulatory modules confer various traits to CSCs. **(D)** Sirtuins utilize NAD^+ to remove acetyl group(s) from histone. This deacetylation affects cell differentiation, tumor initiation, and resistance to therapy.

carcinoma, activation of *de novo* serine synthesis pathway upon limited exogenous serine promotes α-KG-dependent H3K27me3 demethylation, thus facilitating cell differentiation and antagonizing tumor initiation (Baksh et al., 2020). In lung adenocarcinoma, reduction in glucose availability and hence in α-KG levels caused hypermethylation of H3K4me3, H3K9me3, and H3K27me3 (Saggese et al., 2024). An increase in H3K27me3 repressive marks was observed for genes associated with epithelial differentiation. In contrast, an increase in H3K4me3 activation marks was observed in the promoter regions enriched in canonical EMT TFs such as *SNAI1*, *SLUG*, and *ZEB1*. Therefore, understanding how different nutrient availability within different tumor microenvironments converges into intracellular α-KG levels, while α-KG levels can be differentially translated to modulate demethylase reactions of histone at different lysine residues or of DNA/RNA will be of considerable interest. The oncometabolite, 2-HG, can affect cell differentiation and stemness by inhibiting α-KG-dependent demethylation. Furthermore, the IDH gain-of-function mutation produces *R*-2-HG, which mainly inhibits the demethylation of H3K9me3 and H3K27me3 associated with cellular differentiation genes and thus blocks cell differentiation, promoting carcinogenesis in glioma and leukemia (Lu et al., 2012; Rohle et al., 2013; Wang F. et al., 2013)

Ten eleven translocation (TET) DNA demethylases belong to the α-KG-dependent dioxygenase enzyme family, catalyzing multiple oxidation reactions to remove the methyl group from 5-mC in DNA. Additionally, TET enzymatic activity is dysregulated in cancers with IDH mutations. In acute myeloid leukemia (AML) with IDH1 and IDH2 mutations, the global DNA hypermethylation phenotype is commonly induced by impaired TET2 function (Figueroa et al., 2010). Moreover, uniquely hypermethylated DNA regions were identified as GATA1/2 and EVI1 binding promoter regions, thereby inhibiting myeloid differentiation while maintaining stemness features. Branched-chain amino acids (BCAAs) undergo catabolism by transferring the α-amino group to α-KG via a BCAA transaminase (BCAT)-dependent reaction, which decreases intracellular α-KG. In AML stem cells, the BCAT1 enzyme and BCAA catabolic pathway are critical in regulating α-KG-dependent dioxygenase, including TET-mediated DNA demethylation (Raffel et al., 2017). Notably, $BCAT1^{high}$ AML cells showed enrichment of leukemia stemness genes and a DNA hypermethylation signature with augmented tumor-initiating potential. In addition to α-KG, TET family enzymatic activity is regulated by ascorbate (Vitamin C). Among cancer types that frequently present loss-of-function mutations in TET1/2 enzymes, the intracellular levels of ascorbate significantly affect carcinogenesis and cancer cell differentiation. In leukemia, two independent research groups have reported that TET2 deficiency dysregulates stem cell self-renewal via aberrant DNA hypermethylation (Cimmino et al., 2017; Agathocleous et al., 2017). Moreover, ascorbate depletion, in conjunction with Flt3 alteration, can accelerate leukemia formation, mainly by regulating Tet2 enzymatic activity (Agathocleous et al., 2017). Ascorbate treatment of leukemia-induced TET-mediated DNA demethylation inhibits tumor-initiating potential and tumor progression (Cimmino et al., 2017).

RNA methylation of N^6-methyladenosine (m^6A) is a recently recognized epitranscriptomic mark of mRNA that affects the

transcription, translation, alternative splicing, and stability of mRNA (Wang and Tang, 2023). Demethylation of m^6A can be mediated by α-KG-dependent dioxygenase alk/B homolog 5 (ALKBH5) or fat mass and obesity-associated protein (FTO) as an α-KG-dependent enzymatic reaction. In breast cancer, hypoxia-induced ALKBH5 expression positively affects NANOG mRNA expression by its demethylation in the 3′-untranslated region (Zhang et al., 2016). Increased NANOG levels enhanced the breast CSC phenotype and tumor-initiating potential. In gliomas and leukemias harboring IDH1/2 mutations, *R*-2-HG can inhibit FTO activity, thereby increasing m^6A RNA (Su et al., 2018). This compromises the stability of MYC/CEBPA transcripts by downregulating the FTO-mediated demethylase reaction, which may confer anti-tumor activity in IDH1/2-mutant cancers. In clear cell renal carcinoma, methionine derived from tumor-associated pericytes positively regulates the CSC phenotype through mRNA methylation (Zhang et al., 2024). An elevated SAM cycle specifically stabilizes ATPase-family-AAA-domain-containing 2 (ATAD2) mRNA via m^6A modification, thereby promoting the formation of a super-enhancer complex with SOX9 and subsequent transcription of genes associated with CSC features.

An oxidized form of nicotinamide adenine dinucleotide, NAD^+, functions as an essential cofactor in histone deacetylation and deacylation mediated by Sirtuins (SIRTs). Notably, SIRTs are a part of the histone deacetylase family and uniquely utilize NAD^+, translating cellular metabolic and redox conditions into histone modifications, thereby affecting gene expression (Choi and Mostoslavsky, 2014). Furthermore, NAD^+ serves as a substrate in reactions catalyzed by ADP-ribosyltransferases, such as poly (ADP-ribose) polymerase (PARP). In colorectal cancer, the NAD salvage pathway enzyme nicotinamide phosphoribosyl transferase (NAMPT) increases stemness and EMT-related gene expression, resulting in the enrichment of tumor-initiating cells through SIRT1 and PARP (Lucena-Cacace et al., 2018). In glioblastoma, NAMPT can regulate the NAD^+-dependent transcriptional program targeted by E2F2-ID (inhibitor of differentiation) axis (Gujar et al., 2016). Intracellular NAD^+ levels sustained by the NAMPT-mediated salvage pathway are key to GSC self-renewal and therapy resistance to therapy.

4 Epigenetics controls metabolism in CSCs

Epigenetic reprogramming has emerged as a cancer hallmark due to its role in initiating and sustaining malignant tumors (Hanahan, 2022). Exploiting epigenetic reprogramming is beneficial for CSCs, as it enables them to adapt to both extrinsic and intrinsic changes (Wainwright and Scaffidi, 2017; Easwaran et al., 2014). For example, transcriptional reprogramming governed by epigenetic regulation confers plasticity to phenotypic switching. Metabolic adaptation is a critical alteration that enables better survival and growth, and is partly mediated by epigenetic regulation (Miranda-Goncalves et al., 2018).

Epigenetic regulation occurs at various levels ranging from DNA methylation to histone modification and chromatin rearrangement. Epigenetic regulators can be grouped into *cis*-regulatory elements and *trans*-regulatory elements (Maston et al., 2006). *Cis*-regulatory elements are specialized DNA regions capable of regulating the expression of target genes, and include promoters, enhancers, silencers, and insulators (Preissl et al., 2023; Rivera and Ren, 2013). They typically serve as binding platforms for *trans*-regulatory elements. *Trans*-regulatory elements include TFs along with a broader range of DNA-binding proteins that contribute to gene expression regulation. Notably, TFs function by recruiting coactivators and enzymes that modulate the chromatin structure, thereby regulating the accessibility of specific DNA regions to the transcription machinery (Ferrie et al., 2022). These enzymes include histone modifiers, chromatin remodellers, and DNMTs. In this section, we focus on how the aforementioned epigenetic regulators orchestrate tumor metabolism to form and maintain CSC potential.

4.1 Transcription factors

Stem cell pluripotency and EMT TFs are often upregulated in CSCs (Yang L. et al., 2020; Chaudhary et al., 2023). They help CSCs maintain stem cell-like characteristics, partly by changing their metabolic state, preferentially shifting from OXPHOS to glycolysis and FAO (Figure 4) (Lisowski et al., 2018). In basal-like breast cancer, Snail (encoded by *SNAI1*), a critical EMT TF, forms a complex with a G9a histone methyltransferase and DNMT. The Snail-G9a-DNMT complex directly represses the expression of fructose-1,6-biphosphatase, a rate-limiting enzyme in gluconeogenesis. This results in increased glycolysis and reduced reactive oxygen species (ROS) production, conferring stem-like features to breast cancer cells (Dong et al., 2013). Tumor-initiating stem-like cells in hepatocellular carcinoma (HCC) promote self-renewal and support drug resistance through NANOG-mediated expression of FAO gene and concomitant repression of OXPHOS genes (Chen et al., 2016). *c-myc* is an essential TF in the thrombopoietin (TPO)-responsive colorectal $CD110^+$ CSCs that promote liver metastasis. Notably, TPO-induced *c-myc* recruits the histone acetyltransferase HBO1, which increases the H3K14 acetylation of metabolic genes involved in lysine catabolism and fatty acid synthesis (Wu et al., 2015).

The tumor microenvironment influences CSC stemness, in part, through the reprogramming of tumor cell metabolism (Zheng et al., 2021; Elia and Haigis, 2021). Hypoxia, a common characteristic of the tumor microenvironment, epigenetically controls metabolic pathways primarily by activating the hypoxia-inducible factor 1 (HIF-1) (Chen et al., 2023). HIF-1 is a heterodimeric TF consisting of HIF-1α and HIF-1β. Upon activation, HIF-1α interacts with p300/CBP (CREB-binding protein), which in turn acetylates histones and recruits other TFs for gene activation (Gu et al., 2001; Lu et al., 2021). Recruited TFs such as OCT3/4, NANOG, SOX2, Snail, and TWIST contribute to the metabolic adaptation of CSCs by upregulating the expression of metabolic genes and/or their regulators (Zhang et al., 2020; Wang Y. et al., 2013; Jeter et al., 2015). Furthermore, HIF-1α can directly upregulate several glycolytic genes to meet high metabolic demands of

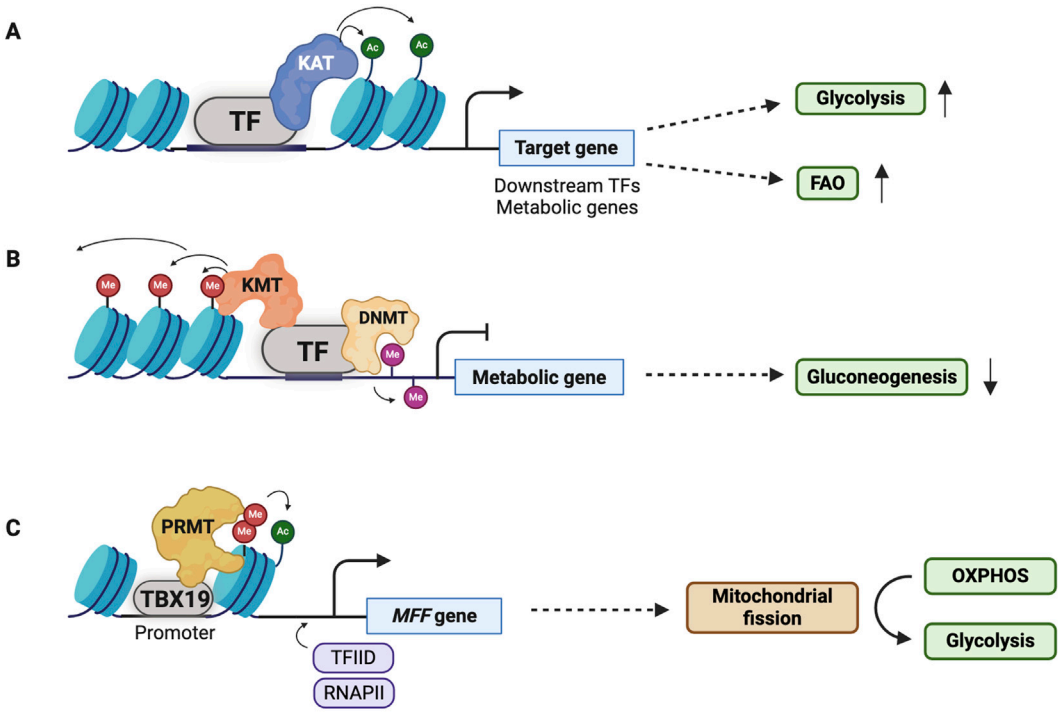

FIGURE 4
Transcription factors (TFs) can modulate metabolic adaptation of CSCs. **(A,B)** Stem cell pluripotency TFs, EMT TFs, and hypoxia-inducible factor-1 (HIF-1) activate or repress expression of metabolic genes through epigenetic modifications in CSCs. Typically, metabolic genes involved in glycolysis and fatty acid oxidation (FAO) or downstream TFs regulating metabolic adaptation are activated while metabolic genes involved in gluconeogenesis and oxidative phosphorylation (OXPHOS) are repressed. **(C)** T-box transcription factor 19 (TBX19), a TF, leads to a metabolic transition from OXPHOS to glycolysis via mitochondrial fission activated by expression of *MFF*. RNAPII; RNA polymerase II.

CSCs, including GLUT1/2, hexokinases, aldolases, phosphoglycerate kinase 1, pyruvate kinase M, and enolases (Taylor and Scholz, 2022; Semenza, 2003).

Another interesting mechanism that strengthens the self-renewal capacity of CSCs is via T-box transcription factor 19 (TBX19)-mediated metabolic adaptation (Figure 4). TBX19 epigenetically regulates mitochondrial fission-mediated metabolic adaptation in liver CSCs (Tang et al., 2021). Specifically, TBX19 interacts with PRMT1, which increases the H4R3me2a/H3K9ac-mediated transcription of the mitochondrial fission factor (MFF) gene. The TBX19/MFF axis induces mitochondrial fission, which promotes the metabolic switch from OXPHOS to glycolysis. This metabolic switch, which involves mitochondrial fission, prevents ROS-mediated OCT4 degradation, thereby maintaining the stemness of liver CSCs.

4.2 Histone modification

Histone modifications can induce chromatin structural rearrangements and recruit chromatin factors, thereby affecting gene expression (Zentner and Henikoff, 2013). A wide array of histone modifications has been identified (Bannister and Kouzarides, 2011). Among these, histone acetylation/deacetylation and histone methylation/demethylation are the most well-characterized. We focus on how these two histone modification modules contribute to CSC metabolic adaptation.

4.2.1 Histone acetylation/deacetylation

Histone acetyltransferases (HATs) and histone deacetylases (HDACs) catalyze the addition or removal, respectively, of acetyl groups from the lysine residues of target proteins (Yang and Seto, 2007). HATs are also known as lysine acetyltransferases. HATs have six families and 17 subtypes in humans, and 18 HDACs are grouped into two families and four classes (Seto and Yoshida, 2014; Wapenaar and Dekker, 2016). Classes I and II HDACs require Zn^{2+} for deacetylation. Class III HDACs belong to the silent information regulator 2 (Sir2)-related protein family (Sirtuins, SIRTs) that contains SIRT1–7. The sirtuin family HDACs use NAD^{+} as the cofactor. Class IV HDAC includes HDAC11.

Acetylation and deacetylation of the ε-amino group of the lysine residue of histones directly affect the transcription of metabolic genes (Figure 5) (Verdone et al., 2006). In HCC, HDAC11 contributes to the maintenance of cancer stemness by regulating glycolysis (Bi et al., 2021). HDAC11 deacetylates H3K9ac in the serine threonine kinase 11 (STK11) promoter region, leading to its suppression. Since STK11 activates the AMP-activated protein kinase signaling pathway, which negatively regulates glucose uptake and glycolysis, HDAC11-mediated downregulation of STK11 promotes glycolysis, thereby maintaining the stemness of HCC CSCs. SIRT6 can deacetylate H3K9ac and H3K56ac, which negatively regulates the transcription of HIF-1α-dependent glycolytic genes, including GLUT1, pyruvate dehydrogenase kinase 1, and lactate dehydrogenase A (Zhong et al., 2010). In a colorectal cancer model with an *Apc* mutation, an increase in glycolysis due to the loss of *Sirt6*

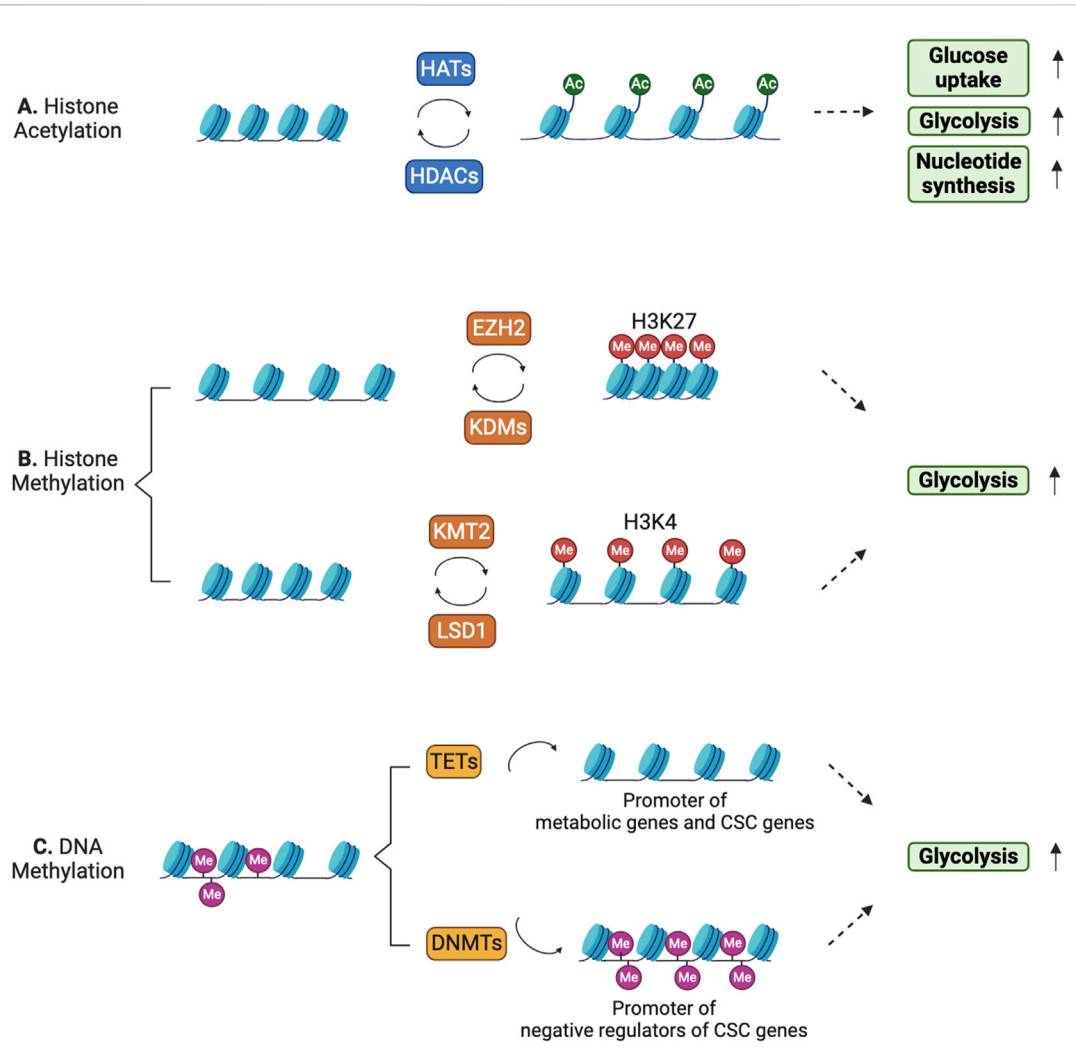

FIGURE 5
Histone and DNA modifications can dynamically control metabolic reprogramming in CSCs. **(A)** Histone acetylation/deacetylation patterns dynamically regulate gene expression in CSCs to meet their high energy demands. **(B)** Histone methylation leads to either gene repression or activation depending on the histone residues that are methylated. **(C)** DNA methylation at the promoter regions of metabolic genes and CSC-related genes is dynamically regulated.

can drive colorectal cancer initiation via aberrant histone acetylation (Sebastián et al., 2012). Furthermore, Sebastian et al. identified a subset of cancer cells with high glycolytic activity as quiescent tumor-initiating cells with better defense against oxidative stress (Sebastian et al., 2022). In line with these findings, in head and neck squamous cell carcinoma, $CD34^{+}$ CSCs with *Sirt6* loss display a high glycolytic phenotype, antioxidant protection, and nucleotide synthesis that collectively confers stemness and malignancy (Choi et al., 2021).

Some HDACs have non-histone targets (Bannister and Kouzarides, 2011). CSCs leverage this noncanonical activity of HDACs for metabolic rewiring. For example, SIRT1 can deacetylate transcription coactivator PGC-1α, leading to increased expression of mitochondrial genes in chronic myeloid leukemia (CML) stem cells (Abraham et al., 2019). Upregulation of mitochondrial gene expression enhances mitochondrial activity and OXPHOS in response to the energy demands of CML stem cells. These findings underscore the multiple levels of metabolic control by epigenetic regulators.

4.2.2 Histone methylation/demethylation

Histone lysine residues are methylated and demethylated by KMTs and KDMs, respectively (Dimitrova et al., 2015; Husmann and Gozani, 2019). Up to three methyl groups can be added to the ε-nitrogen of lysine residues. Canonical lysine methylation sites were found in the N-terminal tails of histones H3 and H4. Dynamic regulation of histone methylation patterns and residues is critical for the epigenetic regulation of transcription (Hyun et al., 2017).

Enhancer of zeste homolog 2 (EZH2), a catalytic subunit of polycomb repressive complex 2, mediates the trimethylation of H3K27 (H3K27me3) (Duan et al., 2020). This histone modification is associated with the repression of gene expression. Additionally, EZH2 plays an essential role in stem cell fate decisions during development (Lee et al., 2022). The aberrant upregulation of EZH2 expression has been observed in CSCs across various cancer types (Wen et al., 2017), suggesting its involvement in CSC features (Figure 5). A recent study suggested that EZH2 epigenetically promotes c-Myc-mediated glycolysis and thus tumor cell

proliferation, invasion, and stemness in pancreatic cancer (Zhai et al., 2021). Specifically, EZH2 silences the expression of long non-coding RNA LINC00261, which subsequently releases IGF2BP1 from its sequestration and thus stabilizing c-Myc RNA. Upregulation of c-Myc activates target genes that regulate CSC identity.

H3K4 methylation is associated with active transcription and is catalyzed by the KMT2 protein family (Van et al., 2024). H3K4 di-methylation (H3K4me2) and H3K4 tri-methylation (H3K4me3) are enriched in leukemia stem cells (LSCs) expressing c-Kit (Wong et al., 2015). This H3K4 methylation pattern was positively correlated with the expression of metabolic genes crucial for maintaining LSC potential (Somervaille et al., 2009; Wong et al., 2015), suggesting that the H3K4 methylation pattern is associated with the transcriptional program of metabolic genes that potentially govern CSC maintenance (Figure 5).

Epigenetic regulators that affect methionine metabolism can alter the H3K4 methylation states, and thus induce the transcription of CSC-related genes. In triple-negative breast cancer, aldehyde dehydrogenase$^+$ CSCs express higher levels of EMSY, a proto-oncogene, than do non-CSCs (Liu et al., 2024). Overexpression of EMSY correlates with poor prognosis, tumorigenesis, and CSC self-renewal. EMSY promotes methionine metabolism and increases SAM and S-adenosylhomocysteine levels. Elevated SAM levels fuel H3K4me2 and H3K4me3, thereby driving the upregulation of CSC-related genes such as *NANOG*, *POU5F1*, and *SOX2*. Additionally, EMSY-mediated H3K4me2 and H3K4me3 are maintained by the competitive binding of EMSY to the JmjC domain of KDM5B, demethylating H3K4 methylation (Liu et al., 2024).

4.3 DNA methylation

DNA methylation typically refers to the methylation of 5-carbon cytosine (5-mC) in CpG dinucleotide repeats found in the promoter regions of most mammalian genes (Moore et al., 2013). DNA methylation is catalyzed by DNMTs (Lyko, 2018), of which DNMT1, DNMT3A, and DNMT3B are canonical DNMTs responsible for 5-mC. DNA methylation is reversed by TET enzymes that convert 5-mC to 5-hydroxymethylcytosine (Lyko, 2018). The counteractive actions of DNMTs and TETs dynamically shape DNA methylation patterns. A recent study has shown that TET3 is overexpressed in LSCs in AML and promotes the expression of glycolytic genes and stem cell signature genes (Pulikkottil et al., 2022). The list includes hexokinase 1/2 and enolase 2, which are involved in glucose metabolism, and HES1 and CCND1, which are associated with early myeloid progenitor gene signatures. Overexpression of TET3 in normal human hematopoietic stem and progenitors disrupts normal hematopoietic differentiation, suggesting that TET3 maintains distinct features of LSCs in AML (Pulikkottil et al., 2022). Zinc finger DHHC-type containing 1 (ZDHHC1, ZNF377) plays a tumor-suppressive function by downregulating stemness-related TFs and providing hostile metabolic conditions for tumor growth (Le et al., 2020). Multiple cancers downregulate ZDHHC1 expression by methylating its promoter region (Le et al., 2020). The expression of stem cell pluripotency TFs and metabolic genes that maintain CSC potential are dynamically regulated at the DNA methylation level (Figure 5).

5 Discussion

Understanding the mechanisms underlying CSC emergence and their ability to self-renew and differentiate has clinical implications and therapeutic potential, given their association with metastasis, therapy resistance, and tumor relapse. Over the past decade, studies have demonstrated an intricate interplay between metabolic pathways and the epigenetic regulation of CSCs. Alterations in metabolic pathways enable CSCs to generate metabolites that reshape the epigenetic landscape and drive transcriptional reprogramming, which is essential for sustaining CSC features. Conversely, epigenetic regulators target metabolic genes and regulators of metabolic genes, preferentially redirecting metabolic pathways toward glycolysis and FAO from OXPHOS. In this section, we discuss the outstanding questions to be answered in this field with the current technological advances.

Recently, acyl-CoA, in addition to acetyl-CoA, has been shown to serve as a direct substrate for generating epigenetic marks that involve distinct functions in gene expression (Simithy et al., 2017). A repertoire of acyl-CoA includes propionyl, butyryl, β-hydroxybutyryl, crotonyl, succinyl, malonyl, glutaryl, and even long-chain fatty acyl groups bound to coenzyme A, capable of generating histone lysine acylation and subsequent signaling to transcriptional activation (Sabari et al., 2017). To date, no studies have investigated how acyl-CoA alters epigenetic states during CSC maintenance. Since diverse metabolites are mainly derived from lipid metabolic pathways, understanding their functional roles in regulating CSC properties through protein lysine modification mechanisms will be of considerable interest. In addition, FAD, a common dietary supplement known as vitamin B_2 (or riboflavin), is a key cofactor of LSD1-mediated lysine demethylation. Its impact on histone (de) methylation and, in turn, CSC characteristics, remains to be explored.

The influence of metabolism on chromatin accessibility and chromatin topology remains another compelling area yet to be investigated in CSCs. The key components of the nucleosome remodeler SWI/SNF (BAF) complex are dependent on the supply of ATP to perform their enzymatic functions (Wilson and Roberts, 2011), which raises questions about how ATP availability affects the activity of the SWI/SNF complex and therefore CSC properties. The seminal paper by Bernstein and colleagues found that DNA hypermethylation in IDH mutant gliomas reduces CCCTC-binding factor (CTCF) binding and presents an associated decrease in insulator function, leading to an aberrant activation of *PDGFRA* oncogene (Flavahan et al., 2016). This paper highlights how chromosomal topology can be dysregulated in cancer under the influence of the oncometabolite. In line with it, poly (ADP-ribose) ylation (PARylation), mediated by PARP with NAD^+ as a cofactor, is a well-known protein modification in the DNA damage response. In addition, PARP1 can regulate transcription, DNA methylation, and the function of CTCF insulator protein via PARylation (Beneke, 2012). Recently, PARylation of CTCF has been shown to affect its insulator function, thereby directly affecting the proper expression of tumor-suppressor genes such as CDH1, p16, and p19ARF (Farrar et al., 2010; Witcher and Emerson, 2009). To date, comprehensive understanding of how the functional interactions between PARP1, PAR, and CTCF can modulate the key characteristics of CSCs due to the dysregulation of NAD^+ metabolism is lacking. Notably, in succinate dehydrogenase deficient

gastrointestinal stromal tumors, global DNA hypermethylation-mediated, defective CTCF binding results in alterations in chromatin topology. The altered genome structure allows the activation of the *FGF4* oncogene by interacting with enhancers (Flavahan et al., 2019). This will be another exciting area that needs future investigation in the context of CSCs, as deficiency in key metabolic enzymes affects the chromatin topology that can drive tumorigenesis.

Furthermore, m^6A modification of RNA can influence gene expression (Jiang et al., 2021). This RNA modification process involves m^6A addition and removal by m^6A methyltransferases and demethylases, respectively. Key m^6A methyltransferases include METTL3/14/16, RBM15/15B, ZC3H3, and VIRMA, whereas demethylases include FTO and ALKBH5. METTL3 directly interacts with and modifies the transcription of metabolic genes, including HK2 and GLUT1 (Shen et al., 2020). The m^6A modification of these transcripts is recognized by readers such as IGF2BP2 or IGFBP2/3, triggering the activation of the glycolysis pathway. This activated glycolytic pathway provides essential sustenance for tumor cell growth. As the relationship between RNA methylation/demethylation and metabolic gene regulation has recently been established, future studies to understand how their interplay drives CSC characteristics should stimulate and expand this research area.

Considering the phenotypic plasticity of CSCs, the interplay between metabolic pathways and epigenetic regulation is dynamically orchestrated, and shapes their characteristics. This interplay can be controlled by external signals received by CSCs, such as the Notch, Hedgehog, and Wnt signaling pathways (Yuan et al., 2024; Takebe et al., 2015). Therefore, investigating how external signals modulate the interaction between metabolism and epigenetic regulation in CSCs will be interesting, albeit challenging. Understanding the distinctions between these signaling pathways in CSCs and normal stem cells and their effect on metabolic enzymes and epigenetic regulators constitutes crucial research questions.

Single-cell-based techniques, such as single-cell RNA-sequencing, single-cell epigenomic profiling, and single-cell metabolomics, in addition to spatially resolved metabolite analyses with cellular resolution (e.g., matrix-assisted laser desorption/ionization-mass spectrometry imaging), offer unprecedented resolution for dissecting the heterogeneity within CSC populations (Vegliante et al., 2022). The identification of metabolically and epigenetically distinct CSC subpopulations can enable us to uncover *bona fide* CSCs associated with cancer stemness (Yuan et al., 2022; Choi et al., 2021). Additionally, single-cell techniques can provide insights into how different cell types within CSC niches affect the metabolic states and epigenetic landscapes of CSCs. Technical advancements that enable the simultaneous capture of metabolic and epigenetic states will further deepen our understanding of the interplay between metabolism and epigenetic regulation in CSC biology.

Notably, CSCs possess the unique ability to initiate and propagate malignant tumors. Their pivotal role in tumors stems from their cellular plasticity. Furthermore, CSCs are capable of self-renewal and differentiation and can dynamically change their fate in response to intrinsic and extrinsic changes, similar to their normal stem cell counterparts. Cellular plasticity is partially achieved via metabolic and epigenetic reprogramming. Markedly, both engage in a complex interplay and fine-tune cellular states. Although various methods of communication between metabolic pathways and epigenetic regulation have been identified in CSCs, further studies are needed to comprehensively understand their interplay in CSCs. Such studies could explore how metabolites, including acyl-CoA and FAD, that are yet to be examined, contribute to epigenetic alterations. Such studies can also address the effects of metabolic reprogramming on spatiotemporal genome organization and identify new pathways of epigenetic influence on metabolic regulation, such as RNA modifications. Another pivotal research direction can be to examine how CSC-associated signaling pathways govern the interplay between metabolic and epigenetic reprogramming.

Intratumor heterogeneity has led to a model in which a tumor subpopulation, now considered CSCs, is responsible for metastasis, drug resistance, and tumor relapse. However, CSCs have been identified based on their functional ability to drive tumor initiation and progression or the expression of CSC biomarkers, such as CD44, CD90, and CD133. Recent advances in single-cell-based approaches for metabolic and epigenomic profiling can enable the identification of *bona fide* CSCs, presenting a promising opportunity for complete cancer remission.

Author contributions

J-EC: Conceptualization, Visualization, Writing–original draft, Writing–review and editing. IB: Conceptualization, Funding acquisition, Visualization, Writing–original draft, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. J-EC is a recipient of the RGC postdoctoral fellowship in Hong Kong SAR (PDFS2223-7S04). This work was supported by a grant from the National Research Foundation of Korea (NRF) funded by the Korea government (MSIT) (RS-2023-00278378) to IB and a grant from Kyung Hee University in 2023 (KHU-20233256) to IB.

Acknowledgments

The authors extend apologies to those colleagues whose important contributions could not be included in this article due to space limitations.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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