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REVIEW

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Bridging epigenomics and tumor immunometabolism: molecular mechanisms and therapeutic implications

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Abstract

Epigenomic modifications—such as DNA methylation, histone acetylation, and histone methylation—and their implications in tumorigenesis, progression, and treatment have emerged as a pivotal field in cancer research. Tumors undergo metabolic reprogramming to sustain proliferation and metastasis in nutrient-deficient conditions, while suppressing anti-tumor immunity in the tumor microenvironment (TME). Concurrently, immune cells within the immunosuppressive TME undergo metabolic adaptations, leading to alterations in their immune function. The complicated interplay between metabolites and epigenomic modulation has spotlighted the significance of epigenomic regulation in tumor immunometabolism. In this review, characteristics of the epigenomic modification associated with tumors are systematically summarized alongside with their regulatory roles in tumor metabolic reprogramming and immunometabolism. Classical and emerging approaches are delineated to broaden the boundaries of research on the crosstalk research on the crosstalk between tumor immunometabolism and epigenomics. Furthermore, we discuss potential therapeutic strategies that target tumor immunometabolism to modulate epigenomic modifications, highlighting the burgeoning synergy between metabolic therapies and immunotherapy as a promising avenue for cancer treatment.

Keywords Tumor, Epigenomics, Metabolic reprogramming, Immunometabolism, ScATAC-seq, Spatial metabolomics, Cancer treatment

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Introduction

In recent decades, research on biology and diseases has transcended the boundaries of genome, with epigenomics emerging as a rapidly growing field. Epigenomics is the study of the effects of chromatin structure on the epigenome, not necessarily genetic memory [1, 2]. It is important to differentiate epigenomics from epigenetics, as the former refers to physical and functional entities associated with DNA and histones, rather than the process of inheriting different cell types or cell states during cell division [3]. Epigenomic alterations, including DNA methylation and histone modifications, with or without mutations in cancer driver genes, have been shown to play critical roles in hematological and solid tumors [4, 5]. Epigenomic regulation participates in tumor cell growth, invasion, metastasis, metabolic reprogramming and immune evasion, suggesting its potential as a target for tumor immunotherapy [6, 7].

After proposing the six basic characteristics of tumor cells, Douglas Hanahan and Robert A. Weinberg identified an emerging signature of tumor cells in 2011—reprogramming energy metabolism, expanding upon their original hallmarks of cancer [8]. To meet the elevated energy demands of rapid growth, invasion and metastasis, tumor cells regulate endogenous and exogenous metabolites in the tumor microenvironment (TME) via multiple signaling pathways, thereby achieving metabolic reprogramming [9, 10]. This metabolic adaptation encompasses a broad spectrum of nutrients, including glucose, lipids, and amino acids, with aerobic glycolysis (the Warburg effect) being the most extensively studied [11]. Under aerobic conditions with preserved mitochondrial respiration, tumor tissues convert more glucose to lactate than normal tissues in the same amount of time, accelerating glucose uptake by tumor cells while simultaneously impairing immune cell infiltration [12, 13]. As a result, immune cells in the TME are compelled to undergo metabolic reprogramming due to excessive acidity, hypoxia, and lack of nutrition, which affects their proliferative and anticancer activities [14]. Moreover, various metabolites and metabolic enzymes serve as key immunological mediators, influencing the differentiation and activity of both innate and adaptive immune cells [15]. Tumor-induced glucose depletion and lactate accumulation lead to T cell exhaustion, promoting the survival of regulatory T cells (Tregs) and augmenting their suppressive effects on anti-tumor immune responses [16]. In the TME, factors such as interleukin-6 (IL-6) and hypoxia induce B cell differentiation into regulatory B cells, which secrete cytokines like IL-10 that facilitate tumor progression and metastasis through modulation of glucose and amino acid metabolism [17]. These findings highlight how targeted immunometabolic therapies present promising avenues for cancer treatment.

Recent research has increasingly focused on the interplay between epigenomics and tumor immunometabolism (Fig. 1). For example, the tumor metabolite 2-hydroxyglutaric acid (2-HG) alters the epigenomic landscape by inhibiting the activity of α-ketoglutaric acid (α-KG)-dependent dioxygenases, which subsequently suppress the function of DNA and histone demethylases [18]. Metabolites created during metabolic reprogramming of tumor and immune cells act as substrates, agonists, or antagonists, influencing the activity of epigenomic enzymes and thereby shaping a diverse epigenomic landscape. Simultaneously, epigenomics regulates metabolic genes at both the transcriptional and post-transcriptional levels, facilitating tumor metabolic reprogramming [5]. This creates a feedback loop where the epigenome and tumor immunometabolism exert reciprocal influences, boosting the proliferation and metastasis of tumor cells. Moreover, current methological landscape and emerging technological resources provide powerful weapons for a deeper insight into immune regulation through the metabolite-epigenomic circuit. This article provides an overview of recent advancements and future prospects regarding the interplay between tumor immunometabolism and epigenomics, as well as current research on therapeutic strategies targeting tumor immunometabolism and epigenomics.

Epigenomic modifications affecting tumorigenesis and progression

The epigenome exhibits cell-type-specific variations and undergoes dynamic changes in response to environmental factors, regulating gene expression through multiple mechanisms [3]. Multiple factors-induced aberrant DNA methylation and histone modifications play a pivotal role in tumor initiation and progression by modulating the expression of tumor-associated genes and influencing processes such as cell death and metabolism (Fig. 2). Moreover, epigenomics provides insights into potential early diagnostic and therapeutic strategies.

DNA methylation

DNA methylation, one of the most extensively studied epigenomic modifications, regulates gene expression without changing the nucleotide order or composition, and is directly linked to normal growth and development as well as a range of disorders. DNA methyltransferases (DNMTs) transfer methyl groups from the cofactor S-adenosyl-L-methionine (SAM) to the fifth carbon of cytosine residues in DNA, forming 5-methylcytosine (5mC), which is ubiquitous in eukaryotic genomes and most prevalent on symmetric CpG dinucleotides. It is

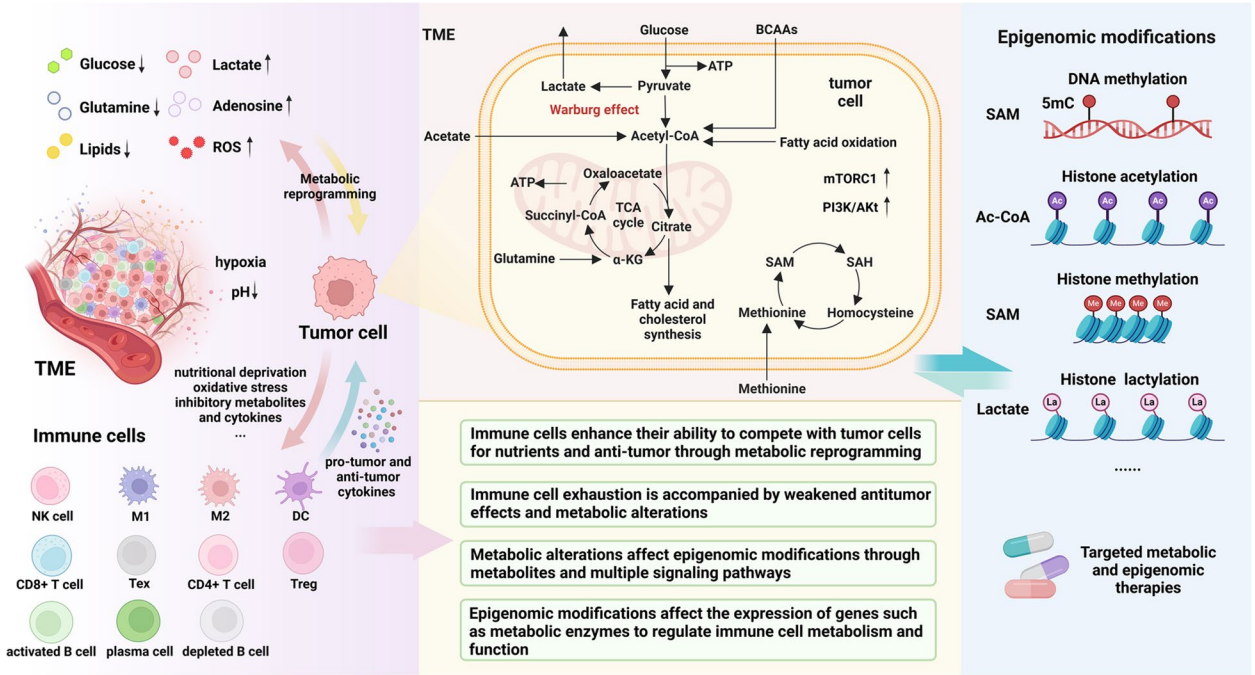

Fig. 1 A brief overview of tumor immunometabolism and epigenomics. Tumor cells undergo metabolic reprogramming for rapid proliferation and metastasis, which leads to deficiencies in essential nutrients, accumulation of metabolic toxicants and immunosuppressive factors in the tumor microenvironment. Immune cells can execute anti-tumor functions, such as the cytotoxic activity of CD8 + T cells, and promote tumor survival and progression, as seen in the pro-tumor effects of regulatory T cells and M2 macrophages. To adapt to the demanding tumor microenvironment, immune cells compete for nutrients and regulate their own differentiation and function through a series of metabolic changes. Metabolites, such as acetyl-CoA and lactate, play important roles in epigenomic alterations, while epigenomics, in turn, affects the metabolism and function of immune cells by regulating the expression of substances such as metabolic enzymes and cytokines. Therefore, the interaction between epigenomics and immunometabolism cannot be ignored, which provides more possibilities for the treatment strategy of tumors. (ROS, reactive oxygen species; NK cell, natural killer cell; DC, dendritic cell; Tex, T cell exhaustion; Treg, regulatory T cell; BCAAs, branched-chain amino acids; Ac-CoA, acetyl-coenzyme A; ATP, adenosine triphosphate; TCA cycle, tricarboxylic acid cycle; α-KG, α-ketoglutaric acid; mTORC1, mechanistic target of rapamycin complex 1; PI3K, phosphatidylinositol-3-kinase; SAM, S-adenosyl-L-methionine; SAH, S-adenosyl-L-homocysteine; 5mC, 5-methylcytosine)

frequently associated with the repression of transposon expression and the maintenance of genomic stability [19]. DNMTs are essential for DNA methylation and can be categorized into two types: de novo DNMT and maintenance DNMT. De novo DNMTs, including DNMT3A and DNMT3B, are primarily responsible for establishing DNA methylation at previously unmethylated sites. In contrast, maintenance DNMTs, such as DNMT1, are localized to the replication center during the mitotic phase, preserving DNA methylation patterns during cell proliferation [20]. DNA methylation removal is primarily connected with passive demethylation during semi-conservative DNA replication and active demethylation by demethylases such as the ten-eleven translocation (TET) protein family [21]. Throughout the lifespan, DNA methylation and demethylation undergo dynamic fluctuations in response to growth and development, aging, and disease. Aberrant DNA methylation patterns can contribute to the initiation and progression of various diseases, exacerbating their pathophysiology [22, 23].

A hallmark of tumor DNA methylation is genome-wide hypomethylation, frequently resulting in chromosomal instability and dysregulated gene expression. Additionally, site-specific hypermethylation, such as hypermethylation of CpG islands in the promoter regions of tumor suppressor genes (TSGs), affects critical processes like apoptosis, DNA repair, carcinogen metabolism, and other factors, all of which play a significant role in carcinogenesis [24]. In breast cancer patients, DNA demethylation and methylation loss have been associated with hypomethylation of oncogenes. Simultaneously, CpG hypermethylation in the promoter regions of tumor suppressor genes, such as superoxide dismutase 3, leads to uncontrolled cell proliferation and metastasis [25]. Furthermore, polycyclic aromatic hydrocarbons in lung cancer can induce mutations in TSGs like p53 and oncogenes such as KRAS by promoting DNA adduct formation. This process, combined with the transcriptional activation and DNA adduct formation of cytochrome P450 through hypomethylation of the aryl hydrocarbon

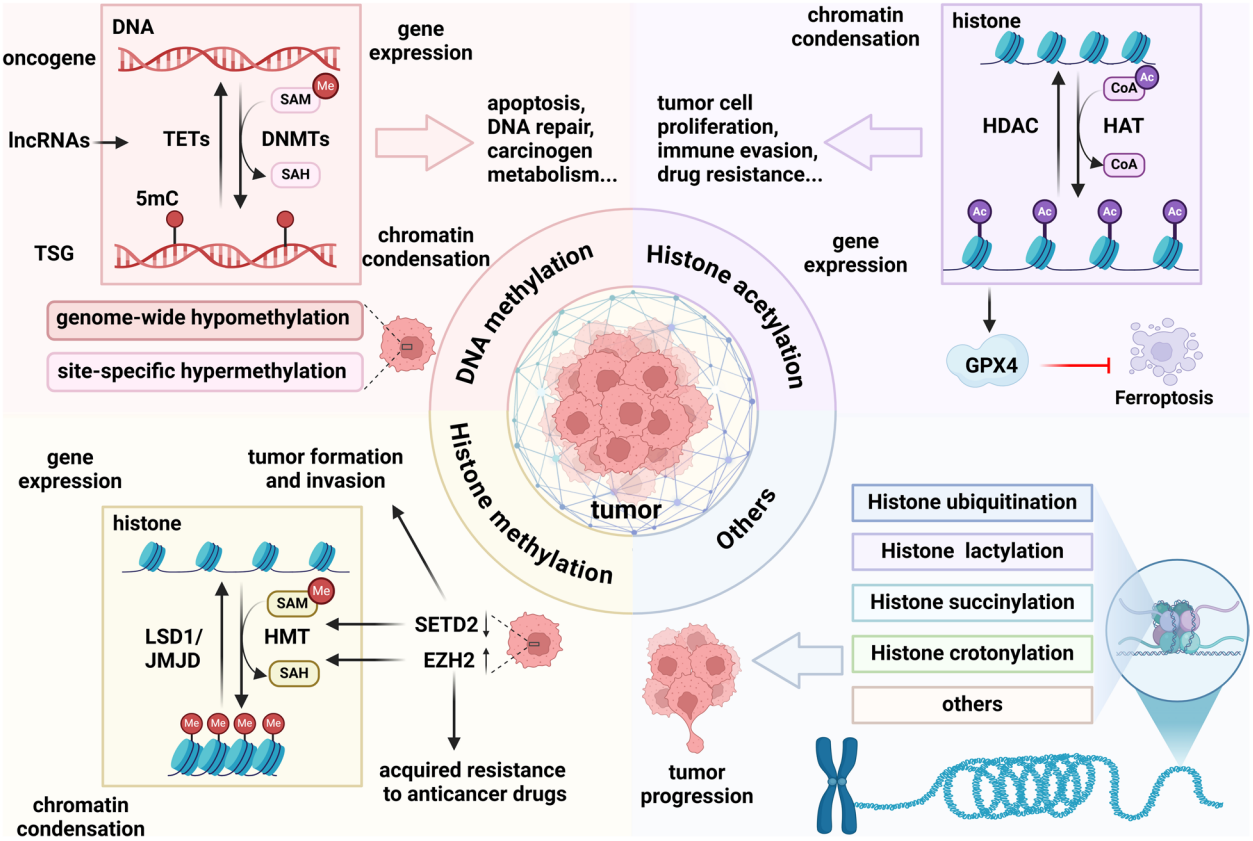

Fig. 2 Epigenomic alterations in tumors. DNA methylation, histone acetylation, and histone methylation are the three most common epigenomic modifications in tumors. Metabolites such as SAM and acetyl-CoA act as donors and participate in epigenomic modifications, which are mediated by related enzymes and are reversible. Methylation modifications cause chromatin to be highly helical, rendering it transcriptionally inactive, while acetylation modifications lead to nucleosome depolymerization, thereby promoting gene expression. Moreover, an increasing number of post-transcriptional modifications, including histone ubiquitination, lactylation, and succinylation, have been found to be implicated in tumor progression. Epigenomic alterations in tumors drive tumor proliferation, metastasis, and drug resistance by activating oncogene expression and silencing tumor suppressor gene transcription, as well as their interactions. (Me, methylation; SAM, S-adenosyl-L-methionine; SAH, S-adenosyl-L-homocysteine; lncRNAs, long non-coding RNAs; TETs, ten-eleven translocation family proteins; DNMTs, DNA methyltransferases; 5mC, 5-methylcytosine; Ac, acetylation; HDAC, histone deacetylase; HAT, histone acetyltransferase; GPX4, glutathione peroxidase 4; LSD1, lysine-specific demethylase 1; JMJD, Jumonji C domain-containing; HMT, histone methyltransferase; SETD2, SET domain containing 2; EZH2, enhancer of zeste homolog 2)

receptor repressor, suggests that both genetic factors and epigenomic alterations, together with their interactions, contribute to tumorigenesis [26]. While it is well-established that aberrant epigenomic modifications can serve as a conduit for carcinogen-induced gene mutations; however, it remains uncertain whether these epigenomic alterations can independently initiate malignancies. Long non-coding RNAs (lncRNAs) have been shown to either directly or indirectly recruit DNMTs and TETs to specific targets or modulate their expression and activity, thereby regulating DNA methylation and driving cancer cell proliferation, migration, and resistance to drugs [27]. Moreover, hypermethylation of TSGs, hypomethylation of oncogenes, and abnormal DNA methylation of other specific genes have been observed in various cancer types and are reversible, indicating their potential as biomarkers for screening, treatment monitoring, and prognosis [28–31]. Overall, aberrant DNA methylation patterns in tumor cells are prevalent but varied, and their underlying mechanisms require further investigation.

Histone acetylation

Different types of post-translational modifications (PTMs) influence histone-DNA interactions, with acetylation being the first and most extensively studied histone modification affecting transcriptional regulation. Histone acetyltransferases (HATs) catalyze the transfer of the acetyl group from the acetyl-CoA molecule to lysine residues in the N-terminal histone tails, facilitating chromatin structure relaxation and enhancing gene expression,

whereas histone deacetylases (HDACs) reverse histone acetylation, acting as repressors of gene expression [32]. In addition, crosstalk between lysine acetylation and other modifications, such as ubiquitination, tyrosination, and phosphorylation, plays a critical regulatory role in both physiological and pathological processes [33].

CREB-binding protein (CBP) and E1A-binding protein (p300) catalyze the acetylation of histone H3 lysine 27 (H3K27ac), a modification originally considered to function as a tumor suppressor. However, subsequent studies have revealed that overexpression of H3K27ac in cancer cells activates oncogene transcription and enhances the function of Tregs and myeloid-derived suppressor cells, thereby promoting cancer cell proliferation, immune evasion, and drug resistance [34]. HAT-mediated acetylation of the signal transducer and activator of transcription factor 3 (STAT3) has been shown to cause the silencing of TSGs, potentially contributing to the pathophysiology of peripheral T-cell lymphoma [35].

A recent study utilizing techniques such as single-cell RNA sequencing (scRNA-seq) analysis revealed that SET domain containing 2 (SETD2) deletion in patients with pancreatic ductal adenocarcinoma induces ectopic deposition of H3K27ac, resulting in transcriptome reprogramming of cancer-associated fibroblasts, altering tumor metabolic adaptation, and accelerating tumor progression [36]. Furthermore, the link between histone acetylation and cell death underscores its important role in diseases like cancer. In hepatocellular carcinoma (HCC), upregulation of HDAC1 and HDAC2 suppresses the expression of fructose-1,6-bisphosphatase and participates in apoptosis, which promotes HCC progression by reducing cell growth and inducing cell death [37]. H3K27ac-induced upregulation of glutathione peroxidase 4 (GPX4) restricts ferroptosis in cancer cells and attenuates the anti-tumor effects of cisplatin in non-small cell lung cancer (NSCLC), suggesting that histone acetylation may modulate cancer progression by regulating ferroptosis [38]. In summary, histone acetylation impacts tumor development through diverse molecular mechanisms, playing context-dependent roles in various environments.

Histone methylation

Histone methylation can occur at various sites on histones, most typically at lysine and arginine residues of histone H3, and it influences gene transcription depending on the specific residue modified, the degree of methylation, and other factors. Like other histone modifications, histone methylation is regulated by multiple positive and negative regulators, including a range of histone methyltransferases and demethylases [39]. Proper dynamic regulation of histone methylation is essential for embryonic development and organogenesis, while dysregulated methylation may induce human genetic diseases, cardiovascular diseases, and various cancers [39–41].

Histone methylation may induce tumors via specific signaling pathways, accelerate tumor growth in the presence of oncogenic factors such as viral infections, and assist tumors in evading immune surveillance through anti-apoptosis mechanisms [42]. Inactivating mutations in the histone methyltransferase SETD2 are frequently observed across various cancers. SETD2 serves as a tumor suppressor, and its loss facilitates tumor initiation and invasion [43]. Additionally, EZH2 promotes tumorigenesis, invasion, and metastasis by modulating H3K27 methylation, and its elevated expression has also been linked to acquired resistance to anticancer therapies [44]. However, studies have found that the carcinogenic effect of EZH2 in ovarian cancer may be independent of its catalytic activity [45]. In recent years, researchers have found the relationship between DNA and histone methylation in tumors. On the one hand, abnormal histone methylation modification and mutations can directly influence DNA methylation reprogramming, driving the initiation and progression of cancer. On the other hand, histone methylation markers in normal cells can predict aberrant DNA methylation associated with cancer [46]. In squamous cell carcinoma (SCC), inactivation of the histone H3K36 methyltransferase, nuclear receptor binding SET domain protein 1 (NSD1), leads to the loss of H3K36 dimethylation and an increase in H3K27 trimethylation (H3K27me3). This imbalance results in DNA hypomethylation, which in turn leads to innate immune gene silencing and decreased tumor immune infiltration [47]. Tumorigenesis is also significantly influenced by the interplay between histone acetylation and methylation. HDAC3 targets the H3K9ac/H3K9me3 transition, and its deactivation triggers hyperacetylation of H3K9, which increases the transcription of tumor-associated genes while impairing H3K9me3-mediated double-strand break repair [32]. Therefore, the role of the interaction between different epigenomic modifications in tumorigenesis and development warrants further investigation.

Others

Other distinct types of histone modifications include phosphorylation, adenylynylate, ubiquitination, lactylation, succinylation, N-acetylglucosamine glycosylation, prenylation, citrullination, cholesterylation, crotonylation, isomerization, and several novel PTMs [48]. These modifications exert more dynamic and flexible effects on chromatin structure and function, often acting synergistically to regulate gene expression and chromatin remodeling.

Ubiquitination is a vital and highly conserved PTM that plays a central role in endogenous protein degradation. Stressors like hypoxia can disrupt the balance between ubiquitination and deubiquitination in cancer cells, thereby influencing the regulation of signaling pathways associated with tumor metabolic reprogramming [49]. Histone H2B monoubiquitination enhances transcriptional elongation and participates in DNA damage repair. Given its tumor-suppressive functions, the absence of H2B monoubiquitination is frequently linked to the advancement of tumors [50]. Besides being the product of glycolysis, lactate has emerged as a hub in energy metabolism and a key signaling molecule. The lactate created by the "Warburg effect" performs as an epigenomic regulator to induce lactylation, which can directly or indirectly influence cancer progression [51]. This role of lactate in epigenetic regulation is an increasingly explored area of research, shedding light on its potential impact on tumor biology. Furthermore, the role of succinylation in tumorigenesis is context-dependent and appears to be closely tied to tumor energy metabolism. General control non-depressible 5 (GCN5)-mediated succinylation of H3K79 promotes gene expression and increases tumor cell proliferation, migration, and invasion, which is involved in liver cancer, human pancreatic ductal adenocarcinoma, and glioma. Meanwhile, sirtuin 5-mediated desuccinylation promotes the growth of various malignancies via several signaling pathways [52]. Lysine crotonylation has been implicated in the proliferation of HCC, with variations in crotonylation expression levels observed across different tumors, suggesting different effects in different tumors [53]. In general, increasing PTMs are being discovered, and their potential roles in tumor etiology and progression call for deeper exploration and discussion.

Crosstalk between tumor metabolic reprogramming and epigenomic alterations

Tumor cells undergo metabolic adaptations driven by intrinsic cellular factors and external stimuli, triggering metabolic reprogramming to support uncontrolled proliferation, which continues to evolve during tumor progression [54]. In addition to influencing immune cells within the TME, metabolites produced by tumor cells can directly regulate epigenomic modifications, further affecting tumor metabolism and other biological processes (Fig. 3). Understanding the role of epigenomics in tumor metabolism holds significant potential for advancing tumor diagnosis, treatment, and monitoring strategies.

Glucose metabolism

The TME regulates glucose absorption, transport, and aerobic and anaerobic metabolic pathways to meet the elevated energy and nutrient demands essential for tumor cell survival and proliferation, with the Warburg effect being the most common metabolic reprogramming. Tumor cells exhibit high glycolytic activity under hypoxic and aerobic conditions, leading to lactate accumulation. Oncogenes such as MYC, alongside key metabolic pathways like phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt), boost glucose uptake and glycolysis in tumor cells by activating transporters and metabolic enzymes, including glucose transporter 1 (GLUT1), phosphofructokinase-1 (PFK1), and lactate dehydrogenase A (LDHA) [55, 56]. Furthermore, enhanced glycolysis in cancer cells promotes tumorigenesis by inhibiting the function of tumor suppressor genes such as p53. p53 has been shown to reduce glucose uptake by directly inhibiting GLUT transcription, downregulate key glycolytic enzymes that impede further glucose metabolism, and restrict the conversion of pyruvate to lactate and its subsequent export, thereby inhibiting glycolysis under most conditions [57].

Epigenomic modifications, such as DNA methylation, affect critical glycolytic enzymes through various mechanisms, promoting tumor growth, metastasis, and medication resistance. In colon cancer, hypermethylation of the LDHB promoter boosts lactate synthesis, whereas hypomethylation of the hexokinase 2 (HK2) promoter increases HK2 expression, driving tumor progression [58]. The increased glycolysis and tricarboxylic acid (TCA) cycle metabolism observed in posterior fossa-group A ependymomas (PFAs) have been linked to H3K27ac enrichment at metabolic enzymes like HK2. Metformin suppresses the inhibitory effect of the overexpressed enhancer of zeste homologs inhibitory protein on H3K27me3 in PFAs, which inhibits TCA cycle metabolism and tumor growth [59]. Histone acetylation in various cancer cells is prevented by decreasing acetyl-CoA levels when HK activity is inhibited, highlighting the interrelationship between glycolysis and global histone hyperacetylation in cancer [60]. In addition to phosphorylation and acetylation, the dynamic O-linked N-acetylglucosamine of phosphoglycerate kinase 1 (PGK1) at threonine 255 enhances PGK1 enzymatic activity. This modification also facilitates translocation to mitochondria, where it impedes pyruvate utilization and inhibits oxidative phosphorylation (OXPHOS), thereby augmenting the Warburg effect and promoting tumor growth [61]. It has been shown that p300/CBP-mediated acetylation of H3K18 and H3K27 in HCC tissues elevated the expression of glycolysis-related metabolic enzymes. Inhibition of p300 using B029-2 effectively disrupts the metabolic

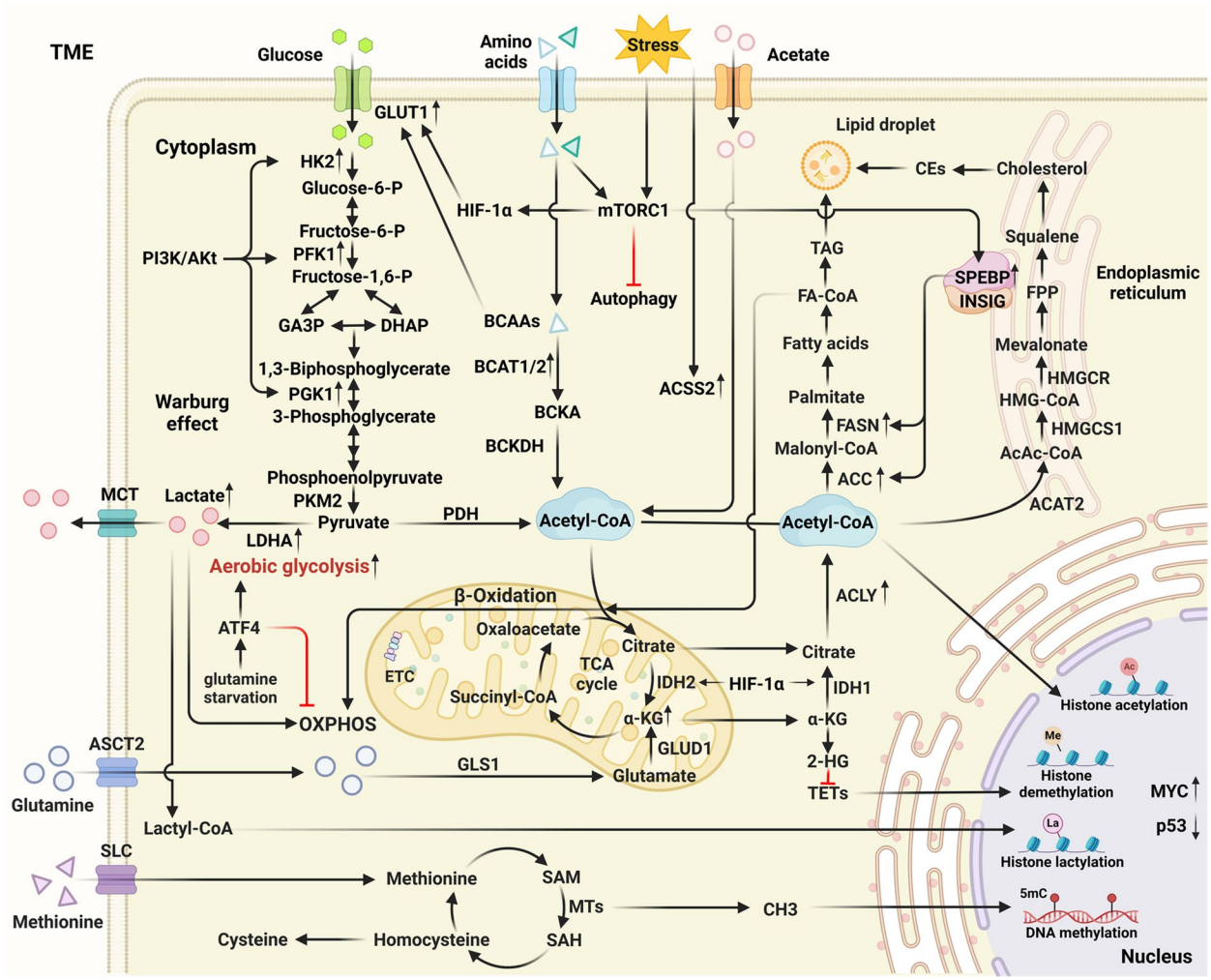

Fig. 3 Crosstalk between tumor metabolic reprogramming and epigenomic alterations. Tumor cells increase the uptake and metabolism of nutrients such as glucose, lipids, and amino acids by upregulating transporters and several metabolic enzymes. The Warburg effect rapidly provides energy to tumor cells and produces large amounts of lactate, which is metabolized to lactyl-CoA to drive histone lactylation. Some tumors rely on glutamine as a key source of energy, and glutamine depletion promotes aerobic glycolysis. Increased glutamine uptake promotes the production of α-ketoglutarate, which in turn affects histone methylation. The glycolytic product pyruvate and metabolites of branched-chain amino acids and acetate can synthesize acetyl-CoA, a key metabolite, which promotes histone acetylation and is further involved in the tricarboxylic acid cycle and lipid metabolism. Moreover, tumor cells increase uptake of methionine to promote the methionine cycle, generating SAM as a methyl donor for DNA and histone methylation modifications. At the same time, these epigenomic modifications affect gene expression of metabolism-related enzymes, thereby promoting metabolic reprogramming in tumors. (GA3P, 3-phosphoglyceric acid; DHAP, dihydroxyacetone phosphate; PKM2, pyruvate kinase isozyme type M2; MCT, monocarboxylate transporter; PI3K, phosphatidylinositol-3-kinase; Akt, protein kinase B; PDH, pyruvate dehydrogenase; TCA cycle, tricarboxylic acid cycle; α-KG, α-ketoglutaric acid; mTORC1, mechanistic target of rapamycin complex 1; IDH1/2, isocitrate dehydrogenase1/2; GLUD1, glutamate dehydrogenase 1; ETC, electron transfer chain; OXPHOS, oxidative phosphorylation; ASCT2, alanine-serine-cysteine transporter 2; GLS1, glutaminase 1; HIF-1α, hypoxia inducible factor-1α; BCAAs, branched-chain amino acids; BCAT1/2, branched-chain amino acid transaminase1/2; BCKA, branched-chain α-keto acid; BCKDH, branched chain ketoacid dehydrogenase; ACSS2, acetyl-CoA synthetase 2; FA, fatty acid; TAG, triacylglycerol; ACLY, ATP-citrate lyase; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; SREBP, sterol regulatory element binding protein; INSIG, insulin-induced gene; ACAT2, acetyl-CoA acetyltransferase 2; AcAc-CoA, acetoacetyl coenzyme A; HMGCS1, 3-hydroxy-3-methylglutaryl-CoA synthase 1; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; FPP, farnesyl pyrophosphate; CEs, cholesteryl esters; SLC, solute carrier family; SAM, S-adenosyl-L-methionine; SAH, S-adenosyl-L-homocysteine; MTs, methyltransferases; CH3, methyl; 5mC, 5-methylcytosine)

reprogramming of HCC cells, exerting anti-tumor effects [62]. Furthermore, in H3K27M mutant gliomas, several mechanisms lead to a reduction in total H3K27me3 levels, promoting enhanced glycolysis and TCA cycle metabolism, increased expression of key enzymes, and the maintenance of low H3K27me3 levels in H3.3K27m

cells, coinciding with elevated α-KG levels [63]. Hypoxic conditions further induce intracellular lactate production and increase histone lysine lactation in human breast cancer cells [64]. A recent study discovered that LDHA, which is highly expressed in tumor-resistant strains, enhances the lactylation of Nijmegen breakage syndrome protein 1 at lysine 388, increasing DNA repair abilities and leading to chemoresistance [65]. Additionally, histone H3K18 lactylation induces methyltransferase-like 3 transcription, which promotes immunosuppression of tumor-infiltrating myeloid cells within the TME characterized by high lactate levels, thus fostering a pro-tumor effect [66]. Therefore, epigenomic modifications in tumor cells are highly correlated with alterations in glucose metabolism, particularly increased aerobic glycolysis, which may serve as a key target for tumor metabolism therapy.

Most studies suggest that tumor cells preferentially rely on aerobic glycolysis as their primary metabolic pathway and avoid OXPHOS to compete with normal cells for glucose, reduce the toxicity of excessive reactive oxygen species (ROS) production, and fulfill the increased demands for other biosynthesis [67]. HIF-1α mediates the metabolic transition from OXPHOS to glycolysis under hypoxic conditions, and the interaction between lysine-specific demethylase 1 and HDAC2 is involved in the regulation of HIF-1α protein stability [68]. However, OXPHOS has been shown to provide cancer cells with ATP and plays an important role in macromolecular anabolism, with some tumors exhibiting a high dependency on OXPHOS for ATP production, rather than glycolysis [69]. The metabolic-epigenomic regulation of OXPHOS in malignancies remains insufficiently explored and warrants further investigation.

Lipid metabolism

In addition to serving as key components of biofilm structure, lipids play a critical role in energy storage, metabolism, and signaling, all of which are necessary for maintaining cellular homeostasis and tumor growth in the TME. As lipid mediators, Prostaglandins drive angiogenesis and chronic inflammation, thereby enhancing tumor progression and suppressing immune cell function [70]. Tumors overexpress lipid transporters and transcriptional regulators of adipogenesis, such as sterol regulatory element-binding protein 1 (SREBP1), which facilitate the uptake of fatty acid and cholesterol and lipid synthesis through various signaling pathways and epigenomic regulation. This dysregulation fosters metabolic crosstalk between TME and surrounding cells, providing energy to tumor cells and promoting tumor metastasis [71]. Furthermore, unsaturated lipids are essential nutrients for certain cancers to adapt and survive in hypoxic environments, with various regulators maintaining the balance of lipid saturation via non-canonical lipid metabolic pathways, preventing cellular stress and death [72]. Increased activity and expression of several lipogenic enzymes are pivotal for de novo lipogenesis in HCC, which contributes to tumor development, progression, and poor prognosis. Acetyl-CoA is converted to malonyl-CoA by acetyl-CoA carboxylase (ACC), which then produces palmitate and other fatty acid synthesis products via fatty acid synthase (FASN) [73]. It has been demonstrated that the tumor-activated stem cell regulator Akt and RAR-associated orphan receptor γ stimulate cholesterol biosynthesis, which is linked to the invasion of mutant TP53 [74]. Moreover, ferroptosis, induced by lipid peroxidation, results in an accumulation of lethal lipid peroxide, which can mediate and suppress antitumor immunity, influencing tumor development, invasion, migration, and resistance to treatment [75]. Overall, by modulating lipid metabolism, tumors fuel their growth and induce nutrient deprivation and the accumulation of metabolic toxicants, thereby creating an immunosuppressive microenvironment and enhancing their proliferation and metastasis.

Epigenomic alterations have an effect on tumor lipid metabolism via various mechanisms, thereby contributing to tumor growth. Promoter DNA hypermethylation in nasopharyngeal carcinoma suppresses the expression of solute carrier family 27 member 6, impairing long-chain fatty acid uptake and lipid storage in cancer cells, which promotes proliferation while inhibiting metastasis [76]. The histone demethylase Jumonji C domain-containing 3 (JMJD3) stimulates the expression of fatty acid oxidation (FAO) transcriptional regulators, including sirtuin 1 and peroxisome proliferators-activated receptors, by decreasing the H3K27me3 of FAO genes [77]. Prostate cancer is linked to interactions between increased lipid metabolism and epigenomic changes, such as Akt and acetyl-CoA synthetase 2 (ACSS2)-mediated histone acetylation generation and maintenance, as well as high-expression acetate-mediated histone acetylation, which increases FASN and ACC expression and promotes tumor cell survival [78]. A study on the immunometabolic phenotyping of clear cell renal cell carcinoma revealed that the M3 subtype, characterized by the lowest metabolic activity in fatty acid metabolism and glycolysis, alongside the highest degree of immune infiltration, demonstrated the highest level of DNA methylation, while the high metabolic status within the TME reduced immune cell infiltration [79]. Moreover, sterol regulatory element binding transcription factor 1 regulates cholesterol and fatty acid biosynthesis, with its overexpression in SCC cells being mediated by elevated levels of H3K27 acetylation, indicating its biological significance in SCC

proliferation and migration [80]. A study integrating transcriptomics, epigenomics, and 3D genomic structural information analysis revealed that the downregulation of overall H3K27me3 and H3K4me3 levels during trastuzumab resistance formation may be involved in driving the reprogramming of lipid metabolism, including arachidonic acid, prostaglandins, and unsaturated fatty acids [81]. Moreover, key enzymes in fatty acid metabolism, such as ATP-citrate lyase and acetyl-CoA carboxylase, are often upregulated in certain cancers and may influence histone acetylation by modulating acetyl-CoA levels. Therefore, DNA methylation, histone acetylation, and histone demethylation play an important role in the metabolic reprogramming of tumor lipids and may serve as potential targets for inhibiting tumor growth by regulating lipid metabolism.

Amino acid metabolism

In the TME, essential and non-essential amino acids are utilized as precursors for synthesizing biological macromolecules and significant metabolites that drive tumor cell proliferation, invasion, immunological escape, as well as immune cell activation and anti-tumor responses. Glutamine, the most abundant amino acid in blood and muscle, serves as a nitrogen donor and is progressively converted to α-KG to participate in the TCA cycle. In renal cell carcinoma, cancer cells utilize glutamine to alleviate oxidative stress, and increased tryptophan metabolism generates immunosuppressive metabolites that promote cancer cell survival [82]. Moreover, the mechanistic target of rapamycin complex 1 (mTORC1)-mediated glutamine absorption has been revealed to decrease glycolysis-related gene expression and glucose metabolism in cancer cells [83]. Glutamine deprivation, resulting from elevated consumption and restricted blood supply, increases the expression of DNA damage-induced transcript 3 via ATF4-mediated transcription, promotes glycolysis, and impairs electron transfer chain (ETC) function, thereby balancing glycolysis with OXPHOS and improving the adaptability of cancer cells to metabolic stress [84]. In certain cancers, high glycolysis promotes glutamine addiction to sustain mitochondrial function under conditions of pyruvate scarcity, potentially leading to CpG hypermethylation [60]. Silencing the amino acid transporter solute carrier family 7 member 11 in breast cancer cells elevates H3K9 methylation at the promoter of transmembrane glycoprotein mucin 1, potentially disrupting glutathione production during ferroptosis [85]. As an energy donor and antioxidant, glutamine interacts with glycolysis and participates in epigenomic regulation, making it an indispensable dependence for many tumors.

Methionine performs diverse physiological roles, including involvement in redox reactions, polyamine production, and conversion to SAM, which provides methyl groups for other methylation reactions [86]. DNA hypermethylation of the key methyl metabolism genes in urothelial carcinoma inhibits gene expression, resulting in a reduced ratio of SAM to S-adenosyl-L-homocysteine and genome-wide DNA hypomethylation [87]. Downregulation of adenosylhomocysteinase, for example, promotes tumourigenesis by inhibiting p53-induced cell cycle arrest and inducing DNA damage [88]. Furthermore, the methionine cycle, together with the folate cycle and the transsulphuration pathway, constitutes one-carbon metabolism, generating metabolites such as SAM, nucleotides, and glutathione while contributing to energy homeostasis, which is essential for tumor growth and progression [89, 90]. Tumor p53 deficiency mediates dysregulation of the methionine uptake transporter Solute Carrier Family 43 Member 2, a key player in one-carbon metabolism, leading to reduced SAM levels, loss of H3K9me, R-loop-associated replication stress, and chromosomal instability [91]. Serine hydroxymethyltransferase-2 catalyzes the synthesis of activated one-carbon units and SAM, which induces the methylation of phosphatase and tensin homolog genes upon AKT activation, resulting in tumor cell metastasis [92]. As an essential amino acid, dietary methionine intake affects the regulation of DNA and histone methylation in tumors to a certain extent, making it a potential and controllable therapeutic strategy.

Leucine, isoleucine, and valine, the three branched-chain amino acids (BCAAs), serve as biomarkers for malignancies, with metabolic alterations influencing the characteristics of a wide range of tumors. In hepatocellular carcinoma patients, inhibition of BCAA catabolic enzyme expression increases circulating BCAAs, and high dietary consumption of BCAAs is related to an increased risk of cancer mortality, probably due to the overactivation of mTOR pathway [93]. BCAAs function as a source of acetyl-CoA and regulate its intracellular distribution, impacting epigenomic landscapes, particularly histone acetylation [94]. High expression of the branched-chain amino acid transaminase 1 (BCAT1) in acute myeloid leukemia diminishes α-KG levels, thereby reducing the activity of histone and DNA demethylases and promoting tumor development [95]. However, another study has demonstrated that metabolic reprogramming of upregulated BCAT1 and BCAA in NSCLC cells facilitated α-KG-dependent demethylation of histone H3K27, resulting in transcriptional derepression of glycolysis-related genes, thus improving glycolysis and promoting tumor progression and drug resistance [96]. BCAT2, which is overexpressed in melanoma, increases the expression of FASN and ATP-citrate lyase (ACLY) via p300-dependent

histone acetylation, enhancing tumor cell proliferation and metastasis [97]. Generally, upregulated BACCs and related metabolic enzymes in tumor cells affect epigenomics and other metabolic pathways through metabolites and multiple signaling pathways, thereby promoting tumor progression. Therefore, inhibition of the BCAA metabolism may be a potential adjuvant therapy.

Furthermore, the reliance on amino acids and the expression of metabolic enzymes differ across tumor types [98]. Other amino acids, such as arginine, also influence tumor growth through metabolic reprogramming, and the relationship between these amino acids and epigenomic regulation is expected to be further investigated [99, 100].

Metabolism and epigenomics cooperate to regulate the activation, differentiation, and function of immune cells

Metabolic competition between tumors and immune cells leads to nutrient deprivation and microenvironmental acidosis, which hinders the function of immune cells. Various immune cells sustain proliferation, differentiation, and effector functions through metabolic reprogramming [101]. Metabolites not only provide energy, but also act as signaling molecules that regulate immune and epigenomic pathways, modulating the activity of immune cells such as T cells and macrophages (Fig. 4) [15, 102]. As metabolic reprogramming of immune cells is closely linked to epigenomic alterations, regulating epigenomic modifications through immunometabolism may provide novel therapeutic insights for cancer treatment.

Innate immune cells

Natural killer cell

Upon being activated by antigen-presenting cells, natural killer (NK) cells regulate adaptive immune responses and other immunological pathways through cytotoxicity and cytokine production, including interferon γ (IFN-γ). In response to restimulation within the TME, NK cells have been proven to exhibit more selective anti-tumor cytotoxicity and differentiate into memory NK cells [103]. The innate immune memory of memory NK cells, referred to as "trained immunity," improves the probability of immune-related gene transcription via several stable and lasting epigenomic alterations. This process is closely linked to metabolism, which provides essential substrates and a steady energy supply [102]. NK cells have been shown to develop memory-like properties following systemic inflammation. The identification of a potential enhancer for H3K4me1 markers at the ifng locus suggests that the memory and protective functions of NK cells are regulated by histone methylation [104]. However, the relationship between this process and metabolism remains unclear.

NK cells rely on c-Myc signaling to promote glycolysis and mitosis, which facilitate long-term anti-tumor responses. However, a glutamine-deficient TME suppresses c-Myc expression, reduces OXPHOS and glycolytic activity, and impairs anti-tumor function in NK cells [105, 106]. Lipids also modulate the anti-tumor activity of innate immune cells, specifically cytotoxic NK cells. Increased lipid uptake and storage in NK cells impair

(See figure on next page.)

Fig. 4 Epigenomic and metabolic reprogramming of immune cells. **A** Nutrient deprivation and oxidative stress in the TME inhibit glucose uptake and glycolysis in natural killer cells, and lipid peroxidation further inhibits glucose metabolism and OXPHOS, resulting in weakened anti-tumor effects. For survival and adaptation, natural killer cells undergo metabolic reprogramming akin to the Warburg effect of tumor cells and inhibit the fatty acids β-oxidation to enhance cytotoxicity. **B** Enhancements in glucose metabolism within M1 macrophages lead to increased acetyl-CoA levels, which subsequently drive histone acetylation and promote the expression of pro-inflammatory cytokine genes. Metabolites and cytokines induce polarization of M2 macrophages with histone acetylation and histone demethylation. Notably, glutamine depletion in the TME can promote anti-tumor immunity by stimulating the release of IL-23. **C** The ability of dendritic cells to present antigens and effectively activate T cell function is impaired by lactate and lipid accumulation, acidification, and amino acid deficiency resulting from tumor metabolism. Enhanced lipid metabolism in DC leads to aberrant lipid accumulation and acetyl-CoA depletion, impairing antigen cross-presentation and histone acetylation in dendritic cells. **D** Methionine deprivation and altered ion concentrations in the TME affect the epigenomics of CD8 + T cells. Metabolism-induced endoplasmic reticulum stress promotes T-cell exhaustion, leading to impaired cytotoxic function, accompanied by upregulation of markers such as programmed cell death protein 1. Regulatory T cells harness the lactate and fatty acids from tumor cells to support their survival and immunosuppressive functions. Additionally, regulatory T cells trigger TCA and promote Foxp3 expression through acetyl-CoA to accommodate low-glucose, high-lactate TME and mediate differentiation and development. **E** Depletion of nutrients in the TME suppresses B cell activation and function. B cells exhibit different metabolic profiles at various stages of activation. Activated B cells and plasma cells exert a dual role as they secrete antibodies to kill tumors while enhancing M2 macrophage function to inhibit the activity of CD8 + T cells. (OXPHOS, oxidative phosphorylation; IFN-γ, interferon γ; STAT3, signal transducer and activator of transcription 3; TLR4, toll-like receptor 4; Ac-CoA, acetyl-CoA; IL-4, interleukin 4; DC, dendritic cell; MHC-I, major histocompatibility complex-I; TCR, T cell receptor; p38-MAPK, p38 mitogen-activated protein kinase; ER, endoplasmic reticulum; PD1, programmed cell death protein 1; LAG-3, lymphocyte activation gene-3; TIM-3, T cell immunoglobulin domain and mucin domain-3; TGF-β, transforming growth factor β; GABA, γ aminobutyric acid)

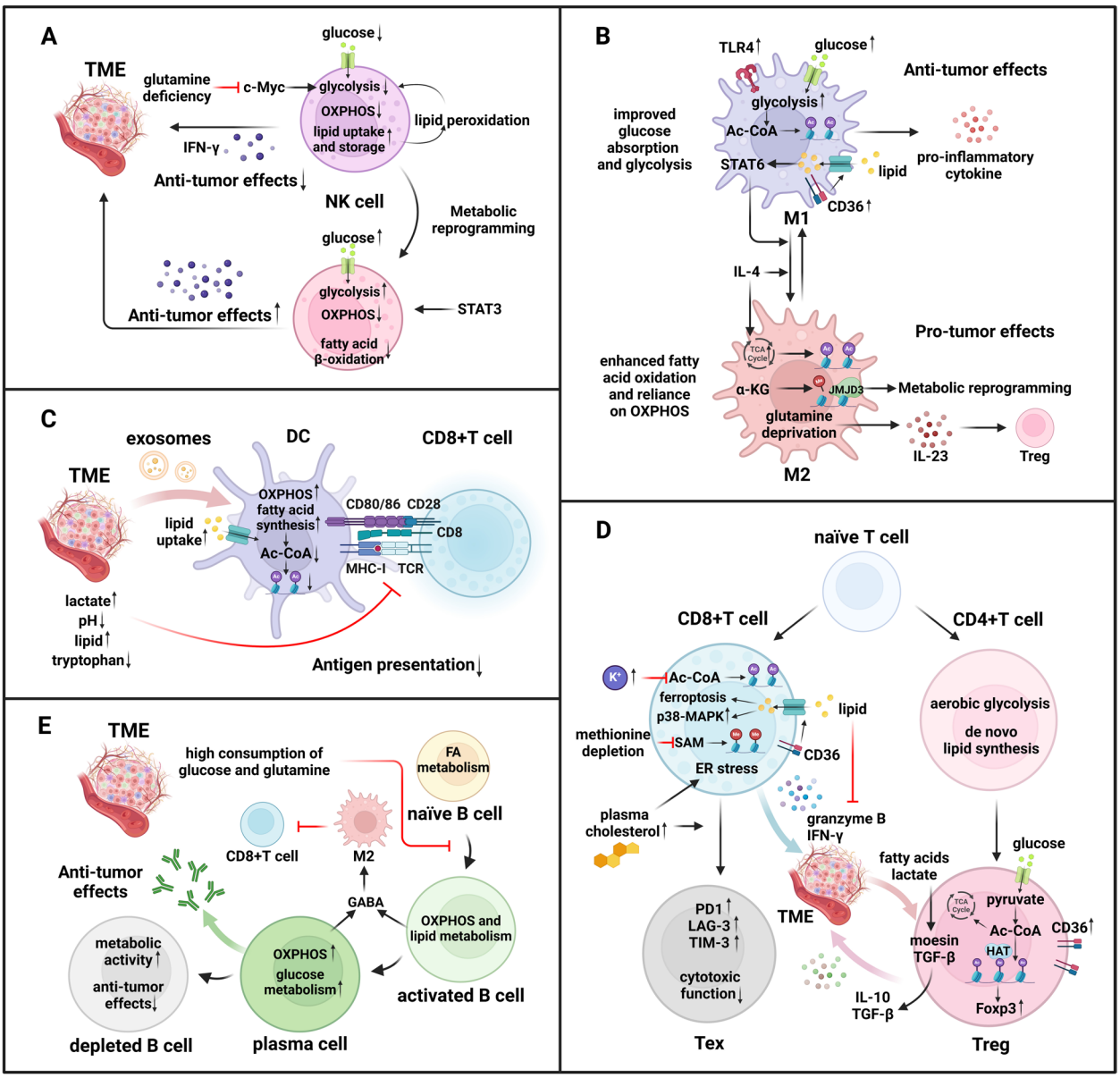

Fig. 4 (See legend on previous page.)

their cytotoxic effects against tumor cells, which may be linked to the disruption of lipid-derived signaling molecules released by tumor cells to the TME [72]. In breast cancer models, lung-resident mesenchymal cells (MCs) cause lipid accumulation during cancer-related inflammation and transport these lipids to tumor cells and NK cells via exosome-like vesicles. Tumor cells use MC-derived lipids to enhance their proliferation and metastasis. In contrast, NK cells store lipids and exhibit lower glycolytic capacity, leading to decreased cytotoxicity and suppression of tumor metastatic colonization [107]. The TME has been found to inhibit glucose metabolism in NK cells via lipid peroxidation-related oxidative stress, whereas NK cells driven by IL-21 signaling via signal transducer and activator of transcription 3 (STAT3) expand and mimic the Warburg effect observed in tumor cells, characterized by upregulation of glycolysis and downregulation of OXPHOS, allowing them to maintain metabolic fitness and tumor-killing capacity in the TME [108]. However, in mice with high serum cholesterol levels, cholesterol buildup in NK cells may improve their cytotoxicity and activate immune signaling against HCC [109]. Nutrient deprivation and metabolite accumulation in the TME weaken the cytotoxicity of NK cells by

influencing their metabolism, while NK cells enhance their adaptation to the environment through metabolic reprogramming. This suggests that promoting the Warburg-like metabolic shift in NK cells may be a promising strategy for immunotherapy. Although there has been little research on epigenomics in the metabolic reprogramming of NK cells, we believe that more studies will be undertaken in this area due to the significant intersection between metabolism and epigenomics.

Macrophage

Macrophages, widely distributed throughout the body, undergo different types of polarization in response to stress and can switch between them. M1 macrophages possess potent anti-tumor and apoptotic cell and necrotic tissue clearance capacities, exhibiting enhanced glucose absorption and glycolysis as metabolic features. On the contrary, M2 macrophages promote tumor growth, immunosuppression, and anti-inflammatory responses, characterized by enhanced fatty acid oxidation and reliance on OXPHOS [60].

Both metabolic reprogramming and epigenomics are crucial for macrophage activation and differentiation. As innate immune cells, macrophages modulate gene accessibility through epigenomic modifications, facilitating gene transcription to maintain innate immune memory and enhance immune responses [110]. Inhibition of mevalonate production leads to H3K4me3 deposition in tumor necrosis factor promoter-associated regions, ultimately reducing tumor necrosis factor production. Therefore, the cholesterol synthesis pathway involving mevalonate is critical for the induction of trained innate immunity [111]. Lipopolysaccharide-stimulated macrophages upregulate the methionine cycle to promote SAM production, support pro-inflammatory macrophages and promote interleukin-1β production via H3K36me3 [112]. Histone lysine lactation has been implicated in the regulation of gene expression during M1 macrophage polarization [64]. A metabolic monitoring study found that activating toll-like receptor 4 boosted glycolysis and the TCA cycle in macrophages, which elevated acetyl-CoA levels and increased histone acetylation [113]. Histone modifications, such as H3K4 methylation and H3K27ac, have been identified in trained macrophages, resulting in chromatin opening at the promoter region of pro-inflammatory cytokine genes, which may be relevant to metabolic changes in these cells [114]. In cancer models, myeloid cells, particularly macrophages, demonstrate a greater capacity for glucose uptake within the TME than cancer cells, which is likely associated with high levels of phosphorylated ribosomal protein S6-activated mTORC1 pathway [83]. M1 macrophages initiate the M1 to M2 transition and employ lactate as a direct substrate for epigenomic lactation in the early stages of cancer development. The polarization of M2 macrophages, induced by IL-4, is accompanied by elevated TCA activity due to metabolic reprogramming, which promotes histone acetylation and immunosuppression [115]. Moreover, glutamine catabolism generates α-KG, which activates M2 macrophages and promotes metabolic reprogramming via JMJD3-dependent demethylation of H3K27 [116]. Histone H3 lysine-27 methylation is known to regulate M2 polarization, but the precise mechanistic pathways linking epigenomic regulation to specific metabolic processes remain poorly understood [117]. Therefore, epigenomics plays a significant role in the activation and differentiation of macrophages in innate immunity and tumors, which may be closely related to metabolism.

Tumor-associated macrophages (TAMs) enhance their glucose consumption and catabolic capacity through metabolic reprogramming, as well as promote tumor proliferation and metastasis and inhibit anti-tumor immunity through endogenous regulation within TAMs and control of their interactions with other cells in TMC [118]. Single-cell and spatial transcriptomic analysis in NSCLC revealed that reprogramming of TAM within the TME facilitates cholesterol efflux and iron output, increasing the availability of neutral lipids in tumors and tumor progression [119]. CD36 has been reported to be highly expressed in TAMs to promote lipid uptake and accumulation, while FAO replaces glycolysis for energy, resulting in STAT6 activation and regulation of TAM differentiation and pro-tumor functions [120]. Additionally, glutamine and its conversion to α-KG promote M2-like macrophage activation. In clear cell renal cell carcinoma, local glutamine depletion stimulates IL-23 release from macrophages, enhancing the immunosuppressive role of Tregs in the TME [121]. Consequently, metabolism-induced activation and differentiation of TAMs promote their immunosuppressive activity and tumor progression through multiple pathways.

Dendritic cell

Dendritic cells (DCs) recognize and capture antigens, differentiate into specialized antigen-presenting cells, and activate naïve T cells to initiate specific immune responses [122]. Epigenomic modifications critically influence the development and activation of DCs by regulating gene expression. For example, variations in inhibitory H3K27me3 levels at the CCR7 locus have been observed in DCs with differing migratory abilities, indicating that epigenomic modifications regulate the migration capacity of distinct DC subsets [123]. Glucose metabolism and lipid metabolism also play crucial roles in regulating the function of DCs and their subsets [124].

Aerobic glycolysis serves as a metabolic marker of activated DCs, forming a positive feedback loop with a stimulator of interferon gene signaling to enhance anti-tumor function [125]. Aberrant fatty acid synthesis leads to lipid accumulation and acetyl-CoA depletion, impairing antigen cross-presentation and histone acetylation in DCs, thereby reducing immune gene expression and compromising their ability to activate CD8 + T cells [126].

Lactate and lipid accumulation, tryptophan deficiency, and other factors in the TME promote metabolic reprogramming of DCs, limiting their immune activity and contributing to tumor progression. The accumulation of lactate in the TME inhibits the activation-related metabolism of DCs and creates an acidic environment, which impairs the antigen uptake capacity of DCs and the stability of antigen-major histocompatibility complex-I complexes [127]. Fatty acids delivered by tumor-derived exosomes induce the expression of peroxisome proliferator-activated receptor αin DCs, resulting in enhanced lipid metabolism and mitochondrial OXPHOS, subsequently leading to DC dysfunction [128]. FASN activation in tumor cells and the increased expression of lipid uptake receptors on tumor-infiltrating DCs lead to abnormal lipid accumulation, inhibiting T cell function and promoting immune evasion [124, 129]. Recently, an in situ nanovaccine that regulates lipid metabolism in tumor-infiltrating DCs has been developed to induce their specific recognition of tumor antigens and enhance their cross-presentation ability [130]. In addition, several studies have shown that HDAC and SAM are involved in critical processes such as DC differentiation, development, and antigen presentation, highlighting the significant role of epigenomics in DC-mediated anti-tumor immunity [131–134]. However, research on the crosstalk between epigenomics and DC metabolism remains limited, which warrants further exploration.

Adaptive immune cells

T cell

As an essential component of the immune response against tumors, CD8 + T cells induce apoptosis in tumor cells through specific recognition and binding, followed by the release of cytotoxic molecules, including granzyme B and perforin. Precursor T cells, upon antigen stimulation, differentiate into memory CD8 + T cells and exhausted T cells [135]. Memory CD8 + T cells are primed for a secondary immune response upon re-exposure to the antigen. In contrast, exhausted T cells suffer from impaired cytotoxic activity due to metabolite deprivation and chronic antigen stimulation within the TME and are overexpressed in depletion-related genes such as programmed cell death protein 1 [136]. The increase of depolarized mitochondria due to hypoxic stress and nutrient scarcity may influence T cell differentiation in response to metabolic damage via epigenomic reprogramming [137].

The balance between glycolysis, OXPHOS, and FAO plays a crucial role in regulating T cell development and function. Like tumor cells, T cells undergo rapid metabolic reprogramming following antigen activation, with the primary energy supply mode shifting from OXPHOS to aerobic glycolysis. This metabolic shift enables rapid ATP production and provides key intermediates necessary for cell proliferation and enhanced function [66]. However, it has been proposed that increased glycolytic activity impairs the function and development of memory CD8 + T cells, driving their conversion into effector T cell phenotypes and subsequent depletion, which ultimately weakens anti-tumor efficacy [138]. Inactivation of GLUT1 impairs glycolysis and promotes OXPHOS pathways, resulting in the accumulation of ROS, which enhances CTL-mediated bystander killing and promotes tumor cell death [139]. FAO, mediated by several signaling pathways, increases the lifespan of memory CD8 + T cells while dampening the effector activity of CD8 + T cells [15]. Moreover, elevated extracellular potassium levels in the TME cause acetyl-CoA depletion and reduced histone acetylation in cytotoxic T cells, which changes their metabolic profile [140].

CD8 + T cell exhaustion is frequently accompanied by aberrant metabolic and epigenomic alterations, as well as diminished proliferative potential and a loss of anti-tumor immune function [141]. High plasma cholesterol levels disturb T cell homeostasis and induce endoplasmic reticulum stress. CD36-mediated lipid absorption in CD8 + T cells triggers ferroptosis and activates the p38-MAPK pathway, resulting in impaired CD8 + T cell function and subsequent depletion [142]. Excess fat intake reduces the synthesis of cytokines like granzyme and IFN-γ, leading to the depletion of CD8 + tumor-infiltrating lymphocytes (TILs). It also limits the activation of CD4 + T helper cells by decreasing autophagy, which promotes tumor growth and metastasis [70]. Moreover, reprogramming the methionine recovery mechanism induces the accumulation of metabolites such as SAM and 5-methylthioadenosine in HCC, promoting T cell exhaustion in the TME and impairing immune function by affecting histone methylation [143]. Tumor cells compete with CD8 + T cells for methionine, leading to methionine depletion in T cells and reduced levels of SAM and H3K79 dimethylation. The loss of H3K79 dimethylation disrupts STAT5 transcription and signaling, thereby impairing T cell activation and anti-tumor immunity [144]. Interestingly, the accumulation of acidic metabolic byproducts in the TME has been found to impair methionine uptake and metabolism by downregulating methionine transporters

in T cells, affecting the deposition of H3K27me3 at gene loci associated with T cell stemness, which improves T cell stemness and enhances resistance to T cell exhaustion [145]. Therefore, inhibiting excessive lipid metabolism and improving methionine utilization may reduce T cell exhaustion, and metabolic therapies targeting T cells require further investigation.

Like cytotoxic CD8 + cells, CD4 + effector T cells, including T helper cell 1 (Th1), Th2, and Th17, primarily rely on aerobic glycolysis, while de novo lipid synthesis stimulates the proliferation of effector T cells [146]. Metabolomic and transcriptomic analyses have revealed that GLUT3 regulates inflammatory cytokine production in pathogenic Th17 via histone acetylation of glycolysis-related genes, promoting Th17 cell differentiation and function [147]. Methionine deprivation-mediated reduction of H3K79me2 downregulates adenosine activated protein kinase in CD4 + T cells, which promotes programmed cell death protein 1 expression and impairs antitumor immunity [148]. Multiple metabolites affect CD4 + T cell differentiation and function by modulating DNA and histone methylation, highlighting a relationship between metabolism and epigenomic alterations.

Tregs, a distinct lineage of CD4 + T cells, play a crucial role in maintaining immune tolerance and homeostasis. However, they can also impair immune surveillance in cancer and suppress anti-tumor immune responses by producing immunosuppressive factors and inhibiting the function of antigen-presenting and effector T cells [149]. Metabolism-related epigenomic modifications regulate the generation, development, and maintenance of Tregs by interacting with immunological signals [150].

Lactate and fatty acids produced by tumor and stromal cells serve as energy sources for Tregs, supporting their survival and immunosuppressive functions. Lactate has been shown to modulate Treg cell formation, promote their activity and stability, and boost signaling of moesin and transforming growth factor β receptors through lactation of lysine 72 in moesin [151]. Moreover, Lactate may increase gene transcription by inhibiting HDAC, linking the metabolism of Tregs to epigenomics [152]. Tregs can convert pyruvate to acetyl-CoA to activate the TCA cycle, enabling them to thrive in the low-glucose, high-extracellular lactate TME [153]. In addition, Tregs in tumor tissues use lipid metabolism as a supplemental metabolic pathway, which is reflected in the enrichment of lipid metabolism-related genes and the significant upregulation of several fatty acid-binding proteins and CD36 [154]. Acetyl-CoA, derived from glucose and lipid metabolism, promotes the differentiation of Tregs by regulating HAT activity and increasing H3K27ac levels in the forkhead box protein P3 (Foxp3) promoter region [155]. The upregulation of GSH and indoleamine 2,3-dioxygenase promotes survival and maturation of Tregs in the TME, leading to weakened antitumor immunity, indicating the crucial role of amino acid metabolism reprogramming in regulating Treg function within the TME [156, 157]. Glutamate and IDH affect the methylation of the Foxp3 gene locus through 2-HG, thereby regulating Treg cell development [155, 158]. It has been found that α-KG enhances OXPHOS and methylation of the Foxp3 gene, resulting in reduced Treg production [159]. Tumor metabolism creates a conducive environment for Tregs, enabling their survival and function. Reducing the accumulation of metabolic toxicants and regulating epigenomic modifications may be effective strategies to weaken the immunosuppressive effects of Tregs.

B cell

B cells play a crucial role in anti-tumor immunity by presenting antigens, producing antibodies to drive humoral immune responses, and secreting cytokines that modulate immune cell activity [160]. Naïve B cells rely on FA as their primary energy source, whereas activated B cells enhance OXPHOS and lipid metabolism to support rapid proliferation and antibody secretion [146].

Glutamine, along with adequate glucose flux and metabolism, is essential for normal B cell development, proliferation, and the humoral immune responses triggered by antibodies and antigens. In the TME, high glucose and glutamine consumption in tumor cells can inhibit B cell function [161]. Plasma cells in HCC tissues exhibit much higher OXPHOS and glucose metabolism activities than activated B cells, possibly contributing to their enhanced tumor-killing capacity. However, in depleted B cells, tyrosine-induced metabolic shifts serve more for cellular adaptation and survival rather than enhancing their immune functions. These B cells exhibit lower effector functions and the downregulation of metabolism-related signaling pathways, but paradoxically, higher levels of overall metabolic activity [162]. Moreover, activated B cells have also been discovered to upregulate glycolysis and OXPHOS to compete with T cells for glucose and oxygen and generate lactate, reducing T cell immune surveillance function, cytokine generation, and T cell proliferation, ultimately promoting tumor progression [163]. Activated B cells and plasma cells synthesize and secrete glutamate-derived γ aminobutyric acid, which promotes the development of anti-inflammatory macrophages. This inhibits the activity of CD8 + T cells and the secretion of IL-10, resulting in enhanced tumor growth [164]. Therefore, activated B cells act as a double-edged sword in the TME, playing different roles under different metabolic conditions.

B-cell-derived tumors are closely associated with epigenomic and metabolic interactions. In Burkitt lymphoma, the Epstein-Barr virus (EBV) elevates the level of amino acid transporters and the MYC oncogene, remodels metabolic pathways in infected B cells to increase methionine input and metabolism, and regulates DNA and histone methylation associated with tumor immune escape [165]. EBV has been shown to regulate viral oncoprotein expression via the epigenomic pathways of germinal center B cells, with DNMT1-mediated DNA methylation playing a pivotal role in suppressing the expression of highly immunogenic latent membrane proteins [166]. Epigenomic alterations in multiple myeloma, including global DNA hypomethylation and the dysregulation of DNA methylation-modifying enzymes, have been linked to tumor initiation, progression, and poor prognosis. However, the potential relationship between these epigenomic alterations and the metabolic reprogramming of B cells remains to be explored [167].

Methodologies contributing to the study of immunometabolism and epigenomics

Research into the intricate interplay between tumor immunometabolism and epigenomics is still in the development stage, yet its significance and necessity are undeniable. The heterogeneity of immune cell phenotypes, the dynamic nature of cellular metabolism, tissue specificity, and the high dependence on the local environment have posed substantial challenges to advancing studies in tumor immunometabolism [168]. However, the advent of innovative methodologies to analyze tumor immunometabolism and epigenomics offers a robust foundation to address these future research obstacles.

Classical approaches

As a bridge between the micro and macro, nuclear magnetic resonance-based and mass spectrometry-based metabolomics enable qualitative and quantitative analysis of small molecule metabolites within specific cells or organisms, which are instrumental in immunological research, track changes in tumor metabolism and predict response to tumor treatment [169, 170]. Untargeted metabolomics is unbiased for the detection of metabolites in samples with high throughput but limited sensitivity, while targeted metabolomics provides precise quantification of specific metabolites to produce more sensitive data with narrower metabolite coverage [171]. A study combining metabolomics with confocal imaging revealed that inhibiting ACC activity promoted FAO and enhanced CD8 + T cell immunity against tumors by reducing the lipid droplet accumulation [172]. Additionally, other mass metabolic analysis methods, such as extracellular flux analysis and fluxomics, and techniques like flow cytometry, mass spectrometry, and clustered regularly interspaced short palindromic repeats screening are extensively employed in immunometabolic research, and their integration with other molecular biology techniques offers innovative avenues for advancing the field [168].

However, these methods possess inherent limitations that cannot be overlooked. For example, the difference between in vivo and in vitro environments results in immune cell metabolism in culture systems failing to accurately mirror in vivo conditions. Moreover, bulk measurement techniques, which assess the average state of cell populations, lack the resolution to investigate the spatiotemporal dynamics of immunometabolism [171]. Consequently, the development of novel metabolic profiling approaches and refined cell isolation techniques is imperative to address these shortcomings.

Emerging techniques

The advent of single-cell sequencing technology has helped us to accurately identify cell types and functions, analyze metabolic profiles, and decipher the immune microenvironment within tumors. This technology has driven significant advancements in fields such as epigenomics, proteomics, and metabolomics. However, limitations like result inaccuracies and poor reproducibility persist [173]. Among these techniques, scRNA-seq stands out as a revolutionary molecular tool, offering high-resolution measurement of gene expression at the individual cell level. Compared to bulk transcriptional analysis, scRNA-seq enables simultaneous transcriptomic profiling of numerous single cells, allowing for the assessment of diverse cell types, states, and functions within cell populations. This capability not only sheds light on cellular heterogeneity but also facilitates the identification of rare or novel cell types and provides insights into cellular dynamics during tumor progression [174]. Recently, an increasing number of studies have revealed the characteristics of tumor immunometabolism and epigenomics through scRNA-seq. For instance, scRNA-seq was employed to investigate the composition, distribution, phenotype, function, and metabolic profile of B cell subsets in HCC mouse models, revealing distinct metabolic differences and alterations among these subsets [162]. In pancreatic tumors, scRNA-seq identified a lipid-rich subset of cancer-associated fibroblasts, highlighting the link between fibroblast heterogeneity, epigenomic dysregulation in tumor cells, and their metabolic interactions [36]. Additionally, an integrated analysis of scRNA-seq and metabolomics revealed that obesity promotes increased fat uptake by tumor cells while reducing fatty acid utilization by CD8 + T cells, leading to impaired anti-tumor immunity and enhanced tumor

growth [175]. The widespread use of scRNA-seq in tumor metabolism has solidified its pivotal role, and its integration with other technologies has allowed them to compensate for their inherent shortcomings to offer a more comprehensive understanding of tumor metabolism and epigenomics.

However, scRNA-seq is unable to capture the diverse and dynamic chromatin landscape that regulates gene expression, which can be addressed by single-cell assay for transposase-accessible chromatin using sequencing (scATAC-seq). Mechanistically, the epigenomic state of cells drives different transcriptional programs by modulating chromatin accessibility. scATAC-seq enables differential accessibility analysis of single-cell epigenomic data by sequencing DNA fragments from open chromatin regions, revealing potential transcription factor binding sites, regulatory elements, and their activity patterns [176, 177]. A study integrating scRNA-seq and scATAC-seq data demonstrated that combined single-cell epigenomics and transcriptomic analyses robustly revealed the metabolic pathways mediating cancer cell-TME communication and highlighted the interplay between epigenomic factors and the TME in driving tumor heterogeneity [178]. Although scATAC-seq has little application in immunometabolism research, it facilitates understanding the epigenomic mechanisms underlying tumor immunometabolism by elucidating the epigenome or in combination with other omics approaches.

Compared to single-cell sequencing, spatial omics excels at preserving spatial location information, thereby capturing high-throughput spatial maps of TME [179]. Spatial metabolomics uses mass spectrometry imaging to analyze metabolite distribution across tissues and organs in terms of qualitative, quantitative and localization, which makes up for the absence of spatial distribution data in conventional metabolomics, facilitating deeper insights into cancer immunity-related biochemical changes in specific structures [180]. However, spatial metabolomics studies must balance spatial resolution and metabolic coverage carefully. Spatial transcriptomics, divided into imaging-based and sequencing-based approaches, is a powerful tool for exploring the metabolic diversity within the TME. Imaging-based spatial transcriptomics is more suitable for targeted analysis due to high precision, but it falls short in capturing the overall metabolic landscape within individual immune cells. Sequencing-based spatial transcriptomics, with its high throughput, has emerged as a crucial tool for investigating the spatial metabolic characteristics of the TME, but its low resolution poses challenges in directly analyzing scattered immune cells in TME [181, 182]. Notably, a recent study utilized spatial single-cell isotope tracing to achieve single-cell spatial probing of the de novo fatty acid synthesis pathway, revealing tumor glucose-dependent fatty acid production and highlighting the potential of metabolic flux analysis in tumor metabolism research [183]. Other spatial omics techniques, including spatial genomics and spatial proteomics, hold significant potential for advancing the study of tumor immunometabolism and epigenomics, despite their limited exploration to date.

Intriguingly, single-cell multiomics, spatial multiomics, and the integration of spatial omics and single-cell omics deepen our understanding of tumorigenesis and immunometabolism [184, 185]. The combined application of spatial metabolomics, spatial lipidomics, and spatial transcriptomics approaches offers a holistic perspective on tumor metabolic reprogramming and immunometabolism by analyzing the associations between metabolites and lipids, gene expression signatures, and their spatial alterations[186]. A study uncovered the transition between glycolysis and OXPHOS during early lymph node metastasis in breast cancer via integrating scRNA-seq and spatial transcriptomics [187]. In conclusion, each technology possesses distinct strengths and collectively enhances the investigation of tumor immunometabolism and epigenomics. While significant gaps persist in cross-disciplinary research between tumor immunometabolism and epigenomics, emerging technologies and multiomics analysis of epigenomics, transcriptome, metabolome, and spatial omics provide valuable tools for future exploration.

Therapeutic strategies targeting tumor immunometabolism to modulate epigenomic modifications

For over a century, immunotherapies, including oncolytic virus therapies, cancer vaccines, cytokine therapies, adoptive cell transfer (including chimeric antigen receptor (CAR)-T cells and T-cell receptor-engineered T cells), and immune checkpoint inhibitors, have been invented and applied in clinical practice, bringing hope to an increasing number of cancer patients [188]. In recent years, strategies based on innate immunity, such as CAR-macrophages or NK cell treatments, have also exhibited considerable anti-tumor efficacy [189]. However, tumor cells compete with immune cells such as TILs, limiting their uptake of essential nutrients and mitochondrial metabolism, thereby impairing the effectiveness of immunotherapies [190]. While the metabolic vulnerabilities of immune and tumor cells in the TME represent a promising therapeutic target, and therapeutics targeting immunometabolism in combination with immunotherapy have also shown promise but remain underexplored [68, 191]. Furthermore, the intricate relationship between metabolism and epigenomics has directed attention to

the potential applications of epigenomic regulation in tumor immunometabolism. In this part, we focus on therapeutic strategies that may regulate epigenomic modifications by targeting tumor immunometabolism (Table 1).

Acetyl-CoA, a product of nutrient metabolism, serves as both a signaling molecule and a substrate for histone acetylation, playing a crucial role in tumor proliferation and immune metabolism. Enzymes involved in acetyl-CoA metabolism have emerged as key regulators of immune cell function within the TME [192]. Therefore, therapies targeting the acetyl-CoA metabolic pathway may inhibit tumor progression by modulating metabolic and epigenomic pathways. For example, upregulated ACSS2 in tumors converts acetic acid to acetyl-CoA in response to nutrient inadequacy and hypoxia and mediates histone acetylation [193, 194]. ACSS2 inhibitors have been shown to block acetate metabolism in breast tumors with elevated ACSS2 expression, resulting in restricted tumor growth and regression [195]. ACLY has also been overexpressed in cancer, where it catalyzes the conversion of citrate to acetyl-CoA, supporting both histone acetylation and de novo lipid synthesis [196]. Caspase-10-mediated cleavage of ACLY inhibits acetyl-CoA synthesis, which in turn suppresses adipogenesis and GCN5-mediated acetylation of histones H3 and H4, resulting in the downregulation of genes related to tumor growth and metastasis [197]. IL-12-induced CD8 + T cells elevate intracellular acetyl-CoA levels through high ACLY expression, which enhances histone acetylation, upregulates fatty acid synthesis genes, and boosts IFN-γ production. This improves the metabolic adaptation and anti-tumor response of CD8 + T cells within the TME [198]. Elevated acetyl-CoA in Kras-mutated pancreatic

Table 1 Therapeutic strategies targeting tumor immunometabolism to modulate epigenomic modifications

Targets	Drugs or agents	Mechanisms	Phase	Trial number	Refs
ACSS2	MTB-9655	Selective inhibiting ACSS2, which allows tumor cells to switch to acetate as the primary carbon source	Phase I	NCT04990739	/
	VY-3–135	Inhibiting ACSS2 to block acetate metabolism	Preclinical	NA	[195]
ACLY	Caspase-10	Promoting cleavage of ACLY to inhibit acetyl-CoA synthesis and suppress adipogenesis and GCN5-mediated acetylation of histones H3 and H4	Preclinical	NA	[197]
	IL-12	Promoting elevated levels of acetyl-CoA and histone acetylation in CD8 + T cells, thereby enhancing lipid synthesis and IFN-γ production	Preclinical	NA	[198]
Glutamine	DON	Blocking glutamine metabolism to inhibit aerobic glycolysis and OXPHOS in cancer cells and promote the transition of TILs to long-lived, highly activated phenotypes	Preclinical	NA	[199]
Wnt signaling	DM-αKG	Inducing DNA hypomethylation of genes involved in cell differentiation and Wnt signaling	Preclinical	NA	[200]
ETC	NEN	Increasing NAD/NADH and α-KG/2-HG ratios, which promotes demethylation of promoter CpG island demethylation downregulating N-Myc and β-catenin signaling	Preclinical	NA	[201]
BET *HMG-CoA reductase*	JQ-1 + atorvastatin	Targeting acetyl-CoA-dependent pathways to inhibit acinar-to-ductal metaplasia	Preclinical	NA	[192]
Methionine	dietary methionine restriction	Promoting the demethylation of H3K4me3 and inhibiting the expression of cancer stem cells and resistance-related genes by decreasing the levels of the SAM	Preclinical	NA	[202]
Methionine	methionine deprivation	Enhancing cell surface expression of TNF-related apoptosis inducing ligand receptor-2	Phase II	NCT03186937	/
Akt/ERK *methionine*	ONC201 + methionine restriction	Enhancing the activity of ONC201 in inhibition of Akt/extracellular regulated protein kinases	Phase II	NCT03733119	/
Methionine *DNA*	dietary methionine restriction + Temozolomide	Interfering with DNA methylation and promoting apoptosis of tumor cells	Phase I	NCT00508456	/
IDH2	Enasidenib	Inhibiting the mutant IDH2 enzyme to decrease 2-HG levels and induce bone marrow differentiation	Phase I and II	NCT01915498	/
	Enasidenib	Preventing the excessive production of metabolites and compounds that aid in the growth of tumors and cancer cells when IDH2 mutations occur	Phase I	NCT03515512	/
	Enasidenib + CAR T cell therapy	Enhancing memory CAR T cell formation through H3K27 acetylation and citric acid accumulation	Preclinical	NA	[206]

acinar cells has been found to upregulate histone H4 acetylation and promote acinar-to-ductal metaplasia via the mevalonate pathway. JQ-1 (carboxylic acid) combined with atorvastatin suppresses tumor growth by targeting acetyl-CoA-dependent pathways [192].

The reliance of tumors on glutamine positions glutamine as a potential target for metabolic therapy. 6-diazo-5-oxo-l-norleucine (DON) restricts both aerobic glycolysis and OXPHOS in cancer cells by blocking glutamine metabolism, while simultaneously promoting oxidative metabolism in TILs and enhancing their proliferation, activation, and anti-tumor immune activity, accompanied by histone methylation changes [199]. However, another study has found that tumor cells can adapt to prolonged low-glutamine conditions, which decrease intracellular α-KG levels and promote adenocarcinoma formation. Cell-permeable α-KG (DM-αKG) induces DNA hypomethylation of genes involved in cell differentiation and wingless-related integration site (Wnt) signaling, which enhances terminal differentiation and hinders tumor growth [200]. In a mouse model of neuroblastoma cells, intervention with the mitochondrial uncoupler niclosamide ethanolamine (NEN) resulted in increased nicotinamide adenine dinucleotide (NAD)/NADH and α-KG/2-HG ratios, which promotes demethylation of promoter CpG island demethylation and downregulates N-Myc and β-catenin signaling, leading to neurological differentiation [201].

Dietary methionine restriction induces the demethylation of H3K4me3 and inhibits the expression of cancer stem cells and resistance-related genes by decreasing the methyl donor SAM levels [202]. Decreased SAM levels in tumor cells mediated by dietary methionine restriction inhibits the expression of programmed cell death ligand 1 and V-domain Ig suppressor of T cell activation, thereby enhancing the proliferation and cytotoxicity of tumor-infiltrating CD8 + T cells [203]. Additionally, dietary methionine restriction is employed as an adjunct therapy alongside other antineoplastic treatments to enhance their efficacy.

Selective mutant isocitrate dehydrogenase (IDH) inhibitors reduce the level of 2-HG produced by IDH mutations, thereby improving histone demethylation and cell differentiation [204, 205]. IDH2 inhibits histone acetylation by restricting intracellular acetyl-CoA levels and suppresses antioxidant metabolism, thereby hindering CAR T cells' metabolic adaptation and function. This effect can be reversed by the IDH2 inhibitor enasidenib [206]. Therefore, metabolic therapies can function independently and in combination with immunotherapy through the epigenomic pathway to achieve synergistic effects. The emergence of novel immunotherapies such as CAR-NK and CAR-macrophage therapies also opens up more possibilities for combining metabolic therapies with immunotherapies [207].

A growing number of drugs targeting epigenomics-modifying enzymes, such as DNMT inhibitors and EZH2 inhibitors, have been studied as therapeutic options for tumors, and their combination with other anti-tumor drugs effectively enhance the sensitivity of chemotherapy [208]. Notably, the resistance and off-target effects of epigenomics-targeted drugs in tumor cells pose challenges to their application. Activation of certain signaling pathways in tumor cells, cytokines secreted by TAMs in the TME, and gene mutations play a crucial role in the development of resistance to epigenomics drugs. Furthermore, some drugs targeting epigenomic enzymes lack localization precision and targeting activity, leading to pan-inhibitory effects and significant off-target effects [209]. However, there is no direct evidence that epigenomics drugs can inhibit tumor growth by regulating immunometabolism, which warrants further investigation.

Conclusions and future perspectives

Over the past decades, gene mutations have dominated the discourse in oncology. However, as research has progressed, the importance of additional factors, such as epigenomics, has become increasingly evident in tumor initiation and progression. Epigenomics enables tumors to adapt to environmental changes by virtue of its relative instability, while imparting significant epigenomic characteristics—genome-wide DNA hypomethylation and variations in CpG island methylation states. DNA methylation and histone modification drive tumor proliferation and metastasis through multiple mechanisms, such as regulating the expression of oncogenes, TSGs, and genes involved in metabolic processes. The ongoing discoveries of new histone modifications highlight the crucial role of epigenomic alterations in tumors.

Metabolic reprogramming and immunometabolism within the TME are also emerging as research hotspots. To support rapid growth and metastatic requirements, tumor cells improve aerobic glycolysis, lipid metabolism, and glutamine absorption and utilization through metabolic reprogramming, exemplified by the "Warburg effect." They compete with immune cells for nutrition and produce signaling molecules that induce immune suppression and evade surveillance. Immune cells in the TME either adopt an immunosuppressive phenotype that facilitates tumor immune evasion or become exhausted due to factors such as metabolite depletion. However, certain immune cells adapt to the environment, enhancing their anti-tumor efficacy through metabolic reprogramming. Intriguingly, several metabolites implicated in tumor metabolism and immunometabolic reprogramming also play a part in epigenomic alterations. For

example, SAM, produced by one-carbon metabolism, serves as the main methyl donor for DNA methylation; acetyl-CoA, derived from the catabolism of the three major nutrients, is essential for histone acetylation; lactate, the end product of glycolysis, functions not only as an energy substrate and signaling molecule but also as a regulator of histone lactylation; and metabolites such as a-KG are key cofactors for enzymes such as TET. In general, tumor metabolites operate as epigenomic remodeling regulators, while epigenomic alterations affect tumor metabolic reprogramming by regulating metabolic enzyme-related genes, and their interactions in the TME should not be disregarded. Recently, emerging technologies such as scRNA-seq, scATAC-seq, spatial transcriptomics, and spatial metabolomics have provided invaluable tools for studying tumor immunometabolism and epigenomics. These technologies enable the decoding of the complex metabolic and immune interactions between diverse cell types within the TME through qualitative, quantitative, and localized analyses of metabolites in the TME.

Given the reversible and pervasive nature of epigenomic changes in tumors, therapies targeting chromatin-binding proteins or enzymes involved in epigenomic regulation have paved new avenues for cancer treatment. Additionally, the relationship between metabolic and epigenomic alterations, which are irreversible in tumor progression, warrants further investigation. How can we ensure the function of anti-tumor immune cells while simultaneously inhibiting tumor metabolism and growth? Metabolic therapies may provide a solution by targeting specific sites of tumor metabolic reprogramming or immunometabolism associated with epigenomics.

However, current research on epigenomic regulation in tumor metabolic reprogramming and immunometabolism represents only the tip of the iceberg. Emerging studies are reshaping our understanding of metabolic reprogramming in cancer. Further research is required to explore the diverse metabolic pathways and epigenomic modifications associated with various tumor phenotypes at different stages of progression. Most studies on epigenomics and immunometabolism focus on glucose metabolism and T cells, with relatively little attention paid to lipid metabolism, amino acid metabolism and non-T cell immune populations, such as B cells and NK cells. While metabolic and epigenomic studies of non-T cell immune populations remain less extensive and comprehensive compared to T cells, these populations significantly contribute to the formation of the TME and facilitate intricate signaling and metabolic communication between tumor cells and surrounding cells, which warrants deeper investigation in the future. Therapeutics that target epigenomics through metabolism are mostly unexplored, yet this represents a promising area for further investigation. We expect that ongoing advancements in epigenomics and tumor immunometabolism will provide novel therapeutic approaches for more cancer patients in the future.

Abbreviations

2-HG	2-Hydroxyglutaric acid
5mC	5-Methylcytosine
α-KG	α-Ketoglutaric acid
Ac	Acetylation
Ac-CoA	Acetyl-coenzyme A
AcAc-CoA	Acetoacetyl coenzyme A
ACAT2	Acetyl-CoA acetyltransferase 2
ACC	Acetyl-CoA carboxylase
ACLY	ATP-citrate lyase
ACSS2	Acetyl-CoA synthetase 2
Akt	Protein kinase B
ASCT2	Alanine-serine-cysteine transporter 2
ATP	Adenosine triphosphate
BCAAs	Branched-chain amino acids
BCAT1/2	Branched-chain amino acid aminotransferase 1/2
BCKA	Branched-chain α-keto acid
BCKDH	Branched chain ketoacid dehydrogenase
CAR	Chimeric antigen receptor
CBP	CREB-binding protein
CEs	Cholesteryl esters
CH3	Methyl
DCs	Dendritic cells
DHAP	Dihydroxyacetone phosphate
DM-αKG	Cell-permeable α-KG
DNMTs	DNA methyltransferases
DON	6-Diazo-5-oxo-l-norleucine
EBV	Epstein-Barr virus
ER	Endoplasmic reticulum
ERK	Extracellular regulated protein kinases
ETC	Electron transfer chain
EZH2	Enhancer of zeste homolog 2
FA	Fatty acid
FAO	Fatty acid oxidation
FASN	Fatty acid synthase
Foxp3	Forkhead box protein P3
FPP	Farnesyl pyrophosphate
GA3P	3-Phosphoglyceric acid
GABA	Glutamate-derived γ aminobutyric acid
GCN5	General control non-depressible 5
GLS1	Glutaminase 1
GLUT1	Glucose transporter 1
GPX4	Glutathione peroxidase 4
H3K27ac	Acetylation of histone H3 lysine 27
H3K27me3	H3K27 trimethylation
HAT	Histone acetyltransferase
HCC	Hepatocellular carcinoma
HDAC	Histone deacetylase
HIF-1α	Hypoxia inducible factor-1α
HK2	Hexokinase 2
HMGCR	3-Hydroxy-3-methylglutaryl-CoA reductase
HMGCS1	3-Hydroxy-3-methylglutaryl-CoA synthase 1
HMT	Histone methyltransferase
IDH	Isocitrate dehydrogenase
IFN-γ	Interferon γ
IL-6	Interleukin-6
INSIG	Insulin-induced gene
JMJD	Jumonji C domain-containing
JQ-1	Carboxylic acid
LDHA	Lactate dehydrogenase A
LAG-3	Lymphocyte activation gene-3
lncRNAs	Long non-coding RNAs
LSD1	Lysine-specific demethylase 1

MCT	Monocarboxylate transporter
MCs	Mesenchymal cells
Me	Methylation
MHC-I	Major histocompatibility complex-I
mTORC1	Mechanistic target of rapamycin complex 1
MTs	Methyltransferases
NAD	Nicotinamide adenine dinucleotide
NEN	Niclosamide ethanolamine
NK cell	Natural killer cell
NSCLC	Non-small cell lung cancer
OXPHOS	Oxidative phosphorylation
P300	E1A-binding protein
p38-MAPK	P38 mitogen-activated protein kinase
PD1	Programmed cell death protein 1
PDH	Pyruvate dehydrogenase
PFAs	Posterior fossa-group A ependymomas
PFK1	Phosphofructokinase-1
PGK1	Phosphoglycerate kinase 1
PI3K	Phosphatidylinositol-3-kinase
PKM2	Pyruvate kinase isozyme type M2
PTMs	Post-translational modifications
ROS	Reactive oxygen species
SAH	S-adenosyl-L-homocysteine
SAM	S-adenosyl-L-methionine
scATAC-seq	Single-cell assay for transposase-accessible chromatin using sequencing
SCC	Squamous cell carcinoma
scRNA-seq	Single-cell RNA sequencing
SETD2	SET domain containing 2
SLC	Solute carrier family
SREBP	Sterol regulatory element binding protein
STAT3	Signal transducer and activator of transcription factor 3
TAG	Triacylglycerol
TAMs	Tumor-associated macrophages
TCA	Tricarboxylic acid
TCR	T cell receptor
TETs	Ten-eleven translocation family proteins
Tex	Exhausted T cell
TGF-β	Growth factor β
Th1	T helper cell 1
TILs	Tumor-infiltrating lymphocytes
TIM-3	T cell immunoglobulin domain and mucin domain-3
TLR4	Toll-like receptor 4
TME	Tumor microenvironment
Tregs	Regulatory T cells
TSGs	Tumor suppressor genes
Wnt	Wingless-related integration site

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Authors' contributions
W.M., H.C. and Z.Y. conceived and supervised this project. X.X. and W.L. wrote the original draft and designed the figures. W.M., H.C. and Z.Y. revised the manuscript. W.M. and H.C. got financial support. All authors reviewed and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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Competing interests
The authors declare no competing interests.

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