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# Metabolic reprogramming and epigenetic modifications in cancer: from the impacts and mechanisms to the treatment potential

Xuemeng Xu<sup>1,2,4</sup>, Qiu Peng<sup>1,4</sup>, Xianjie Jiang<sup>1</sup>, Shiming Tan<sup>1</sup>, Yiqing Yang<sup>1</sup>, Wenjuan Yang<sup>1</sup>, Yaqian Han<sup>1</sup>, Yuyu Chen<sup>1</sup>, Linda Oyang<sup>1</sup>, Jinguan Lin<sup>1</sup>, Longzheng Xia<sup>1</sup>, Mingjing Peng<sup>1</sup>, Nayiyuan Wu<sup>1</sup>, Yanyan Tang<sup>1</sup>, Jinyun Li<sup>1</sup>✉, Qianjin Liao<sup>1,3</sup>✉ and Yujuan Zhou<sup>1,3</sup>✉

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Metabolic reprogramming and epigenetic modifications are hallmarks of cancer cells. In cancer cells, metabolic pathway activity varies during tumorigenesis and cancer progression, indicating regulated metabolic plasticity. Metabolic changes are often closely related to epigenetic changes, such as alterations in the expression or activity of epigenetically modified enzymes, which may exert a direct or an indirect influence on cellular metabolism. Therefore, exploring the mechanisms underlying epigenetic modifications regulating the reprogramming of tumor cell metabolism is important for further understanding tumor pathogenesis. Here, we mainly focus on the latest studies on epigenetic modifications related to cancer cell metabolism regulations, including changes in glucose, lipid and amino acid metabolism in the cancer context, and then emphasize the mechanisms related to tumor cell epigenetic modifications. Specifically, we discuss the role played by DNA methylation, chromatin remodeling, noncoding RNAs and histone lactylation in tumor growth and progression. Finally, we summarize the prospects of potential cancer therapeutic strategies based on metabolic reprogramming and epigenetic changes in tumor cells.

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## INTRODUCTION

Cancer is a complicated disease resulting from the proliferation and metastasis of malignant cells. Although some progress has been made in understanding cancer etiology over the years, tumor pathogenesis has not been clarified<sup>1</sup>. Cell metabolism maintains the normal life activities in the body, providing energy and growth products needed for life activities and maintaining the balance in cellular redox. In the process of tumorigenesis and tumor development, cell metabolism is changed, meeting the energy and biosynthetic needs of the uncontrolled proliferation of cancer cells<sup>2,3</sup>. For example, the oxygenated glycolysis rate (Warburg effect) is increased in tumors<sup>4</sup>. Although different cancer types exhibit broad heterogeneity and genetic diversity, some metabolic changes are common to cancer cells, and these types of metabolic reprogramming are thought to be hallmarks of cancers<sup>5,6</sup>. Our understanding of cancer cell metabolic reprogramming is far from sufficient. Therefore, it is important to elucidate the specific molecular mechanisms underlying metabolic reprogramming. Epigenetics was first proposed by Conrad Waddington, a British developmental biologist, in the 1950s. He defined epigenetics as “a branch of biology that studies the relationship between genes and their products, thus forming phenotypes”<sup>7</sup>. On the basis of this definition, epigenetics originally referred to all the molecular pathways in which the expression of a genotype is regulated to generate a specific phenotype. With the advent of

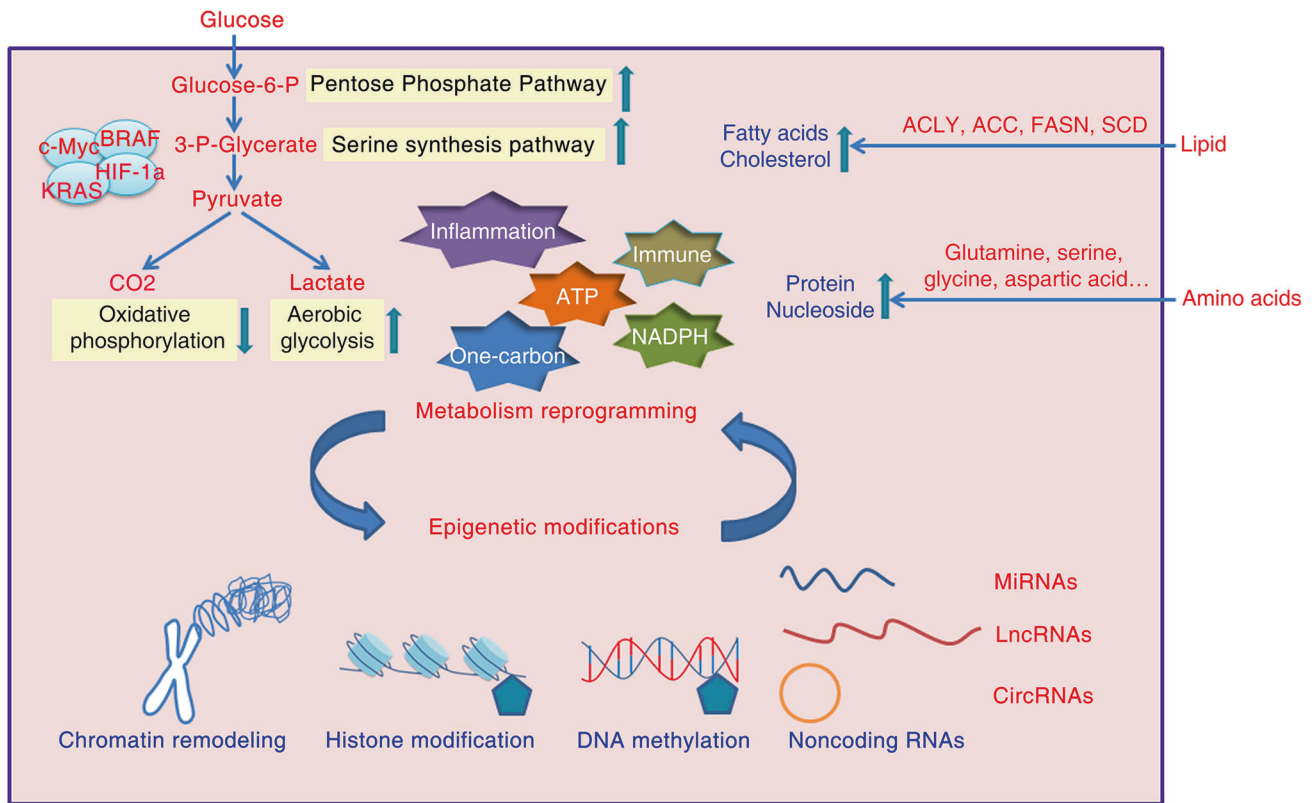
genetics, the definition of epigenetics has changed, and now, it mainly refers to both mitotically and meiotically stable and heritable variations in gene expression that do not involve alteration to the DNA sequence<sup>8</sup>. Epigenetic modifications mainly include DNA methylation, posttranslational modifications of histone proteins, chromatin remodeling and noncoding RNA-induced regulation. Epigenetic modifications impact physical and psychological development<sup>9,10</sup>, and abnormal epigenetic modification has been shown to be involved in the development and progression of various diseases<sup>11</sup>. Numerous studies have reported that aberrant regulation of epigenetic modifications can induce tumorigenesis and tumor progression through metabolic reprogramming of cancer cells<sup>12</sup>.

In recent years, with the implementation of cancer cell genome sequencing projects and advances in cancer research, the role of epigenetics in tumorigenesis has been widely accepted<sup>12–16</sup>. An increasing number of studies have shown that cancers are the results of multiple factors, such as the environment and genetics<sup>17</sup>. Epigenetic modification regulation of metabolic reprogramming in cancer cells provides a reasonable explanation for gene-related phenotype changes in the absence of changes to the DNA sequence during tumorigenesis. The effects of epigenetic modification and metabolic reprogramming on cancer cells are not independent of each other. Studies have revealed that metabolic reprogramming in cancer cells remodels tumor

<sup>1</sup>Hunan Key Laboratory of Cancer Metabolism, Hunan Cancer Hospital and the Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha 410013 Hunan, China. <sup>2</sup>University of South China, Hengyang 421001 Hunan, China. <sup>3</sup>Hunan Key Laboratory of Translational Radiation Oncology, 283 Tongzipo Road, Changsha 410013 Hunan, China. <sup>4</sup>These authors contributed equally: Xuemeng Xu, Qiu Peng. ✉email: [lijinyun@hnca.org.cn](mailto:lijinyun@hnca.org.cn); [march-on@126.com](mailto:march-on@126.com); [yujany\\_zhou@163.com](mailto:yujany_zhou@163.com)

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**Fig. 1 Metabolic reprogramming pathways and epigenetic modification marks interact in cancer.** In cancer cells, metabolic pathways are altered during tumorigenesis and development, exhibiting regulated metabolic plasticity. Cancer metabolic reprogramming involves mainly a shift from oxidative phosphorylation to aerobic glycolysis, increased pentose phosphate pathway and serine synthesis pathway activation, and enhanced lipid and amino acid metabolism in cancer cells, providing essential raw materials and energy support for tumor growth, participating in the tumor immune response, and maintaining redox homeostasis in the tumor microenvironment. Metabolic changes are often closely related to epigenetic changes. The mechanisms of epigenetic modification mainly include DNA methylation, histone modification, chromatin remodeling and noncoding RNA functions. Epigenetic modification marks and metabolic reprogramming pathways interact to play an essential role in tumorigenesis and development.

epigenetic modifications<sup>18,19</sup>. In this review, we focus mainly on the regulatory role played by different epigenetic modifications during metabolic reprogramming in cancer cells (Fig. 1). First, we briefly introduce the changes in glucose, lipid, and amino acid metabolism in cancer cells. Then, we discussed the regulatory effects of DNA methylation, histone modification, chromatin remodeling, and noncoding RNA on metabolic reprogramming in tumor cells. Finally, we discuss the treatment of tumors based on metabolic reprogramming and epigenetic modification.

## METABOLIC REPROGRAMMING IN CANCER

### Glucose metabolism

Glucose is the main source of energy for cell proliferation. Glucose metabolism includes the glycolytic pathway, pentose phosphate pathway (PPP), and serine synthesis pathway (SSP) in the cytoplasm, as well as oxidative phosphorylation, that is, the tricarboxylic acid cycle (TCA), in mitochondria. Glycolysis is the common process through which glucose is metabolized. Pyruvate, a metabolic product of glycolysis, can be converted to lactate and secreted out of a cell, or it can enter the mitochondria for consumption in the TCA. The intermediate products from glycolysis can enter the PPP pathway and SSP pathway. Warburg first discovered that cancer cells produce lactic acid through glycolysis to provide energy even when the oxygen level is sufficient for oxidative phosphorylation; this metabolic feature of cancer cells is called the “Warburg effect” or “aerobic glycolysis”<sup>20</sup>. This change in the glucose metabolism pathway is the most

common and representative phenotype of the glucose metabolism change in cancer cells and constitutes the main driving factor in cancer progression<sup>21</sup>. Research has shown that abnormal metabolism in cancer cells is related to abnormal expression of the proto-oncogenes cMyc, KRAS, and BRAF. cMyc regulates the expression of most glycolytic enzymes, thereby transforming the metabolism of cancer cells from oxidative phosphorylation to glycolysis, and abnormal expression of cMyc drives serine synthesis pathway activation in tumors under nutrient-deficient conditions<sup>22</sup>. Oncogene KRAS mutations alter cancer cell metabolism by inducing upregulated transcription of glucose transporters and glycolytic enzymes. Hypoxia-inducible factor (HIF) is the main regulatory factor in glucose metabolism in the hypoxic microenvironment of tumor cells. HIF-1a enhances hypoxia-related glycolysis in cancer cells by activating the expression of multiple glycolytic enzymes, which is crucial for the growth and proliferation of cancer cells under hypoxic conditions<sup>23–25</sup>. In addition, the stability and activity of HIFs are affected by the TCA cycle, electron transport chain components, mitochondrial respiration, and mitochondrion-associated proteins. Activation of HIF is associated with mitochondrial dysfunction, including the oxidative capacity in mitochondria, biogenesis, apoptosis, and autophagy<sup>26</sup>. Glycolysis is an important carbon process in cancer cell metabolism, providing nutrients for the unlimited proliferation of cancer cells. The intermediates of glycolysis are consumed to promote the biosynthesis of biomolecules, such as nucleotides, amino acids, and fats<sup>27</sup>. Glycolysis leads to high levels of accumulated lactic acid in the tumor microenvironment. Lactate

is a signaling molecule in cancer, regulating inflammation and immune responses in tumors<sup>28</sup>. In addition, enhanced aerobic glycolysis in cancer cells promotes angiogenesis<sup>29</sup>. Abnormal glucose metabolism as a hallmark of cancer has been used in clinical diagnostics and treatment. For example, fluorodeoxyglucose positron emission tomography (18F-FDG-PET) has been widely used in tumor diagnosis, exploiting the difference between glucose metabolism in tumors and normal tissues<sup>30,31</sup>. Specifically, glucose metabolism provides preferential targets for cancer therapy. Tumor growth can be limited by inhibiting glycolysis; for example, the ruthenium-based anticancer compound BOLD-100 targets glycolysis and renders cells vulnerable to glucose-deficient metabolism<sup>32</sup>.

### Lipid metabolism

Lipids are biological macromolecules that are the bases of biological membrane structure and function as signaling molecules and energy sources<sup>33</sup>. During the development of cancer, fat metabolism dramatically changes<sup>34</sup>. Some key enzymes such as ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), and fatty acid synthesis enzyme (FASN) involved in fatty acid metabolism in cancer cells are upregulated in certain cancers, including liver cancer, and are related to clinical prognosis<sup>35–37</sup>. Under hypoxic conditions, the fatty acid synthesis rate in cancer cells increases. Fatty acid intake and metabolism promote cancer progression. Studies have shown that rapidly proliferating cholangiocarcinoma cells depend on the uptake of lipids and lipoproteins to promote FA catabolism<sup>38</sup>. Recently, fatty acid metabolism pathways as potential antitumor targets have attracted increasing attention<sup>39</sup>.

The involvement of abnormal cholesterol metabolism is also important in cancer development. A recent study found that dysregulation of cholesterol homeostasis leads to resistance to iron, dyslipidemia, or hypercholesterolemia, thereby increasing tumorigenesis and metastasis by resisting ferroptosis<sup>40</sup>. Cholesterol participates in the inflammatory response by regulating various immune cell functions. Thus, controlling cholesterol metabolism may increase the cancer immune response<sup>41</sup>. For example, regulatory T cells (Treg cells) drive immunosuppression in the tumor microenvironment. Lipid synthesis and metabolic signals in Treg cells rely on steroid regulatory element-binding proteins (SREBPs) to induce potent antitumor immune responses without increasing toxicity related to autoimmunity. Recent research has shown that the activity of SREBPs is upregulated in Treg cells within tumors. SREBP lysis activation protein (SCAP) is required for SREBP activity. SCAP-deficient Treg cells suppressed tumor proliferation and promoted the initiation of immunotherapy by targeting the immune checkpoint protein PD-1. The lipid signaling pathway enhances the specialized function of Treg cells in tumors<sup>42</sup>.

### Amino acid metabolism

In addition to increased aerobic glycolysis and fatty acid synthesis, cancer cells show an increased demand for amino acids. An adequate provision of amino acids is vital for cancer cells to sustain their proliferative dynamics. In addition to a substrate for protein synthesis, amino acids are important for energy production, driving nucleoside synthesis, and maintaining cellular redox balance<sup>43</sup>.

Although the energy needed for cancer metabolism is derived mainly from aerobic glycolysis, amino acids such as glutamine, serine, and glycine play key roles in cancer metabolism<sup>44,45</sup>. Serine, a major source of one-carbon units, plays an essential role in tumor development. The rapid proliferation of tumor cells depends on the supply of extracellular serine. Baksh et al.<sup>46</sup> found that epidermal stem cells (EpdSCs) rely on extracellular serine for metabolic reprogramming that inhibits their differentiation, thereby boosting the proliferation of cancer-causing cells. Restricting serine intake can limit tumor growth by altering

sphingolipid diversity<sup>47</sup>. Moreover, inhibition of the serine synthesis pathway and reduced dietary serine and glycine levels showed clear positive effects on cancer treatment<sup>48</sup>. Nucleotide synthesis also depends on amino acids. Glycine, glutamine, and aspartate provide carbon and nitrogen for the biosynthesis of purines. Glycine, serine, and methionine provide carbon units through the methionine–folate cycle. Amino acid metabolism is also important in maintaining redox homeostasis. Glutathione is an important intracellular reactive oxygen scavenger. In tumors, high reactive oxygen species (ROS) levels disrupt the redox homeostasis of the tumor microenvironment. Tumor cells show an increase NADPH levels, mediated through various mechanisms, enabling their adaptation to high ROS levels, including activation of AMPK and the pentose phosphate pathway (PPP) and reduced glutamine levels and folate pathway activation<sup>49</sup>. Glutamine promotes NADPH production through malic enzyme 1 (ME1), and malate from glutamine in mitochondria is shuttled to the cytoplasm to generate NADPH<sup>50</sup>.

Other substances, such as nucleotides, are subjected to metabolic reprogramming in cancer cells. Metabolic such as 6-phosphate-glucose and one-carbon metabolism link nucleotide metabolism with glucose metabolism and amino acid metabolism. In summary, metabolic reprogramming regulates tumor progression and significantly affects many biological properties of cancer cells, promoting their proliferation, growth, invasion, and distant metastasis.

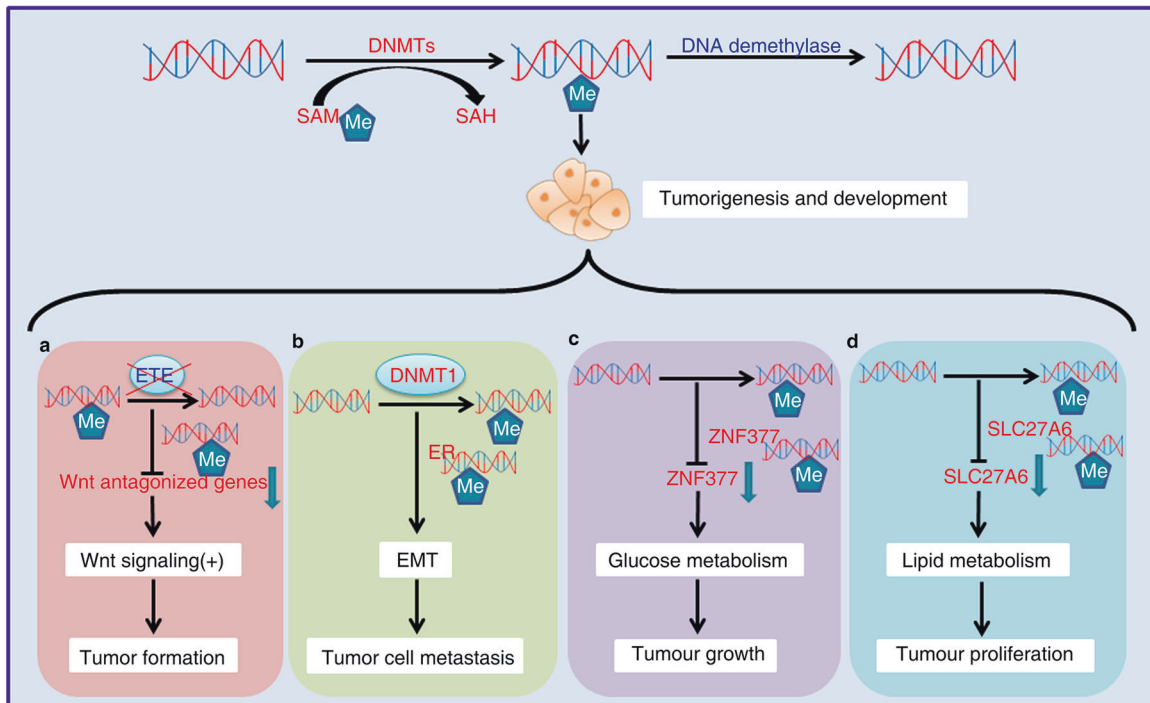
### EPIGENETIC MODIFICATIONS REGULATE METABOLIC REPROGRAMMING IN CANCER CELLS

Four main types of epigenetic modifications have been reported: DNA methylation, histone modification, chromatin remodeling, and noncoding RNA-induced modification. DNA methylation maintains a dynamic balance in the body to maintain normal physiological functions. Most histone modification targets are conserved lysine residues in histone tails. The N-terminus of histones can be posttranslationally modified by methylation, acetylation, lactylation, glycosylation, propionylation, or butyrylation. These modifications change DNA–histone interactions, regulating the loosening and condensation of chromatin, thereby activating and repressing transcription, respectively, to alter gene expression. Chromatin remodeling refers to changes in chromatin structure without changes in the covalent modifications of DNA and histones; that is, nucleosome disassembly (separation of DNA and histones), nucleotide translocation, DNA–histone affinity and chromatin three-dimensional structure are unchanged. Noncoding RNAs (ncRNAs), mainly composed of microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs), have been gradually shown in recent years to be crucial to various biological processes.

Epigenetic modifications may influence gene expression and do not alter the DNA sequence. Notably, epigenetic modifications determine the phenotypes of cells and even individuals in a heritable fashion, but the metabolic reprogramming they induce does not involve DNA sequence changes such as those induced by genetic mechanisms. The impact of epigenetic regulation on metabolic reprogramming in cancer cells cannot be ignored. An in-depth understanding of the mechanisms underlying epigenetic regulation of metabolic reprogramming in cancer has far-reaching scientific significance.

### DNA methylation regulates metabolic reprogramming in cancer cells

DNA methylation, referring mainly to the methylation of the 5-carbon cytosine residue (5mC) in a cytosine-guanine (CpG) dinucleotide, was one of the first discovered and most extensively studied epigenetic modifications. Methylation in the body maintains a dynamic balance to maintain normal physiological



**Fig. 2 DNA methylation affects tumor initiation and progression.** **a** In pre-adenocarcinoma in the lung, DNA hypermethylation caused by functional mutation of TET downregulates the expression of Wnt antagonist genes, triggering abnormal activation of Wnt signaling and accelerating the formation of early tumor lesions. **b** DNMT1-mediated hypermethylation of the estrogen receptor (ER) promoter region inhibits the expression of the ER gene during the epithelial-mesenchymal transition, promoting the EMT, which required for metastasis, thereby promoting the proliferation of cancer stem cells in triple-negative breast cancer (TNBC). **c** Zinc finger ZNF377 negatively regulates the glucose metabolism pathway in tumor cells to exert a significant antitumor effect. **d** SLC27A6 increases the tumor cell metastatic potential by promoting lipid biosynthesis. DNA hypermethylation downregulates the expression of SLC27A6, which promotes the proliferation of nasopharyngeal carcinoma via the regulation of lipid metabolism.

functions. Abnormal methylation of DNA in cells may contribute to the development of tumors and cardiovascular and autoimmune diseases<sup>51–53</sup>. In tumor cells, abnormal methylation leads to the activation of some important proto-oncogenes, leading to tumor suppressor gene silencing, genomic instability, and chromatin changes. These factors promote tumorigenesis by altering cancer metabolic pathways<sup>53</sup>.

Epigenetic modifications are reversible. The dioxygenase ten-eleven translocation (TET) enzyme promotes DNA demethylation, which is often dysregulated in cancer. In lung adenocarcinoma tissues with functional TET mutations, DNA hypermethylation downregulates the expression of Wnt-antagonized genes, thereby triggering aberrant Wnt signaling activation and accelerating tumor formation (Fig. 2a)<sup>54</sup>. Hypermethylation of the DNA methyltransferase 1 (DNMT1) gene is thought to be a cause of triple-negative breast cancer (TNBC). DNMT1 inhibits the expression of downstream EMT-related target genes through hypermethylation of the estrogen receptor (ER) promoter region, thereby promoting tumor cell metastasis (Fig. 2b)<sup>55</sup>. Brain-expressed X-catenin 1 (BEX1) is highly expressed in hepatoblastoma (HB) and the cancer stem cells of hepatocellular carcinoma (CSC-HCC) patients but expressed at low levels in non-CSC-HCC patients. The differential expression of BEX1 in tumor and normal tissues is regulated by DNMT1, which maintains the self-renewal capacity of the hepatocellular carcinoma CSCs by activating the Wnt/ $\beta$ -catenin signaling pathway. Therefore, BEX1 may be a potential therapeutic target in HB and CSC-HCC. Abnormal glucose metabolism in cancer is linked to DNA methylation. Studies have shown that hyperglycemia levels inhibit DNA 5-hydroxymethylation. The stability of the DNA demethylase TET2 depends on the phosphorylation of AMPK at serine 99. Increased glucose levels hinder the AMPK-mediated phosphorylation of serine 99, causing TET2 instability, which in turn leads to the

dysregulation of 5-hydroxymethylcytosine (5HmC), limiting the tumor suppressor function of TET2<sup>56</sup>. The TET3 protein is commonly upregulated in AML patients and human leukemia stem cells (LSCs). Overexpression of TET3 induces the expression of genes related to glucose metabolism and promotes AML progression<sup>57</sup>. A recent study revealed that the zinc finger DHHC-1 (ZDHHHC1, also known as ZNF377) negatively regulated the tumor glucose metabolism pathway and pentose phosphate pathway (PPP), thereby playing a significant antitumor role, making it a potential new tumor suppressor (Fig. 2c). ZDHHHC1 is silenced in multiple cancers because of promoter methylation. A study showed that the methylation level of the ZDHHHC1 promoter was markedly increased in tumor tissue compared with neighboring normal tissue. In ZDHHHC1-deficient cells, ZDHHHC1 was expressed after demethylation. These results showed that the methylation of the ZDHHHC1 promoter silenced its expression in tumors, thereby inhibiting its regulatory metabolic function<sup>58</sup>. In gliomas, the low expression of ankyrin repeat and death domain-containing 1A (ANKDD1A) was due to the aberrant methylation of a promoter CpG. ANKDD1A directly interacts with FIH1 to inhibit HIF1 transcriptional activity and shortens the half-life of HIF1 by upregulating FIH1 expression, thereby reducing glucose uptake and lactate production, inhibiting autophagy, and inducing the apoptosis of glioblastoma multiforme cells. However, in glioma multiforme, the high level of ANKDD1A methylation changes the metabolism of the cancer cells, thereby inhibiting the antitumor effect of ANKDD1A<sup>59</sup>. DNA methylation can also affect the development of tumors by regulating the lipid metabolism pathway. For example, solute carrier family 27 member 6 (SLC27A6) increased the levels of triglyceride (TG) and total cholesterol (T-CHO) in nasopharyngeal carcinoma (NPC) cells by promoting lipid biosynthesis. Downregulation of SLC27A6 expression by DNA hypermethylation promoted the proliferation but



inhibited NPC cell metastasis by regulating lipid metabolism (Fig. 2d)<sup>60</sup>.

### Histone modification regulates metabolic reprogramming in cancer cells

**Histone methylation.** Methylation modulate cell physiology by regulating the state and activity of histones. Histones H3 and H4 are methylated mainly on a lysine or arginine residue. Histone methylation alters cellular metabolic processes by activating or repressing gene expression<sup>61,62</sup>. The expression of various histone methylases and demethylases plays an important role in histone methylation.

Elevated histone methylation activity of the histone H3 lysine 36 (H3K36) methyltransferase NSD3 has been related to squamous cell lung cancer. According to previous studies, NSD3 increased the transformation of tracheobronchial cells and the growth of transplanted human lung squamous cell carcinoma (LUSC) cells by amplifying 8p11-12 in a catalytic activity-dependent manner<sup>63</sup>. Lysine methyltransferase 2D (KMT2D) regulates tumorigenesis through metabolic reprogramming. KMT2D was transcriptionally repressed by DNA methylation in pancreatic tumors. Inhibition of KMT2D promotes the metabolic transition to aerobic glycolysis by regulating glucose transporter 3 (SLC2A3), increasing the aerobic glycolysis rate and changing the lipid composition of pancreatic cancer cells. The mechanisms regulating KMT2D expression and its downstream effects in pancreatic tumorigenesis represent a potential therapeutic approach to pancreatic cancer as an epigenome-regulated metabolic disease<sup>64</sup>. KMT2D is often mutated in pulmonary cancer. Lung-specific KMT2D deletion facilitates pulmonary tumorigenesis by impairing the super-enhancer of PER2 and upregulates tumorigenesis, including an increase in the glycolysis rate<sup>65</sup>. In melanoma cells, KMT2D deletion led to a genome-wide reduction in the H3K4me1 mark, a gene-activating factor, and subsequent inhibition of IGF1R-activated IGF1R-AKT, resulting in increased glycolysis in cancer cells<sup>66</sup>. SETD1A is an H3K4 methyltransferase. In gastric cancer tissues, SETD1A promoted GC cell glycolysis by upregulating HIF1 $\alpha$  expression. Hence, SETD1A is thought to be an important regulator of HIF1 $\alpha$ -mediated glycolysis<sup>67</sup>.

Histone demethylases participate in metabolic reprogramming in cancer cells. JMJD1A is highly expressed in bladder carcinoma and contributes to the proliferation of bladder cancer cells by increasing cellular glucose metabolism<sup>68</sup>. JMJD1A promotes the transcription of PGK1 by regulating H3K9me2 levels in the PGK1 promoter region and interacting with HIF-1 $\alpha$  to regulate the glucose metabolism pathway in bladder cancer cells, thus regulating the progression of bladder carcinoma. The histone demethylase KDM5B also acts as an oncogene in breast cancer cell proliferation and migration<sup>69</sup>. KDM5B promotes breast cancer cell proliferation and migration by reprogramming lipid metabolism. KDM5B knockdown in breast cancer cells activated the AMPK protein, reduced the level of lipid metabolism, and inhibited the epithelial-mesenchymal transition (EMT), and reduced their growth and migration ability, revealing novel theoretical evidence for the clinical regulation of tumor metabolism by targeting related genes.

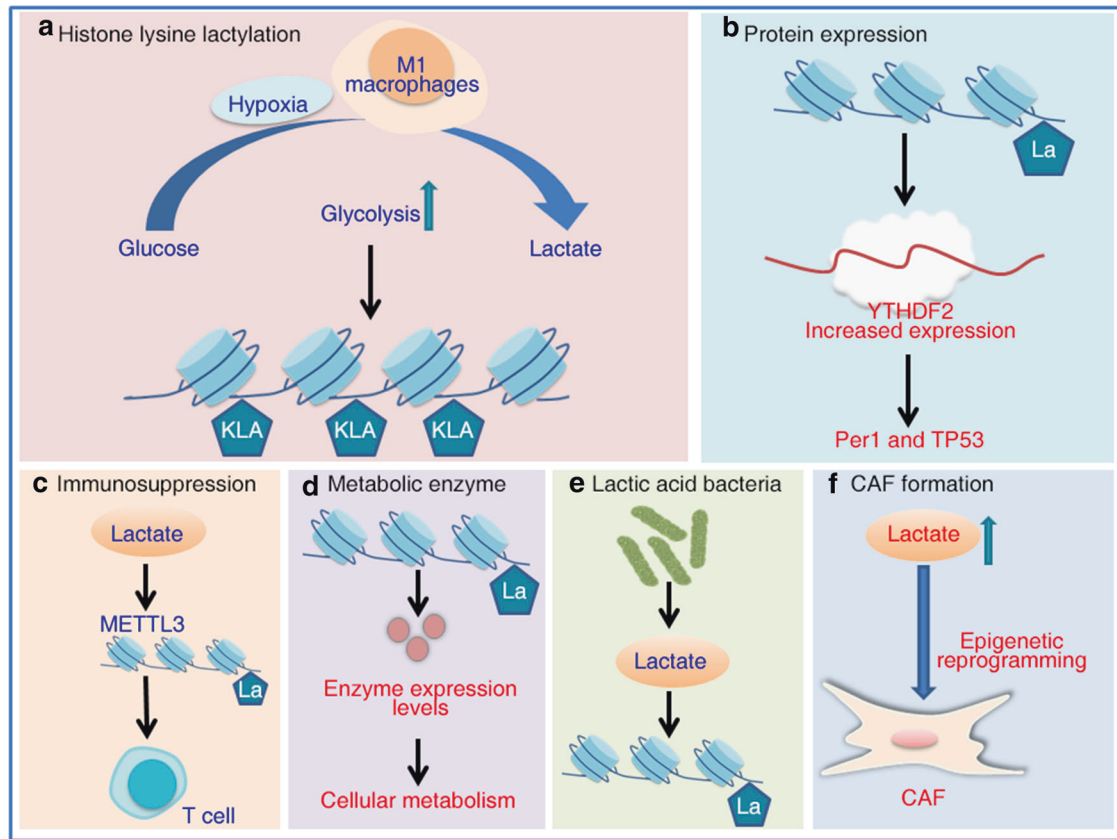
**Histone acetylation.** Histone acetylases (HATs) and histone deacetylases (HDACs) work together to maintain normal levels of histone acetylation. Imbalances in histone acetylation modifications lead to the development of various tumors. Aberrant binding of HDACs at specific promoter regions suppresses normal functional gene transcription, inducing malignancy, such as promyelocytic leukemia-retinoic acid receptor- $\alpha$  (PML-RAR $\alpha$ ) fusion proteins that reactivate HDACs and inhibit the expression of genes associated with hematopoietic cell differentiation, leading to the progression of acute promyelocytic leukemia (APL)<sup>70</sup>.

Histone acetylation is closely related to lipid metabolism in tumors. The histone deacetylase HDAC3 interacts with SREBP2, a key regulator of cholesterol synthesis, and HMGCR, a cholesterol synthesis-limiting enzyme. Downregulation of HDAC3 activates cholesterol synthesis in gastric cancer cells, which induces ROS production, thereby inducing oxidative stress and apoptosis. The use of the histone deacetylase inhibitor trichostatin A (TSA) enhanced the acetylation of H3 and inhibited PI3K/AKT pathway activation, thereby inhibiting gastric cancer cell proliferation and inducing apoptosis<sup>71</sup>. P300/CBP regulates the expression of metabolism-related enzymes by regulating the acetylation of histone H3K18/K27. Inhibition of p300/CBP expression significantly prevented liver cancer cell proliferation and metastasis<sup>72</sup>. Histone acetylation also plays roles in tumor vascular mimicry by regulating glucose metabolism reprogramming and thus affects tumorigenesis. Bactericidal/permeability-increasing fold-containing family B member 1 (BPIFB1) is hyperexpressed in nasopharyngeal epithelial cells and is markedly downregulated in nasopharyngeal carcinoma tissues; its expression is related to the prognosis of patients with nasopharyngeal carcinoma. Recent studies have shown that BPIFB1 reduced GLUT1 transcription through the regulation of the JNK/AP1 signaling pathway, leading to altered glycolysis. BPIFB1 reduced the acetylation level of histones, further inhibiting the expression of the angiogenic mimicry-related genes VEGFA, VE-cadherin, and MMP2, ultimately leading to the inhibition of angiogenic mimicry in nasopharyngeal carcinoma<sup>73</sup>. Histone acetylation is involved in regulating amino acid metabolism. Arginine is a semi-essential amino acid. It plays an essential role in cellular physiology and is an epigenetic regulator of cancer cell metabolic reprogramming because it regulates epigenetic modifications. In prostate carcinoma, arginine upregulated the expression of a nuclear oxidative phosphorylation (OXPHOS) gene mediated through histone acetylation. Arginine-activated expression of lysine acetyltransferases (KATs) increased the overall levels of histone acetylation and acetyl-CoA and promoted the retention of transcriptional enhancer factor domain 4 (TEAD4) at the promoter/enhancer regions of the aforementioned OXPHOS gene, thereby upregulating the OXPHOS gene and maintaining mitochondrial OXPHOS function<sup>74</sup>.

**Histone lactylation.** Historically, lactate was regarded as a metabolic waste product of anaerobic glycolysis in cells. New findings suggest that in addition to being a key metabolite, lactate is a multifunctional biological signaling molecule. Lactate regulates metabolic processes both inside and outside a cell. Additionally, it plays multiple biological roles and is important to cell signaling and immune regulation (Fig. 3)<sup>28,75-78</sup>. Glycolysis produces lactic acid, leading to an acidic tumor microenvironment, which adds complexity to the metabolic heterogeneity of cancer cells.

**Discovery and mechanism of histone lysine lactylation:** In recent years, lactate has been identified as a substrate for the posttranslational modification of lysine residues in histones. This novel epigenetic modification is called histone lysine lactylation (KLA). Zhang et al.<sup>79</sup> identified 26 and 16 histone KLA sites in human HeLa cells and mouse bone marrow-derived macrophages (BMDMs), respectively. Experiments performed by metabolic labeling with the isotope sodium L-lactate (13C3) and detection by high-performance liquid chromatography (HPLC)-tandem mass spectrometry (MS/MS) indicated that the lactylation of a lysine is based on the lactic acid level. Glucose is the main source of lactate in the body. Glycolysis induces lactate production and regulates histone KLA levels. In addition, both hypoxia and macrophage M1 polarization promote histone lactylation<sup>79</sup>.

**The role played by KLA in reprogramming cancer cell metabolism:** The modification disorder of histone KLA destroys the balance in gene transcription and leads to cancer and other diseases. Higher levels of histone lactylation are associated with poor prognosis in



**Fig. 3 Lactate metabolism and histone lysine lactylation in cancer cells.** **a** Lactic acid in the body is derived mainly from the metabolites of glycolysis. Histone lactylation refers mainly to the posttranslational modification of histone lysine residues with lactate as the substrate. Hypoxia and M1 macrophages promote histone lactylation. **b** Histone lactylation promotes the expression of YTHDF2, which promotes the degradation of the mRNA of tumor suppressor genes Per1 and TP53, accelerating ocular melanoma tumorigenesis. **c** The M6A modification of JAK1 mRNA in TIM cells is mediated by the lactylation of METTL3 at K281 and K345 and promotes the immunosuppression of tumor-infiltrating myeloid cells. **d** In non-small cell lung cancer, histone lactylation regulates the expression levels of metabolic enzymes that modulate cancer cell glycolysis. **e** Lactic acid-producing bacteria may promote gastric carcinogenesis by increasing lactate levels and lactylation rates. **f** In pancreatic ductal adenocarcinoma, increased tumor cell-produced lactate flux mediates epigenetic reprogramming to regulate the formation of human pancreatic CAFs.

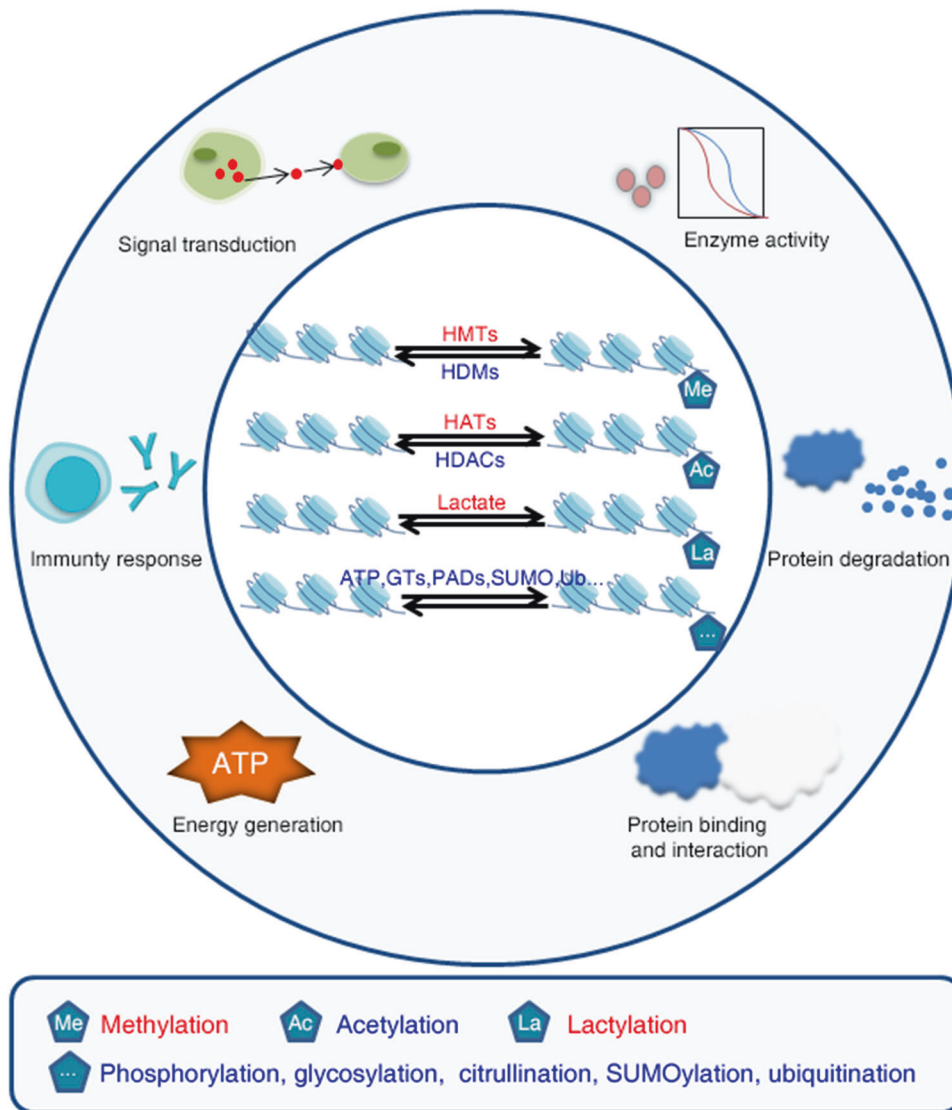
ocular melanoma. Histone lactylation promotes the expression of YTHDF2, which specifically recognizes the m6A modification sites on oncogene Per1 and TP53 RNA and promotes Per1 and TP53 mRNA degradation, thereby accelerating the development of ocular melanoma<sup>80</sup>. Lactylation drives tumor-infiltrating myeloid (TIM) cell immunosuppression. Accumulation of lactate in the tumor microenvironment (TME) significantly induces the expression of methyltransferase-like 3 (METTL3) in infiltrating myeloid cells in colon cancer mediated through H3K18 lactylation, which is essential for the transcription of immunosuppressive genes in TIM cells. This recent finding helps in understanding the molecular mechanisms underlying tumor cell immune escape. Exploring strategies to target TIM cells is important to enhance the T-cell response to tumors<sup>81</sup>. In non-small cell lung cancer, lactic acid regulates cellular metabolism through histone lactylation-mediated expression of oncogenes. Lactic acid inhibits glucose uptake, glycolysis and mitochondrial homeostasis mediated by changes in metabolic enzyme expression levels induced by histone lactylation of gene promoters<sup>82</sup>. In addition, the number of lactic acid-producing bacteria is significantly increased in patients with gastric cancer. Lactic acid-producing bacteria may contribute to the development of gastric cancer by regulating the levels of lactic acid and lactylation modification<sup>83</sup>. In pancreatic ductal adenocarcinoma, increased lactic acid levels have been associated with epigenome reprogramming during cancer-associated fibroblast formation<sup>84</sup>. In hepatocellular carcinoma,

KLA plays an important role in the regulation of cellular metabolism. Researchers have found that KLA regulates amino acid, lipid and nucleic acid metabolism by affecting metabolic enzymes. Moreover, researchers have verified that lactylation promotes the progression of liver cancer<sup>85</sup>.

As a recently discovered posttranslational modification, histone lactylation links cell metabolism to gene regulation, which may indicate its many effects on cancer progression. Studying the functional and regulatory mechanisms of histone lactylation in physiological and pathological processes is crucial and will contribute to an in-depth understanding of the pathogenesis of diseases, including cancers.

**Other types of histone modifications.** In addition to methylation, acetylation, and lactylation, the N-terminus and C-terminus of histones can be modified by phosphorylation, glycosylation, citrullination, succinylation, SUMOylation, and ubiquitination (Fig. 4)<sup>18</sup>. All of these posttranscriptional modifications alter the charge and structure of the histone terminus that binds to DNA, thereby altering chromatin status and gene expression<sup>86</sup>. To date, various histone modifications have been identified as important in the metabolic reprogramming of cancer cells<sup>18</sup>.

Histone phosphorylation is not only closely related to ATP production or the energy supply but has been shown to be involved in metabolic reprogramming in cancer cells. For example, Rab26 induces the autophagic degradation of phosphorylated Src



**Fig. 4 Histone modifications in cancer.** Histone tails can be posttranslationally modified by various molecules in the presence of enzymes. Examples include histone methylation, acetylation, phosphorylation, glycosylation, guanylation, succinate, SUMO, and ubiquitination. These histone posttranslational modifications are involved in protein expression and degradation, changes in enzymatic activity, signaling, energy production, the immune response, and various other cancer cell activities.

by coordinating with autophagy-related 16-like protein 1 (ATG16L1) in breast cancer cells, resulting in the inhibition of cancer cell migration and invasion<sup>87</sup>. Histone citrullination is a posttranscriptional modification that is catalyzed by peptide arginine deiminase (PAD) and is important in physiological and tumor cell regulation. In cancer cells, histone citrullination is related to the formation of neutrophil extracellular traps (NETs), which is conducive to innate immunity and tumor progression<sup>88</sup>. Glycosylation is important in the cellular environment and microenvironment. N-glycosylation and O-glycosylation are the two main glycosylation modifications. A sugar chain is added to the amino group of an asparagine (ASN) residue or the hydroxyl oxygen of a serine/threonine (Ser/Thr) residue. N-glycosylation donors include various branched sugars. O-glycosylation donors include mainly galactose, mannose, fucose, and N-acetylgalactosamine (GalNAc)<sup>89</sup>. Abnormal glycosylation of proteins modulates the acquisition of a malignant phenotype. Epigenetic changes to glycosylation patterns enable cancer cells to evade immune surveillance mechanisms, and targeting glycosylated PD-1 induces effective antitumor immunity<sup>90</sup>. Ubiquitin mediates the proteolysis of cell cycle protein

chaperones and kinase inhibitors (CKIs), ensuring precise regulation of the cell cycle. Cell cycle dysregulation caused by inefficient proteolytic regulation leads to an imbalance in cell proliferation and ultimately to tumorigenesis. Therefore, E3 ubiquitin ligases are involved in cell cycle regulation and hold promise as new therapeutic targets in cancer<sup>91</sup>. For example, cullin 3 (CUL3)-mediated beclin 1 (BECN1) degradation inhibits autophagy and promotes cancer progression<sup>92</sup>. UFMylation can maintain the stability of the tumor suppressor p53 by antagonizing its ubiquitination<sup>93</sup>. Taken together, various histone modifications have been shown to exert an essential regulatory effect on metabolic reprogramming in cancer cells, thereby increasing or decreasing tumor progression.

#### CHROMATIN REMODELING REGULATES METABOLIC REPROGRAMMING IN CANCER CELLS

Chromatin remodeling is usually catalyzed by a number of ATP-dependent subunit complexes called chromatin complexes; these subunits affect chromatin structure by utilizing energy obtained

via ATP hydrolysis and regulate transcription, replication, and DNA damage repair processes, thus playing essential roles in cell growth and tissue development<sup>94</sup>. The dynamically regulated structure of the genome is necessary for timely and proper gene expression in almost all cells. In recent years, complex three-dimensional structure and biochemical properties of proteins have attracted considerable attention. The discovery of chromosome-remodeling complexes has enabled investigations into how alterations to the complicated topology of a protein and the histone landscape mediate crosstalk that leads to oncogenic and carcinogenic effects<sup>95</sup>.

In recent years, chromatin complexes such as SWI/SNF, ISWI, and ANDO80, but especially SWI/SNF complexes, have been found to be linked to a variety of cancers. The SWI/SNF family of chromatin remodeling complexes, also known as BRG1/BRM-related factor (BAF) complexes, are crucial regulators of nucleosome localization. The incidence of mutations in a SWI/SNF subunit is very high, with nearly 25% of cancers having one or more of SWI/SNF gene abnormalities<sup>96</sup>. SWI/SNF gene mutations exert cancer-promoting effects. For example, SWI/SNF complex mutations promote the progression of thyroid tumors<sup>97</sup>. Loss of SNF5, a highly conserved subunit in the SWI/SNF complex, has been found in multiple tumors. Decreased expression of SNF5 promotes bladder cancer progression through the activation of STAT3<sup>98</sup>. The loss of SNF5 expression in melanoma has been associated with a low patient survival rate<sup>99</sup>. ARID1A encodes an SWI/SNF chromatin-remodeling factor. In ovarian clear cell carcinoma cells, ARID1A inactivation increased the accessibility of the GLS1 promoter and upregulated glutaminase (GLS) expression, which depended on glutamine metabolism<sup>100</sup>. In another study, ARID1A deficiency in ovarian cancer cells was shown to impair SWI/SNF recruitment to the SLC7A11 transcriptional start site, thereby reducing cystine uptake and glutathione (GSH) synthesis<sup>101</sup>. Chromatin complexes also participate in the regulation of noncoding RNAs. The SWI/SNF complex regulates the expression of the oncogene miR-222 in lung adenocarcinoma. The SWI/SNF chromosome-remodeling complex has also been associated with lipid metabolism in tumor cells. BRG1 is the catalytic ATPase of the SWI/SNF chromatin-remodeling enzyme. It is a tumor suppressor with obvious effects on certain tumors and is overexpressed in other cancers, thereby increasing or decreasing metabolic pathway activation in cancer cells. For example, BRG1 is overexpressed in breast cancer and promotes tumor cell proliferation by promoting adipogenesis<sup>102</sup>. Knocking out the BRG1 gene reduced the lipid synthesis rate by disrupting enzyme transcription. Targeting BRG1 reduced lipid metabolism, thereby reducing tumor cell proliferation, and therefore, BRG1 is expected to be used in the epigenetic treatment of TNBC. ISWI and INO80 family members show high gene expression and many genetic abnormalities in human cancers<sup>103</sup>. Loss of the ISWI ATPase SmarC5 (SNF2H) inhibited cell proliferation and chromatid cohesion in the AML context<sup>104</sup>. In the melanoma context, INO80 regulated superenhancer (SE)-mediated oncogenic transcription and tumor progression<sup>105</sup>. Decomposition of an r-loop by INO80 facilitated DNA replication and sustained the capacity of cancer cells to proliferate and survive<sup>106</sup>. These studies summarize the link between ATP-dependent chromosome-remodeling complexes and cancer metabolism and demonstrate the mechanisms by which aberrant chromosome-remodeling complex components play roles in tumorigenesis, suggesting possible new ideas for tumor therapy.

#### NONCODING RNAs (NCRNAS) REGULATE METABOLIC REPROGRAMMING IN CANCER CELLS

DNA methylation, histone modification, and chromatin remodeling are major epigenetic modifications and have been extensively studied thus far. Noncoding RNAs (ncRNAs) do not encode

proteins in the genome and mainly comprise miRNAs, lncRNAs, and circRNAs. ncRNAs account for approximately 80% of the human genome, which contains millions of noncoding regulatory regions. Recently, an increasing number of studies have reported that ncRNAs play important roles in gene expression, epigenetic regulation, and metabolic reprogramming in cancer (Table 1)<sup>107</sup>.

#### MiRNAs regulate metabolic reprogramming in cancer cells

MiRNAs constitute a class of regulatory transcripts that are approximately 19–22 nucleotides in length. MiRNA can be cancer suppressors, such as mir-431-5p, inhibit tumor progression in pancreatic ductal adenocarcinoma cells<sup>108</sup>. MiRNAs can also be oncogenes; for example, miR-601 promotes the proliferation of human glioblastoma cells by inhibiting the expression of TINP1<sup>109</sup>.

Studies have reported that miRNAs are involved in cancerogenesis through various regulatory mechanisms. MiRNAs are key regulators in endoplasmic reticulum stress-related diseases, including cancer. Factors involved in the unfolded protein response (UPR), ER-related degradation (ERAD) and cell death caused by endoplasmic reticulum stress are targeted and regulated by various miRNAs<sup>110</sup>. MiRNAs interact with endothelial cells during tumor progression, promoting or inhibiting tumor angiogenesis or lymphangiogenesis. MiR-9 and miR-494 are usually highly expressed in tumors and induce the expression of angiogenesis-related genes in endothelial cells, while the levels of miR-200 and miR-128, which inhibit angiogenesis and lymphangiogenesis, are frequently reduced<sup>111</sup>. MicroRNAs are mostly involved in regulating all aspects of immune cell development and differentiation. Studies have shown that miRNAs are involved in maintaining lymphocyte tolerance. Moreover, dysregulation of microRNAs contributes to the development of autoimmune diseases and lymphomas<sup>112</sup>. MiRNAs regulate tumor development by regulating metabolic reprogramming in cancer cells. MiR-30d/RUNX1 regulates aerobic glycolysis in pancreatic ductal adenocarcinoma (PDAC) cells. MiR-30d has been recently identified as a target for YTHDC1 m6A modification. YTHDC1-mediated m6A promoted mRNA stability and regulated the biogenesis of mature miR-30d. MiR-30d targets RUNX1, a transcription factor that binds to the promoters of the SLC2A1 and HK1 genes, to regulate the expression of SLC2A1 and HK1, thereby inhibiting the transcriptional activation of the RUNX1-induced Warburg effect and suppressing pancreatic tumorigenesis<sup>113</sup>. LIX1-like protein upregulates miR-21-3p expression and promotes hepatocellular carcinoma growth and metastasis by inhibiting fructose-1,6-bisphosphatase (FBP1)<sup>114</sup>. MiR-378a inhibits prostate (PCa) cell proliferation by inhibiting glucose metabolism that is mediated by GLUT1<sup>115</sup>. Ectopic expression of miR-612 partially decreased HADHA levels, reduced invasive pseudopodia formation through HADHA-mediated changes in cell membrane cholesterol levels, and inhibited the metastasis and invasion of HCC cells via its effect on lipid reprogramming<sup>116</sup>. MiR-4646-5p regulates the secretion of ABHD16A and the lysophospholipid metabolites to promote gastric cancer cell metastasis<sup>117</sup>. In addition, miRNAs generated by tumor cells modulate fibroblast protein synthesis and amino acid-induced mTORC1 activation<sup>118</sup>.

#### LncRNAs regulate metabolic reprogramming in cancer cells

LncRNAs are RNA transcripts that carry more than 200 nucleotides and show no or limited protein-coding potential. Recently, many studies have revealed that lncRNAs exhibit complex regulatory roles in metabolic reprogramming in cancer cells and that these effects are mediated through various mechanisms.

LncRNAs affect the glucose metabolism in cancer cells through a wide range of mechanisms. The lncRNA H19/miR-675-5p/PFKFB3 signaling pathway promotes oral cancer development by reprogramming glycolysis in cancer-associated fibroblasts (CAFs)<sup>119</sup>. The relationship between the gut microbiota and glucose metabolism is also mediated via lncRNAs. In patients, *Fusarium*



**Table 1.** The regulatory role of noncoding RNAs in cancer cells.

	Noncoding RNAs	Roles in cancer	Cancer	Reference	
MiRNA	MiR-431-5p	Inhibits tumor progression	PDAC	108	
	MiR-601	Promotes cell proliferation by inhibiting the expression of TINP1	GBM	109	
	MiR-30d	Targets the transcription factor RUNX1 and inhibits the transcriptional activation of the RUNX1-induced Warburg effect	PDAC	113	
	MiR-21-3p	Promotes cell growth and metastasis	Liver cancer	114	
	MiR-378a	Inhibits PCa cell proliferation	Prostate cancer	115	
	MiR-612	Suppresses HCC cell invasion and migration	HCC	116	
	MiR-4646-5p	Promotes metastasis	GC	117	
	LncRNA	LncRNA H19	Promotes the growth of oral tumors	Oral cancer	119
		LncRNA ENO1-IT1	Promotes glycolysis and tumorigenesis	CRC	120
		LncRNA NRCP	Promotes cancer cell growth	Ovarian cancer	121
LINC00842		Leads to a metabolic switch from mitochondrial oxidative catabolic processes to fatty acid synthesis, enhancing the malignant phenotype of PDAC cells	PDAC	122	
LncRNA romp		Regulates the properties of breast cancer stem cells (BCSCs) by mediating lipid metabolism	Breast cancer	123	
		Promotes the survival of glucose-deficient hepatoma cells by activating the serine synthesis pathway	HHC	124	
LINC00467		Promotes cell proliferation	CRC	125	
Lnc-NA		Regulates the expression of the nuclear receptor NR4A1 and then increases caspase signaling pathway activation, promoting apoptosis in endometrial cell lines	EC	126	
CircRNA		CircRPN2	Increases the expression of FOXO1 to suppress glucose metabolism and tumor progression	HCC	130
		CircMAT2B	Promotes glycolysis through the activation of circMAT2B/miR-338-3p/PKM2 axis to promote HCC progression under hypoxic conditions	HCC	131
	CircEZH2	Promotes tumorigenesis and metastasis by sponging miR-217-5p and establishing a new feedback loop consisting of FUS/circEZH2/KLF5	Breast cancer	132	
	CircECE1	Interacts with c-Myc to prevent POZ-mediated c-Myc ubiquitination and degradation	OS	133	
	CircErbin	Promotes angiogenesis by increasing the expression of HIF-1 $\alpha$	CRC	135	
	CircRNF13	Inhibits proliferation and metastasis	NPC	136	
	CircFNDC3B	Inhibits tumor progression by encoding the protein CircFNDC3B-218aa	Colon cancer	138	

*nucleatum* (F.) abundance is associated with increased glucose metabolism. *F. nucleatum* increases the binding effectiveness of the transcription factor SP1 to the lncRNA ENO1-IT1 promoter region, activating transcription. Elevated ENO1-IT directs the histone modification of target genes to promote glycolysis and tumorigenesis<sup>120</sup>. The long noncoding RNA ceruloplasmin (the lncRNA NRCP) promotes the development by modifying the glycolysis of tumor cells. NRCP expression is upregulated in ovarian cancer. Silencing NRCP markedly reduces glycolysis and increase mitochondrial respiration in cancer cells, ultimately leading to an increased apoptosis and reduced proliferation rates of cancer cells<sup>121</sup>. LncRNAs are also engaged in lipid and amino acid metabolism in cancer cells. LINC00842 is upregulated in pancreatic ductal adenocarcinoma (PDAC). pGC-1 $\alpha$  is an important transcriptional cofactor that participates in regulating cellular metabolism. By binding to acetylated pGC-1, LINC00842 blocks SIRT1 deacetylation of pGC-1, stabilizing the pGC-1 level. The malignant phenotype of PDAC cells was enhanced by over-expression of LINC00842, which triggered metabolic switching from mitochondrial oxidative catabolic processes to fatty acid production<sup>122</sup>. The lncRNA romp regulates the characteristics of breast cancer stem cells (BCSCs) by mediating lipid metabolic processes. The XVI phospholipase A2 PLA2G16 is a prominent promoter of Group phospholipid metabolism and free fatty acid synthesis, specifically arachidonic acid. lncRPM binds to the

PLA2G16's 3' UTR to regulate PLA2G16 expression, which in turn activates PI3K/AKT, WNT/Catenin, and HIPPO/YAP signaling, which maintains BCSC stemness<sup>123</sup>. Lnc01564 promotes the survival of glucose-deficient hepatoma cells by activating the SSP. PHGDH is a rate-limiting enzyme in the SPP. Lnc01564 binds to PHGDH in a competitive manner, weakening the suppression of PHGDH induced by miR-107/103a-3p, leading to an increase in PHGDH expression and promoting hepatocellular carcinogenesis and cancer cell survival<sup>124</sup>. A 94-amino acid micropeptide adenosine triphosphate synthase-associated peptide (ASAP) encoded by LINC00467 has been identified in colorectal cancer. The peptide facilitates the assembly of adenosine triphosphate synthase subunits (ATP5A and ATP5C) by interacting with them to increase their activity levels and mitochondrial oxygen consumption rate, thereby favoring colorectal cancer cell proliferation<sup>125</sup>. In addition, lncRNAs are involved in cell apoptosis. Lnc-NA specifically regulates the expression of the nuclear receptor NR4A1 and increasing caspase apoptosis signaling pathway activation, thereby inhibiting tumor cell proliferation, invasion, and migration and promoting apoptosis in endometrial cell lineages<sup>126</sup>.

#### CircRNAs regulate metabolic reprogramming in cancer cells

CircRNAs are among the most extensively studied noncoding RNAs in the past few years. CircRNAs are derived from pre-mRNA reverse splicing and form a closed loop structure without a 5' end

cap or a 3' end polyA tail. Due to their unique closed loop structure, circRNAs are not degraded by exonucleases and have a long half-life<sup>127</sup>. The main finding thus far is that circRNAs function by interacting with RNA-binding proteins (RBPs), sponging mRNAs or being directly translated into peptides<sup>128</sup>. CircRNAs regulate cancer cell metabolism through regulatory mechanisms that have also been increasingly clarified<sup>129</sup>.

CircRNAs regulate metabolic reprogramming through as competitive endogenous RNAs (ceRNAs). CircRNAs adsorb (sponge) miRNAs to prevent miRNA binding to target genes and thus modulate the expression of miRNA-targeted genes. For example, circRPN2 has been shown to bind to enolase 1 (ENO1), accelerating its degradation. CircRPN2 promotes glycolytic reprogramming via the AKT/mTOR pathway to inhibit hepatocellular carcinoma cell metastasis. CircRPN2 is also an endogenous competitor for miR-183-5p binding, which upregulates forkhead box protein O1 (FOXO1) expression to suppress glucose metabolism and tumor progression<sup>130</sup>. The expression of circMAT2B is upregulated in HCC and is linked to the overall survival of HCC patients. Studies have shown that circMAT2B promotes glycolysis by activating the circMAT2B/miR-338-3p/PKM2 axis to induce HCC progression under hypoxic conditions. CircMAT2B positively regulates the expression level of PKM2 by sponging miR-338-3p. The PKM2 gene encodes a key enzyme in glycolysis<sup>131</sup>. CircEZH2 expression is upregulated in breast cancer (BC) liver metastases and is associated with a poor patient prognosis. Mechanistically, circEZH2 upregulates KLF5 expression by sponging miR-217-5p to promote tumorigenesis and metastasis. Moreover, transcriptional activation of FUS induced by KLF5 promotes circEZH2 reverse splicing. Thus, a novel FUS/CircEZH2-KLF5 feedback loop is established. Ultimately, KLF5 upregulates CXCR4 transcription and contributes to the liver metastasis of BC cells by promoting the epithelial-mesenchymal transition<sup>132</sup>.

CircRNAs affect metabolic reprogramming by regulating the expression of transcription factors. circECE1 is expressed at high levels in osteosarcoma (OS) tissues and cells. Knocking down circECE1 inhibits the proliferation and metastasis of tumor cells in vitro and in vivo. Mechanistically, circECE1 and c-Myc interact to hinder POZ-mediated degradation of ubiquitinated c-Myc. c-Myc represses the transcription of thioredoxin-binding protein (TXNIP), which in turn activates aerobic glycolysis<sup>133</sup>. Circ\_0010729 was overexpressed in human umbilical vein endothelial cells (HUVECs). Under hypoxic conditions, HUVECs promote endothelial cell proliferation by upregulating the expression of HIF-1 $\alpha$  due to miR-186 sponging<sup>134</sup>. Overexpression of circ-Erbin in colorectal cancer cells significantly increased the angiogenesis rate by upregulating HIF-1 $\alpha$  expression. Circ-Erbin sponges miR-125a-5p and miR-138-5p, targeting eukaryotic translation initiation factor 4E-binding protein 1 (4EBP-1) and accelerating HIF-1 $\alpha$  capsid protein translation in colorectal cancer cells<sup>135</sup>.

CircRNAs exert effects on cancer metabolism by regulating metabolism-related transporter and enzyme expression. Notably, circRNF13 expression is low in nasopharyngeal carcinoma clinical tissues and nasopharyngeal carcinoma cells. CircRNF13 inhibits the proliferation and metastasis of nasopharyngeal carcinoma cells in vitro and in vivo. Mechanistically, the binding of circRNF13 to the 3'-untranslated region (3'-UTR) of SUMO2 prolonged the SUMO2 gene half-life. SUMO2 glycosylation and GLUT1 ubiquitination promoted GLUT1 degradation and activated the AMPK-mTOR pathway through glycolytic inhibition, leading to nasopharyngeal carcinoma cell proliferation and metastasis<sup>136</sup>. CircACC1 is derived from ACC1 pre-mRNA and is critical to the cellular response to metabolic stress. Under serum deprivation conditions, the transcription factor c-Jun upregulates the expression of circACC1, which destabilizes and promotes AMPK enzyme activity, thereby promoting fatty acid oxidation and glycolysis<sup>137</sup>.

CircRNAs play important roles when they are translated into proteins. The circFNDC3B-encoded protein regulates Snail

expression to suppress colon cancer progression. Studies have indicated that circFNDC3B encodes proteins. Through functional experiments, circFNDC3B-218aa was shown to promote cell proliferation, invasion, migration, and glucose metabolism<sup>138</sup>.

How these epigenetic processes are coordinated remains unclear, despite the abundant research being reported. ncRNAs contribute to tumor development through their epigenetic roles in metabolic reprogramming. The functions of ncRNAs in regulating metabolic reprogramming are much more complex and deserve further exploration.

## EPIGENETIC MODIFICATION IN METABOLIC REPROGRAMMING AND CANCER THERAPY

In contrast to genetic mutations, abnormal changes in epigenetic signatures are usually reversible. Leveraging the reversibility of epigenetic modification to normalize abnormal epigenetic modification is a strategy for tumor treatment. For example, DNA methyltransferase inhibitors (DNMTis) and histone deacetylase inhibitors (HDACis) can be used to treat cancers because they change the patterns of DNA methylation and histone modification. DNMT3a catalyzes elevated DNA methylation of gene promoters in prostate cancer (PCa). Polo-like kinase 1 is involved in multiple aspects of the cell cycle. The combined application of Plk1 inhibition and the DNMT3a inhibitor 5-aza-2'-deoxycytidine (5-aza) is a novel and efficient treatment of prostate cancer<sup>139</sup>. KA2507 has been validated as a selective HDAC6 inhibitor. Apostolia M Tsimberidou et al.<sup>140</sup> conducted the first preclinical model and human evaluations of KA2507, and the results showed its antitumor efficacy and immunomodulatory effect. To date, a variety of DNMT inhibitors and HDAC inhibitors, such as azacitidine, decitabine, vorinostat, belinostat, and romidepsin, have been used to treat certain diseases, such as AML and myelodysplastic syndrome, increasing the choice for cancer patients, especially for those with hematological tumors<sup>141</sup>.

The immune system plays a major antitumor role. Cancer cells undergoing metabolism reprogramming interact with immune cells to disrupt normal immune function<sup>142</sup>. Epigenetic mechanisms are crucial for the activation, differentiation, and effector functions of immune cells. Some important immune-related genes, such as granzyme B, interferon- $\gamma$ , IL-2, IL-12, FoxP3, and STING, and immune checkpoint molecules (such as PD-1, CTLA-4, TIM-3, LAG-3, and TIGIT) can all be regulated in immune and cancer cells through epigenetic mechanisms. Small-molecule inhibitors of epigenetic regulators are expected to strengthen antitumor immune responses<sup>141,143</sup>. In mouse melanomas that are resistant to checkpoint inhibition, for instance, histone demethylase LSD1 knockdown increased tumor immunogenicity and T-cell infiltration, leading to a considerable response to anti-PD-1 therapy. LSD1 combined with anti-PD-1 immunotherapy may be effective against tumors<sup>144</sup>. Researchers found that using DNMTis combined with HDACis to treat NSCLC mice reversed tumor cell immune escape and promoted an increased response of NSCLC cells to immunotherapy<sup>145</sup>. Recently, chimeric antigen receptor (CAR) T-cell therapy has shown great success against cancer. However, several barriers have limited the efficacy of CAR T cells in cancer treatments. These challenges include the actions of immunosuppressive cells and molecules in the TME, inferior durability of CAR T cell expansion in vitro, and barriers to CAR T-cell infiltration and transport to tumor locations. Compared with T cells from healthy people, T cells from individuals with cancer have shown dysregulated epigenetic modification. Several barriers to CAR T-cell therapy may be overcome through epigenetic remodeling that increases T-cell endurance and viability, reduces their depletion, increases their infiltration to facilitate the acquisition of a memory phenotype<sup>146</sup>.

Furthermore, with the emergence of gene therapy, editing the epigenome has become increasingly important to epigenetic

modification-based therapy and is worth further exploration. Epigenetic modification editing therapies require agent binding to target DNA while regulating DNA methylation and mediating histone modifications. Long-term studies of DNA-binding domains have led to the discovery of enzymes capable of writing or erasing epigenetic marks. Precise editing of the epigenome is at the forefront of research. Several companies, such as Chroma Medicine and Tune Therapeutics, are working on epigenome editing, and both companies are developing DNA-binding proteins, inactivated versions of Cas9 (“dead” Cas9, dCas9) or zinc finger structural proteins that target different enzymes. The aim is to create therapies that act on specific gene loci to control gene expression at the genome level<sup>147</sup>. Gersbach’s group is conducting large-scale screening to identify candidate epigenome sequences for editing. They have identified a CRISPR–Cas9-based acetyltransferase that activates promoters and enhancers in the epigenome, providing a powerful tool for manipulating gene regulation<sup>148</sup>. “Epigenome editing” offers a precise therapeutic pathway for targeting site-specific epigenetic disorders, preventing the effects of untargeted editing. In summary, targeted epigenetic mark are reprogrammed. Various gene-editing technologies, such as zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and short palindromic repeat sequences (CRISPR–CAS9), have transformed the landscape of genome editing by offering extraordinary control and accuracy<sup>149</sup>. Future epigenome-editing therapies are expected to lead to revolutionary breakthrough therapies in cancer.

Alterations in the three-dimensional structure of chromatin show promise for cancer therapy. Almossalha et al.<sup>150</sup> combined simulation, systematic modeling and in vitro experiments to establish a physically regulated framework for regulating genomic information based on heterogeneous chromatin-packing density. CBL0137 is an anticancer compound that restores the function of the tumor suppressors TP53 and RB. Furthermore, the combined use of CBL0137 and panobinostat markedly prolonged the viability of mice transplanted with diffuse intrinsic pontine glioma (DIPG) cells, offering a promising treatment strategy for DIPG<sup>151</sup>.

## CONCLUSIONS

In the past two decades, epigenetics in cancer has been greatly advanced, and numerous studies have suggested that epigenetic modifications exert an important regulatory effect on metabolic reprogramming in tumor cells. Similarly, studies have shown that the epigenome is sensitive to the metabolic state of cells and that metabolites play critical roles in the epigenetic reprogramming of oncogenic pathways. Metabolites produced via the glycolytic cycle and in oxidative phosphorylation and other pathways are cofactors or substrates for enzymatic reactions involved in epigenetic modifications and transcriptional regulation, such as S-adenosylmethionine (SAM) and methylation, acetyl coenzyme A and acetylation, and ATP and phosphorylation<sup>18</sup>. Metabolic reprogramming can influence the activity of epigenetic chromatin regulators. Metabolites can function as competitive inhibitors of chromatin modifications<sup>152</sup>. Therefore, the effects of altered metabolism in cancer cells on epigenetic modifications cannot be ignored. Metabolic reprogramming and epigenetic modifications in cancer cells interact in a bidirectional manner. These interactions may contribute to tumorigenesis.

Metabolic variations and aberrant epigenetic regulation are common in many cancers. They are promising targets for anticancer therapy. The reversibility of epigenetic modifications provides opportunities to correct their abnormal modifications. Therefore, using epigenome-targeted drugs to promote the normalization of metabolic reprogramming in cancer cells will become an important strategy for cancer treatment. Although the field has made great progress in recent years, some new problems have emerged, such as poor drug specificity and toxic side effects.

Therefore, the development of targeted strategies for specific genes has important scientific and clinical significance.

The EZH2 inhibitor tazemetostat has been approved for EZH2-mutant lymphoma and INI1-deficient soft tissue sarcoma, signaling is a major breakthrough in epigenetics-based medicine. An innovative therapy for epithelioid sarcoma indicates that EZH2 inhibitors show very promising prospects for the treatment of solid tumors that have been difficult to achieve by previously developed epigenetics-based drugs. These major breakthroughs continue to increase the research and development of epigenetic drugs. In addition, the mechanisms by which different epigenetic modifications work together in the same cell are intriguing areas of research. Studies have shown interactions between different modifications<sup>153</sup>. For example, interactions between m6A RNA methylation modifications and other epigenetic marks are involved in tumor progression<sup>154</sup>. Bidirectional regulation between DNA methylation marks and chromatin triggers the methylation or demethylation of DNA<sup>155</sup>. In the future, considerable effort will be needed to characterize the interactions of these epigenetic marks with metabolic reprogramming factors in cancer cells. Exploring potential remedies to correct aberrant epigenetic remodeling and establish metabolic balance in cancer cells show potential for cancer treatments.

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### AUTHOR CONTRIBUTIONS

X.X., Q.P., X.J., S.T., Y.Y., W.Y., Y.H., Y.C., L.O., J.L., L.X., M.P., N.W., and Y.T. collected the related papers and drafted the manuscript. J.L., Q.L., and Y.Z. revised and finalized the manuscript. All authors read and approved the final manuscript.

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### COMPETING INTERESTS

The authors declare no competing interests.

### ADDITIONAL INFORMATION

**Correspondence** and requests for materials should be addressed to Jinyun Li, Qianjin Liao or Yujuan Zhou.

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