Understanding the epigenetic regulation of lactylation and aberrant lactate metabolism in cancer: From mechanisms to therapeutic strategies (Review)

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Received October 9, 2025; Accepted January 29, 2026

DOI: 10.3892/ijo.2026.5906

Abstract. Tumor metabolic reprogramming is a hallmark of cancer, supporting adaptation to hostile microenvironments and sustained malignancy. Among these changes, abnormal lactate metabolism is central to tumor progression, immune evasion and therapy resistance. Lactate, once considered a mere glycolytic byproduct, also acts as a signaling molecule influencing cancer behavior. Epigenetic mechanisms, including DNA/RNA methylation, histone modifications and non-coding RNAs, serve key roles in regulating lactate metabolism. Notably, lactylation, a novel post-translational modification, links lactate metabolism with epigenetic control. The present review outlines the molecular basis of lactate dysregulation, its epigenetic control and its biological impact on cancer, and highlights emerging therapeutic strategies targeting lactate metabolism.

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Key words: tumor metabolic reprogramming, lactate metabolism, epigenetic regulation, lactylation, antitumor drugs

Contents

1. Introduction

Cancer cells undergo metabolic reprogramming to support their rapid proliferation and survival by adapting to environmental challenges and altering metabolic pathways (1). These adaptive changes provide essential energy and biosynthetic precursors, thereby promoting tumorigenesis and progression. As a result, metabolic dysregulation has been recognized as a hallmark of cancer (2). In addition to fueling growth, tumor metabolic reprogramming serves a central role in modulating oncogenic signaling pathways and shaping the tumor immune microenvironment through the release of metabolites and regulation of immune modulators, ultimately contributing to immune evasion and resistance (3). Among these alterations, the reprogramming of lactate metabolism has emerged as a critical driver of tumor progression and microenvironmental remodeling. Lactate, which was traditionally considered a metabolic waste product of glycolysis, is now recognized as a multifunctional metabolite that can act as a signaling molecule to regulate essential oncogenic processes, including cell proliferation, angiogenesis, immune suppression and therapy resistance (4,5). This paradigm shift underscores the broader biological importance of lactate in tumor development.

Epigenetic modifications, as dynamic regulators of gene expression in response to environmental cues, serve a key role in the control of cancer metabolism (6). Mechanisms such as DNA methylation, RNA methylation, histone modifications and non-coding RNA (ncRNA)-mediated regulation are closely involved in the expression of key enzymes and transporters associated with lactate metabolism. These epigenetic alterations often interact with aberrant lactate metabolism to synergistically sustain malignant phenotypes (7). Notably, lactylation is a relatively recently identified post-translational modification (PTM); this phenomenon has emerged as a potential epigenetic link between lactate metabolism and gene regulation (8). However, its functional role in cancer remains largely unclear.

The present review provides a comprehensive overview of the molecular mechanisms underlying dysregulated lactate metabolism in tumors, the role of epigenetic regulation and the biological importance of lactylation. It further discusses therapeutic strategies targeting lactate metabolism, aiming to offer novel insights and theoretical foundations for cancer metabolism research and the development of metabolism-based cancer therapies.

2. Molecular basis of aberrant lactate metabolism in cancer

Lactate synthesis: Glycolysis and lactate dehydrogenase (LDH). Under physiological conditions, glucose undergoes glycolysis in the cytoplasm of normal cells (Fig. 1), yielding two molecules of pyruvate along with a small amount of ATP and NADH. Depending on oxygen availability, pyruvate enters the mitochondria under aerobic conditions for complete oxidation via the tricarboxylic acid (TCA) cycle, where it produces CO_2, H_2O, NADH and FADH2 to fuel oxidative phosphorylation (OXPHOS). Under anaerobic conditions, pyruvate is instead reduced to lactate, regenerating NAD^+ to sustain glycolysis.

In healthy cells, glycolysis and mitochondrial respiration operate synergistically, enabling the complete oxidation of glucose and the production of up to 38 ATP molecules, ensuring sufficient energy for cellular functions. However, cancer cells exhibit a distinct metabolic preference known as the Warburg effect, whereby they rely heavily on aerobic glycolysis even in the presence of oxygen (9). This less efficient pathway generates only two ATP molecules per glucose molecule, with lactate as the major end product. Several factors contribute to this metabolic shift in cancer cells (Fig. 2): i) Tumor cells have a high demand for energy that relies more on efficient glycolysis than on the TCA cycle and OXPHOS (9). ii) Intracellular regulatory mechanisms: Compared with normal cells, cancer cells have a lower dependence on OXPHOS, which helps to avoid the inhibition of glycolytic pathways by ATP, citrate and reactive oxygen species (ROS) (10). Additionally, a reduction in ROS production can decrease cytotoxicity and improve survival rates (11). Furthermore, lactate production helps convert NADH to NAD^+, thus preventing the depletion of NAD^+, which could lead to cell death (12). iii) Importance of intermediates: The intermediates of glycolysis can serve as precursors for the synthesis of amino acids, nucleotides, fatty acids and glycogen, promoting the growth of tumor cells (9). iv) Impact of the tumor microenvironment (TME): The hypoxic conditions present in the TME enhance glycolysis while inhibiting the activity of OXPHOS (13). Moreover, lactate, the final product of glycolysis, acts as a signaling molecule, helping shape the TME and enhancing the adaptability of cancer cells under hypoxic conditions. The enzyme LDH serves a central role in the reversible conversion of pyruvate to lactate while maintaining the NAD^+/NADH redox balance. LDH exists as five tetrameric isoenzymes, LDH1-LDH5, which are composed of varying combinations of two subunits, LDHA and LDHB. These isoenzymes exhibit distinct tissue distributions and functional roles (14,15). Notably, LDHA (also known as LDH-M) predominantly catalyzes the conversion of pyruvate to lactate and is frequently upregulated in cancer cells with high glycolytic activity, thereby promoting the Warburg effect and contributing to malignant progression (16).

Lactate transport: Monocarboxylate transporters (MCTs). As aforementioned, tumor cells predominantly generate large amounts of lactate through aerobic glycolysis. The accumulation of intracellular lactate can lead to acidification of the cytosol, necessitating timely and efficient export of lactate to maintain the intracellular pH balance and metabolic homeostasis. The transport of lactate across the plasma membrane is primarily mediated by MCTs, a family of transmembrane proteins that specifically facilitate the proton-coupled transport of monocarboxylates such as lactate and pyruvate (17). In this mechanism, lactate forms a complex with protons and is transported out of the cell via MCTs (18). Initially, MCTs were considered merely passive channels for metabolic waste disposal; however, increasing evidence has suggested that MCTs serve crucial roles in shaping the TME and facilitating immune evasion (19,20). Among them, MCT1 and MCT4 are key isoforms involved in lactate transport, and are frequently upregulated in breast cancer, colorectal cancer (CRC), lung cancer and glioma (21).

The expression of these genes is closely associated with increased glycolytic activity, and enhanced potential for cell migration and invasion. MCT1 is broadly expressed in both normal and tumor tissues, with high affinity for both lactate and pyruvate, and is involved primarily in lactate uptake (22,23). By contrast, MCT4 is highly expressed in glycolytic tumor cells, has a relatively high affinity for lactate (24) and mainly mediates lactate efflux (25,26). The expression and activity of MCTs are regulated by multiple mechanisms. Hypoxia, a hallmark of solid tumors, activates hypoxia-inducible factor-1 (HIF-1), which transcriptionally upregulates MCT4 and other lactate transport-related genes. Additionally, signaling pathways such as p53 can influence lactate transport by modulating the expression and function of MCTs (21). Intracellular factors such as pH (27) and calcium concentration (28) also contribute to the fine-tuning of MCT activity.

In summary, through MCT-mediated lactate transport, tumor cells efficiently export excessive lactate to adapt to their metabolic demands and microenvironmental challenges. This process supports sustained tumor growth and progression, highlighting the potential of MCTs as therapeutic targets in cancer metabolism.

3. Epigenetic regulation of tumor lactate metabolism

DNA methylation and tumor lactate metabolism. DNA methylation is a pivotal epigenetic modification involving

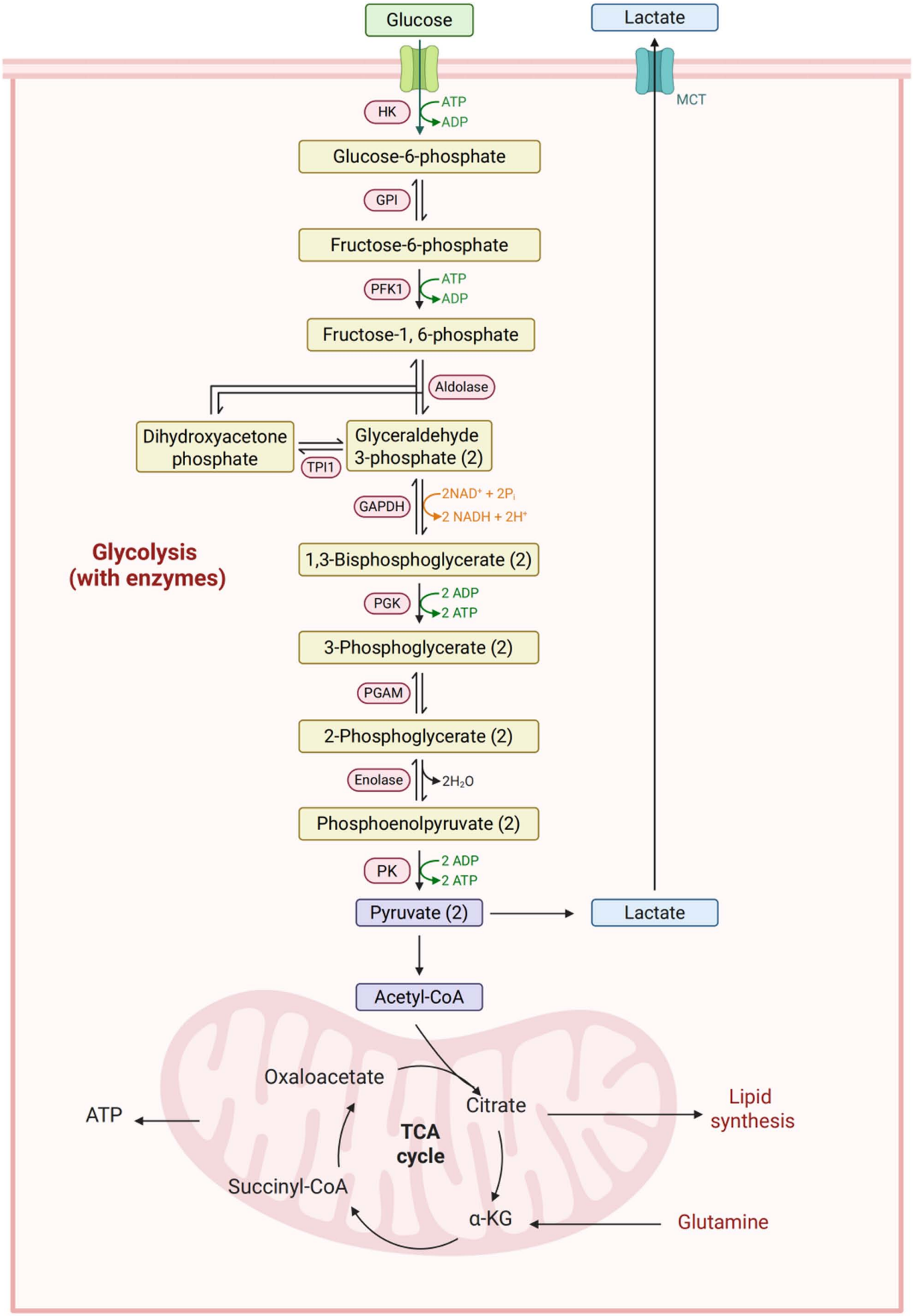

Figure 1. Schematic representation of the lactate metabolism pathway in normal cells. This figure was created by BioRender (https://app.biorender.com/illustrations/685841de2c2cb4570b690-737). HK, hexokinase; MCT, monocarboxylate transporter; GPI, glucose-6-phosphate isomerase; PFK1, phosphofructokinase-1; TPI1, triosephosphate isomerase; GAPDH glyceraldehyde-3-phosphate dehydrogenase; PGK, phosphoglycerate kinase; PGAM, phosphoglycerate mutase; PK, pyruvate kinase; α-KG, α-ketoglutarate; TCA, tricarboxylic acid.

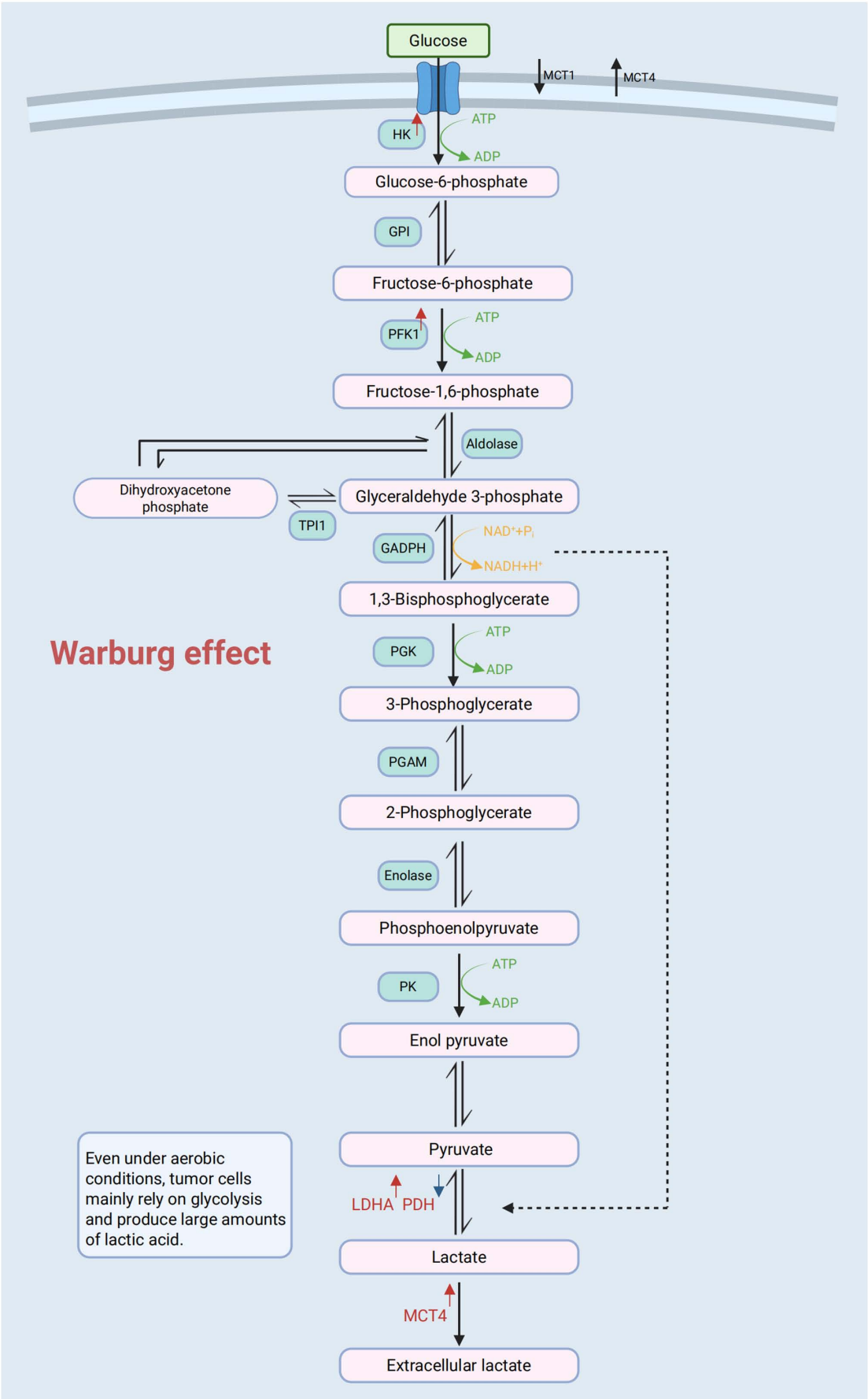

Figure 2. Schematic representation of the accelerated lactate metabolism and glycolytic flux in tumor cells. This figure was created by BioRender (https://app.biorender.com/illustrations/6888bcd4da40e158a01eaaed). MCT, monocarboxylate transporter; HK, hexokinase; GPI, glucose-6-phosphate isomerase; PFK1, phosphofructokinase-1; TPI1, triosephosphate isomerase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; PGK, phosphoglycerate kinase; PGAM, phosphoglycerate mutase; PK, pyruvate kinase; LDHA, lactate dehydrogenase A; PDH, pyruvate dehydrogenase.

the covalent addition of a methyl group to a DNA molecule, which is typically catalyzed by DNA methyltransferases (DNMTs) (29-31). This process commonly occurs at cytosine residues within CpG dinucleotides, particularly within CpG islands (32). Under the catalytic activity of DNMTs, a methyl group from S-adenosylmethionine is transferred to cytosine, forming 5-methylcytosine (5-mC). Although DNA methylation does not alter the DNA sequence, it serves a crucial role in regulating gene expression and maintaining cellular identity (33).

In cancer biology, aberrant DNA methylation is closely associated with tumor initiation, progression and metastasis. Notably, research has highlighted its role in modulating lactate metabolism in tumors, a hallmark of cancer metabolism (34). By regulating genes involved in glycolysis, lactate production, transport and utilization, DNA methylation contributes to the metabolic reprogramming of tumor cells and shapes the TME, ultimately influencing tumor growth, survival and immune escape. To meet the high energy demands of rapid proliferation, tumor cells preferentially utilize aerobic glycolysis, or the Warburg effect, which leads to excessive lactate production (35). DNA methylation acts as a key regulator in this metabolic shift. It alters the expression of critical metabolic enzymes such as hexokinase 2 (HK2) (36) and LDHA, as well as signaling molecules, thereby reshaping tumor metabolic phenotypes. For example, hypermethylation of the HK2 promoter has been shown to suppress its transcription, reducing glycolytic flux and lactate production, and ultimately impeding CRC progression (37). In ovarian cancer, DNMT3A-mediated methylation of the microRNA (miRNA/miR)-603 promoter silences miR-603, which normally suppresses HK2. The resulting upregulation of HK2 promotes glucose uptake and lactate generation, enhancing tumor cell growth and invasion (38). Similarly, in isocitrate dehydrogenase (IDH)-mutant glioma, hypermethylation of the LDHA promoter inhibits transcription factor binding, downregulates LDHA expression (39) and reduces lactate production, impairing glycolytic capacity and tumor growth (40).

Lactate transport across the cell membrane is essential for maintaining metabolic homeostasis and promoting cancer progression. DNA methylation also regulates this process by modulating the expression of MCTs (41). In renal cancer, methylation of the SLC16A3 promoter reduces MCT4 expression, hindering lactate export and leading to intracellular lactate accumulation and microenvironmental alterations (42). Conversely, the inhibition of DNMTs with agents such as 5-azacytidine can induce methylation at the MCT1 promoter, downregulating its expression and impairing lactate uptake, which inhibits tumor cell survival (43). Notably, some enzymes, such as histone-lysine (K) N-methyltransferase SETDB (SETDB1), promote MCT1 expression via histone H3K9 trimethylation, increasing lactate uptake and activating oncogenic pathways, such as the PI3K/AKT and MAPK pathways, to support cancer progression (41). Moreover, DNA methylation influences upstream regulators of glucose metabolism. In esophageal squamous cell carcinoma, DNMT1-mediated hypermethylation of the RAR related orphan receptor A (RORA) promoter suppresses RORA expression, reducing its inhibitory effect on SLC2A3 [a glucose transporter (GLUT)], thereby increasing glucose uptake and glycolytic activity, leading to lactate accumulation and tumor progression (44).

Intracellular lactate metabolism is tightly regulated by enzymes such as LDHB. In breast cancer, frequent methylation of the LDHB promoter silences its expression, disrupting lactate-to-pyruvate conversion, leading to lactate accumulation that supports tumor growth and immune evasion (45). Similarly, in hepatocellular carcinoma (HCC), LDHB promoter methylation suppresses lactate clearance, exacerbating acidosis in the TME, and promoting proliferation and metastasis while inhibiting immune cell function (46). Additionally, in melanoma, hypomethylation of the transketolase-like-1 promoter enhances its expression, linking the pentose phosphate pathway to glycolysis, and increasing aerobic glycolysis and lactate production, thereby supporting immune escape and tumor progression (47). Notably, epigenetic regulation does not act in isolation. Transcription factors such as HIF-1α are central to lactate metabolism and simultaneously regulate glycolytic gene expression, MCT expression and mitochondrial function (48). For example, in oral squamous cell carcinoma, ASC stabilizes HIF-1α, which in turn enhances the transcription of glycolysis-related genes (49). In hypoxic pancreatic tumors, HIF-1α activation further drives glycolytic reprogramming by binding to hypoxia response elements (50). DNA methylation serves as a pivotal epigenetic mechanism that drives the tumor glycolytic phenotype through three core pathways in coordination with HIF-1α: i) Silencing negative regulators of HIF-1α via hypermethylation, enabling sustained HIF-1α activation to establish the foundation for metabolic reprogramming (51); ii) activating HIF-1α downstream glycolytic genes through hypomethylation, enhancing glucose uptake and lactate fermentation; and iii) suppressing mitochondrial aerobic respiration genes via hypermethylation, epigenetically obstructing OXPHOS and redirecting metabolic flux toward glycolysis (52).

In summary, DNA methylation is a key epigenetic mechanism that regulates various aspects of lactate metabolism in cancer, including glycolysis, lactate transport and downstream metabolic pathways. By influencing genes such as HK2, LDHA, LDHB, MCT1 and MCT4, as well as modulators such as HIF-1α, DNA methylation reshapes tumor metabolism and contributes to immune suppression, microenvironmental changes and tumor aggressiveness. Understanding these mechanisms may pave the way for novel therapeutic strategies targeting epigenetic and metabolic vulnerabilities in cancer.

RNA methylation and tumor lactate metabolism. RNA methylation, accounting for >60% of all RNA modifications, has emerged as a crucial mechanism in the epitranscriptomic regulation of gene expression (53). The major RNA methylation types include N6-methyladenosine (m6A), N1-methyladenosine, 2'-O-dimethyladenosine, 7-methylguanine (m7G) and 5-mC (Table I) (54). Among these, m6A is the most abundant and functionally diverse modification and is enriched near stop codons, 3' untranslated regions (3'UTRs), and both intronic and exonic regions of precursor and mature mRNAs. It serves key roles in mRNA decay, splicing and translation (55). RNA methylation (Fig. 3) is dynamically regulated by three groups of proteins: Methyltransferases [‘writers’, such as methyltransferase 3, N6-adenosine-methyltransferase

Table I. Key regulatory targets of RNA methylation in tumor lactate metabolism.

First author, year	Molecule	Cancer type	Biological function	(Refs.)
A, m6A methylation				
Mei, 2024	NAT10	Osteosarcoma	Stabilizes YTHDC1 mRNA → Upregulates LDHA/PFKM → Promotes glycolysis in osteosarcoma (oncogenic)	(62)
Liu, 2023	ALKBH5	LUAD	Reduction of m6A modification level on Wnt5B mRNA → Decreased expression of PFKFB3 → Inhibition of glycolysis in LUAD (tumor suppressive effect)	(65)
Sun, 2024	IGF2BP3	LUSC	Stabilization of CTCF mRNA → Upregulation of NT5DC2 → Enhancement of glycolysis in LUSC (tumor-promoting)	(66)
Mei, 2024	YTHDC1	Osteosarcoma	Mediation of LDHA/PFKM mRNA stability → Promotion of glycolysis in osteosarcoma (tumor-promoting)	(62)
B, m7G				
Wang, 2024	METTL1	CRC	Upregulation of PKM2 expression → Promotion of lactate production and histone lactylation → Driving CRC progression (tumor-promoting)	(64)

ALKBH5, AlkB homolog 5, RNA demethylase; CRC, colorectal cancer; CTCF, CCCTC-binding factor; IGF2BP, insulin-like growth factor 2 mRNA-binding protein; LDHA, lactate dehydrogenase A; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; m6A, N6-methyladenosine; METTL3, methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit; NAT10, N-actetyltransferase 10; NT5DC2, 5'-nucleotidase domain containing 2; PRMT7, protein arginine methyltransferase 7; TNBC, triple-negative breast cancer; YTHDC1, YTH m6A RNA binding protein C1.

complex catalytic subunit (METTL3), methyltransferase 1, transfer (t)RNA methylguanosine (METTL1) and N-actetyltransferase 10 (NAT10)], binding proteins ['readers', such as insulin-like growth factor 2 mRNA-binding protein (IGF2BP)1, IGF2BP3 and YTH m6A RNA binding protein C1 (YTHDC1)] and demethylases ['erasers', such as fat mass and obesity-associated protein and AlkB homolog 5, RNA demethylase (ALKBH5)]. These factors collectively orchestrate the methylation landscape, thereby influencing the processing, localization, translation (56) and stability of various RNA species, including mRNAs, tRNAs and long ncRNAs (lncRNAs) (57).

Studies have revealed that dysregulated RNA methylation is closely associated with tumorigenesis and progression in a wide range of cancers, including HCC, CRC, gastric cancer, lung cancer and prostate cancer, underscoring its potential value in cancer diagnosis and therapy (58-60). RNA methylation modulates lactate metabolism primarily by influencing the stability, splicing or translational efficiency of key glycolytic enzymes. For example, lactate, which is primarily generated by LDHA, can be regulated at multiple levels via RNA modifications. In lung adenocarcinoma (LUAD), lactate uptake via MCT1 induces K lactylation (Kla) of RNA binding motif protein 15 (RBM15) at K850, which prevents RBM15 degradation and enhances m6A methylation. This stabilizes LDHA mRNA and promotes lactate production, forming a lactate-RBM15-m6A-LDHA positive-feedback loop that promotes cancer progression via sustained metabolic and epigenetic signaling (61).

Additionally, NAT10-mediated N4-acetylcytidine acetylation stabilizes YTHDC1 mRNA, which in turn promotes the expression of glycolytic enzymes such as LDHA and phosphofructokinase (PFK)M, increasing glucose uptake and lactate production in osteosarcoma (62). In triple-negative breast cancer, the METTL3/IGF2BP1 axis stabilizes protein arginine methyltransferase 7 mRNA through an m6A-dependent mechanism, activating the WNT/β-catenin pathway and specifically enhancing glycolytic activity (63). Similarly, METTL1-mediated m7G modification promotes pyruvate kinase isozymes M1/M2 (PKM2) expression in CRC, forming a METTL1/PKM2/H3K9la loop that not only drives lactate production but also facilitates histone lactylation, thereby integrating metabolic changes with transcriptional regulation (64).

Moreover, increased lactate export acidifies the TME, which further activates METTL3 and perpetuates a pro-tumorigenic feedback loop (61). On the other hand, demethylases can reverse RNA methylation and inhibit lactate metabolism. For example, IL-37 suppresses ALKBH5 expression, increasing m6A methylation of Wnt5B mRNA and downregulating its expression. Concurrently, IL-37 reduces the expression of the glycolytic enzyme PFKFB3, leading to decreased glucose uptake and lactate production, thereby impeding LUAD progression (65). Reader proteins further contribute to lactate metabolism by selectively recognizing methylated

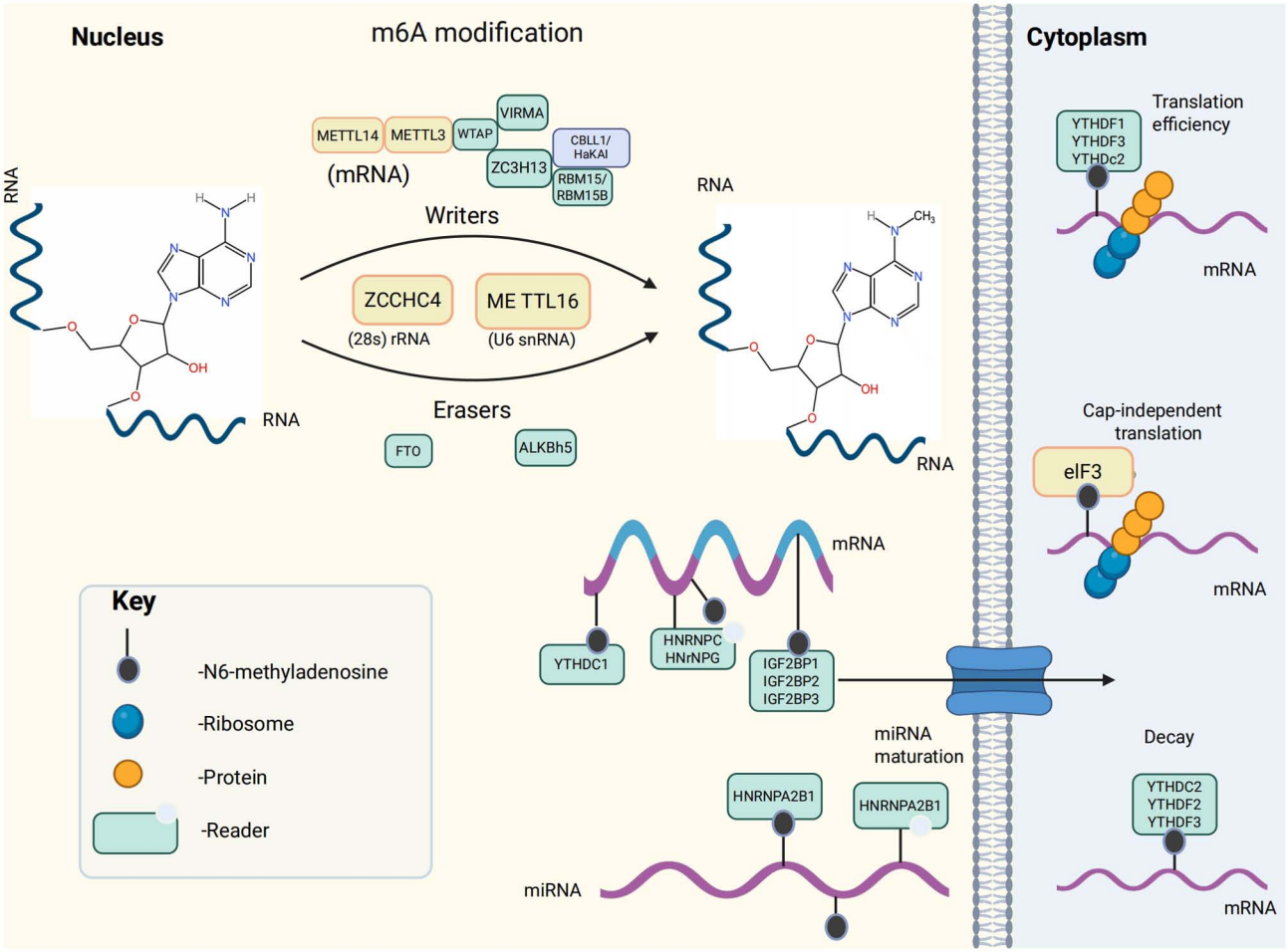

Figure 3. Overview of RNA methylation patterns across diverse RNA species. This figure was created by BioRender (https://app.biorender.com/illustrations/68897e3dc97a6429d4aab32b). m6A, N6-methyladenosine; miRNA, microRNA; rRNA, ribosomal RNA; snRNA, small nuclear RNA.

RNAs. In lung squamous cell carcinoma, IGF2BP3 binds to m6A-modified CCCTC-binding factor (CTCF) mRNA and activates the IGF2BP3/CTCF/5'-nucleotidase domain containing 2 (NT5DC2) axis, which enhances glycolysis through the upregulation of NT5DC2 (66). In CRC, IGF2BP2 binds to the m6A-modified lncRNA ZFAS1 and activates the ATPase activity of Obg like ATPase 1 (OLA1), forming a metabolism-epigenetics regulatory network that drives the Warburg effect (66).

Overall, RNA methylation serves as a multilayered and multidimensional regulator of lactate metabolism in tumors. Multiple positive feedback loops between RNA methylation and lactate production reinforce metabolic adaptation and tumor growth. The involvement of readers and erasers further adds dynamic complexity to this regulatory network. These findings highlight the critical role of RNA modifications in tumor metabolic reprogramming and suggest novel therapeutic opportunities for targeting the epitranscriptome in cancer.

Histone methylation and tumor lactate metabolism. In eukaryotic cells, genetic information is stored in a highly organized chromatin structure. The fundamental unit of chromatin, the nucleosome, consists of DNA wrapped around histone octamers composed of H2A, H2B, H3 and H4 (67). PTMs, such as methylation, occur on the N-terminal tails and globular domains of histones, modulating gene expression and DNA repair by altering chromatin structure or recruiting transcriptional regulators (68). Histone methylation is dynamically regulated by methyltransferases ['writers' such as SET and MYND domain containing 2 (SMYD2), SETD1A and SETDB1] and demethylases ['erasers' such as K demethylase 6A/B (KDM)6A/B and KDM8], and is recognized by specific 'reader' proteins (such as CHD1 and BPTF) (67). Aberrant histone methylation is closely linked to tumor development and serves a key role in metabolic reprogramming (69).

As with RNA methylation, histone methylation enzymes can deposit methyl marks (such as H3K4me3, H3K9me3 and H3K27me3) at the promoters or enhancers of genes involved in lactate metabolism, thus regulating their transcription. In cervical cancer, SMYD2 suppresses p53 transcriptional activity via K370 methylation, thereby impairing its tumor suppressive function. This modification also downregulates genes involved in OXPHOS, shifting tumor metabolism toward glycolysis, as evidenced by increased glucose uptake and lactate production (70). In gastric cancer, SMYD2 enhances apolipoprotein C1 expression through H3K4me3 modification, promoting glycolysis and cell proliferation (71). Similarly, SETD1A, another H3K4 methyltransferase, interacts with HIF-1α to increase its transcriptional activity, thereby upregulating the expression of glycolytic genes such as GLUT1, HK2

and LDHA, and ultimately accelerating tumor glycolysis and progression (72).

SETDB1 serves dual regulatory roles in breast cancer. It promotes the nuclear transport-dependent activation of the c-MYC/LDHA axis and directly methylates LDHA at K155 (73). Notably, SETDB1 also catalyzes K473 trimethylation on MCT1, a novel PTM that blocks Toll-interacting protein-mediated autophagic degradation, prolonging the MCT1 half-life. The resulting increase in lactate secretion maintains high glycolytic flux in tumor cells and induces M2 polarization of tumor-associated macrophages (TAMs) via G protein-coupled receptor (GPR)132 activation, linking tumor metabolic reprogramming with immune microenvironment remodeling (42).

Demethylases also serve pivotal roles in lactate metabolism. KDM6A/B promotes the expression of glycolytic genes such as GLUT1, HK2 and LDHA by removing H3K27me3 marks, enabling detached tumor cells to maintain their glycolytic activity and energy supply during metastasis (74). JMJD5 contributes to metabolic adaptation under hypoxia by demethylating H3K36me2, thereby stabilizing HIF-1α and facilitating PKM2-dependent glycolysis (75).

Histone acetylation and tumor lactate metabolism. Histone acetylation is a key epigenetic modification that regulates chromatin structure and gene expression, and serves a pivotal role in various biological processes. In the context of tumor metabolic reprogramming, histone acetylation is closely linked to lactate metabolism, influencing cancer cell energy production, shaping the TME and contributing to therapeutic resistance (76). This modification is dynamically regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). These enzymes not only acetylate histones but also target non-histone proteins, including metabolic enzymes and transcription factors, thereby altering their activity, stability or subcellular localization. Through these mechanisms, HATs and HDACs modulate the glycolytic pathway and lactate production, ultimately promoting metabolic adaptation in tumor cells (77).

HATs and tumor lactate metabolism. HATs catalyze the acetylation of K residues on histone tails and non-histone proteins, thereby modulating their transcriptional activity and participating in diverse biological processes. HATs are broadly classified into three major families on the basis of their structural and functional features: GCN5-related N-acetyltransferase, MYST and p300/CREB-binding protein (CBP). Dysregulation of HAT activity has been closely associated with the initiation and progression of multiple types of cancer (78).

The MYST family, a highly conserved class of HATs, includes KAT5 (Tip60), KAT6A, KAT6B, KAT7 (HBO1/MYST2) and KAT8. These enzymes contain a characteristic MYST domain composed of an acetyl-CoA binding motif and a zinc finger, enabling the acetylation of nuclear and cytoplasmic proteins involved in chromatin remodeling, transcription regulation, DNA damage repair and tumorigenesis (79). KAT5 (Tip60) acetylates both histone and non-histone substrates, and serves a critical role in chromatin dynamics and the DNA damage response (80). In cancer cells exhibiting elevated lactate production due to the Warburg effect, KAT5 directly interacts with nibrin (NBS1) and catalyzes lactylation at K388, promoting the assembly of the MRE11-RAD50-NBS1 complex. This enhances DNA repair efficiency and contributes to chemoresistance (81). KAT7 (HBO1) requires association with scaffold proteins such as bromodomain and PHD finger containing 1 or jade family PHD finger 1 to exert its function. Depending on the complex formed, KAT7 acetylates histone H3 (at K14 and K23) or H4 (at K5, K8 and K12), participating in physiological processes such as DNA replication, transcription regulation, protein ubiquitination, immune modulation and stem cell pluripotency (82). Notably, KAT7 acetylates LDHA at K118, increasing its enzymatic activity and expression. This promotes lactate production and facilitates tumor proliferation and metastasis in head and neck squamous cell carcinoma (HNSCC), acting as a pro-oncogenic factor (83).

The p300/CBP family comprises two paralogous coactivators, CBP and p300, each containing a bromodomain. These HATs regulate a wide array of transcription factors, including HIF-1α, and are essential for cell cycle progression, differentiation and growth, with strong implications for cancer development (84,85). In multiple myeloma, acute inhibition of p300/CBP reduces histone acetylation and promotes chromatin condensation, resulting in transcriptional repression. However, this suppression can be antagonized by the loss of the nuclear receptor corepressor 1 (NCOR1)/HDAC3 corepressor complex, identifying NCOR1 and HDAC3 as key modulators of p300/CBP activity (86). In lung cancer, Notch1 interacts functionally with p300 and p300/CBP-associated factor (PCAF) to upregulate glycolytic gene expression. Moreover, it forms a positive feedback loop with TAZ, whereby the Notch1/TAZ axis promotes glycolysis, enhances glucose uptake and lactate production, and suppresses cytotoxic T-cell and natural killer (NK) cell activity, ultimately facilitating immune evasion (87).

In LUAD, upregulation of uridine phosphorylase 1 promotes glycolytic metabolism and reduces sensitivity to the glycolysis inhibitor 2-deoxy-D-glucose (2-DG). This process is epigenetically regulated via p300/CBP-mediated histone acetylation, which contributes to enhanced cancer cell proliferation (88). Furthermore, even under aerobic conditions, cancer cells preferentially rely on glycolysis. PCAF influences cellular energy metabolism through HIF-1α and p53-dependent regulation of SCO2 and TIGAR expression. Notably, the effects of PCAF vary by cellular context: In the human osteosarcoma cell line U2OS, PCAF HAT activity increases glycolysis and lactate production, whereas in SaOS2 osteosarcoma cells, it suppresses these processes (89). These tissue-specific effects may be explained by differences in chromatin accessibility at glycolytic gene loci, as well as variations in acetyl-CoA availability, the essential substrate for PCAF-mediated acetylation (90). Together, these findings underscore the tight coupling between epigenetic regulation and metabolic state, highlighting the importance of cellular context in shaping metabolic phenotypes in cancer. The mechanisms underlying the tissue-specific effects of PCAF include: First, PCAF must access the regulatory regions of its target genes to function; in U2OS cells, the promoters of glycolysis-related genes may exist in an open chromatin state, allowing PCAF binding and transcriptional activation. By contrast, the same regions in SaOS2 cells might be embedded in heterochromatin or carry pre-existing repressive histone marks, preventing PCAF

access or nullifying its activation function (91). Second, the enzymatic activity of PCAF is directly influenced by substrate availability. The catalytic substrate of PCAF is acetyl-CoA, a central metabolic metabolite. U2OS cells may maintain higher acetyl-CoA levels, providing ample 'fuel' for PCAF HAT activity, and thereby promoting acetylation and activation of glycolytic genes. Conversely, lower acetyl-CoA levels in SaOS2 cells may restrict the activity of PCAF (92).

HDACs and tumor lactate metabolism. HDACs are enzymes that remove acetyl groups from K residues on histones, thereby regulating chromatin structure and gene expression. HDACs are grouped into four classes (I-IV) and include 18 isoforms. In addition to their roles in controlling cell proliferation and differentiation, HDACs influence non-histone protein acetylation in the nucleus, cytoplasm and mitochondria (84,93).

Class I HDACs. Class I HDACs serve as crucial mediators of the crosstalk between lactate metabolism and epigenetic regulation. Studies have demonstrated that lactate functions as an endogenous inhibitor of class I HDACs (primarily HDAC1/2/3) in a concentration-dependent manner, thereby relieving their transcriptional repression of target genes, reshaping the histone acetylation landscape and driving tumor progression (94,95). Across different cancer types, lactate exerts specific inhibitory effects on HDAC1/2/3 to differentially regulate cell cycle progression, immune responses and survival gene expression (94), establishing a critical bridge connecting tumor metabolic reprogramming with epigenetic dysregulation.

Lactate has emerged as an endogenous inhibitor of HDAC activity in a concentration-dependent manner. The lactate-induced gene expression profile notably overlaps with that induced by potent HDAC inhibitors, such as trichostatin A (TSA) and butyrate, suggesting that lactate primarily functions to upregulate gene expression by relieving HDAC-mediated transcriptional repression (94). In ovarian cancer, enhanced glycolysis mediated by paired like homeodomain 2 leads to intranuclear lactate accumulation, selectively inhibiting HDAC1/2 activity, increasing acetylation of histone H3/H4 and ultimately promoting the expression of cell cycle-related genes, such as CCND1, CDK4 and PCNA, ultimately enhancing tumor cell proliferation and tumor cell proliferation (96). In HNSCC, upregulated PKM2 enhances glycolytic flux and lactate production. Lactate inhibits HDAC3, which in turn lifts transcriptional repression of the immunosuppressive molecule galectin-9, aiding immune evasion (97). Conversely, in CRC, epigenetic silencing of LDHB and loss of the SLC5A8 transporter lead to decreased pyruvate and elevated lactate levels. This removes the basal inhibitory effect of pyruvate on HDAC1/3, enhancing HDAC activity and promoting survival gene expression, such as BCL2, MCL1 and BIRC5 (98). Various targeted strategies based on the intricate lactate-HDAC regulatory network have been developed. For example, somatostatin receptor-targeted micelles carrying the HDAC inhibitor thailandepsin A enhance drug accumulation in neuroendocrine tumors while minimizing systemic toxicity (99). Additionally, gold nanoparticles loaded with quercetin inhibit HDAC1/2 activity and simultaneously activate the p53-ROS apoptotic pathway, demonstrating dual anticancer mechanisms with high tumor selectivity (100).

Class II and IV HDACs. Class II HDACs are tissue-specific regulators of differentiation processes, including neurogenesis and myogenesis. They are subdivided into class IIa (HDAC4/5/7/9), which shuttle between the nucleus and cytoplasm, and class IIb (HDAC6/10), which possesses dual catalytic domains (101). Notably, HDAC6 regulates cell motility by modulating microtubule acetylation. In addition to its deacetylase activity, HDAC6 can catalyze lactylation at the K40 site of α-tubulin (102). This modification is lactate concentration-dependent: At low lactate levels (<1 mM), HDAC6 exhibits delactylase activity to stabilize microtubules, whereas at high levels (>1 mM), it promotes lactylation, enhances microtubule dynamics, and promotes neurite outgrowth and axonal regeneration (103). HDAC6 and the class IV enzyme HDAC11 physically interact in antigen-presenting cells and exert opposing regulatory effects on IL-10 expression. HDAC6 is essential for IL-10 transcriptional activation, whereas HDAC11 acts as a repressor (104). Tumor-derived lactate acts as a metabolic signal that fosters an immunosuppressive microenvironment by enhancing H3K27 acetylation in B cells and macrophages. This epigenetic reprogramming, which is dynamically balanced by HDAC-mediated deacetylation, leads to the transcriptional upregulation of IL-10, thereby driving the expansion of regulatory B cells and orchestrating tumor immune evasion (105).

Class III HDACs [sirtuins (SIRTs)]. Class III HDACs, also known as SIRTs (SIRT1-7), are NAD^+-dependent enzymes involved in diverse cellular functions (106). Each SIRT exhibits distinct subcellular localization and primarily targets nonhistone substrates (107). SIRT1, located in the nucleus, regulates the cell cycle, proliferation, differentiation and apoptosis. Myeloid CD38-mediated NAD^+ depletion suppresses SIRT1 activity, thereby promoting glycolytic lactate production and shifting macrophage polarization toward a pro-tumorigenic phenotype that facilitates cancer progression (108) In renal cell carcinoma, lactate downregulates SIRT1 expression, leading to increased acetylation of histones H3 and H3K9, promoting epithelial-mesenchymal transition (EMT), and enhancing tumor cell migration and invasion (109). SIRT2 is expressed mainly in the cytoplasm and regulates diverse biological functions, including metabolism, mitosis and neurotoxicity. In hepatocellular carcinoma, SIRT2 acts as a pro-tumorigenic regulator by deacetylating PGAM2 at K100, which leads to its degradation and subsequent loss of its tumor-suppressive function. This SIRT2-mediated depletion of PGAM2 triggers LDHA upregulation and enhances lactate production through STAT3 activation, thereby driving aerobic glycolysis and HCC progression (110). SIRT3 is a mitochondrial deacetylase that modulates enzymes involved in the TCA cycle and fatty acid metabolism (106). In renal cell carcinoma, SIRT3 acts as a critical regulator of mitochondrial metabolism by controlling the lactylation of MDH2 at the K239 site. This SIRT3-mediated metabolic reprogramming allows tumor cells to utilize lactate to drive ATP production and antioxidant defense, ultimately fostering oxidative stress resistance and renal cell carcinoma progression (111).

ncRNAs and tumor lactate metabolism. ncRNAs serve pivotal roles in regulating gene expression and tumor metabolism through direct interactions with DNA, RNA and

proteins. In particular, ncRNAs contribute to tumor growth by modulating glycolysis and lactate metabolism. They influence the activity of key glycolytic enzymes, alter metabolic reprogramming and affect various signaling pathways, thereby regulating the production, transport and utilization of lactate. By targeting critical enzymes involved in glycolysis and participating in signaling cascades, ncRNAs exert notable control over glucose metabolism, which in turn promotes tumor initiation and progression. Furthermore, metabolic reprogramming driven by ncRNAs provides malignant tumors with the necessary energy to sustain rapid proliferation and metastasis, making them promising targets for novel cancer therapies.

lncRNAs and tumor lactate metabolism. Enhanced glycolysis is a hallmark of cancer metabolism. Notably, viral infections can also hijack this metabolic pathway, promoting aerobic glycolysis to support viral replication. lncRNAs serve critical roles in regulating glycolysis and lactate metabolism through diverse molecular mechanisms, thereby influencing tumor initiation, progression, metastasis and therapeutic response (112).

Multiple studies have revealed that lncRNAs modulate glycolytic enzyme expression, stabilize mRNAs, interact with signaling proteins and act as competing endogenous RNAs (ceRNAs) to regulate metabolic pathways. Protein interactions are essential for lncRNA-mediated metabolic regulation. For example, HULC binds to both LDHA and PKM2, thereby facilitating aerobic glycolysis and tumor growth of HCC (113). In liver cancer cells, LINC01419 interacts with Y-box binding protein 1 to stabilize PDK1 mRNA, promoting lactate production and metabolic reprogramming (114). Additionally, in the context of m6A modification, the m6A reader IMP2 stabilizes the lncRNA ZFAS1, which in turn activates the OLA1 axis and enhances glycolysis, contributing to CRC progression (115). lncRNAs also regulate glycolysis by interacting with miRNAs. For example, CASC9 negatively regulates miR-383-5p, which targets LDHA, thus indirectly increasing LDHA levels. While this mechanism has been studied in the context of spinal cord injury, the regulatory axis may have broader implications in cancer and other diseases (116). In osteosarcoma, a risk model was constructed from differentially expressed lncRNAs associated with lactate metabolism pathways (117), and RP11-472M19.2 was identified as an important regulator of immune infiltration and metastasis by modulating chemokine expression and glycolysis. RP11-472M19.2 upregulates LDHA-mediated lactate production, which promotes an immunosuppressive microenvironment and supports tumor metastasis (117). In cervical cancer, NEAT1 is consistently upregulated; its silencing inhibits glycolysis and cellular aggressiveness, whereas its overexpression has the opposite effect. Mechanistically, NEAT1 upregulates PDK1 via the WNT/β-catenin pathway and stabilizes the β-catenin protein without affecting its mRNA level. RNA pull-down assays have excluded direct interactions between NEAT1 and the β-catenin protein (118). In LUAD, HOXA11-AS promotes proliferation and glycolysis via the miR-148b-3p/PKM2 axis (119). Furthermore, lactate can be metabolized within tumor cells to sustain growth, and lncRNAs markedly influence lactate reutilization.

The immune microenvironment also exhibits lncRNA-mediated glycolytic regulation. PVT1, for example, is upregulated during $CD4^+$ T-cell activation and enhances glycolytic reprogramming (120). The macrophage-derived lncRNA HISLA is transmitted to breast cancer cells via extracellular vesicles, where it stabilizes HIF-1α to drive aerobic glycolysis and apoptotic resistance. This creates a metabolic feed-forward loop in the tumor microenvironment, as tumor-derived lactate reciprocally upregulates HISLA in macrophages to fuel chemoresistance and disease progression (121). In breast cancer, TAMs deliver the lncRNA HISLA via extracellular vesicles, stabilizing HIF-1α in cancer cells, and promoting aerobic glycolysis and resistance to apoptosis (121). In addition, HITT directly interacts with PKM2 in HCC, preventing its oligomerization, reducing pyruvate kinase activity, and consequently suppressing lactate production and tumor growth while modulating macrophage polarization (122). The exosomal lncRNA TUG1, which is secreted by cancer-associated fibroblasts (CAFs), enhances glycolysis and lactate metabolism in HCC via the miR-524-5p/SIX1 axis, highlighting the key regulatory roles of lncRNAs within the TME (123).

lncRNAs form a sophisticated regulatory network for glycolysis and lactate metabolism through multiple molecular mechanisms, including direct binding to metabolic enzymes, functioning as ceRNAs to sequester miRNAs and mediating intercellular communication within the TME. By remodeling the energy metabolism of tumor cells, these lncRNAs have pivotal roles in driving tumor progression, immune evasion and therapy resistance.

Small ncRNAs and tumor lactate metabolism. miRNAs, including canonical miRNAs and circular RNAs, are small ncRNAs ~22 nucleotides in length. They predominantly regulate gene expression by binding to complementary sequences in the 3'UTRs of target mRNAs, leading to translational repression or mRNA degradation (124). In cancer metabolism, miRNAs are extensively involved in diverse metabolic pathways, including glycolysis, mitochondrial respiration and lipid metabolism. Their regulatory effects can be exerted either by directly targeting metabolic enzymes, or by modulating transcription factors and key signaling pathways (125,126), thereby indirectly reshaping the metabolic network.

During glucose uptake, miRNAs influence the expression of GLUTs, thereby modulating glucose influx into tumor cells. For example, miR-92b-mediated regulation of glucose GLUTs has been shown to promote glycolysis, and support tumor cell proliferation and survival in lung, liver and stomach cancer cells, highlighting its potential role in the metabolic reprogramming of these malignancies (127). In HCC, miR-34a is markedly downregulated, and its restoration suppresses glycolysis by directly targeting key enzymes such as HK1, PKM2 and LDHA. This results in reduced ATP production, energy imbalance, G_1 cell cycle arrest, mitochondrial apoptosis and ultimately tumor growth inhibition (128). Similarly, miR-122-5p directly targets LDHA to suppress glycolysis, but MYC suppresses miR-122-5p, leading to LDHA upregulation and increased glycolysis in liver cancer. The accumulation of lactate not only supports survival under hypoxia but also contributes to tumor progression and metastasis (129).

miRNAs also serve critical roles in regulating glycolysis through ceRNA networks. In LUAD, LUCAT1 functions as a ceRNA to sponge miR-4316, leading to the upregulation of VEGFA, and increased glycolysis and cell migration (130). In cervical cancer, members of the C14MC cluster (such as miR-379/miR-656) modulate ROS production, intracellular Ca^{2+} levels and lipid peroxidation, and inhibit EMT, indicating their potential suppressive roles in cancer metabolism and invasiveness (131). Activation of C14MC promotes glucose uptake, enhances lactate production and upregulates PDK3 expression in HCC, collectively constituting pivotal molecular events that drive tumor metabolic reprogramming. This effect appears to contrast with the tumor-suppressive role of C14MC reported in cervical cancer, suggesting that the function of this miRNA cluster may be context-dependent and tissue-specific (132). Several miRNAs, such as miR-9-1 (132), miR-323a (133), miR-34a (134) and miR-124 (135), inhibit glycolysis by directly targeting HK2, reducing glucose flux and lactate output. Conversely, miR-92b (128), miR-19a-3p (136) and miR-182 (137) enhance glycolysis by upregulating enzymes such as HK2, PFK, PKM2 and LDHA, supporting tumor growth in hypoxic environments. p53, a key tumor suppressor and metabolic regulator, governs glycolysis, OXPHOS and lipid metabolism (138). The miR-34 family, as direct transcriptional targets of p53, mediates cell cycle arrest and apoptosis while modulating cancer metabolism by targeting LDHA, MYC and SIRT1 (139,140). As p53 is frequently mutated in >50% of human cancers, the p53/miR-34 axis represents a critical node in metabolic regulation and a promising therapeutic target (124).

Lactate, the end-product of glycolysis, is exported via MCTs, which are also regulated by miRNAs and lncRNAs. For example, miR-34a inhibits glycolysis and tumor growth by downregulating LDHA (134). Similarly, miR-124-5p targets MCT1, modulating lactate transport, and potentially contributing to hypoxia adaptation and metabolic regulation (141). miR-342-3p functions as a potent tumor suppressor in HCC, whereas miR-29a/b suppresses lactate efflux by inhibiting MCT1, leading to intracellular lactate accumulation, metabolic stress and cell death (142). miRNAs orchestrate tumor metabolic reprogramming at multiple levels, including glycolysis, lactate metabolism, mitochondrial function and TME adaptation. For example, exosomal miR-105 derived from cancer cells promotes tumor growth through MYC-dependent metabolic reprogramming of CAFs. Under nutrient-rich conditions, CAFs display increased glucose and glutamine metabolism, whereas in nutrient-poor environments, they metabolize metabolic byproducts to sustain tumor survival, reflecting a complex metabolic interplay (143). In non-small cell lung cancer (NSCLC), miR-182 upregulates HIF-1α, facilitating metabolic reprogramming and adaptation to hypoxic conditions (137).

In conclusion, miRNAs are integral regulators of cancer metabolism, affecting not only tumor-intrinsic metabolic pathways but also the metabolic landscape of the TME. Further elucidation of miRNA-mediated metabolic circuits may reveal novel diagnostic markers and therapeutic targets for metabolic intervention in cancer.

Lactylation has emerged as a pivotal metabolic-epigenetic regulator that interfaces with histone acetylation and RNA methylation to influence tumor progression. It can directly activate transcription (8) and shares substrates and writers with acetylation, including p300/CBP (144,145), allowing cooperative or competitive regulation of chromatin accessibility. Mechanistically, elevated intracellular lactate generates lactyl-CoA, which serves as the donor for p300/CBP-mediated Kla. This modifies both histone tails and non-histone proteins, including chromatin- and RNA-modifying enzymes, thereby altering their activity, stability and recruitment to target loci. For example, key m6A RNA methyltransferases such as METTL3 and METTL16 undergo Kla, which modulates their enzymatic activity and nuclear localization. Lactylation-enhanced METTL3 increases m6A deposition on transcripts encoding glycolytic enzymes, immune checkpoint molecules and hypoxia-responsive factors, thereby reinforcing lactate-driven metabolic adaptation and immunosuppressive programs (145,146). Beyond m6A, lactylation may influence additional RNA methylation systems and affect lncRNA-mediated recruitment of chromatin modifiers, further integrating transcriptional and post-transcriptional control.

Collectively, these interactions establish a multilayered, lactate-responsive regulatory network, where lactylation acts as a molecular switch linking metabolic status to chromatin remodeling and RNA epigenetic regulation, enabling fine-tuning of gene expression programs that drive tumor progression.

4. Lactate fate: Dysregulated lactate metabolism in tumor progression

As aforementioned, lactate is not only the end product of glycolysis but also a critical metabolite and signaling molecule within the TME. In tumor cells with high glycolytic activity, lactate is produced in large quantities and exported extracellularly via MCTs. In contrast to its traditional classification as a metabolic waste product, extracellular lactate is actively utilized by various cell types within the TME to meet specific metabolic demands. For example, CAFs take up lactate through MCT1 and convert it to pyruvate via LDHB; the resulting pyruvate enters the TCA cycle to fuel CAFs and generate metabolites that support tumor cell growth. This 'lactate-pyruvate metabolic loop' facilitates metabolic crosstalk between tumor and stromal cells (5). Immune cells respond differently to extracellular lactate. M2-polarized macrophages can utilize lactate as an energy source, promoting an anti-inflammatory and immunosuppressive phenotype that favors tumor progression (147). By contrast, the glycolytic metabolism of effector T cells is inhibited by lactate, resulting in functional exhaustion (148,149). Regulatory T cells however adapt well to lactate-rich conditions and further contribute to immunosuppression (20). Lactate efflux via MCT4 leads to acidification of the TME, lowering the extracellular pH; this acidic microenvironment promotes EMT, enhances matrix degradation, and increases the invasive and metastatic potential of tumor cells (150,151). Low pH also impairs dendritic cell maturation and antigen presentation, and weakens the cytotoxic functions of T cells and NK cells, thereby facilitating immune evasion (149,152).

In addition to its metabolic role, lactate functions as a signaling molecule by activating pathways such as the GPR81 axis. Activation of GPR81 suppresses intracellular cAMP

levels, thereby reducing oxidative stress and enhancing tumor cell survival (153,154). Beyond this, lactate actively reshapes lipid metabolism by promoting fatty acid synthesis, which further strengthens cancer cell resilience (155). Notably, lactate can also directly regulate gene expression through histone lactylation, highlighting its emerging role as a metabolic-epigenetic regulator that links altered metabolism to transcriptional reprogramming in cancer.

Consistent with these multifaceted functions, elevated lactate markedly influences the tumor immune microenvironment, although its impact varies across tumor types. In solid tumors, high lactate concentrations promote the polarization of macrophages specifically toward an immunosuppressive M2-like phenotype, rather than pro-inflammatory M1, and stimulate CAFs to undergo metabolic reprogramming and secrete tumor-supportive factors, collectively facilitating tumor progression. Mechanistically, lactate is transported into macrophages via MCT1, where intracellular accumulation stabilizes HIF-1α, activates STAT3/STAT6 and suppresses NF-κB-dependent inflammatory pathways, whereas histone lactylation further reinforces M2-associated transcriptional programs (for example, ARG1, IL10 and VEGFA) (156,157). These pathways collectively constitute the molecular basis of tumor-stromal-immune crosstalk in solid tumors.

By contrast, in hematological malignancies, where tumor cells are in more direct and dynamic contact with immune populations, lactate-mediated effects tend to be more immediate and cell-intrinsic. For example, in acute myeloid leukemia, aberrant activation of STAT5 enhances glycolysis and results in excessive lactate accumulation. Nuclear lactate subsequently induces histone lactylation, upregulates programmed death-ligand 1 (PD-L1) expression, and suppresses $CD8^+$ T-cell function, an immunosuppressive state that can be partially reversed by programmed cell death protein 1/PD-L1 blockade (158). Similarly, in lymphoma, Epstein-Barr virus infection upregulates MCT1/MCT4 expression, thereby increasing lactate export and acidifying the TME, which dampens immune cell activity and underscores the therapeutic potential of targeting lactate transporters (159). In multiple myeloma, lactate not only drives macrophage polarization toward an M2-like immunosuppressive phenotype via STAT2-PFKFB4-mediated glycolytic remodeling but also directly inhibits T-cell cytotoxicity, further accelerating disease progression (160).

Taken together, these observations suggest that aberrant lactate metabolism is closely associated with epigenetic reprogramming and immune modulation. Lactate-induced histone lactylation alters the expression of genes governing immune escape and metabolic adaptation, and the extent and consequences of these changes differ between solid tumors and hematological malignancies, ultimately contributing to distinct patterns of cell-cell communication within the TME.

Lactate metabolism is not confined to the TME. Excess lactate enters systemic circulation and is metabolized in organs such as the liver and kidneys to maintain overall metabolic homeostasis. In the liver, circulating lactate is converted to pyruvate and used for gluconeogenesis, regenerating glucose that can be redistributed to peripheral tissues as an energy source (161). This active recycling loop may exacerbate tumor progression by fueling cancer metabolism. In the kidneys, lactate is taken up via MCTs and oxidized in the TCA cycle. During conditions of elevated lactate levels (such as lactic acidosis), the kidneys can also excrete lactate via tubular secretion to maintain acid-base balance (162).

Due to its multifaceted role in tumor biology, targeting lactate metabolism, such as through MCT4 inhibitors, LDHA inhibitors or GPR81 antagonists, has emerged as a promising anticancer strategy. These interventions aim to remodel the TME, restore immune function and enhance therapeutic efficacy.

Lactate has emerged not only as a metabolic byproduct but also as a direct epigenetic regulator through Kla, a novel PTM that modulates gene expression. Under metabolic stress conditions such as hypoxia or bacterial infection, elevated intracellular lactate serves as a donor for lactylation of K residues of histones, affecting multiple histone sites, including well-studied marks such as H3K18la, H4K5la and H4K18la. For example, in M1-type macrophages responding to bacterial infection, increased lactate levels enhance H3K18la modification, activating genes involved in tissue repair and inflammatory resistance, such as PD-1 (163). Notably, the HAT p300 has been identified as a 'writer' enzyme for histone lactylation that is capable of transferring lactate onto histones and thereby increasing lactylation levels upon upregulation. Conversely, HDACs possess delactylase activity, suggesting a dynamic regulatory system of lactylation. This discovery provides novel mechanistic insight into metabolic-epigenetic crosstalk, with potential implications for cancer, inflammation and immune regulation (8).

In addition to histones, lactylation occurs on numerous non-histone proteins, including metabolic enzymes and signaling molecules, influencing their stability and activity (164-166). Global lactylome analyses in hepatitis B virus (HBV)-associated HCC have identified thousands of lactylation sites predominantly on non-histone proteins (167), underscoring the widespread nature of this modification. Functionally, lactylation serves a critical oncogenic role by regulating metabolism, signaling pathways and drug resistance, thereby promoting tumor proliferation, metastasis and poor prognosis. For example, under hypoxia, lactylation stabilizes β-catenin, enhancing CRC cell proliferation (168). In HBV-related liver cancer, lactylation inhibits adenylate kinase 2 function, accelerating tumor growth and metastasis. Similarly, in clear cell renal cell carcinoma, lactylation activates platelet-derived growth factor receptor β transcription, facilitating disease progression; targeting lactylation effectively suppresses proliferation and metastasis (167,169). Lactylation also promotes the transcription of the m6A reader YTHDF2, leading to the degradation of the tumor suppressor mRNAs PER1 and TP53, thereby increasing uveal melanoma cell proliferation and migration (170). Moreover, lactylation is linked to therapeutic resistance in ocular melanoma (170). It can upregulate RUBCNL expression, mediating resistance to bevacizumab in CRC. Aberrant lactylation patterns may serve as prognostic and diagnostic biomarkers (171); for example, lactylation of the ubiquitin-specific peptidase 14 and ABCF1 proteins is associated with liver cancer diagnosis, and lactylation-associated genes have been proposed as markers of treatment response (172,173). Notably, lactylation can also

exhibit tumor-suppressive effects. Increased histone lactylation has been shown to repress glycolytic enzymes, such as HK1 and PKM, while upregulating key TCA cycle enzymes, such as SDHA and IDH3γ, leading to metabolic reprogramming that inhibits tumor cell proliferation and migration in NSCLC (174).

Furthermore, lactate-induced H3K18la modification has been implicated in cell cycle arrest and the inhibition of uveal melanoma progression. Lactate and lactylation also impact various cell types within the TME, offering novel avenues to overcome immune suppression and enhance immunotherapy efficacy (175). Collectively, advances in understanding lactylation and its regulatory enzymes hold promise for the development of innovative anticancer therapies.

Previous studies have indicated that lactylation extends beyond cancer cell biology, and has important regulatory roles in the differentiation and function of multiple immune cell types within the TME. Lactate-driven histone and non-histone Kla can promote macrophage polarization toward an immunosuppressive M2-like phenotype, and amplify expression programs that favor tissue repair and tumor tolerance, thereby facilitating immune evasion (176-178). Lactylation also modulates T-cell metabolic fitness and effector functions, suppressing proliferation and cytokine production in the high-lactate tumor milieu, and may bias $CD4^+$ T-cell differentiation under certain conditions (179). Emerging evidence has further suggested that persistent histone lactylation can contribute to epigenetic 'memory' in innate immune cells, with potential implications for trained immunity and long-term modulation of antitumor responses (180). Together, these findings highlight that lactylation is a critical link between tumor metabolism and immune regulation, and should be integrated into discussions of tumor immunobiology and therapeutic strategies aiming to reverse metabolic immune suppression (181,182).

5. Therapeutic strategies targeting dysregulated lactate metabolism in tumors

In summary, interventions targeting lactate metabolism have emerged as promising new directions in cancer therapy. The present review highlights key strategies, including targeting enzymes involved in lactate metabolism, lactate transporters, lactylation modifications and epigenetic regulatory mechanisms (Fig. 4).

Targeting lactate metabolism-related enzymes. Lactate metabolism is regulated by key enzymes such as LDHA, HK2, PFK1 and PKM2. Pharmacological inhibition of these enzymes can reduce lactate production, increase oxidative metabolism and ultimately impede tumor progression (21). Among them, CHK-336, a first-in-class orally bioavailable LDHA inhibitor that has been evaluated in a first-in-human clinical study, represents the only reported clinical agent targeting lactate metabolism (183); however, its antitumor efficacy in patients with cancer remains to be fully established.

Targeting lactate transporter signaling. Transmembrane lactate transport is facilitated primarily by MCTs. Inhibiting MCTs can effectively reduce lactate accumulation within the TME, alleviate immunosuppressive conditions and restore immune cell function (184).

Targeting lactylation modifications. Lactylation serves a critical role in cancer progression, and several studies have explored the targeting of lactate or lactylation as a therapeutic approach, highlighting lactylation as a promising novel option for cancer treatment (185,186). Due to the notable role of lactylation in tumors, future strategies may go beyond indirectly reducing lactate levels via inhibitors of lactate metabolism, such as LDH and MCT1/4 inhibitors, and focus on directly targeting the regulation of lactylation to improve therapeutic outcomes. Drugs targeting lactylation-regulating enzymes, particularly HAT inhibitors such as C646 (187), and HDAC inhibitors such as suberanilohydroxamic acid and TSA (188), represent promising therapeutic strategies.

6. Conclusions

Lactylation, a PTM derived from intracellular lactate, has reshaped the understanding of the interplay between cellular metabolism and epigenetic regulation. In addition to serving as a metabolic byproduct, lactate functions as a donor for Kla, particularly on histones and various non-histone proteins. Lactylation has been shown to influence gene transcription, enzyme activity, protein stability and chromatin structure, thereby contributing to diverse biological processes, including tumor proliferation, metastasis, immune modulation and therapeutic resistance. In cancer, aberrant lactylation promotes tumor progression by enhancing glycolysis, regulating key oncogenic signaling pathways and reshaping the TME. It serves dual roles in facilitating tumorigenesis in some contexts while exhibiting tumor-suppressive effects in others by reprogramming metabolic pathways and inhibiting proliferation. Notably, key enzymes such as p300 and HDACs have been identified as potential 'writers' and 'erasers' of lactylation, respectively, suggesting promising therapeutic targets.

Despite notable progress, numerous critical questions remain unanswered. The full repertoire of lactylated proteins, their site-specific regulatory mechanisms, and their functional implications in different cancer types and stages remain to be fully elucidated. Moreover, the crosstalk between lactylation and other epigenetic modifications, such as acetylation and methylation, as well as its roles in immune and stromal cells within the TME, require further investigation. Future studies should focus on the development of specific tools to detect, modulate and visualize lactylation dynamics *in vivo*. In addition, therapeutic strategies targeting the lactylation machinery, either alone or in combination with existing cancer therapies, may offer novel opportunities to overcome resistance and improve treatment efficacy. Overall, lactylation represents a novel and promising epigenetic mechanism with broad implications in tumor biology and clinical oncology.

The present study comprehensively elucidates the synergistic role of lactate metabolic reprogramming and epigenetic regulation in tumor progression, establishing a complete regulatory axis of 'lactate-lactylation-epigenetics-tumor malignant progression' that reveals a new paradigm of direct metabolite involvement in epigenetic regulation. Secondly, the study systematically summarizes preclinical evidence targeting key lactate metabolism enzymes and lactylation modifications, laying the foundation for developing 'metabolism-epigenetics'

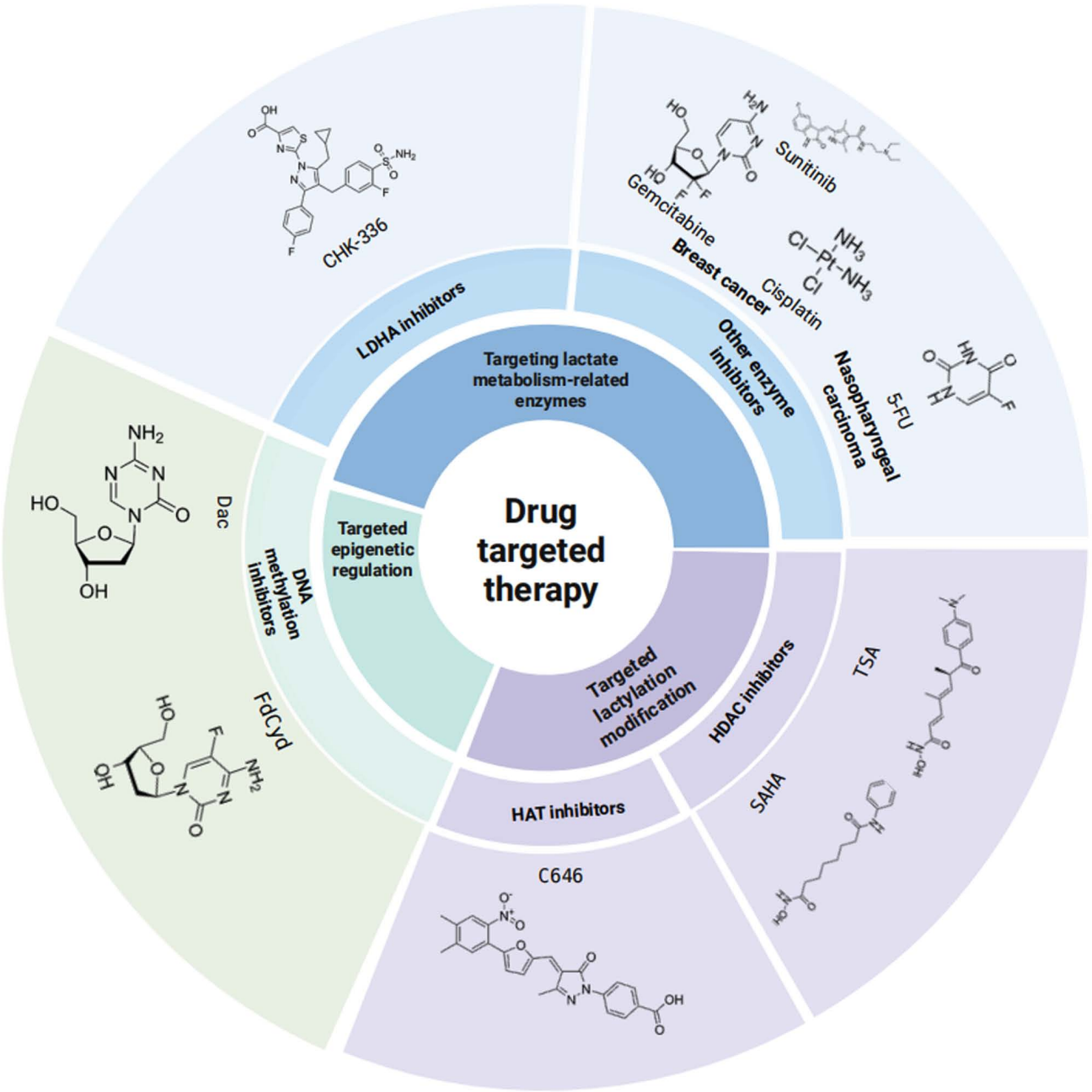

Figure 4. Drugs targeting dysregulated lactate metabolism in tumors. This figure was created by BioRender (https://app.biorender.com/illustrations/6981983 8e1a01138b0bbeb49). 5-FU, 5-fluorouracil; HAT, histone acetyltransferase; HDAC, histone deacetylase; LDHA, lactate dehydrogenase A; monocarboxylate transporter; SAHA, suberanilohydroxamic acid; TSA, trichostatin A.

dual-targeting therapies. Finally, it proposes a cross-cellular regulatory network of lactate metabolism in the TME, providing new insights for combination immunotherapy. However, the study still has limitations; for example, notable heterogeneity in lactate metabolism exists across different tumor types, stages and microenvironmental regions, and there is not currently an established, stratified evaluation system, which may weaken the universality of targeted therapies. Additionally, there is a lack of standardized models to evaluate the synergistic effects of combining lactate metabolism inhibitors with epigenetic drugs. Future research could seek breakthroughs in developing lactylation-specific probes and inhibitors and establishing humanized TME models.

Acknowledgements

Not applicable.

Funding

This study was funded by the National Natural Science Foundation of China (grant no. 82273352), the Scientific Research Foundation of Hangzhou City College (grant no. X-202305), the Zhejiang Province College Students' Scientific and Technological Innovation Activity Plan (grant no. 2024R436A007) and the National College Students' Innovation and Entrepreneurship Training Program (grant nos. 202413021037 and 202513021029).

Availability of data and materials

Not applicable.

Authors' contributions

XZ, JZ, YS, CC, MG and TX wrote the original draft. XZ reviewed and edited the manuscript, and supervised the review. ChuZ, CM and HH wrote the original draft and supervised the review. ChoZ and YL reviewed and edited the manuscript, and supervised and conceptualized the review. ChoZ, YL, JZ and CM acquired funding. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools (Gemini) were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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