Research progress of lactylation modification in tumors (Review)

SHI-CHAO FANG and ZHI-ZHOU SHI

Laboratory of Molecular Neurobiology, Faculty of Medicine, Kunming University of Science and Technology, Kunming, Yunnan 650500, P.R. China

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Abstract. Lactic acid was once thought to be only a metabolic product of glycolysis. An increasing number of studies, however, have reported that lactic acid produced by glycolysis is a multifunctional signaling molecule that not only serves as an essential energy source, signaling molecule and immunomodulatory molecule but also controls metabolism, the immune response and intercellular communication. It has been discovered that lactylation is a posttranslational modification of proteins that regulates and creates an acidic tumor microenvironment, directly regulates gene expression and promotes the recruitment and management of immune signaling molecules, among other processes, to promote tumor survival and progression. The lactylation of histones and non-histone proteins, which is regulated by different mechanisms, is a notable subject of current research on the tumor microenvironment and tumor progression. The present review covered the discovery of lactylation and the research advances on the role of lactylation in metabolism, immunity, metastasis and cell proliferation across different tumors. These findings open up the possibility for in-depth investigation of the role of lactylation in tumors.

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Correspondence to: Professor Zhi-Zhou Shi, Laboratory of Molecular Neurobiology, Faculty of Medicine, Kunming University of Science and Technology, 727 Jingming South Road, Kunming, Yunnan 650500, P.R. China
E-mail: zhizhoushi@126.com

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1. Introduction

Lactate, the end product of glycolysis, has long been considered a metabolic waste product of glucose metabolism under hypoxic conditions, and was therefore not considered a notable research topic (1). In the Warburg effect, tumor cells tend to undergo glycolysis and produce large amounts of lactate even in the presence of sufficient oxygen. Lactate accumulates in the cells and is exported to the extracellular environment through the activation of transporters on the cell membrane, ultimately leading to the formation of an acidic tumor microenvironment (TME) (2). In 2019, Zhang *et al* (3) identified the lysine lactylation (Kla) of histones for the first time, discovering a new metabolite-associated posttranslational modification (PTM). In addition to histones, there is growing evidence that non-histone proteins can also be modified by lactylation (4). Both L-lactate and lactyl-coenzyme A are the direct substrates for protein lactylation (5,6). The discovery of protein lactylation generated a new era for more in-depth analysis of lactate metabolism and provided a novel mechanism for determining the pathophysiological mechanisms of lactate in tumors and inflammatory diseases (7,8).

Over the years, protein lactylation, as a key regulatory mechanism in cellular metabolism, immune response and tumor biology, has gradually become a cutting-edge focus of scientific research. Lactylation not only plays a marked role in the regulation of energy metabolism, but also notably affects the regulation of gene expression, the activation of signaling pathways and cell proliferation and migration (1,2) (Fig. 1). Specifically, lactylation provides tumor cells with a notable energetic and survival advantage by altering the chemistry of specific histone sites [such as histone H3 lysine 18 (H3K18)], increasing the activity of glycolysis-related enzymes and facilitating the activation of a variety of signaling pathways that promote tumor development (9,10). At the metabolic level, lactylation promotes glycolysis and other metabolic pathways by upregulating the expression or activity of key enzymes, creating a malignant positive feedback loop that further exacerbates the process of tumor development (11,12). In addition, lactylation promotes the expression of specific genes, such as NF-kB (p65), YY1, CCND1 and NRP2, which play key roles in tumor cell proliferation, migration and invasion, by regulating their transcription (13,14). In terms of the immune response, lactylation results in the formation of an immunosuppressive microenvironment that is conducive to tumor growth by increasing the generation and stability of regulatory T cells

(Tregs) while suppressing the function of effector T cells. For example, in pancreatic ductal adenocarcinoma (PDAC), the increased lactylation level at the K72 of the moesin protein promotes its interaction with transforming growth factor β (TGF-β) receptor I and its downstream SMAD family member 3 (SMAD3) signaling, which promotes the generation and stabilization of Tregs and consequently enhances the immunosuppressive state (10). Similarly, in non-small cell lung cancer (NSCLC), increased lactylation at the K70 of the apolipoprotein C2 (APOC2) protein promotes extracellular lipolysis and induces Treg accumulation, which further exacerbates the phenomenon of immunoresistance (9). Notably, lactylation also plays a role in tumor metastasis. Studies have shown that lactylation promotes the migration and invasion ability of tumor cells by activating specific signaling pathways [such as Hippo and platelet derived growth factor receptor beta (PDGFRβ)]. For example, in glioblastoma (GBM), histone H3 lysine 9 lactylation (H3K9la) activates LUC7-like 2 (LUC7L2) transcription to promote its expression, and LUC7L2 mediates the retention of intron 7 of MutL homolog 1 (*MLH1*) and reduces MLH1 expression, leading to temozolomide resistance (15).

In the present review the associations between lactylation and tumorigenesis are discussed in depth, laying the foundation for further understanding of its role in disease progression and aimed to provide some insights for new therapeutic strategies (16).

2. Lactylation in tumor immunity

Lactate is notable metabolite in the TME that serves as fuel for mitochondrial metabolism and plays an integral role in shaping the function of immune cells, which should not be overlooked in cancer immunotherapy because it can regulate immune cell metabolism and inhibit the activation and proliferation of immune cells (17-19) (Fig. 2). Lactate is a signaling molecule that plays a notable role in regulating the immune response of tumor cells and influencing immune surveillance and escape related behaviors (17-19) (Fig. 2). The present section specifically discusses lactate-mediated anti-tumor immunity and focuses on the research investigating NSCLC, gastric cancer (GC) and glioma.

The accumulation of lactate in the TME induces histone H3K18 lactylation (H3K18la), upregulating the expression of the RNA methyltransferase methyltransferase-like 3 (METTL3) in tumor-infiltrating myeloid cells. METTL3 enhances the translation of Janus kinase 1 (*JAK1*) mRNA through m6A modification, activating the JAK1-STAT3 signaling pathway. This activity strengthens the immunosuppressive functions of myeloid cells (such as promoting T-cell exhaustion and Treg-cell infiltration), thereby driving tumor immune evasion and malignant progression. Notably, a preclinical study confirmed that genetic ablation of METTL3 in myeloid cells, treatment with the METTL3 inhibitor STM2457 or blockade of lactylation (for example using the p300 inhibitor C646) can notably inhibit tumor growth and remodel the immune microenvironment (20). Recent findings suggest that targeting the lactylation-immunosuppression axis represents a potential antitumor immunotherapy strategy for patients with NSCLC (21), GC (22), glioma (23), ovarian cancer (OC) (24), cervical cancer (CC) (25), colorectal cancer (CRC) (26), GBM (27), head and neck squamous cell carcinoma (HNSCC) (28), acute myeloid leukemia (AML) (29) and PDAC (30). These studies have revealed that histone lactylation not only participates in the malignant transformation process of tumor cells themselves but also promotes immune escape and immunosuppressive states in the TME through complex molecular mechanisms.

Specifically, a study in NSCLC has shown that elevated H3K18la levels directly activate the POM121 transmembrane nucleoporin/MYC/programmed death ligand 1 (PD-L1) pathway, increase PD-L1 expression and enhance the immune escape ability of tumor cells (21).

In GC, H3K18la upregulates vascular cell adhesion molecule-1 (VCAM1) transcription, activates the AKT-mTOR-C-X-C motif ligand (CXCL)1 signaling pathway, and promotes the recruitment of human GC-derived mesenchymal stem cells and M2 macrophages. Both *in vivo* and *in vitro* experiments confirmed that MK2206 (an AKT inhibitor) notably inhibits the proliferation, migration and tumor growth of GC cells induced by VCAM1 overexpression. Targeting the AKT pathway effectively reverses its procancer effects (22). In addition, lysyl oxidase (LOX) secreted by cancer-associated fibroblasts upregulates insulin-like growth factor 1 (IGF1) expression through activation of the TGF-β signaling pathway, which increases the rate of glycolysis and lactate accumulation, leading in turn to an increase in the level of H3K18la, which further facilitates the transcription of PD-L1 and enhances immune evasion in GC cells. Targeting LOX, IGF1 or glycolysis [such as with dasatinib or lactate dehydrogenase A (LDHA) inhibitors] can effectively block lactylation, thereby inhibiting PD-L1 expression and tumor progression (31).

Similarly, in gliomas, lactate-induced H3K18la promotes the expression of tumor necrosis factor superfamily member 9 in a histone-lactylation-dependent manner, leading to M2 polarization and enhanced immune escape and promoting the migration, invasion, colony formation and *in vivo* tumor growth of glioma cells (23). In other types of cancers such as OC (24), CC (25), CRC (26) and GBM (27), H3K18la promotes tumor progression and constructs an immunosuppressive microenvironment by regulating specific gene promoter activities (such as PD-L1 and glycerol-3-phosphate dehydrogenase 2) and transcriptional repression of the retinoic acid receptor γ gene.

In HNSCC, elevated levels of H3K9la promote interlukin-11 (IL-11) transcription and $CD8^+$ T cell depletion and upregulate immune checkpoints such as programmed death-1 (PD-1), TIGIT, cytotoxic T-lymphocyte antigen-4 (CTLA-4) and TIM-3 on $CD8^+$ T cells, resulting in T-cell exhaustion and immune escape. Targeting IL-11 (for example with chol-siIL11) effectively blocks the lactate/H3K9la/IL-11/JAK2/STAT3 axis, reversing $CD8^+$ T-cell exhaustion and restoring their cytotoxic function. Combining this approach with anti-PD-1 therapy can result in synergistic effects, offering a novel combination strategy for HNSCC immunotherapy (28). In AML, high expression of STAT5 promotes glycolysis and lactate accumulation, increases E3-binding protein nuclear translocation, raises the level of histone H4 lysine 5 lactylation and promotes

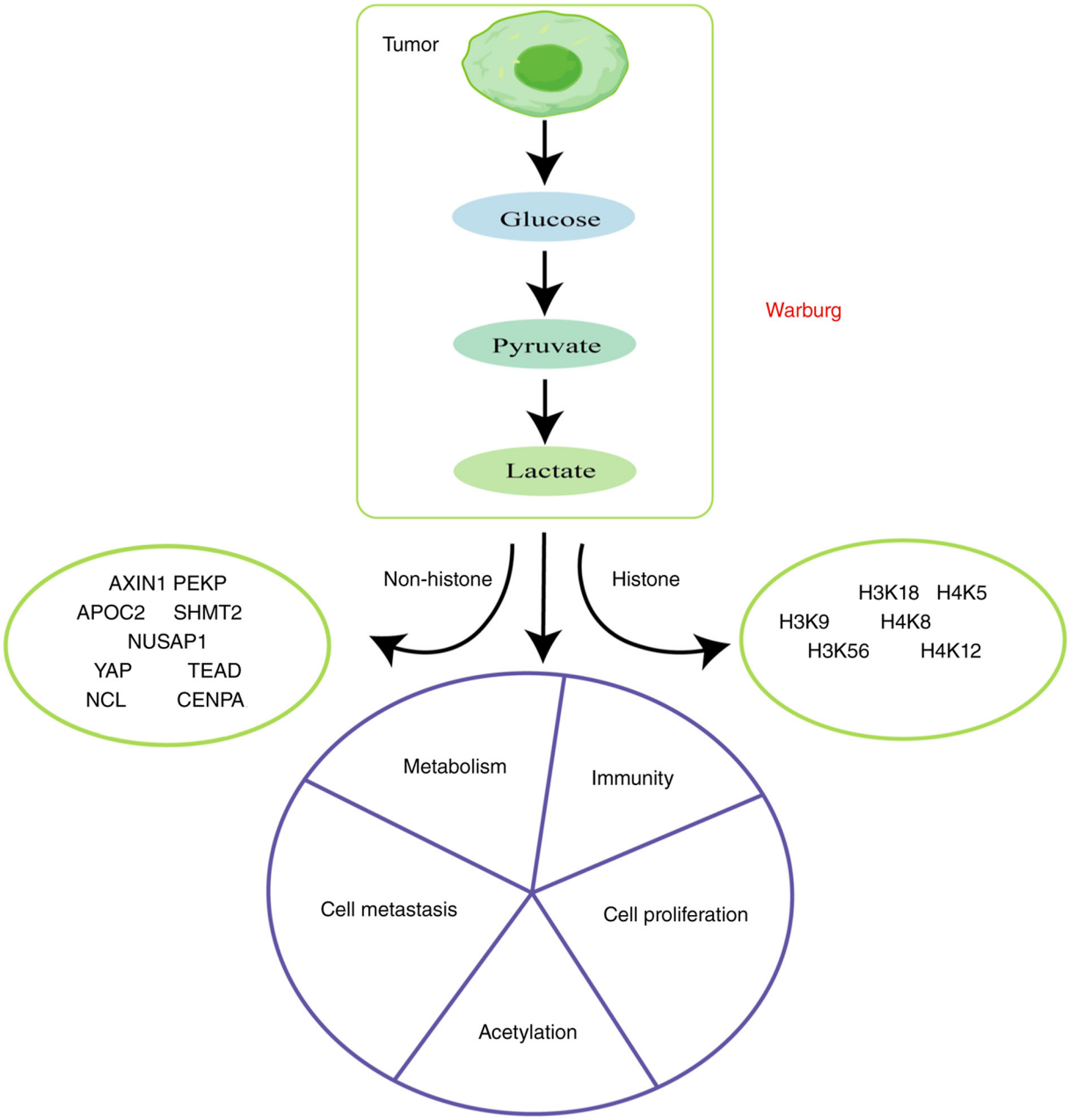

Figure 1. Tumor cells produce lactic acid through the Warburg effect. The produced lactic acid can serve as a substrate for lactylation modification, promoting the lactylation of histones and non-histones during cell proliferation, metastasis, immunity and metabolism. AXIN1, axis inhibition protein 1; PEKP, phosphofructokinase, platelet; APOC2, Apolipoprotein C2; NUSAP1, nucleolar and spindle-associated protein 1; YAP, yes-associated protein; TEAD, TEA domain; NCL, nucleocapsid; CENPA, centromeric protein A; SHMT2, serine hydroxymethyltransferase-2; H3K18, histone H3 lysine 18; H4K5, histone H4 lysine 5; H3K9, histone H3 lysine 9; H4K8, histone H4 lysine 8; H3K56, histone H3 lysine 56; H4K12, H4 lysine 12.

PD-L1 transcription, thereby inhibiting $CD8^+$ T cell activation through PD-1/PD-L1 interaction, leading to immune escape. Patients with high STAT5 expression may benefit from PD-1/PD-L1 blockade therapy (29). The epidermal growth factor receptor/extracellular signal-regulated kinase (ERK)/acetyl coenzyme A synthetase 2 (ACSS2)/lysine acetyltransferase 2A (KAT2A) axis directly upregulates PD-L1 expression via H3K18la, leading to $CD8^+$ T-cell dysfunction and immune escape. Targeting the interaction between ACSS2 and KAT2A with a blocking peptide effectively suppresses PD-L1 expression, restores T-cell function, and synergizes with anti-PD-1 therapy, offering a novel metabolic-immune combination strategy for GBM immunotherapy (6). In PDAC, CCCTC-binding factor interacts with heterogeneous nuclear ribonucleoprotein U through a FLG-AS1-dependent mechanism, promotes E1A-associated protein recruitment and m6A reader IGF2BP2 activation, enhances colony-stimulating factor 1 (*CSF1*) and *MYC* mRNA stability, regulates CSF1-selective splicing and promotes M2 polarization of tumor associated macrophages and enhances immune escape (30).

In summary, elevated levels of lactylation not only promote the transcription of specific genes (such as IL-11 and PD-L1) but also affect the function of immune cells through specific signaling pathways (such as JAK2/STAT3), especially by weakening $CD8^+$ T-cell activity or promoting the polarization of

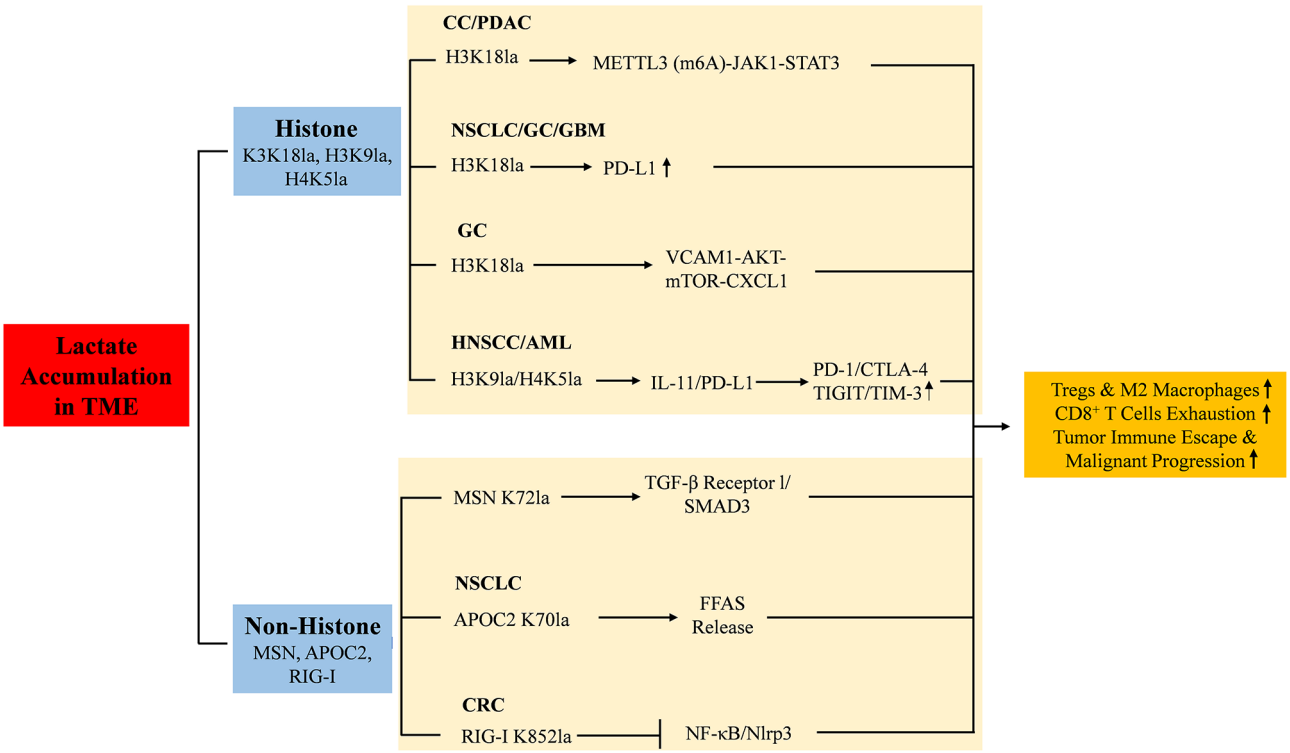

Figure 2. Histone and non-histone lactylation in tumor immunity. Lactate accumulation in TME reshapes the immunomicroenvironment. IL-11, interlukin-11; H3K9, histone H3 lysine 9; JAK1, janus kinase 1; STAT3, signal transducer and activator of transcription 3; H3K18, histone H3 lysine 18; PD-L1, Programmed death-ligand 1; STAT5, signal transducer and activator of transcription 5; H4K5, histone H4 lysine 5; VCAM1, vascular cell adhesion molecule-1; CXCL1, C-X-C motif ligand 1; SMAD3, small mother against decapentaplegic family member 3; Rig-1, retinoic acid-inducible gene I; Nlrp3, nod-like receptor protein 3; APOC2, apolipoprotein C2; METTL3, methyltransferase-like 3; TME, tumor microenvironment; Tregs, regulatory T cells; FFAS, free fatty acids; MSN, moesin; CC, cervical cancer; PDAC, pancreatic ductal adenocarcinoma; NSCLC, non-small cell lung cancer; GC, gastric cancer; GBM, glioblastoma; HNSCC, head and neck squamous cell carcinoma; AML, acute myeloid leukemia; CRC, colorectal cancer.

immunosuppressive cells such as M2 macrophages. Together, these changes construct an immunosuppressive microenvironment that is conducive to tumor growth and development. Thus, the marked role of histone lactylation modifications in a variety of cancer types provides a theoretical basis and new perspectives for the development of novel anticancer therapies based on this mechanism. A deeper understanding of these complex regulatory networks can aid in more precisely understanding the cancer process and improve therapeutic outcomes.

Protein lactylation plays notable roles in the progression and immune escape of numerous cancers. First, lactylation promotes the generation and stabilization of Tregs in the TME by enhancing the interaction of key proteins with signaling pathways, as revealed by Chen *et al* (9) and Gu *et al* (10) and. An increase in the lactylation level of the K72 locus of the moesin protein enhanced its interaction with TGF-β receptor I and its downstream SMAD3 signaling, which promoted the generation and stabilization of Tregs in the TME, thereby contributing to the formation of an immunosuppressive TME. Targeting lactate metabolism [for example with LDHi (GSK2837808A)] or directly blocking moesin lactylation inhibited Treg function and enhanced the efficacy of anti-PD-1 therapy. Clinical samples also show that moesin lactylation levels are negatively associated with the response to PD-1 therapy (10). In NSCLC, tumor-derived lactate, via P300-mediated lactylation of APOC2 at K70, stabilizes the APOC2 protein, promoting extracellular lipolysis and the release of free fatty acids (FFAs). These FFAs drive the accumulation of Tregs and the upregulation of immune checkpoints such as CTLA-4, thereby suppressing the function of PD-1^{+} CD8^{+} T-cells and leading to resistance to anti-PD-1 therapy. Targeting APOC2 lactylation (using an anti-APOC2 K70-lactylation antibody) or lactate metabolism (with FX11) reverses this resistance and synergizes with anti-PD-1 treatment. In clinical samples, APOC2 K70 lactylation levels are positively associated with immunotherapy resistance, suggesting a novel combination strategy and a potential predictive biomarker for NSCLC immunotherapy (9). Second, lactylation inhibits the transcription of immune-related genes. In CRC, the tumor-resident microbiota (for example *E. coli*) enhances glycolysis and lactate production in tumor cells, driving RIG-I lactylation at K852 in macrophages. This activity inhibits the NF-κB-Nlrp3 axis, promoting M2 polarization and Treg accumulation (along with the upregulation of the expression of checkpoints such as CTLA-4), thereby suppressing CD8^{+} T-cell function and facilitating CRC liver metastasis. Targeting RIG-I lactylation [for example with 7-(carboxymethyl)-10-methyl-10H-phenothiazin-2-yl acetic acid] reverses this immunosuppression and increases the efficacy of chemotherapy (32). In summary, protein lactylation promotes tumor development and immune escape through diverse mechanisms in different types of cancers, suggesting that this modification may be a potential therapeutic target.

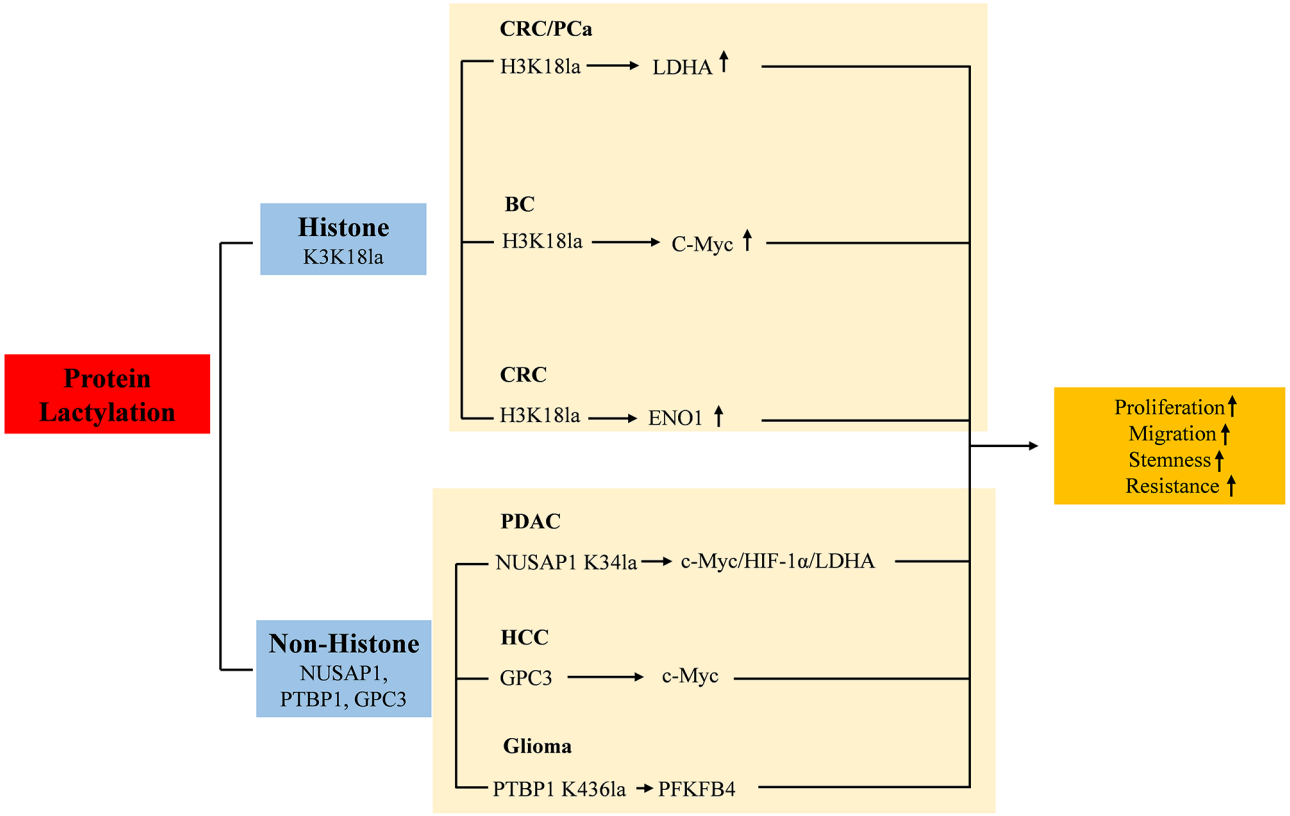

Figure 3. Histone and non-histone lactylation in tumor metabolism. The tumor metabolism was regulated by H3K18la and the lactylation of NUSAP1, YAP and GPC3. NUSAP1, nucleolar and spindle-associated protein 1; LDHA, lactate dehydrogenase A; PFKP, phosphofructokinase, platelet; YAP, yes-associated protein; PFKFB4, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4; H3K18, histone H3 lysine 18; LDHA, lactate dehydrogenase A; ENO1, enolase 1; HIF-1α, hypoxia-inducible factor-1α; GPC3, glypican-3; CRC, colorectal cancer; PCa, prostate cancer; BC, bladder cancer; PDAC, pancreatic ductal adenocarcinoma; HCC, hepatocellular carcinoma.

3. Lactylation in tumor metabolism

A major hallmark of cancer is metabolic reprogramming (33). Metabolism regulates glycolysis, oxidative phosphorylation and other metabolic pathways by modulating gene expression and signaling pathways (34) (Fig. 3). The most well-known example is the Warburg effect, where tumor cells preferentially use glycolysis for energy production, even in the presence of oxygen, instead of oxidative phosphorylation. This metabolic switch leads to the accumulation of large amounts of lactate, which in tumors not only exists as a metabolic byproduct but also functions as a metabolic intermediate and signaling molecule (35,36).

Histone lactylation contributes to tumorigenesis and progression through complex metabolic and signaling networks in multiple cancer types. In PDAC, P300 acts as a potential writer leading to elevated levels of H3K18la, which activates the transcription of TTK protein kinase (TTK) and BUB1 mitotic checkpoint serine/threonine kinase B (BUB1B) to form a positive feedback loop of glycolysis/H3K18la/TTK/BUB1B. It was observed that knockdown of TTK inhibited the activation of LDHA via Y239 phosphorylation, which established a positive feedback loop of glycolysis and histone lactylation and positive feedback loops of cell cycle genes, suggesting a new mechanism of PDAC and providing new insights for its treatment (37). In CRC, G protein-coupled receptor 37 promotes LDHA expression through the hippo pathway, increases H3K18la levels and upregulates the expression of the chemokines CXCL1 and CXCL5 (38). Chen *et al* (39) reported that enolase 1 (ENO1) upregulation enhances glycolysis and lactate accumulation. On the one hand, lactate activates NSUN2 transcription through H3K18 lactylation; on the other hand, it directly induces K356 lactylation of the NSUN2 protein, increasing its RNA capture ability. This establishes a self-reinforcing 'NSUN2-ENO1-lactate-NSUN2' positive feedback loop. Targeting this circuit with the small-molecule inhibitor Nsu2-i4 effectively blocks this feedback mechanism. In anaplastic thyroid carcinoma, the BRAFV600E mutation enhances aerobic glycolytic flux, leading to elevated levels of histone H4 lysine 12 lactylation (40). In endometrial carcinoma, H3K18la is enriched in the ubiquitin-specific protease 39 (USP39) promoter region. USP39 deubiquitinates and stabilizes phosphoglycerate kinase 1 (PGK1) and activates glycolysis through the phosphatidylinositol 3-kinase (PI3K)/AKT/hypoxia-inducible factor-1alpha (HIF-1α) signaling pathway, promoting cell proliferation and migration. The lactic acid produced by glycolysis further stimulates histone lactylation. Targeting lactylation or USP39 can effectively block this loop (41). In breast cancer, glycolysis-derived lactate directly activates c-Myc transcription through H3K18 lactylation. c-Myc in turn upregulates SRSF10, driving the protumor effects of MDM4 and Bcl-x and forming a positive feedback loop of 'lactate-H3K18la/c-Myc/SRSF10/glycolysis', and targeting glycolysis or P300 could disrupt this axis (42). In

gliomas, NF-κB activation drives glycolysis and lactate accumulation, promoting H3K18la deposition and subsequently activating LINC01127 transcription. LINC01127, which acts as an RNA scaffold, recruits RNA polymerase II subunit A to the promoter of mitogen-activated protein kinase kinase kinase kinase 4 (MAP4K4) in a cis manner, thereby activating the MAP4K4-c-Jun N-terminal kinase (JNK) pathway and subsequently activating NF-κB. This positive feedback loop sustains glioma stem cell stemness and drives tumor progression. The targeting of LINC01127 or JNK effectively disrupts this axis (43). In prostate cancer, DNA topoisomerase II α (TOP2A) results in the production of lactate through the upregulation of LDHA activity and glycolysis, forming a positive feedback loop of TOP2A/LDHA/lactylation and thus promoting the proliferation, migration, invasion and epithelial-mesenchymal transition (EMT) of prostate cancer cells (44). Together, these mechanisms increase glycolysis and lactate accumulation through the upregulation of key enzymes (such as LDHA and PGK1) and the formation of a positive feedback loop that further exacerbates tumor progression. In addition, lactate modification regulates the transcription of specific genes (such as TTK, BUB1B, CXCL1, CXCL5, USP39 and c-Myc) and affects metabolic pathways and signaling pathways, thereby promoting the proliferation and survival of tumor cells.

Protein lactylation in multiple cancer types collectively contributes to tumor development by promoting metabolic reprogramming, stabilizing key proteins, modulating signaling pathways and influencing gene expression; specifically, lactylation enhances glycolysis and other metabolic pathways by upregulating key enzymes [such as LDHA, alanyl-tRNA synthetase 1 (AARS1), phosphofructokinase, platelet (PFKP)], which provide an energetic advantage to tumor cells. In addition, lactylation stabilizes key proteins [such as nucleolar and spindle-associated protein 1 (NUSAP1) and X-ray cross complementing 1 (XRCC1)], which prolongs their half-life and enhances their functions. Furthermore, lactylation affects multiple aspects of the TME by activating or inhibiting specific signaling pathways (such as TGF-β/SMAD3, Hippo and MAPK/ERK). Lactylation is also enriched in promoter regions that regulate the transcription of specific genes, further contributing to tumorigenesis and progression. In PDAC, the binding of NUSAP1 to c-Myc and HIF-1α promotes LDHA expression, after which the lactylation of NUSAP1 stabilizes its expression, resulting in the formation of a positive feedback loop that promotes metastasis; targeting NUSAP1 or blocking its lactylation can effectively inhibit this loop (45).

In GC, AARS1 is translocated to the nucleus as a lactylation writer, and lactylation of yes-associated protein (YAP) and TEA domain transcription factor (TEAD) promotes AARS1 transcription through the Hippo signaling pathway, driving the malignant progression of GC. AARS1 is notably expressed in GC tissues and is positively associated with YAP/TEAD1 expression and poor patient prognosis. Moreover, the GC-associated R77Q mutation increases the lactyltransferase activity of AARS1 (46). In GBM, interaction of aldehyde dehydrogenase 1 family member A3 (ALDH1A3) and pyruvate kinase M2 (PKM2) increases glucose metabolism, and promotes lactylation of XRCC1 at lysine 247 and enhances DNA repair, leading to resistance to chemoradiotherapy; the small molecule D34-919, which targets the ALDH1A3-PKM2 interaction, effectively reverses this mechanism and synergizes with chemoradiotherapy to inhibit tumor growth both *in vivo* and *in vitro* (11).

In intrahepatic cholangiocarcinoma, nucleolin (NCL) is lactylated by P300 at lysine 477, and lactylated NCL binds to MAP kinase-activating death domain protein (*MADD*) pre-mRNA to prevent aberrant splicing, thereby ensuring efficient translation of MADD and activating ERK signaling through the MAPK pathway, thus driving tumorigenesis (47). In pancreatic adenocarcinoma, P300 catalyzes the lactylation of lysine 128 of nicotinamide nucleotide adenylyltransferase 1 (NMNAT1), inhibits DNA damage-inducible transcript 3 transcription and promotes the survival of tumor cells under glucose-deprived conditions. Targeting the lactylation of NMNAT1 or its upstream metabolic pathways could inhibit tumor growth (48). In lung adenocarcinoma, basic leucine zipper and W2 domains 2 (BZW2) promotes glycolysis to increase lactate accumulation, which in turn upregulates isocitrate dehydrogenase subunit expression via H3K18 lactylation, thereby driving tumor cell proliferation, migration, invasion and apoptosis resistance. Targeting glycolysis (for example with 2-DG or oxamate) or BZW2 effectively inhibits this axis (12).

In gliomas, polypyrimidine tract-binding protein 1 (PTBP1) promotes glycolysis by promoting the lactylation at lysine 436 of PTBP1, increasing the RNA binding capacity and stabilizing the mRNA of the metabolic enzyme 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 (49). In the hypoxic TME of hepatocellular carcinoma (HCC), the upregulation of glypican-3 (GPC3) stabilizes the c-Myc protein by increasing its lactylation, thereby promoting the proliferation, migration, invasion, stemness and glycolysis of HCC cells. Targeting GPC3 or inhibiting glycolysis reduces c-Myc lactylation and suppresses the malignant phenotype of tumors (50). In OC, lactylation of PFKP upregulates phosphatase and tensin homolog expression and inhibits glycolytic processes (51). In esophageal cancer, hypoxia induces an increase in the level of Axin1 protein lactylation at lysine 147, promotes Axin1 ubiquitination degradation and relieves the inhibition of glycolysis, driving metabolic reprogramming and stemness maintenance in esophageal cancer cells (52).

4. Lactylation in tumor cell proliferation

The lactic acid produced by glycolysis affects not only the transcription of the downstream molecule laminin γ 2 (LAMC2), AP001885.4, through histone lactylation, but also affects the transcription of cyclin D1 (CCND1)/neuropilin-2 (NRP2) through the non-histone lactylation of centromeric protein A (CENPA). In esophageal squamous cell carcinoma (ESCC), hypoxia specifically activates LAMC2 transcription by inducing H3K9la, thereby driving the proliferation, migration, invasion and metastasis of ESCC cells through the PI3K/AKT/VEGFA axis (53). Fu *et al* (13) reported that elevated H3K18la promotes the transcription of AP001885.4, thereby promoting the proliferation of ESCC cells. In HCC, CENPA is lactylated at lysine 124, and then promotes the transcription of CCND1/NRP2,

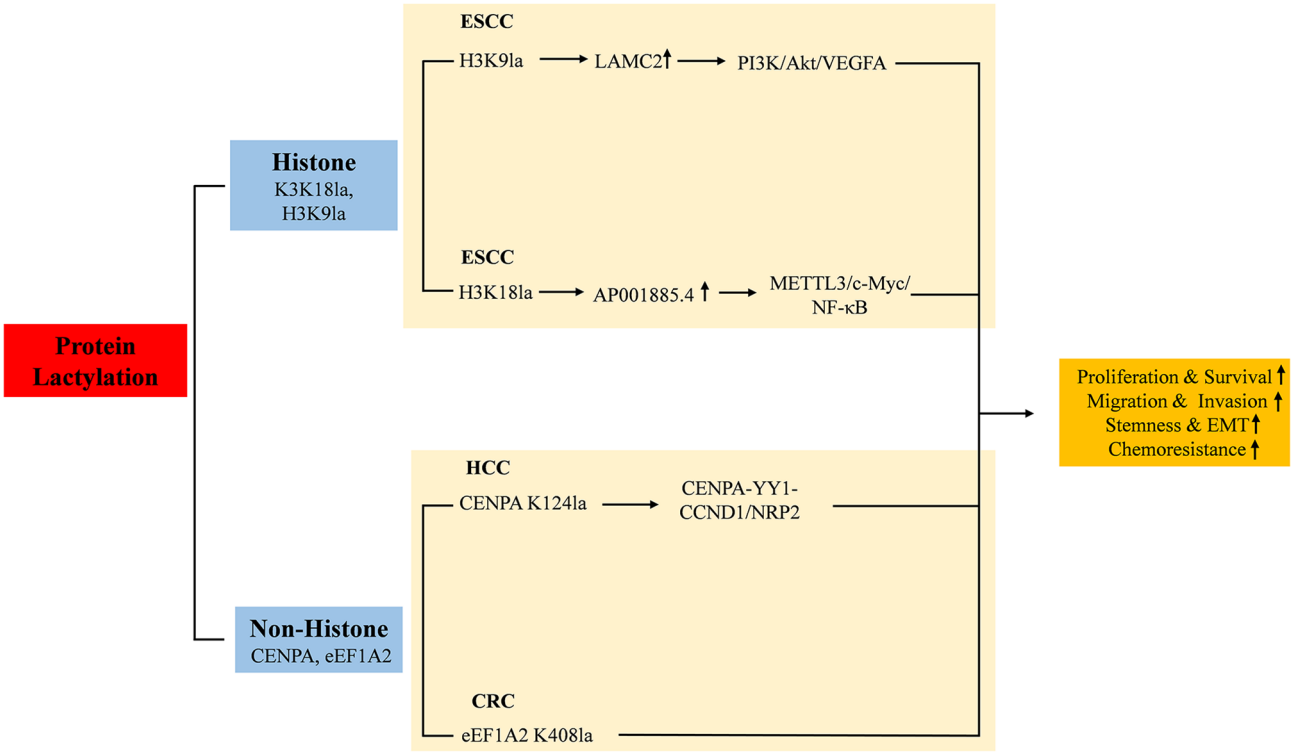

Figure 4. Histone and non-histone lactylation in tumor cell proliferation. Protein lactylation promotes the proliferation of tumor cells by regulating PI3K/Akt/VEGFA, METTL3/c-Myc/NF-kB, and CENPA-YY1-CCND1/NRP2 signaling pathways. H3K9, histone H3 lysine 9; LAMC2, laminin γ 2; CENPA, centromeric protein A; YY1, yin yang 1; CCND1, cyclin D1; NRP2, neuropilin-2; METTL3, methyltransferase-like 3; NF-κb, nuclear factor κB; H3K18, histone H3 lysine 18; VEGFA, vascular endothelial growth factor A; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; CRC, colorectal cancer; EMT, epithelial-mesenchymal transition.

thereby enhancing the proliferation of hepatoma cells (14). In CRC, lysine acetyltransferase 8 (KAT8) was identified as a lactate transferase, lactylating eukaryotic translation elongation factor-1, α-2 at lysine 408, increasing translation elongation and protein synthesis and driving malignant tumor progression; targeting KAT8 can effectively suppress tumor growth (54).

Taken together, these findings suggest that protein lactylation collectively promotes cell proliferation in different types of cancers by increasing the transcription of key genes, activating specific signaling pathways, and promoting metabolic reprogramming (Fig. 4).

5. Lactate in cell metastasis

Protein lactylation promotes migration and invasion by regulating the transcription and signaling pathways of key genes in multiple cancer types. Specifically, in bladder cancer, the expression of circXRN2 is aberrantly downregulated in bladder cancer tissues and cell lines. CircXRN2 prevents large tumor suppressor 1 from speckle-type POZ protein (SPOP)-mediated degradation by binding to SPOP degron, which then activates the Hippo signaling pathway, reducing the levels of H3K18la and lipocalin 2 (LCN2) expression, thus inhibiting migration of cancer cells (55). In addition, Wang *et al* (56) reported that phosphofructokinase-1 (PFK-1) inhibited histone lactylation and transcription activity of zinc-finger E-box-binding homeobox 1, thereby inhibiting the migration and invasion of bladder cancer cells (56).

In breast cancer, potassium two pore domain channel subfamily K member 1 increases glycolysis and lactate production by binding to and activating LDHA, which results in elevated levels of H3K18la and thus creates malignant positive feedback that reduces tumor cell stiffness and adhesion, ultimately leading to the proliferation, invasion and metastasis of breast cancer cells (57). In clear cell renal cell carcinoma (ccRCC), the inactivation of von Hippel-Lindau activates PDGFRβ transcription via the HIF-glycolysis-lactate-H3K18la axis, while PDGFRβ signaling in turn promotes glycolysis and lactylation, resulting in the formation of a positive feedback loop that drives malignant progression of ccRCC. Targeting glycolysis (for example with oxamate) or PDGFRβ (for example with axitinib) can effectively disrupt this loop, and the combination therapy has synergistic effects (58).

In CRC, intestinal bacteria-derived lipopolysaccharide promotes the transcription and upregulates the expression of LINC00152 by increasing the level of lactylation of histone H4 lysine 8 on the promoter, and the overexpression of LINC00152 promotes the migration and invasion of cells (59). In GC, elevated glucose transporter protein 3 promotes elevated levels of LDHA, L-lactyl, H3K9la, H3K18la and histone H3 lysine 56 lactylation (H3K56la), and promotes the metastasis and invasive ability of GC cells (60). In esophageal cancer, hypoxia induces elevated levels of serine hydroxymethyltransferase-2 (SHMT2) protein lactylation and upregulates SHMT2 expression, which in turn increases methylenetetrahydrofolate dehydrogenase 1 like expression

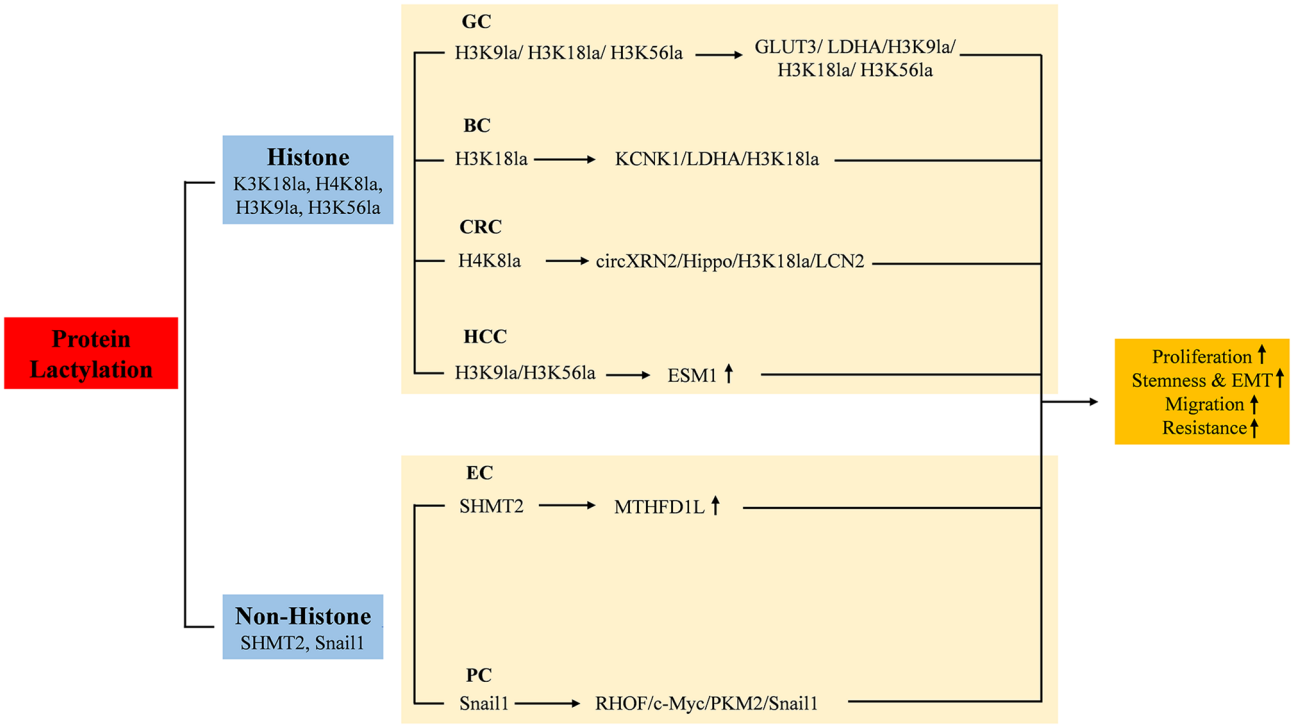

Figure 5. Histone and non-histone lactylation in tumor cell metastasis. Protein lactylation enhances tumor cell metastasis by mediating several pathways such as GLUT3/LDHA/H3K9la/H3K18la/H3K56la, KCNK1/LDHA/H3K18la, and RHOF/c-Myc/PKM2/Snail1. GLUT3, glucose transporter protein 3; LDHA, lactate dehydrogenase A; H3K9, histone H3 lysine 9; H3K18, histone H3 lysine 18; H3K56, histone H3 lysine 56; H4K8, histone H4 lysine 8; SHMT2, serine hydroxymethyltransferase-2; MTHFD1L, methylenetetrahydrofolate dehydrogenase 1 like; KCNK1, potassium two pore domain channel subfamily K member 1; LCN2, lipocalin 2; RHOF, Rho GTPase Rif; ESM1, endothelial cell-specific molecule 1; EMT, epithelial-mesenchymal transition; GC, gastric cancer; BC, bladder cancer; CRC, colorectal cancer; HCC, hepatocellular carcinoma; PC, pancreatic cancer; EC, esophageal cancer.

and promotes esophageal cancer cell migration and invasion (61). In pancreatic cancer (PC), overexpression of the small Rho GTPase Rif promotes the upregulation of c-Myc to promote PKM2 transcription, which in turn promotes the production of lactic acid from glycolysis and subsequently induces the lactylation of Snail1, which facilitates EMT and accelerates PC cell migration and invasion (62). In HCC, elevated levels of H3K9la and H3K56la promote endothelial cell-specific molecule 1 (ESM1) transcription, upregulate ESM1 expression and promote the metastasis of HCC cells (63).

In summary, protein lactylation promotes migration and invasion in different types of cancers through the following common mechanisms. First, lactylation promotes glycolysis and other metabolic pathways by upregulating key enzymes (such as LDHA and PFK-1), providing an energy advantage to tumor cells and forming a malignant positive feedback loop. Second, lactylation is enriched in the promoter region, regulating the transcription of specific genes (such as LCN2, LINC00152 and ESM1) and promoting tumor cell migration and invasion. Furthermore, lactylation affects multiple aspects of the TME by activating or inhibiting specific signaling pathways (such as Hippo, PDGFRβ and EMT). Finally, lactylation stabilizes key proteins (such as SHMT2 and Snail1), prolonging their half-life and enhancing their function, thereby further promoting tumor development (Fig. 5). These findings suggest that further attention to molecules related to protein lactylation is important for the treatment of different tumors.

6. Acetylation and lactylation

As two notable PTMs, acetylation and lactylation play distinct but interrelated roles in cellular metabolism, gene expression regulation and tumor biology. Compared with acetylation, lactylation is more prominent in the TME, especially under hypoxia and high glycolytic conditions, where it increases glycolytic activity by upregulating the expression of key enzymes (such as LDHA) and promotes tumor cell proliferation, migration and invasion (11,21). Although both types of modification regulate gene expression by altering the chemistry of lysine residues, lactylation is more directly associated with cellular metabolic states, whereas acetylation is more involved in a broad network of gene regulation, such as protein stability, liquid-liquid phase separation and enzyme activity (64).

Studies have also shown that specific enzymes such as KAT8 catalyze not only acetylation but also lactylation reactions, indicating a potential cross-regulatory mechanism between these modifications (54). Elucidating the differences between acetylation and lactylation and their potential synergistic effects is required to fully resolve the complex intracellular regulatory network, and this understanding should provide a theoretical basis for the development of new anticancer therapies.

7. Summary and discussion

As an emerging PTM of proteins, lactate modification overturns the traditional perception of lactate as a metabolic waste

product only, revealing its central regulatory role in tumorigenesis and development. Histone lactylation (such as H3K18la and H3K9la) induces an immunosuppressive microenvironment by activating the transcription of genes such as PD-L1 and IL-11 or by recruiting immunosuppressive cells such as M2 macrophages and Tregs, whereas non-histone lactylation (such as APOC2) promotes immune escape by enhancing the signaling pathway interactions or metabolic reprogramming. Histone lactylation (for example H3K18la activates TTK/BUB1B in PDAC) and non-histone lactylation (for example NUSAP1 and XRCC1 stabilize metabolism-critical enzymes) work together to increase glycolysis, resulting in the formation of a 'lactate production-lactylation' positive feedback loop that provides an energetic advantage to tumor cells.

In terms of mechanistic depth, although multiple studies have revealed the lactylation sites of specific proteins and their functions, the specific lactylation transferases (writers) and delactylation enzymes (erasers) that catalyze these modifications have mostly not been identified. Furthermore, the interplay between lactylation and other PTMs (such as acetylation, phosphorylation and ubiquitination), for example, competing for the same lysine residue or synergistically regulating protein function, remains largely unexplored. At the level of modeling and validation, numerous studies rely on *in vitro* cell experiments and mouse xenograft models but lack validation in spontaneous tumor models or gene knock-in/knockout animal models. In terms of clinical translation, the development of drugs targeting lactylation is still in its early stages. Although some studies have demonstrated the efficacy of small-molecule inhibitors or specific antibodies *in vitro* and *in vivo*, the specificity, pharmacokinetic properties and long-term toxicity of these compounds have not yet been systematically evaluated. Furthermore, although lactylation modification has shown potential as a biomarker for predicting response to immunotherapy in some studies (65,66), it lacks validation in prospective clinical trials, and its combined application value in combination with other known biomarkers remains unexplored.

The discovery of lactylation has opened up a new dimension of metabolism-epigenetic intersection for tumor research, and its key role in tumor immunity, metabolism, metastasis and other aspects makes it a promising therapeutic target. In the future, it needs to be synergistically promoted through mechanistic research, technological innovation and clinical translation, which is expected to overcome the bottleneck of traditional treatment and provide a brand-new strategy for precision tumor medicine.

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SCF was responsible for topic selection, literature search and manuscript writing. ZZS conceptualized the review, confirmed the final draft and supervised the work. Both authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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