From mechanism to targeted therapy: Advances in histone lactylation-driven cancer progression (Review)

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Abstract. As a novel lactate-derived post-translational modification, histone lactylation links metabolic reprogramming and epigenetic regulation in cancer. Histone lactylation, particularly at histone H3 lysine 18 lactylation (H3K18la), has been implicated in tumor initiation, progression, metastasis, immune evasion and therapy resistance. It modulates oncogenic pathways (such as PI3K/Akt/mTOR, NF-κB, JAK/STAT) and metabolic pathways (such as glycolysis enhancement, fatty acid synthesis via stearoyl-CoA desaturase and glutamine metabolism) and by altering chromatin structure and gene transcription. In the tumor microenvironment, lactate-induced H3K18la polarizes macrophages toward an M2 phenotype, upregulates immune checkpoints and induces $CD8^+$ T cells dysfunction, which promotes immunosuppression. However, $CD8^+$ T cell-intrinsic lactylation may enhance antitumor immunity during checkpoint blockade. Histone lactylation also induces chemoresistance via autophagy activation, DNA repair and ferroptosis suppression. Therapeutic strategies targeting lactylation include inhibiting lactate transporters, glycolysis or regulation enzymes (such as E1A-binding protein, lysine acetyltransferase 2A and brahma-related gene 1). Furthermore, the clinical potential is emerging, with H3K18la and H4K5la serving as prognostic biomarkers in multiple types of cancer. However, key questions regarding the non-enzymatic modification mechanisms, identification of histone lactation regulatory enzymes and pan-cancer functional heterogeneity are yet to be elucidated. Future research should prioritize translational validation of lactylation-targeted therapies and their integration with existing regimens to overcome resistance and improve immunotherapy efficacy.

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Abbreviations: ACAT2, acetyl-CoA acetyltransferase 2; ACOX1, acyl-CoA oxidase 1; ACSS2, acyl-CoA synthetase short chain family member 2; ALDH1A3, aldehyde dehydrogenase 1 family member A3; BC, breast cancer BLCA, bladder cancer; B7-H3, B7 homologue 3; Brg1, brahma-related gene 1; CEA, carcinoembryonic antigen; CRLM, colorectal cancer liver metastasis; CRC, colorectal cancer; CAFs, cancer-associated fibroblasts; CXCL, chemokine (C-X-C motif) ligand; CBX3, chromobox homolog 3; CTHRC1, collagen triple helix repeat-containing 1; DNAJC12, DnaJ heat shock protein family (Hsp40) member C12; DPF2, double plant homeodomain finger 2; ESCC, esophageal squamous cell carcinoma; GBM, glioblastoma; GCN5, general control non-depressible 5; HCC, hepatocellular carcinoma; H3K27ac, histone H3 lysine 27 acetylation; H3K18la, histone H3 lysine 18 lactylation; HECTD2, HECT domain E3 ubiquitin protein ligase 2; HDAC, histone deacetylase; IRS1, insulin receptor substrate 1; Kla, lysine lactylation; KEAP1, Kelch-like ECH associated protein 1; KAT2A, lysine acetyltransferase 2A; LDH, lactate dehydrogenase; LUAD, lung adenocarcinoma; LAMC2, laminin subunit γ 2; MCTs, monocarboxylate transporters; NEAT1, nuclear paraspeckle assembly transcript 1; NB, neuroblastoma; NSCLC, non-small cell lung cancer; NUPR1, nuclear protein 1; OC, ovarian cancer; PTMs, post-translational modifications; PYCR1, pyrroline-5-carboxylate reductase 1; PCA, pancreatic cancer; PKM2, pyruvate kinase M2; RUBCNL, rubicon-like autophagy enhancer; SCD, stearoyl-CoA desaturase; SLFN5, Schlafen 5; SIRT, sirtuin; TME, tumor microenvironment; TNBC, triple-negative breast cancer; TAMs, tumor-associated macrophages; TMZ, temozolomide; TRIM33, tripartite motif containing 33; USP, ubiquitin-specific peptidase; YTHDF2, YTH N^6-methyladenosine RNA-binding protein F2

Key words: histone lactylation, epigenetic regulation, lactate metabolism, therapeutic targets

Contents

1. Introduction

Post-translational modifications (PTMs) are regulatory mechanisms that modulate protein function, serving roles in

cellular signaling and disease pathogenesis (1-4). Chromatin is a dynamic nucleoprotein complex localized in cell nuclei, consisting of DNA, histones, non-histone proteins and small regulatory RNAs. It serves a role in essential nuclear processes, including the regulation of gene expression, DNA replication and repair and mitotic chromosome segregation (5-8). The N-terminal tails of core histones represent the major sites for post-translational chromatin modifications, which dynamically regulate chromatin accessibility and function (9). Aberrant histone PTMs constitute a fundamental epigenetic mechanism in oncogenesis that dysregulates transcriptional networks, DNA repair fidelity and the fate of the cell, which promotes tumor development and metastatic competence (10-14).

Lactate is a key signaling molecule that mediates intercellular communication, with protein lactylation, a novel PTM, emerging as a central mechanism underlying lactate-dependent regulation. This epigenetic modification promotes tumor progression through lactate accumulation-dependent mechanisms and the subsequent activation of specific lactylation-promoting acyltransferases (15,16). First identified as a novel PTM in a study by Zhang *et al* (17) in 2019, histone lactylation is a ubiquitously present, evolutionarily conserved and dynamically regulated lactate-mediated epigenetic mark. Furthermore, it is preferentially enriched at gene promoters and enhancers, serving as a potential indicator of transcriptionally active chromatin (17,18). As an epigenetic regulation, histone lactylation mediates transcriptional control through lactyl group deposition on histone lysines, which alters nucleosome dynamics and DNA-histone interactions (19). Histone lactylation serves a role in cancer progression and treatment resistance, with aberrant histone lactylation levels serving as a prognostic indicator for patients with cancer (20,21). Targeting histone lactylation may potentially be used for precision cancer therapy (22,23).

The present review discussed the current knowledge on histone lactylation and emphasized its role as a pivotal metabolic-epigenetic nexus in cancer. The present review described its mechanistic contributions to tumor progression, immune evasion and therapy resistance. Furthermore, the cascading interplay between lactylation and other PTMs (histone acetylation and histone methylation) were evaluated and emerging therapeutic strategies targeting the lactylation axis were discussed.

2. Lactate metabolism and lactate transport

During glycolysis, glucose undergoes sequential enzymatic breakdown to yield pyruvate, which is subsequently converted to lactate via NADH-dependent reduction. This process is catalyzed by lactate dehydrogenase (LDH), resulting in lactate accumulation (24). Lactate is actively shuttled across cellular membranes via monocarboxylate transporters (MCTs) (25). Under conditions of adenosine triphosphate (ATP) depletion and hypoxia, oxidative phosphorylation is compromised, leading to suppression of the tricarboxylic acid cycle and the upregulation of glycolytic flux to maintain cellular ATP levels (26). During physiological stress, such as intense exercise, skeletal muscle cells exhibit marked lactate production. This metabolic byproduct contributes to an increase in the carbon dioxide concentrations, which stimulates the respiratory center to enhance pulmonary ventilation, thereby meeting the increased oxygen demands (27). During inflammation, lactate functions as a pleiotropic signaling molecule that orchestrates immune cell responses during inflammation (28).

The core function of mitochondria is to generate energy through oxidative phosphorylation. Under normal physiological conditions, pyruvate enters the mitochondria and is metabolized, resulting in minimal lactate production. However, during mitochondrial dysfunction, the transport of pyruvate into mitochondria is impaired, resulting in cells being reliant on glycolysis, which leads to lactate accumulation. Therefore, the metabolic state of mitochondria determines the intracellular levels of lactate (29-31). Abnormal lactate accumulation promotes tumorigenesis and progression through histone lactylation (25,32,33). In the Warburg effect, glucose is preferentially converted into lactate to facilitate rapid energy production, which is concomitant with metabolic reprogramming that is characterized by enhanced aerobic glycolysis, lactate accumulation, suppressed mitochondrial oxidative phosphorylation and compromised mitochondrial function (34,35).

3. Histone lactylation in tumor progression

Histones are highly conserved, nuclear-encoded basic proteins characterized by their abundance of positively charged amino acids (lysine and arginine residues) (16). As the core structural components of nucleosomes, they organize and compact eukaryotic DNA into chromatin (36). In addition to their architectural role, histones dynamically regulate essential nuclear processes including transcriptional control, DNA damage response and mitotic chromosome segregation (36). Histones are classified into two categories, namely core and linker histones. The core histones (H2A, H2B, H3 and H4) form the octameric structural scaffold of nucleosomes, while the H1 linker histone binds to the inter-nucleosomal DNA regions (16,37,38).

Histone H3 lysine 18 lactylation (H3K18la) in tumor progression. Multiple histone lactylation sites are identified on histone H3 and H4 (39,40). Since its initial identification, H3K18la is the most studied histone lactylation site (17). Previous studies demonstrate that H3K18la influences tumor initiation, progression and metastasis through transcriptional regulation (41,42). In uveal melanoma, H3K18la transcriptionally upregulates YTH N6-methyladenosine RNA-binding protein F2 (YTHDF2), which promotes uveal melanoma pathogenesis. Mechanistically, YTHDF2 recognizes and binds to N6-methyladenosine (m6A)-modified period circadian regulator 1 and TP53 mRNAs, which facilitates their degradation and accelerates uveal melanoma tumorigenesis (43). In ocular melanoma, increased levels of H3K18la epigenetically activates the transcription of α-ketoglutarate-dependent dioxygenase homolog 3 (ALKBH3). ALKBH3 mediates the N1-methyladenosine demethylation of SP100A mRNA, which promotes malignant transformation (44). In hepatocellular carcinoma (HCC), histone lactylation (H3K18la) and histone H3 lysine 27 acetylation (H3K27ac) cooperatively regulate tumor progression through an epigenetic cascade mechanism. H3K18la upregulates the expression of the m6A reader

protein YTH m6A RNA binding protein C1 (YTHDC1), which stabilizes m6A-modified long non-coding RNA nuclear paraspeckle assembly transcript 1 (NEAT1) and recruits histone acetyltransferase p300 to the promoter region of the stearoyl-CoA desaturase (SCD) gene. This leads to increased histone H3K27ac levels, which activates the expression of SCD, induces fatty acid metabolic reprogramming and promotes HCC progression (45). This exemplifies a complex cascade of epigenetic modifications, in which histone lactylation (H3K18la) acts as an upstream regulator that promotes downstream histone acetylation (H3K27ac), and induces oncogenic metabolic reprogramming. This exemplifies a complex cascade of epigenetic modifications, in which histone lactylation acts as an upstream regulator that directly promotes downstream histone acetylation, thereby driving oncogenic metabolic reprogramming. It underscores that histone PTMs do not function in isolation but can form a hierarchical cascade, with upstream modifications dictating downstream epigenetic events. In glioblastoma (GBM), the NF-κB pathway promotes H3K18la via the Warburg effect, which enhances the expression of the long non-coding RNA LINC01127. Subsequently, LINC01127 activates the mitogen-activated protein kinase kinase kinase kinase 4/JNK/NF-κB signaling axis, promoting self-renewal of GBM stem cells (46).

Dysfunctional mitochondrial processes (including impaired mitochondrial oxidative phosphorylation and dysregulated mitophagy) and proteins [such as sirtuin (SIRT), Parkin and Numb] serve as central therapeutic targets in various diseases (such as neurodegenerative diseases, cancer and metabolic disorders) (47-55). Glycolysis and oxidative phosphorylation are the primary pathways for cellular energy production. When mitochondrial oxidative phosphorylation is impaired, glycolysis is enhanced, leading to an increased accumulation of lactic acid in cells, which further influences histone lactylation (34). SIRT 4, a member of the mitochondrial SIRT family, serves a key role in regulating mitochondrial function. As a mitochondrial protein, SIRT4 deacetylates glycolytic enzyme α-enolase at lysine 358. This promotes a metabolic shift from mitochondrial oxidative phosphorylation to glycolysis and enhances lactate production. The accumulated lactate subsequently induces histone lactylation (H3K18la and H3K9la), which activates stemness-related pathways via epigenetic reprogramming, and enhances the stem-like properties of pancreatic cancer (PCA) cells (52).

Mitophagy is a highly conserved and crucial cellular self-cleaning process. Its function is to maintain intracellular homeostasis by removing damaged mitochondria. This ensures that there is an energy supply and prevents the release of pro-apoptotic factors (such as cytochrome c and second mitochondria-derived activator of caspases) and excessive reactive oxygen species (ROS) that could lead to cellular damage or death (53,54). The regulation of mitophagy influences cancer development (47). In prostate and lung cancer, the cell fate determinant Numb binds to and promotes Parkin-mediated mitophagy, which maintains mitochondrial stability. When the Numb/Parkin axis is impaired, damaged mitochondria accumulate, which triggers a metabolic reprogramming toward aerobic glycolysis. This shift increases lactate production, which subsequently induces epigenetic reprogramming via histone lactylation (H3K18la), activating the transcription of neuroendocrine-related genes such as synaptophysin, neural cell adhesion molecule-1 and neuron-specific enolase. Ultimately, this process promotes the transformation of cancer cells toward a neuroendocrine phenotype and confers therapy resistance (55).

H3K18la also functions as a key epigenetic promoter of metastatic progression in multiple types of cancer, such as HCC, CRC, endometrial carcinoma and BC (33,41,42,56,57). A study by Wang *et al* (56) demonstrates using *in vitro* and *in vivo* experiments that pyrroline-5-carboxylate reductase 1 (PYCR1) increases insulin receptor substrate 1 (IRS1) expression levels by promoting H3K18la at the IRS1 promoter region. This PYCR1/H3K18la/IRS1 axis subsequently activates the PI3K/Akt/mTOR signaling pathway, which promotes the proliferation and migration of HCC cells. H3K18la promotes colorectal cancer (CRC) liver metastasis (CRLM) by upregulating the expression of cell division cycle 27. Mechanistically, this is promoted by lactate accumulation, which results from the ubiquitin-specific peptidase 3 (USP3)-antisense RNA 1/USP3/MYC axis-mediated activation of the glycolytic pathway (41). Bioinformatic analysis reveals that histone lysine lactylation (Kla) serves as a poor prognostic biomarker in breast cancer (BC), which under high glycolytic flux promotes BC cell proliferation and migration by increasing c-Myc expression levels, upregulating serine/arginine-rich splicing factor 10 and consequently modulating the alternative splicing of murine double minute 4 and Bcl-x (33,57). In endometrial carcinoma, H3K18la positively regulates the expression of USP39. Subsequently, USP39 activates the PI3K/AKT/hypoxia inducible factor 1α signaling pathway, promoting lactate production, proliferation and metastasis (42).

Histone lactylation at other sites. In addition to the well-characterized H3K18la, other known lactylation sites include H3K27la, H3K14la, H3K9la and H3K56la on histone H3, as well as histone H4 lysine 5 lactylation (H4K5la), H4K8la, H4K12la and H4K16la on histone H4 (39,40,58). These modifications exhibit distinct regulatory roles in tumor progression, with mechanisms that include: i) Inhibition of tumor apoptosis (59,60); ii) regulation of tumor metastasis and invasion (61,62); and iii) induction of cellular senescence and telomerase inhibition (58).

Bioinformatics analysis and experimental validation using clinical samples reveals H4K12la as a novel prognostic biomarker for triple-negative BC (TNBC) (59). A study by Li *et al* (60) demonstrates that lactate mediates H4K12la binding to the Schlafen 5 (SLFN5) promoter region, which suppresses the transcription of SLFN5 and subsequently inhibits apoptosis in TNBC. Hypoxia-induced H3K9la promotes migration and invasion in esophageal squamous cell carcinoma (ESCC) by upregulating the expression of laminin subunit g 2 (LAMC2). Mechanistic study further revealed that LAMC2 enhances the expression of vascular endothelial growth factor by activating the PI3K/Akt signaling pathway (61).

In patients with neuroblastoma (NB), low expression levels of DnaJ heat shock protein family member C12 (DNAJC12) is associated with poor clinical outcomes. Functionally, DNAJC12 deficiency upregulates the expression of collagen type Iα1 through H4K5la-mediated epigenetic regulation, which promotes NB cell invasion and metastasis. Mechanistically,

this process involves DNAJC12 downregulation enhances the glycolytic pathway by upregulating key enzymes such as hexokinase 2, pyruvate kinase M1/M2 (PKM), lactate dehydrogenase A (LDHA) and LDHB. This activation leads to lactate accumulation, which in turn promotes H4K5la (62).

In lung adenocarcinoma (LUAD), liver kinase B1 regulates lactate metabolism to suppress H4K8la and H4K16la, which inhibits telomerase reverse transcriptase gene expression and represses telomerase activity, leading to senescence in LUAD cells (58).

Histone lactylation, particularly H3K18la, promotes oncogenesis across various types of cancer (such as HCC, CRC, BC, GBM and LUAD) through epigenetic reprogramming, metabolic rewiring and the activation of oncogenic signaling pathways (such as the PI3K/Akt/mTOR signaling pathway and PI3K/AKT/HIF-1α signaling pathway) by modulating chromatin architecture and transcriptional regulation. Additional lactylation sites (H4K8la, H4K16la, H4K12la, H3K9la, H4K5la) are implicated in tumor progression through diverse mechanisms including apoptosis inhibition, metastasis promotion and cellular senescence inhibition (Table I). However, notable gaps in the knowledge remain regarding the functional roles and specific downstream targets of H3K27la and H3K56la in carcinogenesis. Furthermore, studies on histone lactylation sites predominantly focus on a single type of cancer, highlighting the need for systematic pan-cancer analyses (58-61).

4. Histone lactylation modulates tumor progression by remodeling the tumor microenvironment (TME)

Tumor-associated macrophages (TAMs). First revealed in macrophage research, histone lactylation promotes the expression of M2-like macrophage-associated genes (17). Further studies reveal that histone lactylation promotes tumor progression by inducing M2 polarization of TAMs (21,63-66).

A study by Li *et al* (21) demonstrates that lactate derived from CRC cells promotes tumorigenesis by inducing H3K18la in macrophages, which suppresses the expression of retinoic acid receptor γ and activates the TNF receptor associated factor 6-IL-6-STAT3 signaling axis.

In bladder cancer (BLCA), combining single-cell RNA sequencing with computational biology and functional assays, a study by Deng *et al* (63) reveals that H3K18la epigenetically enhances parkin RBR E3 ubiquitin protein ligase transcription. This promotes both mitochondrial autophagy and M2-like polarization in TAMs, which forms an immunosuppressive microenvironment that increases BLCA progression. Additionally, under hypoxic conditions, lactate produced by glioma cells promotes M2 polarization of TAMs through the MCT1/H3K18la/TNF superfamily member 9 axis (64). In addition, H3K18la in macrophages upregulates the expression of nuclear protein 1 (NUPR1), which promotes M2-like polarization through the suppression of ERK and JNK signaling pathways. This NUPR1-mediated reprogramming increases the levels of immune checkpoint molecules programmed death ligand 1 (PD-L1) and signal regulatory protein α, which induces $CD8^+$ T-cell dysfunction and compromises the efficacy of immunotherapy (65). In PCA, lactate-induced H3K18la activates acetyl-CoA acetyltransferase 2 (ACAT2) at the transcriptional level, establishing a positive feedback loop of lactate/H3K18la/ACAT2/mitochondrial carrier homolog 2, which impairs mitochondrial oxidative phosphorylation and promotes lactate accumulation. In addition, ACAT2 facilitates cholesterol transport via small extracellular vesicles, which promotes the M2 polarization of TAMs (66).

In addition to its role in macrophage polarization, histone lactylation can also regulate the phagocytic capacity of macrophages. In PTEN/p53-deficient aggressive PCA, tumor-derived lactate suppresses the phagocytic function of TAMs via H3K18la, which promotes tumor progression (67). Elevated H3K18la levels in tumor-infiltrating myeloid cells upregulates the expression of methyltransferase-like 3, which increases the RNA m6A modification. This subsequently increases the mRNA translation efficiency of Janus kinase 1 (JAK1) and activates the JAK1/STAT3 signaling pathway, which amplifies the immunosuppressive function of tumor-infiltrating myeloid cells in tumors (68).

Cancer-associated fibroblasts (CAFs). Functioning as critical microenvironmental modulators, CAFs contribute to tumor pathogenesis (69). Lactate derived from lung cancer cells promotes the expression of collagen triple helix repeat-containing 1 (CTHRC1) in CAFs via H3K18la, which maintains their $CTHRC1^+$ CAF phenotype. These activated $CTHRC1^+$ CAFs subsequently upregulate the expression of hexokinase 2 in tumor cells through the activation of TGF-β/Smad signaling. This then induces a resistance to epidermal growth factor receptor tyrosine kinase inhibitors and enhances glycolytic metabolism in lung cancer cells (70).

Neutrophils. G protein-coupled receptor 37 promotes CRLM progression through dual mechanisms: i) It activates the Hippo signaling pathway to enhance tumor cell proliferation; and ii) it upregulates the expression of chemokine (C-X-C motif) ligand (CXCL) 1 and 5 via H3K18la, which promotes neutrophil accumulation in the TME. These coordinated actions establish a pro-metastatic niche that facilitates CRLM development (71). Hypoxia-induced glycolytic activation in neutrophils increases lactate-dependent histone lactylation, which transcriptionally activates arginase-1 to enhance immunosuppression. Inhibition of this lactylation pathway reverses neutrophil-mediated immune evasion and improves the response of brain tumors to immunotherapy (72).

$CD8^+$ T cells. Histone lactylation exhibits dual roles in modulating $CD8^+$ T cell function in the TME. Tumor cell-intrinsic histone lactylation induces $CD8^+$ T cell exhaustion; however, $CD8^+$ T cell-autonomous histone lactylation enhances their antitumor immunity. In head and neck squamous cell carcinoma, H3K9la upregulates the expression of IL-11 in tumor cells. This tumor-derived IL-11 then induces $CD8^+$ T cell exhaustion via the JAK2/STAT3 signaling pathway (73). A study using the MB49 tumor model demonstrates that combination therapy with anti-programmed cell death protein 1 (PD-1) and anti-cytotoxic T-lymphocyte associated protein 4 (CTLA-4) antibodies markedly elevates the H3K18la and H3K9la levels in tumor-infiltrating $CD8^+$ T cells, which is associated with marked tumor growth inhibition (74).

Table I. Effects of histone lactylation on tumor cells.

First author, year	Type of cancer	Lactylation site	Downstream targets	Associated molecules or pathways	Effects	(Refs.)
Zhou *et al*, 2025	CRC	H3K18la	CDC27	Not mentioned	Liver metastases	(41)
Wei *et al*, 2024	EC	H3K18la	USP39	PI3K/AKT/HIF-1α signaling pathway	Proliferation and metastasis	(42)
Yu *et al*, 2021	Uveal melanoma	H3K18la	YTHDF2	PER1 and TP53	Oncogenesis	(43)
Gu *et al*, 2024	Ocular melanoma	H3K18la	ALKBH3	SP100A	Progression	(44)
Du *et al*, 2024	HCC	H3K18la	YTHDC1	NEAT1, p300 and H3K27ac	Progression	(45)
Li *et al*, 2023	GBM	H3K18la	LINC01127	MAP4K4/JNK/NF-κB axis	Stem cells self-renew	(46)
Wang *et al*, 2024	HCC	H3K18la	IRS1	PI3K/Akt/mTOR signaling pathway	Proliferation and migration	(56)
Pandkar *et al*, 2023	BC	H3K18la	c-Myc	SRSF10, MDM4 and Bcl-x	Proliferation and migration	(33)
Liu *et al*, 2024	LUAD	H4K8la and H4K16la	TERT	Not mentioned	Cellular senescence	(58)
Li *et al*, 2024	TNBC	H4K12la	SLFN5	Not mentioned	Progression	(60)
Zang *et al*, 2024	ESCC	H3K9la	Not mentioned	PI3K/Akt signaling pathway and VEGFA	Migration and invasion	(61)
Yang *et al*, 2025	NB	H4K5la	COL1A1	Not mentioned	Migration and invasion	(62)

HCC, hepatocellular carcinoma; BC, breast cancer; EC, esophageal cancer; CRC, colorectal cancer; GBM, glioblastoma; TNBC, triple-negative breast cancer; LUAD, lung adenocarcinoma; ESCC, esophageal squamous cell carcinoma; NB, neuroblastoma; CDC27, cell division cycle 27; YTHDF2, YTH N6-methyladenosine RNA binding protein F2; PER1, period1; NEAT1, nuclear enriched abundant transcript1; ALKBH3, α-ketoglutarate-dependent dioxygenase homolog 3; H3K27ac, histone H3 lysine 27 acetylation; H3K18la, histone H3 lysine 18 lactylation; SRSF10, serine and arginine rich splicing factor 10; MDM4, murine double minute 4; USP39, ubiquitin specific peptidase 39; IRS1, insulin receptor substrate 1; SLFN5, schlafen family member 5; TERT, telomerase reverse transcriptase; COL1A1, collagen type I α1 chain; LINC, long intergenic non-protein coding RNA; HIF-1α, hypoxia-inducible factor-1α; SP100A, speckled protein 100A; MAP4K4, mitogen-activated protein kinase kinase kinase kinase 4; VEGFA, vascular endothelial growth factor A.

In summary, histone lactylation, particularly H3K18la, is a pivotal epigenetic mechanism that orchestrates the immunosuppressive TME through multifaceted pathways including immune cell reprogramming, stromal cell activation and therapy resistance. Mechanistically, histone lactylation mediates immunosuppression by polarizing myeloid cells toward an M2-like phenotype, promoting $CD8^+$ T cell exhaustion and enhancing neutrophil-mediated immunosuppression. Additionally, $CD8^+$ T cell-intrinsic histone lactylation exhibits context-dependent effects, potentiating antitumor activity when induced by immune checkpoint blockades (Table II).

5. Histone lactylation and chemoresistance

Emerging evidence demonstrates that this epigenetic modification regulates chemotherapeutic responses through multiple molecular mechanisms, which contributes to chemoresistance in malignant tumors.

Modulation of cellular autophagy pathways. Compared with bevacizumab-sensitive patients, the histone lactylation level is markedly higher in bevacizumab-resistant patients with CRC. In patient-derived tumor xenograft models and patient-derived organoids, the combination of bevacizumab and histone lactylation inhibitor (oxamate) relieves the bevacizumab resistance in CRC. Mechanistically, H3K18la activates the transcription of the autophagy-enhancing gene rubicon-like autophagy enhancer (RUBCNL). RUBCNL interacts with Beclin 1 to mediate the recruitment and function of the class III phosphatidylinositol 3-kinase complex, which promotes autophagosome maturation (75).

Regulation of transcriptional activity and activation of proliferation-associated signaling pathways. In BLCA, H3K18la promotes cisplatin resistance by facilitating the transcriptional induction of Y-Box binding protein 1 and Yin Yang 1 transcription factor (76). In HCC, H3K18la exacerbates resistance to lenvatinib by promoting the transcription of the HECT domain E3 ubiquitin protein ligase 2 (*HECTD2*) gene. HECTD2 acts as an E3 ubiquitin ligase for Kelch-like ECH associated protein 1 (KEAP1), facilitating the degradation of KEAP1 protein and activating the antioxidant response, which induces lenvatinib resistance in HCC cells (77). H3K14la promotes multi-drug (oxaliplatin and 5-fluorouracil) resistance through neural precursor cell expressed, developmentally downregulated protein 4 E3 ubiquitin protein ligase-mediated phosphatase and PTEN ubiquitination and degradation, which leads to the subsequent activation of the PI3K/Akt/mTOR signaling pathway in HCC (78). However, the suppression of histone lactylation enhances the sensitivity of cancer to chemotherapy.

In GBM, peroxisome proliferator-activated receptor α activates the p38 MAPK signaling pathway, which in turn upregulates acyl-CoA oxidase 1 (ACOX1). ACOX1 suppresses lactate-mediated H3K18la by promoting ROS-dependent downregulation of PKM2, which enhances the sensitivity of GBM to temozolomide (TMZ) (79). Transfer RNA-derived small RNA (tsRNA)-08614 enhances the sensitivity of CRC to oxaliplatin by targeting aldehyde dehydrogenase 1 family member A3 (ALDH1A3) to inhibit glycolysis and histone lactylation modifications. Mechanistically, tsRNA-08614 downregulates the expression of ALDH1A3, which reduces lactate production and decreases the level of H3K18la. The decreased H3K18la level suppresses the transcriptional activity of EF-hand domain family member D2, which promotes the sensitivity of CRC to oxaliplatin (80).

Inhibition of ferroptosis. H4K12la in CRC stem cells suppresses ferroptosis signaling by upregulating the expression of glutamate-cysteine ligase, which enhances oxaliplatin resistance. This epigenetic modification is dynamically regulated by p300-mediated lactylation and histone deacetylase (HDAC) 1-mediated delactylation (81). Lactate derived from CAFs promotes doxorubicin resistance in TNBC cells by enhancing the expression of zinc finger protein 64 through H3K18la-mediated epigenetic regulation, which suppresses ferroptosis (82).

Modulation of DNA damage repair pathways. In lung cancer brain metastasis, aldo-keto reductase family 1 member B10 enhances lactate accumulation. Lactate-induced H4K12la transcriptionally activates the cell cycle gene cyclin B1, which promotes DNA replication and cell cycle progression, inducing an acquired resistance to pemetrexed (83). In ovarian cancer (OC), H4K12la activates super-enhancers to recruit the oncogenic transcription factor MYC, which upregulates the expression of the nucleotide excision repair-related gene radiation sensitive protein (RAD)23 homolog A, nucleotide excision repair protein (84). Additionally, general control non-depressible 5 (GCN5) promotes cisplatin resistance in OC by upregulating H3K9la and RAD51 Kla to enhance homologous recombination repair (85). H3K9la promotes the transcription of LUC7-like 2, pre-mRNA splicing factor (LUC7L2). However, in GBM, LUC7L2 downregulation reduces the expression of MLH1, which suppresses mismatch repair and leads to TMZ resistance (86).

In summary, histone lactylation acts as a crucial mediator in chemoresistance across various types of cancer. It promotes chemoresistance through multiple mechanisms, including activation of autophagy-related pathways, modulation of transcription factor activity, regulation of DNA repair, interference with apoptosis, reprogramming of cellular metabolism and stimulation of proliferation-related signaling pathways (Table III).

6. Histone lactylation and immune checkpoint inhibitors

Immune checkpoint inhibitors, such as CTLA-4 and PD-1, function by blocking immune checkpoints to restore the ability of the immune system to recognize and attack cancer cells (87). Notable clinical success is demonstrated with checkpoint proteins such as PD-1/PD-L1 and CTLA-4 in cancer treatment (88). Emerging evidence reveals histone lactylation-mediated immune evasion mechanisms across various types of cancer (Table IV). In non-small cell lung cancer (NSCLC), H3K18la activates pore membrane protein 121 transcription, which facilitates MYC nuclear translocation. This enhances MYC binding to the CD274 promoter, which upregulates the expression of PD-L1 and promotes immune evasion (89). In acute myeloid leukemia, STAT5-induced

Table II. Effects of histone lactylation on the tumor microenvironment.

First author, year	Type of cancer	Cell type	Lactylation site	Downstream targets	Associated molecules or pathways	Effects	(Refs.)
Li *et al*, 2024	CRC	TAMs	H3K18la	RARγ	TRAF6/IL-6/STAT3	Oncogenesis	(21)
Deng *et al*, 2025	BLCA	TAMs	H3K18la	PRKN	Not mentioned	Mitophagy and M2 polarization	(63)
Li *et al*, 2024	GBM	TAMs	H3K18la	TNFSF9	Not mentioned	M2 polarization	(64)
Cai *et al*, 2025	HCC	TAMs	H3K18la	NUPR1	ERK and JNK signaling pathways	M2 polarization	(65)
Yang *et al*, 2025	PCA	TAMs	H3K18la	ACAT2	Not mentioned	M2 polarization	(66)
Chaudagar *et al*, 2023	Prostate cancer	TAMs	H3K18la	Not mentioned	Not mentioned	Inhibition of phagocytosis in TAMs	(67)
Xiong *et al*, 2022	CRC	TIMs	H3K18la	METTL3	JAK1/STAT3	Tumor immune evasion	(68)
Zhang *et al*, 2025	Lung cancer	CAFs	H3K18la	Cthrc1	TGF-β/Smad	Resistance to EGFR-TKI	(70)
Zhou *et al*, 2023	CRC	Neutrophils	H3K18la	CXCL1 and 5	Not mentioned	Immunosuppression	(71)
Ugolini *et al*, 2025	Brain tumor	TIMs	Not mentione2	ARG1	Not mentioned	Immunosuppression	(72)
Wang *et al*, 2024	HNSCC	$CD8^+$ T cells	H3K9la	IL-11	JAK2/STAT3	Dysfunction of $CD8^+$ T cells	(73)
Raychaudhuri *et al*, 2024	BLCA	$CD8^+$ T cells	H3K18la and H3K9la	Not mentioned	Not mentioned	Tumor suppression	(74)

CRC, colorectal cancer; BLCA, bladder cancer; GBM, glioblastoma; HCC, hepatocellular carcinoma; PCA, pancreatic cancer; HNSCC, head and neck squamous cell carcinoma; TAMs, tumor-associated macrophages; RARγ, retinoic acid receptor γ; TRAF6, TNF receptor-associated factor 6; IL, interleukin; STAT3, signal transducer and activator of transcription 3; JAK, janus kinase; PRKN, parkin RBR E3 ubiquitin protein ligase; TNFSF9, TNF superfamily member 9; NUPR1, nuclear protein 1; Cthrc1, collagen triple helix repeat containing-1; METTL3, methyltransferase like 3; TIMs, tumor-infiltrating myeloid cells; CAFs, cancer-associated fibroblasts; CXCL, C-X-C motif chemokine ligand; ACAT2, acetyl-coA acetyltransferase 2; ARG1, arginase 1; H3K18la, histone H3 lysine 18 lactylation; TKI, tyrosine kinase inhibitor.

Table III. An overview of the effects of histone lactylation on chemotherapy.

First author, year	Type of cancer	Drug	Lactylation site	Downstream targets	Effects	(Refs.)
Li *et al*, 2024	CRC	Bevacizumab	H3K18la	RUBCNL	Autophagosome maturation	(75)
Li *et al*, 2024	BLCA	Cisplatin	H3K18la	YBX1 and YY1	Reduction in the sensitivity of tumor cells to cisplatin	(76)
Dong *et al*, 2025	HCC	Lenvatinib	H3K18la	HECTD2	Reduction in the sensitivity of tumor cells to lenvatinib	(77)
Zeng *et al*, 2025	HCC	Oxaliplatin and 5-fluorouracil	H3K14la	The ubiquitin E3 ligase NEDD4	Activation of PI3K/Akt/mTOR signaling pathway	(78)
Wang *et al*, 2025	GBM	Temozolomide	H3K18la	Not mentioned	Reduction in the sensitivity of tumor cells to temozolomide	(79)
Chen *et al*, 2025	CRC	Oxaliplatin	H3K18la	EFHD2	Reduction in the sensitivity of tumor cells to oxaliplatin	(80)
Deng *et al*, 2025	CRC	Oxaliplatin	H4K12la	Glutamate-cysteine ligase	Reduction in the sensitivity of tumor cells to oxaliplatin	(81)
Zhang *et al*, 2025	TNBC	Doxorubicin	H3K18la	ZFP64	Reduction in ferroptosis	(82)
Duan *et al*, 2023	Lung cancer	Pemetrexed	H4K12la	*CCNB1*	Increases in DNA replication and the acceleration of the cell cycle	(83)
Lu *et al*, 2025	Ovarian cancer	Niraparib	H4K12la	Super-enhancer	Increases in DNA damage repair	(84)
Sun *et al*, 2025	Ovarian cancer	Cisplatin	H3K9la	Not mentioned	Increases in homologous recombination repair	(85)
Yue *et al*, 2024	GBM	Temozolomide	H3K9la	LUC7L2	Reductions in mismatch repair	(86)

CRC, colorectal cancer; BLCA, bladder cancer; GBM, glioblastoma; HCC, hepatocellular carcinoma; TNBC, triple-negative breast cancer; RUBCNL, rubicon-like autophagy enhancer; YBX1, Y-Box binding protein 1; YY1, Yin Yang 1; EFHD2, EF-hand domain family member D2; HECTD2, HECT domain E3 ubiquitin protein ligase 2; NEDD4, neural precursor cell expressed, developmentally down-regulated protein 4; CCNB1, cyclin B1; LUC7L2, LUC7-like 2; H3K18la, histone H3 lysine 18 lactylation; ZFP64, zinc finger protein 64.

Table IV. An overview of the effects of histone lactylation on immunotherapy.

First author, year	Type of cancer	Lactylation site	Downstream targets	Immune checkpoint	(Refs.)
Zhang *et al*, 2024	Non-small cell lung cancer	H3K18la	Pore membrane protein 121	PD-L1	(89)
Huang *et al*, 2023	Acute myeloid leukemia	H4K5la	PD-L1	PD-L1	(90)
Li *et al*, 2024	Gastric cancer	H3K18la	PD-L1	PD-L1	(91)
Chao *et al*, 2024	Ovarian cancer	H3K18la	PD-L1	PD-L1	(92)
Ding *et al*, 2025	HCC	H3K18la	PD-L1	PD-L1	(94)
Ma *et al*, 2025	HCC	H3K18la	CD276	CD276	(95)
Wang *et al*, 2024	Glioblastoma	Not mentioned	CD47	CD47	(98)

HCC, hepatocellular carcinoma; H3K18la, histone H3 lysine 18 lactylation; PD-L1, programmed death ligand 1.

lactate accumulation promotes E3 binding protein nuclear translocation, which increases H4K5la levels. H4K15la further elevates the expression of PD-L1, which establishes a metabolic-epigenetic cascade linking lactate metabolism to immune escape (90).

CAF-derived lysyl oxidase activates the TGF-β/insulin-like growth factor 1 signaling pathway to promote the epithelial-mesenchymal transition and glycolysis in GC. The resulting lactate accumulation enhances the H3K18la-mediated expression of PD-L1 (91). Elevated H3K18la levels are associated with poor prognosis in OC (92). LDHB, a subunit of lactate LDH, facilitates immune evasion in OC by modulating H3K18la at the PD-L1 promoter to upregulate the expression of PD-L1 (93). Protein arginine methyltransferase 3 methylates pyruvate dehydrogenase kinase isoform 1 at residues R363 and R368, which enhances its kinase activity to promote glycolysis and the accumulation of lactate. The resulting lactate induces H3K18la, which directly binds to the PD-L1 promoter to upregulate its expression, which promotes immune evasion in HCC (94). Histone lactylation modulates the expression of PD-L1, which impairs the immune system recognition and attack of cancer cells (91,93,94). However, the role of histone lactylation in regulating CTLA-4 during cancer therapy is yet to be fully elucidated, which may be an avenue for future investigation.

In addition to PD-L1 and CTLA-4, new immune checkpoints, including B7 homologue 3 (B7-H3), are being investigated (88). Lactate upregulates the expression of B7-H3/CD276 in HCC cells via histone lactylation modifications, particularly H3K18la, which suppresses the proportion and function of tumor-infiltrating $CD8^+$ T cells and promotes tumor immune escape. Inhibiting lactate metabolism reduces the expression of B7-H3 and synergizes with anti-PD-1 therapy, which markedly suppresses tumor progression (95).

CD47 (integrin-associated protein) is expressed on the surface of various cell types, including tumor cells. Its ligand, signal-regulatory protein α (SIRPα), is primarily expressed on immune cells such as macrophages. When CD47 binds to SIRPα, a signal is transmitted to macrophages, which inhibits their phagocytic activity against the tumor cells (96,97). In GBM stem cells, histone lactylation promotes the expression of CD47, which inhibits the phagocytic activity of microglia/macrophages against tumor cells and facilitates tumor immune escape. Histone lactylation also enhances the substrate specificity of histone acetyltransferase p300 for lactyl-CoA through its interaction with heterochromatin protein chromobox homolog 3 (CBX3), which further promotes the expression of immunosuppressive cytokines (IL-4, IL-10 and IL-13) (98).

In summary, histone lactylation serves as a critical epigenetic regulatory mechanism mediating tumor immune evasion. This modification orchestrates the expression levels of immune checkpoint molecules through multiple pathways, impairing immune cell recognition and cytotoxic functions against tumor cells, which leads to immune escape. Elucidating the precise mechanisms of histone lactylation in tumor immune evasion may provide a theoretical foundation for identifying novel immunotherapy targets and may also facilitate the rational design of combination therapies.

7. Current research status and future directions of histone lactylation in cancer diagnosis or treatment

Histone lactylation has the potential to serve as a biomarker for cancer diagnosis and prognosis. The levels of histone lactylation modification show marked differences in various types of cancer and may be a potential diagnostic biomarker (57,99). Combined with multi-omics analysis techniques, genes modified by histone lactylation may also serve as novel biomarkers for predicting the prognosis of cancer or evaluating therapeutic efficacy (100).

The study by Hou *et al* (20) first reveals an association between H3K18la and both severity and prognosis in PCA. The aforementioned study demonstrates an elevated expression of H3K18la in PCA tissues, which shows notable associations with serum lactate levels as well as tumor markers such as carbohydrate antigen 19-9 and carcinoembryonic antigen (CEA). These findings indicate that H3K18la may be a promising novel biomarker for PCA diagnosis and prognostic evaluation. A study by Zhu *et al* (99) performs a comprehensive evaluation of the clinical significance of H4K5la in BC. The aforementioned study demonstrates elevated H4K5la levels across multiple sample types, including TNBC tissues, non-TNBC tissues and peripheral blood mononuclear cells. Furthermore, the authors identify positive associations between the expression of H4K5la and tumor progression markers such as proliferation index Ki-67, CEA levels and lymph node metastasis status. However, higher H4K5la expression levels show a negative association with overall survival time, suggesting its potential as both a prognostic indicator and therapeutic monitoring marker in BC management. The study by He *et al* (101) uses an integrated analysis of transcriptomic and single-cell RNA sequencing data to identify five histone lactylation-related prognostic genes (synuclein α interacting protein, transmembrane protein 100, NLR family pyrin domain containing 11, homeobox C11 and D10) in GBM. Based on these molecular signatures, the aforementioned study presents a risk prediction model that demonstrates robust prognostic performance in patients with GBM.

Potential therapeutic strategies targeting histone lactylation
Inhibition of histone lactylation through targeting lactate transportation and glycolysis. MCTs, particularly MCT1 and MCT4, are key lactate transporters that maintain cellular metabolic balance. MCT1 mediates bidirectional lactate transport and MCT4 primarily facilitates lactate efflux, especially in highly glycolytic cells such as cancer cells and immune cells (102). The MCT1 inhibitor AZD3965 can increase the accumulation of lactate (103). At present, AZD3965, as the first-in-class drug targeting tumor lactate metabolism, has entered phase I/II clinical trials for the treatment of diffuse large B-cell lymphoma and neuroendocrine tumors (NCT01791595) (104). The effects of MCT1 inhibition on histone lactylation exhibit notable cell-type specificity and microenvironmental dependency (105).

Glycolysis, a central metabolic pathway that converts glucose into pyruvate and lactate to generate ATP and key intermediates, promotes lactate accumulation in cells with a Warburg effect. This links cellular metabolic status to histone lactylation modifications (106). Inhibition of glycolysis-related genes reduces lactate production, which decreases histone lactylation levels. LDHA inhibitors suppress tumor growth and synergize with immunotherapy (107). A study by Guo *et al* (23) demonstrates that Fargesin inhibits aerobic glycolysis in NSCLC cell lines by targeting glycolysis-related genes such as LDHA, solute carrier family 2 member 1, and PKM2. The aforementioned study also reveals that Fargesin suppresses the lactylation of histone H3, which inhibits the growth of NSCLC. Tanshinone I, a bioactive diterpenoid derived from *Salvia miltiorrhiza* (Danshen), suppresses OC progression by downregulating glycolysis-related genes and subsequently reducing H3K18la levels (22). Additionally, administration of sodium dichloroacetate, the pyruvate dehydrogenase kinase 1 inhibitor, attenuates histone lactylation modifications (17).

Writers, erasers and readers of histone lactylation. Histone lactylation is a dynamically regulated process that is installed and removed by regulatory enzymes, instead of being a spontaneous chemical reaction. It involves 'writers', 'erasers' and 'readers'. These regulatory enzymes regulate the dynamic balance of histone lactylation, which influences gene expression levels and cellular functions (108-110).

The 'writers' refer to enzymes that add lactate groups to lysine residues on histones. At present, known 'writers' for histone lactylation include acetyltransferase p300 (17,111), GCN5 (also known as lysine acetyltransferase 2A), lysine acetyltransferase 2A (KAT2A) (81,112,113), histone acetyltransferase binding to ORC1 (HBO1; also known as KAT7) (114), KAT5 and KAT8 (115). After histone lactylation was first demonstrated in 2019, p300 emerged as a candidate 'writer' (17). Since identifying p300 as a histone acetyltransferase, a key question is how it specifically catalyzes histone lactylation without affecting histone acetylation. In GBM, CBX3 enhances the specificity of p300 for lactyl-CoA through their interaction, which specifically catalyzes histone lactylation without affecting histone acetylation. This promotes tumor progression (99). In atherosclerosis, the histone chaperone protein anti-silencing function 1A histone chaperone acts as a cofactor for p300, and regulates the enrichment of H3K18la at the snail family transcriptional repressor 1 (SNAI1) promoter region to activate the transcription of SNAI. This in turn induces the endothelial-to-mesenchymal transition, and the use of the p300 agonist cholera toxin B markedly enhances H3K18la levels (116).

A study by Niu *et al* (114) demonstrates that HBO1 functions as a lactyltransferase that preferentially catalyzes H3K9la to enhance malignant behaviors, including proliferation, migration and invasion in various cancer cell lines [including HeLa, HepG2 (HCC), U87MG (gliomas), KYSE-30 (ESCC), MDA-MB-231 (BC), HCT116 (CRC) and H460 (NSCLC)]. In GBM, it is KAT2A, instead of p300, that is the 'writer' and it promotes endothelial growth factor-induced H3K14la and H3K18la. In addition, acyl-CoA synthetase short chain family member 2 (ACSS2) binds to KAT2A, which then acts as a lactyltransferase to catalyze the lactylation of histone H3 at K14 and K18 residues. This regulates gene expression levels and promotes the proliferation and immune evasion of GBM cells. KAT2A carried out distinct histone acylation in different protein complexes and the interaction between ACSS2 and KAT2A promotes the catalytic activity of KAT2A toward

histone lactylation instead of acetylation (113). A study by Zou *et al* (115) demonstrates that KAT5 and KAT8 function synergistically as 'writers' to mediate lactate-induced H4K12la in macrophages. The aforementioned study demonstrates that H4K12la is not influenced by other 'writers', such as p300 and KAT2A.

'Erasers' are enzymes that remove lactylation modifications from histones. Previous studies indicate that a number of deacetylases, such as HDAC1-3 and SIRT1-3, act as 'erasers' to remove lactyl modifications (109,110,117-120). A study by Moreno-Yruela *et al* (110) reports that HDAC1-3 function as 'erasers' to remove histone lactylation modifications. At the H3K9 and H4K12 sites, HDAC3 has greater delactylation activity compared with its deacetylation activity. Additionally, HDAC1 and HDAC3, but not HDAC2, appear to preferentially regulate H4K5la. A study by Xu *et al* (121) demonstrates that HDAC2 and HDAC3 function as 'erasers' for H3 Kla, participating in the regulation of H3K18la-mediated BC cell proliferation. However, the aforementioned study, reveals that HDAC1 levels show no association with H3K18la. SIRT1 acts as a histone delactylase, inhibiting the oncogenic positive feedback loop of long non-coding RNA H19-glycolysis-H3K18la. Moreover, the combined use of the SIRT1-specific activator SRT2104 and the LDHA inhibitor oxamate markedly suppresses the growth of GC cells, with limited effects on normal GC cells; thus, potentially providing a novel strategy for GC treatment (122). A study by Yang *et al* (62) also demonstrates that SIRT2 and p300/CBP act as the 'eraser' and 'writer' of H4K5la, respectively, to regulate the metastatic phenotype of NB cells. In a study on esophageal cancer, SIRT3 is found to act as a specific 'eraser' of H3K9la, which inhibits the progression of ESCC cells (123). In addition, a study by Fan *et al* (109) suggests that SIRT3 also acts as an 'eraser' for H4K16la. The development of small-molecule modulators targeting erasers may potentially be useful in cancer therapy.

'Readers' are proteins that recognize and bind to lactylated histones, regulating gene expression levels and other cellular processes, such as chromatin remodeling and accessibility regulation, cell survival and tumorigenesis, and gene transcription program regulation. Known histone lactylation 'readers' include brahma-related gene 1 (Brg1) (108), double plant homeodomain finger 2 (DPF2) (124) and tripartite motif containing 33 (TRIM33) (125). In 2024, the study by Hu *et al* (108) first reports that Brg1 interacts with H3K18la and functions as a 'reader' of H3K18la and is potentially involved in facilitating the accessibility of chromatin regions-thereby promoting an open chromatin state and enhancing gene expression. DPF2 recognizes H3K14la and binds to it through its DPF domain, which modulates gene transcription and cell survival. In cervical cancer, the accumulation of lactate leads to increased levels of H3K14la, and DPF2 promotes the expression of oncogenes by recognizing H3K14la, which promotes tumorigenesis (124). The bromodomain of TRIM33 specifically recognizes Kla on histones. It is demonstrated that the bromodomain of TRIM33 selectively binds to Kla via a unique glutamic acid residue (E981), establishing it as a Kla-specific 'reader' protein (125). However, a previous study, focusing on H3K18la as the primary subject of investigation, did not demonstrate direct evidence regarding whether TRIM33 functions as a 'reader' at other histone sites (125).

In summary, the primary strategies for targeting histone lactylation include: i) Modulation of lactate transport; ii) regulation of lactate production; and iii) inhibition or activation of enzymes mediating histone lactylation modifications. The present evidence regarding the 'readers', 'erasers' and 'writers' of histone lactylation is yet to be fully elucidated. Further identification and validation of specific targets are required to enhance therapeutic precision. Moreover, there may be a potential for the development of small-molecule inhibitors and activators targeting these regulatory proteins (Fig. 1).

8. Conclusions and research perspectives

Histone lactylation is an epigenetic modification that links cellular metabolism with gene regulation, serving a role in cancer initiation, progression, metastasis, drug resistance and immune evasion. The present review highlighted several key findings. Histone lactylation, particularly at H3K18la, regulates oncogenic pathways and metabolic reprogramming. Other lactylation sites (such as H4K12la, H3K9la and H4K5la) contribute to tumorigenesis in a context-dependent manner, influencing apoptosis suppression, immune evasion and therapy resistance.

Hypoxia and mitochondrial dysfunction often lead to the accumulation of lactic acid within cells. By acting as a metabolic 'gatekeeper' controlling lactate metabolism, mitochondrial targets serve as upstream regulators of histone lactylation. At present, it is indicated that SIRT4 enhances histone lactylation by promoting a metabolic shift from mitochondrial oxidative phosphorylation to glycolysis, which increases lactate accumulation (52). When the Numb/Parkin axis is impaired, the accumulation of damaged mitochondria triggers metabolic reprogramming toward aerobic glycolysis, which leads to lactate accumulation and the promotion of histone lactylation (55). In addition, histone lactylation can also influence mitochondrial function, which affects intracellular lactate accumulation and forms a positive feedback loop. H3K18la disrupts mitochondrial oxidative phosphorylation by promoting the transcriptional activation of ACAT2, exacerbates lactate accumulation and forms a protumorigenic positive feedback loop (66). In Alzheimer's disease, the shift from oxidative phosphorylation to glycolysis in microglia promotes proinflammatory activation. During this process, the glycolysis/H4K12la/PKM2 positive feedback loop exacerbates microglial dysfunction (126).

In the context of cancer, targeting mitochondria with regards to histone lactylation is yet to be fully elucidated. However, understanding its implications in non-cancer contexts (such as inflammation and hypoxic pulmonary hypertension) may be significant (127,128). In the context of inflammation, mitochondrial fragmentation promotes a metabolic shift that increases lactate, which in turn promotes histone lactylation, enhancing macrophage phagocytosis and inflammation resolution (127). Hypoxia-induced mitochondrial ROS stabilizes hypoxia-inducible factor-1α (HIF-1α) via inhibition of its hydroxylation, which upregulates pyruvate dehydrogenase kinase 1/2 to promote glycolytic switching and lactate accumulation in pulmonary arterial smooth muscle cells (PASMCs). H3K18la, induced by accumulated lactate, activates HIF-1α target genes, which facilitates PASMC proliferation and vascular remodeling (128).

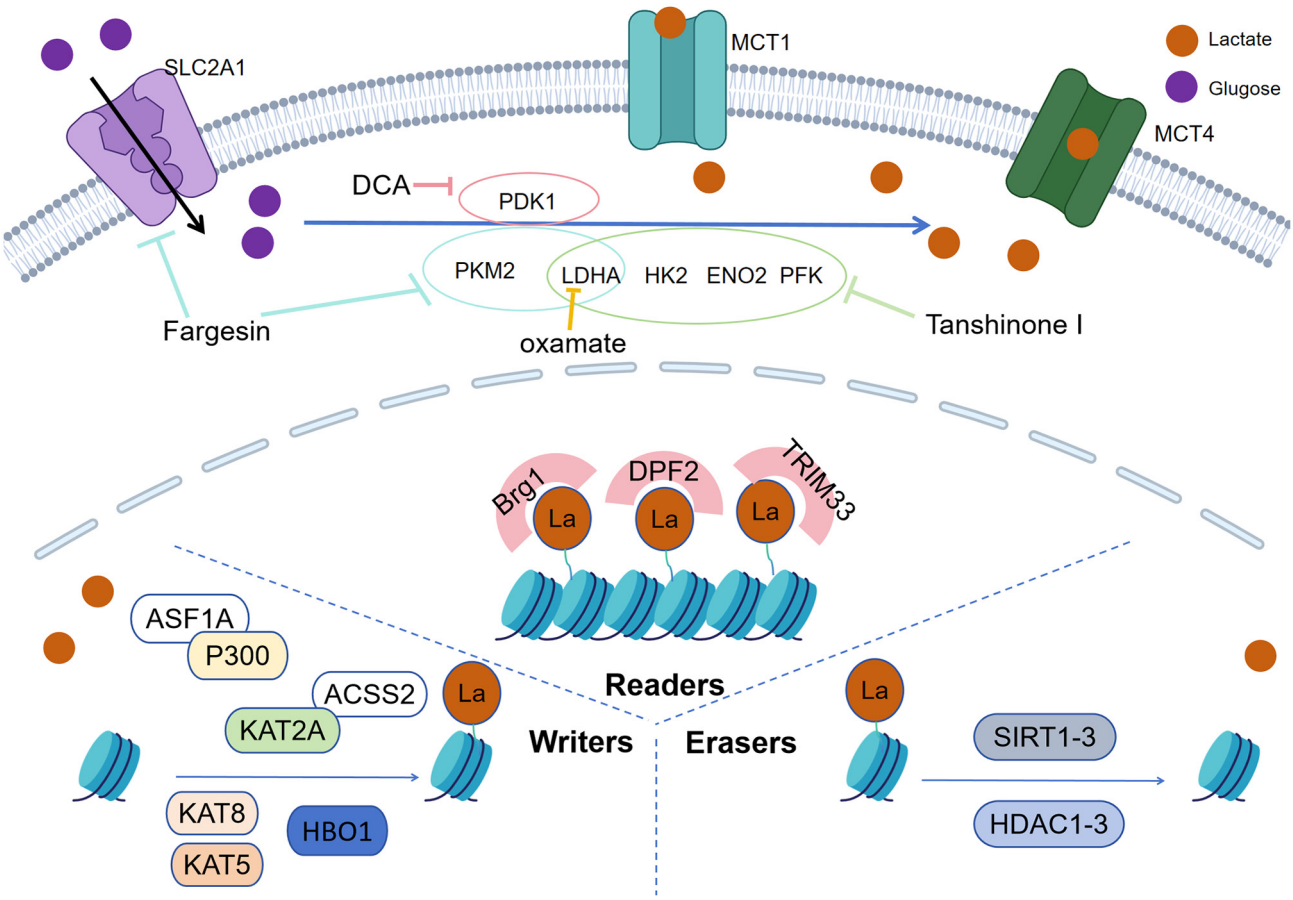

Figure 1. Potential therapeutic strategies targeting histone lactylation. Key strategies to modulate histone lactylation include: i) Downregulating lactate flux (via MCT1/4 inhibition); ii) inhibition of the expression of glycolytic genes (such as *HK2*, *LDHA*, *ENO2*, *PFK*, *PKM2*, *PDK1* and *SLC2A1*); iii) blocking lactylation-recognizing 'readers' (e.g., Brg1, DPF2, TRIM33) and modifying 'writers' (e.g., P300, KAT2A, KAT5, KAT8, HBO1); and iv) enhancing the enzymatic activity of 'erasers' (e.g., SIRT1-3, HDAC1-3). 'T' shaped arrows denote the inhibitions of the pathways. DCA, sodium dichloroacetate; SLC2A1, solute carrier family 2 member 1; MCT1, monocarboxylate transporter 1; MCT4, monocarboxylate transporter 4; HK2, hexokinase 2; LDHA, lactate dehydrogenase; ENO2, enolase 2; PFK, phosphofructokinase; PKM2, pyruvate kinase isozyme type M2; PDK1, pyruvate dehydrogenase kinase 1; HBO1, home box office 1; La, lactate; Brg1, brahma-related gene 1; DPF2, double PHD fingers 2; TRIM33, tripartite motif containing 33; ASF1A, anti-silencing function 1A histone chaperone; P300, E1A-binding protein; ACSS2, acyl-CoA synthetase short chain family member 2; KAT, lysine acetyltransferase; HDAC, histone deacetylase; SIRT, sirtuin.

Selenium deficiency induces mitochondrial dysfunction via the ROS/HIF-1α pathway, leading to enhanced glycolysis and lactate production. The accumulated lactate promotes H3K18la, which activates the NLRP3 inflammasome promoter and induces pyroptosis and the release of inflammatory factors (including TNF-α, IL-6, IL-8, IFN-γ) (129). Methyltransferase-like 15 deficiency impairs mitochondrial ribosome function, leading to reduced oxidative phosphorylation, increased ROS and diminished membrane potential. This promotes enhanced glycolysis and lactate secretion, and leads to a notable increase in histone lactylation at the H4K12 and H3K9 sites (130). In summary, mitochondrial dysfunction is a key regulator of histone lactylation, primarily through its impact on glycolysis and intracellular lactate levels. Enhanced glycolysis fuels lactate production, which in turn promotes histone lactylation by substrate provision. This establishes a key mechanistic link through which mitochondrial dysfunction influences histone lactylation (34,118,126,131).

The present review highlighted that histone PTMs do not function in isolation. A key emerging concept is the cascading interplay between lactylation and other PTMs, which regulate oncogenic programs. For example, in HCC, H3K18la upregulates the expression of YTHDC1, stabilizes NEAT1 RNA and recruits p300 to the SCD gene promoter. This subsequently promotes H3K27ac, forming a cascade of epigenetic modifications that promotes tumor progression by activating fatty acid metabolic reprogramming (45). This 'lactylation-acetylation axis' links lactate metabolism to lipid metabolic reprogramming and tumor progression. In addition to acetylation, the potential crosstalk between lactylation and lysine methylation warrants further investigation. A study by Yang *et al* (132) reveals that H3K18la upregulates the expression of suppressor of zeste 12 (SUZ12), which enhances the level of trimethylated histone H3 at K27 (H3K27me3). Subsequently, SUZ12/H3K27me3 inhibits the transcription of Krüppel-like factor 4 (KLF4). The downregulation of KLF4 relieves its inhibitory effect on LDHA, a key enzyme in glycolysis, leading to lactate production. In turn, the accumulated lactate further promotes histone lactylation, thus forming a self-amplifying positive feedback loop that promotes the Warburg effect and malignant progression of retinoblastoma. Elucidating these cascading interactions may be important to

understand the full scope of histone lactylation in cancer and may contribute to clinical translation strategies from single target to 'PTM cascade' targeting therapies.

Lactate-induced H3K18la in TAMs and myeloid cells promotes an immunosuppressive TME via PD-L1 upregulation, M2 polarization and $CD8^+$ T cell exhaustion. However, $CD8^+$ T cell-intrinsic lactylation may enhance antitumor immunity after induction by immune checkpoint blockade, which suggests a dual role in immunotherapy. Histone lactylation promotes resistance to chemotherapy such as oxaliplatin, cisplatin, lenvatinib and targeted therapies through autophagy activation, DNA repair enhancement and ferroptosis suppression. Lactylation-mediated immune checkpoint upregulation (such as via PD-L1, CD47 and B7-H3) contributes to immunotherapy resistance, which highlights the potential of combination strategies.

However, despite notable progress in associated research, numerous questions are yet to be investigated. At present, a hypothesis regarding the process of histone lactylation is that lactate condenses with CoA within the cell to form lac-CoA. Lac-CoA is then acted upon by a 'writer', which transfers the lactyl group to lysine residues. Subsequently, the lactylated histones are recognized by a 'reader', leading to changes in the transcription levels of downstream genes. Finally, after the modification is complete, an 'eraser' recognizes and removes the lactyl group from the lysine residues, restoring the normal chromatin structure (19). Previous studies demonstrate direct experimental evidence for non-enzymatic histone lactylation. Non-enzymatic Kla is experimentally demonstrated on glycolytic enzymes *in vitro* (45,133). The study by Zhang *et al* (17) provides evidence for its occurrence on histones and demonstrate the modification after incubating histones with sodium lactate in the absence of enzymes. Subsequently, the study by Tan *et al* (134) demonstrates that lactoyl-CoA and lactoylglutathione are the direct inducers of this spontaneous reaction. It is hypothesized that in cellular environments with high lactate and low pH (such as the TME), lactate accumulation may promote histone lactylation through similar non-enzymatic mechanisms (133,135,136). However, at present, it is challenging for the majority of cellular studies to delineate whether lactylation at a specific site arises from enzymatic catalysis or non-enzymatic mechanisms, which is a notable limitation in the field. Therefore, non-enzymatic modification should be considered as a potential confounding factor when interpreting associated physiological or pathological data. Future studies should aim to resolve this by developing site-specific probes or constructing enzyme-deficient models.

At present, multiple 'writers' of histone lactylation (such as P300, GCN5, HBO1, KAT5 and KAT8) and 'erasers' (such as HDAC1-3 and SIRT1-3) are identified. Previous studies suggest that HBO1 preferentially catalyzes H3K9la. Furthermore, compared with HDAC2, HDAC1 and 3 more preferentially regulate H4K5la. These findings indicate that future studies on histone lactylation should select appropriate regulatory enzymes based on specific sites. However, at present, studies on regulatory enzymes for histone lactylation are limited. Therefore, further studies are needed to provide evidence regarding whether these enzymes specifically or preferentially regulate lactylation at particular histone sites. In addition, the specific functions and mechanisms of these enzymes in different types of cancer are yet to be fully elucidated.

Additionally, studies on the 'readers' of histone lactylation is limited, and their functions and regulatory mechanisms in cancer still requires thorough investigation. Due to the high degree of conservation and acetyl-lysine specificity of bromodomain modules, and the structural, functional and evolutionary parallels between histone lactylation and acetylation, it is hypothesized that bromodomain-containing proteins may function as 'readers' of histone lactylation (108,125). It is suggested that future studies further identify and validate the specific targets of these enzymes and possibly develop small-molecule inhibitors or modulators targeting them to potentially achieve more precise cancer therapy.

At present, the majority of studies are still in the basic research stage, and further translational research is required to verify the safety and efficacy of histone lactylation-targeting therapeutic strategies in cancer. Histone lactylation represents a dynamic link between metabolism and epigenetics and may potentially offer novel insights into cancer biology and therapy. Future studies may potentially investigate the enzymatic regulation and functional outcomes of lactylation, develop lactylation-targeted drugs and rational combinations, and validate lactylation as a biomarker and therapeutic target in clinical trials.

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Authors' contributions

ZJ and PG conceived and designed the present study. ZJ, SL and ZW drafted the initial manuscript. ZJ prepared the figures and tables. PG revised figures, tables and manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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.

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