Lactylation in gastric cancer: From mechanisms to clinical applications (Review)

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Abstract. Gastric cancer (GC) is one of the most common malignant tumors worldwide. Metabolic reprogramming and epigenetic dysregulation represent its key pathological characteristics. As a novel lactate-mediated post-translational modification, lactylation converts metabolic signals into epigenetic and protein functional regulation, and it is extensively and aberrantly activated in GC. Lactylation drives the malignant progression of GC by promoting cell proliferation, invasion, metastasis and stemness. In addition, lactylation suppresses antitumor immune cell functions, and mediates immune escape and therapeutic resistance. Clinically, global lactylation levels and specific lactylation sites can serve as independent prognostic biomarkers, and corresponding risk models enable prognostic stratification and prediction of immunotherapy response. Intervention strategies targeting lactate production, lactyltransferases and downstream effector axes have emerged as promising directions for GC treatment. The present review summarizes the regulatory mechanisms, biological functions and clinical translational value of lactylation in GC, aiming to provide novel insights for precision diagnostics and therapeutics.

Contents

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1. Introduction

Gastric cancer (GC) is a highly prevalent gastrointestinal malignancy with poor prognosis worldwide. It ranks as the fifth most common malignant cancer and the fourth leading cause of cancer-related death. GC poses clinical challenges, including high heterogeneity, strong invasiveness and metastasis, frequent chemoresistance and limited response to immunotherapy, thus threatening human health (1,2). The development and progression of GC constitutes a complex, multifactorial and multistep process involving genetic abnormalities, disordered signaling pathways, tumor microenvironment (TME) remodeling and dysregulated metabolic-epigenetic control (3-5). Despite recent advances in targeted therapy and immunotherapy for GC, the overall survival of patients with advanced disease remains unsatisfactory (6,7). Therefore, exploring the key molecular mechanisms underlying GC progression, and identifying novel, precise diagnostic and therapeutic targets have become urgent demands in current GC research.

Metabolic reprogramming is one of the core hallmarks of cancer. Enhanced aerobic glycolysis, known as the Warburg effect, is the most typical metabolic phenotype of cancer cells. Even under sufficient oxygen supply, cancer cells preferentially generate energy through glycolysis, which is accompanied by large lactate production and extracellular secretion, thereby shaping an acidic TME (8,9). In the past, lactate was regarded merely as a metabolic waste product. However, emerging evidence has demonstrated that lactate acts as a key signaling molecule widely involved in the regulation of tumor growth, invasion, immune escape and therapeutic resistance (10,11). In GC, aberrant upregulation of glycolytic key enzymes, including glucose transporter (GLUT)3, lactate dehydrogenase (LDH)A, LDHB and pyruvate kinase M2 (PKM2), drives excessive lactate production and accumulation. Lactate subsequently serves as a sufficient substrate for a novel type of post-translational modification (PTM) termed lactylation, acting as a pivotal link connecting metabolic disturbance and epigenetic dysregulation (12,13).

Lactylation is a newly identified PTM that covalently modifies lysine residues of proteins using lactate as the donor, mainly comprising of histone lactylation and non-histone lactylation (14,15). As a key epigenetic mechanism linking cellular metabolic status to gene transcription, lactylation participates extensively in tumor progression, TME remodeling and therapeutic resistance by altering chromatin accessibility, regulating target gene transcription, and affecting protein stability, subcellular localization and protein-protein interactions (16-18). To date, several functional histone lactylation sites have been identified, including H3K18la, H3K9la, H4K8la and H4K12la, as well as key non-histone substrates such as LDHB, glutathione (GSH) peroxidase 4 (GPX4) and methyltransferase-like (METTL)3 (19-21). These modifications are dynamically regulated by 'writers' such as alanyl-tRNA synthetase 1 (AARS1) and p300, and 'erasers' such as sirtuins (SIRTs) and histone deacetylases (HDACs) (22,23). However, the site-specific functions, signaling networks and clinical translational value of lactylation in GC remain to be systematically summarized and comprehensively elucidated.

Collectively, lactylation serves as a hub connecting metabolic reprogramming, epigenetic regulation and TME remodeling in GC, and plays a key role in driving GC malignant progression. The present review systematically focuses on lactylation in GC, elaborates the classification and dynamic regulatory mechanisms of lactylation, highlights the biological functions and molecular mechanisms of lactylation in GC cell proliferation, invasion, metastasis, immune escape and therapeutic resistance, summarizes research advances in lactylation-related prognostic biomarkers and proposes potential therapeutic strategies targeting lactylation. The present review aims to provide a systematic theoretical basis and research perspective for further understanding the metabolic-epigenetic regulatory network of GC, and for developing novel diagnostic biomarkers and precise therapeutic targets.

2. Overview of lactylation

Lactate metabolism and lactylation. Lactate is the end-product of the glycolytic pathway, and fulfills a key role in cellular energy metabolism and redox homeostasis. Under physiological conditions, cells convert glucose to pyruvate via glycolysis. Pyruvate is then reduced to lactate by LDH, and lactate is transported across the plasma membrane by monocarboxylate transporters (MCTs) to maintain lactate homeostasis (24,25). In pathological conditions such as cancer, metabolic reprogramming triggers a marked increase in aerobic glycolysis (the Warburg effect). Aberrant activation of key molecules, including GLUTs, LDHA and PKM2, drives excessive lactate production and accumulation in cells and in the microenvironment, resulting in lactate concentrations far exceeding physiological levels (26,27).

Lactylation is directly dependent on lactate availability. Lactate serves not only as a metabolite but also as the direct donor for lactylation, with a strict dose-dependent and dynamic association (28). Elevated intracellular lactate promotes the synthesis of lactoyl-coenzyme A (lactoyl-CoA), which provides the lactoyl group for modification of lysine residues and initiates lactylation (29,30). Previous studies have indicated that glycolytic inhibitors such as 2-deoxy-D-glucose and oxamate markedly reduce cellular lactate levels and globally downregulate lactylation, whereas exogenous lactate directly increases lactylation levels (31,32). Furthermore, lactate transport, cellular stress [such as hypoxia or endoplasmic reticulum (ER) stress] and pathogenic infection indirectly regulate the intensity and specificity of lactylation by altering glycolytic flux (33,34). Thus, lactate metabolism acts as the upstream core regulator of lactylation, and lactylation represents the key molecular mechanism by which lactate exerts signaling and epigenetic functions.

Classification and molecular mechanisms of lactylation. Lactylation is a novel PTM that covalently adds a lactoyl group to protein lysine residues using lactate as a donor. It is dynamically reversible and site-specific, acts on a wide range of substrates and can be mainly classified into histone lactylation and non-histone lactylation (32,35).

Histone lactylation was first identified and remains the most extensively studied subtype of lactylation. In 2019, Zhang *et al* (36) first identified 28 histone lactylation sites and demonstrated that lactate drives histone lactylation via p300 to directly regulate gene transcription. To date, multiple functional sites have been identified in various cell and disease models, including H3K9la, H3K14la, H3K18la, H4K8la and H4K12la. These sites are mostly enriched in gene promoters or enhancers, and participate in transcriptional regulation by altering chromatin accessibility (37,38). For example, H4K12la enhances glycolysis in endometrial cells by regulating HIF1α, thereby improving pregnancy outcomes (39). H3K18la plays a role in gene regulation in bone marrow stromal cells, and is closely associated with osteogenesis and osteoporosis (40). H4K12la promotes pemetrexed resistance in lung cancer brain metastasis by regulating cyclin B1 transcription (41).

Non-histone lactylation is a regulatory modification that has been recently identified, with substrates covering metabolic enzymes, signaling proteins, RNA-binding proteins, nuclear membrane proteins, immune checkpoints and other functional proteins (42). Previous studies have shown that non-histone lactylation sites are more numerous than histone sites, and can alter protein stability, enzymatic activity, subcellular localization and protein-protein interactions (43,44). For example, MECP2-K271la stabilizes atherosclerotic plaques by inhibiting epiregulin expression and pro-inflammatory cytokine secretion (45). Lactylation of β-catenin activates the Wnt pathway by enhancing its stability, thus promoting proliferation and stemness in colorectal cancer cells (46). In addition, lactylation of metabolic enzymes, including aldolase B, PKM2 and enolase, directly participates in glycolytic reprogramming by modifying substrate binding or enzyme activity (27,47,48).

Elevated lactate levels are a prerequisite for lactylation, but they cannot determine which proteins undergo this modification. Protein lactylation is tightly controlled by three families of regulatory enzymes: Writers, erasers and readers. Writers facilitate lactylation by catalyzing the transfer of lactoyl groups. p300/CBP act as primary lactyltransferases that rely on lactoyl-CoA to carry out such modification (49,50). Previous studies have demonstrated that AARS1 directly catalyzes lactylation with lactate and ATP as substrates, independent of lactoyl-CoA, thus serving as a *bona fide* lactyltransferase (51,52). Furthermore, HBO1 and NAA10 also

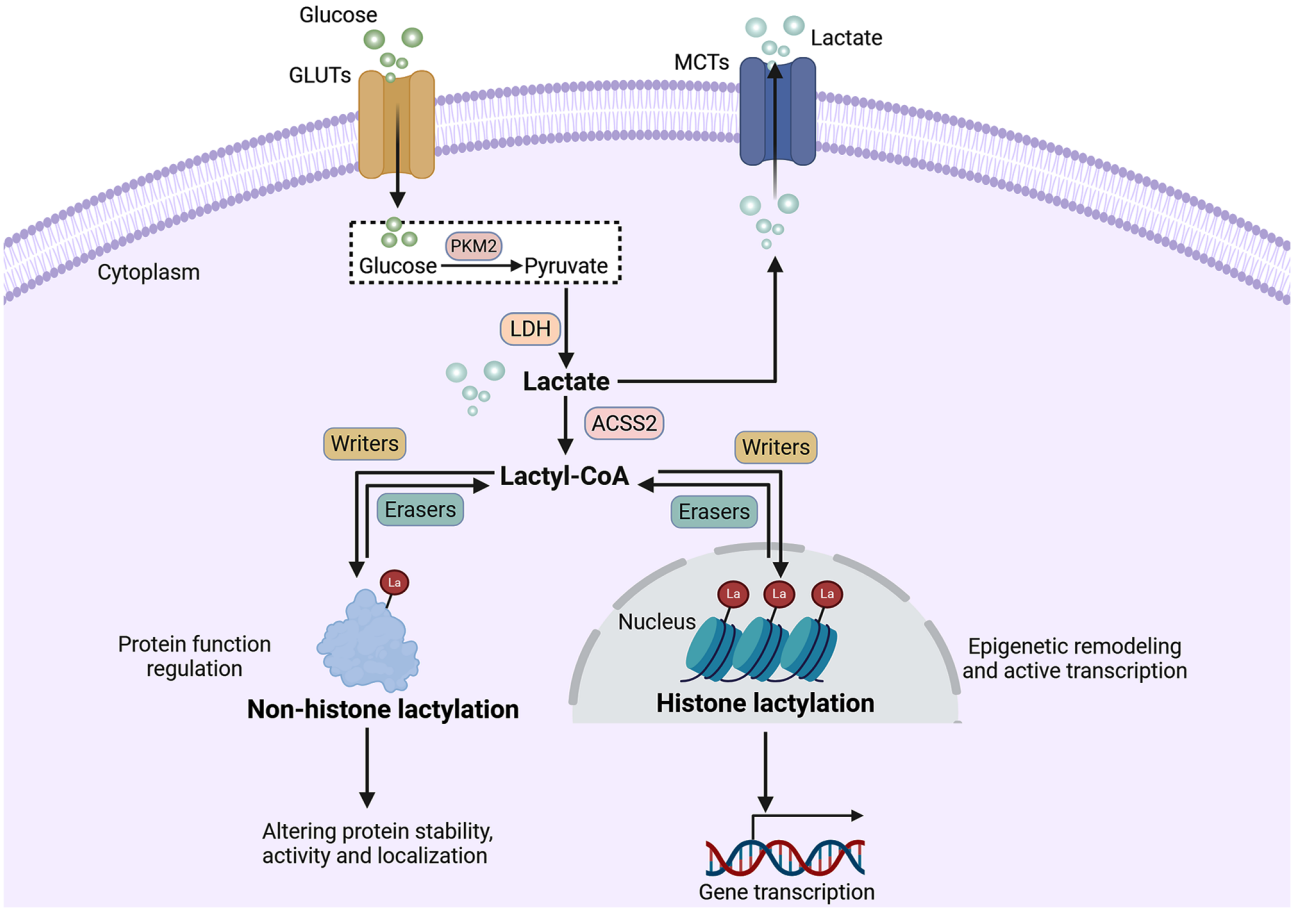

Figure 1. Lactylation classification and molecular regulatory mechanisms. ACSS2, acetyl-CoA synthetase 2; GLUTs, glucose transporters; LDH, lactate dehydrogenase; MCTs, monocarboxylate transporters; PKM2, pyruvate kinase M2.

exhibit site-specific lactylation catalytic activity (53,54). On the other hand, erasers reverse lactylation by removing lactyl groups. Deacetylases such as SIRT1, SIRT2 and HDAC1-3 can remove lactylation modifications, forming a reversible regulatory loop. For example, SIRT1 mediates the delactylation of H3K18la (55), and SIRT2 targets METTL16 K229la for erasure (56). After lactylation occurs, readers are required to recognize the modification and trigger downstream biological effects, and relevant studies in this topic remain limited to date. Known readers include DPF2, BRG1 and TRIM33. DPF2 drives cancer-related gene transcription and tumorigenesis by recognizing H3K14la (57), whereas BRG1 promotes the mesenchymal-epithelial transition of pluripotent stem cells by reading H3K18la (37), and TRIM33 regulates inflammatory gene expression in activated macrophages and mediates M2 macrophage polarization (58). Notably, certain lactylation modifications occur non-enzymatically, particularly under extreme microenvironmental conditions such as high lactate and acidic stress (59). Fig. 1 depicts the classification and molecular mechanisms of lactylation.

Lactylation does not exist in isolation; rather, it engages in extensive competitive and synergistic crosstalk with other PTMs, particularly in GC. Regarding ubiquitination, lactylation of PCBP2 blocks its interaction with the E3 ubiquitin ligase ARIH2, thereby inhibiting ubiquitin-mediated degradation and stabilizing the protein, which confers oxaliplatin resistance to GC cells (60). Meanwhile, NLRP12 competitively binds to TRIM25, suppressing TRIM25-mediated ubiquitination of HK2, thereby promoting glycolysis and H3K18la in GC cells (61). In terms of phosphorylation, BASP1-AS1 facilitates ULK1-mediated phosphorylation of LDHA, enhancing its enzymatic activity and consequently inducing H3K14la in GC cells (60). Regarding RNA modifications, lactylation exhibits a clear synergistic relationship with m^6A and m^5C modifications: H3K18la can directly transcriptionally activate the m^6A writers METTL3 (62) and METTL14 (63), enhancing m^6A modification of downstream target genes; lactylation of METTL16 itself enhances its m^6A enzymatic activity and stabilizes FDX1 mRNA (56); and lactylation of NSUN2 enhances its m^5C methyltransferase activity, promoting the stabilization of GCLC mRNA (54). Notably, the interplay between lactylation and acetylation or succinylation has been demonstrated in other diseases. For example, it has been found that acetylation of the HNRNPU competitively inhibits lactylation at the same site, thereby influencing the progression of cervical cancer. In addition, another study has reported that succinylation of PCK2 enhances its own stability by antagonizing ubiquitination, which further promotes lactylation of the downstream protein PQBP1 and ultimately aggravates asthma (64-66). but the interplay has not been reported in GC. In addition, lactylation exhibits marked cell-type specificity. The expression profiles of lactylation substrates and catalytic enzymes differ substantially across distinct cell subpopulations (67),

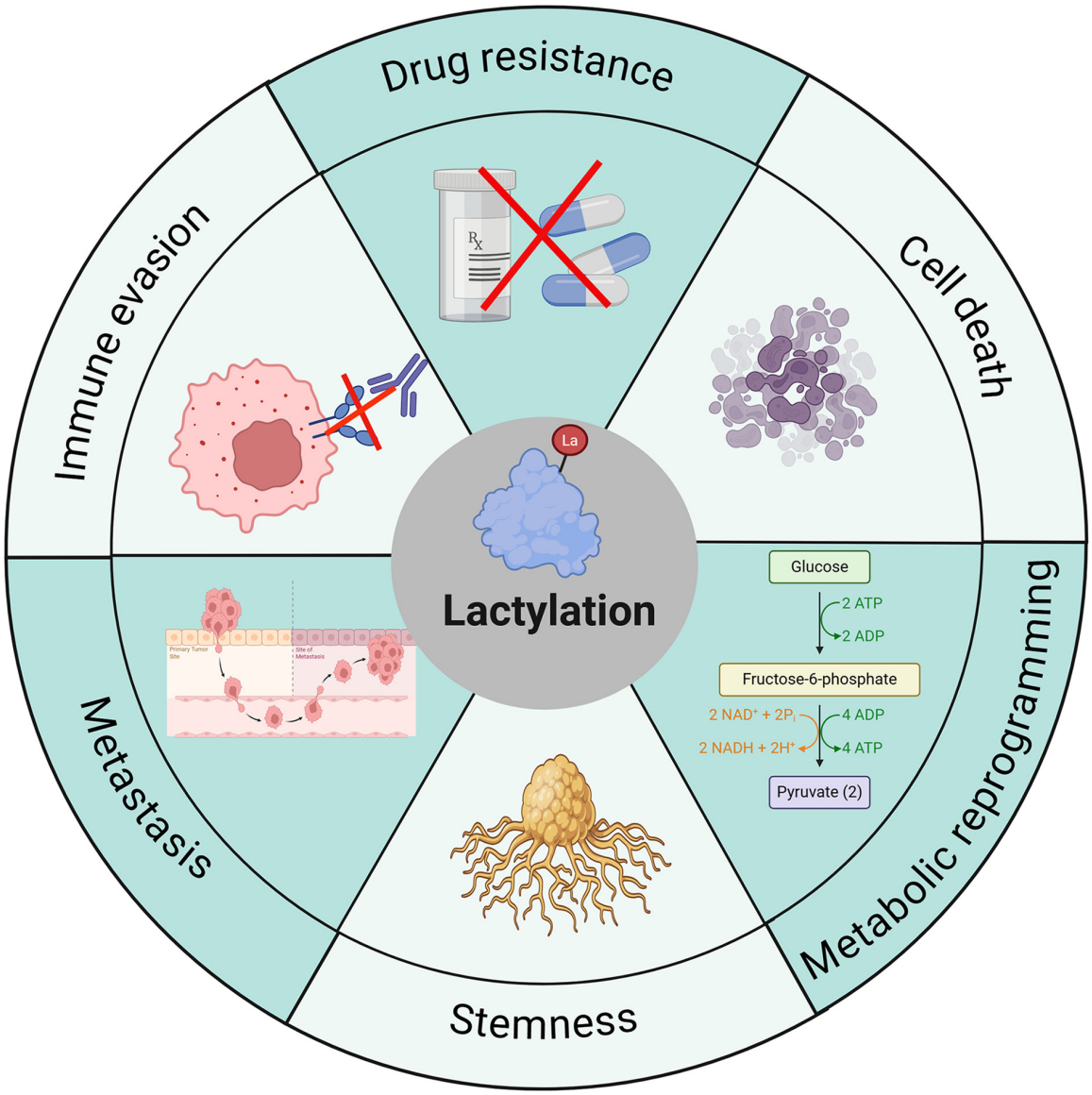

Figure 2. Biological functions of lactylation in malignant tumors. Lactylation participates in multiple core malignant phenotypes of cancer, including metabolic reprogramming, tumor growth and metastasis, cancer stem cell maintenance, immune evasion, regulation of programmed cell death and the development of drug resistance.

which is a key determinant of the occurrence and magnitude of lactylation in a cell-type-dependent manner.

3. Roles of lactylation in cancer

As a key node linking metabolic reprogramming and epigenetic regulation, lactylation plays a regulatory role in tumorigenesis and progression. It is involved in malignant phenotypes, including proliferation, metastasis, stemness, immune escape, cell death and therapeutic resistance (Fig. 2), and has become a hotspot in pan-cancer research (68,69).

In the regulation of tumor metabolic reprogramming, lactylation sustains and strengthens aerobic glycolysis through positive feedback loops, further promoting lactate accumulation and malignant progression (70,71). In colorectal cancer, lactylation enhances glycolytic flux by stabilizing ENO1 mRNA and forming a metabolic-epigenetic positive feedback loop to drive persistent metabolic abnormalities (72). In hepatocellular carcinoma, lactylation increases the stability of the c-Myc protein, which directly transactivates a series of glycolytic genes, including GLUT1 and LDHA, forming a positive feedback pathway to maintain the hypermetabolic state of tumor cells (73). In clear cell renal cell carcinoma, the Von Hippel-Lindau mutation activates the HIF pathway, increases lactate production, upregulates H3K18la and activates downstream metabolic genes to promote metabolic reprogramming (74). The aforementioned findings suggest that lactylation is a key executor and amplifier of tumor metabolic imbalance.

In the regulation of tumor cell proliferation, invasion and metastasis, lactylation promotes malignant progression through both epigenetic modification and protein functional remodeling. Regarding histone lactylation, lactate secreted by cancer-associated fibroblasts (CAFs) in triple-negative breast cancer upregulates H3K18la, transcriptionally activates ZFP64, inhibits ferroptosis, and enhances invasion and

chemoresistance (75). Regarding non-histone lactylation, the lactylation of metabolic enzymes, including HK1 and IDH3G, directly alters catalytic activity, reshapes energy metabolism and drives cell proliferation in non-small cell lung cancer (74). In colorectal cancer, hypoxia induces β-catenin lactylation, enhances its stability, constitutively activates the Wnt pathway, and promotes stemness and distant metastasis (46).

In tumor immune escape, lactylation serves as a molecular mechanism that shapes an immunosuppressive microenvironment. In $CD8^+$ T cells, lactate induces H3K18la and activates programmed cell death 1 (PD-1) transcription, leading to T-cell exhaustion and reduced immunotherapy response (76). In glioblastoma, H3K18la upregulates TNFSF9 and drives macrophage polarization toward a protumor M2 phenotype (77). In colorectal cancer, lactylation activates METTL1 and upregulates CD155, suppressing the antitumor activity of natural killer and $CD8^+$ T cells (78). In regulatory T cells (Tregs), lactylation of moesin enhances TGF-β signaling, promotes Treg differentiation and immunosuppressive function, and further impairs antitumor immunity (79).

In the regulation of cell death and therapeutic resistance, lactylation exerts a dual regulatory role and mediates resistance in multiple types of cancer. For example, lactylation of HDAC1 in colorectal cancer increases protein stability, upregulates FSP1, inhibits ferroptosis and reduces chemosensitivity (80). In bladder cancer, H3K18la notably enhances the cisplatin resistance of tumor cells by upregulating YY1 and YBX1 expression (81). In glioblastoma, H3K9la inhibits mismatch repair by activating LUC7L2 expression, resulting in temozolomide resistance (82). In terms of DNA damage repair-mediated drug resistance, RAD51 K73 lactylation in ovarian cancer enhances homologous recombination repair efficiency and directly leads to platinum resistance (83).

Collectively, lactylation is a key regulatory mechanism of malignant phenotypes. It can serve as a pan-cancer prognostic biomarker and as a broad-spectrum therapeutic target, offering novel directions for overcoming drug resistance and improving immunotherapy efficacy.

4. Roles and mechanisms of lactylation in GC progression

Roles and mechanisms of histone lactylation in GC. Histone lactylation is the most widely reported lactylation subtype in GC research. In GC cells, abnormally enhanced glycolysis leads to substantial lactate accumulation. Lactate serves as a substrate to induce lactylation on specific lysine residues of histones, thereby widely regulating GC proliferation, metastasis, immune escape and therapeutic resistance by transcriptionally activating downstream target genes (Fig. 3; Table I).

Histone lactylation promotes GC proliferation and metastasis. Histone lactylation plays a driving role in GC proliferation, epithelial-mesenchymal transition (EMT) and distant metastasis by activating multiple oncogenic signaling pathways and transcriptional programs. Among these sites, H3K18la is the most extensively studied, and promotes GC malignant progression through multiple positive feedback loops and downstream target genes.

Key glycolytic enzymes promote histone lactylation by regulating glycolysis and lactate production, thereby enhancing GC proliferation and migration. CSDE1 enhances glycolysis and lactate synthesis by stabilizing LDHA mRNA. Lactate further induces H3K18la and upregulates HOXD9 transcription, ultimately promoting GC cell proliferation and migration (84). GLUT3 upregulates LDHA expression and elevates global lactylation, inducing multi-site histone lactylation, including H3K9la, H3K18la and H3K56la, thus strengthening GC cell proliferation, migration and invasion (85). PFKM promotes H3K18la by increasing glycolytic flux and lactate levels, further activating CNTN1 transcription to drive GC cell proliferation and metastasis (86). HKDC1 similarly triggers H3K18la by enhancing glycolysis and lactate accumulation, and by transcriptionally activating VCAM1 to promote GC cell proliferation, migration and invasion (87). As another key rate-limiting glycolytic enzyme, PKM2 can be directly bound and inhibited by the natural product saikosaponin D, which downregulates PKM2 expression, suppresses glycolysis and lactate accumulation, markedly reduces H3K9la, H3K14la and H3K18la levels, and inhibits GC cell proliferation, colony formation, migration and invasion (88). P4HA2 increases glycolysis and lactate production to increase H3K9la and H3K18la levels, thereby increasing TTK transcription and ultimately inhibiting GC cell proliferation (53).

In addition to glycolytic enzymes, deubiquitinases and other regulatory proteins also form oncogenic positive feedback loops via histone lactylation. PSMD14, which is highly expressed in GC, enhances PFKFB2 activity by removing K63-linked ubiquitination from PFKFB2, thereby promoting SCYL2-mediated PFKFB2 phosphorylation and subsequent glycolysis and lactate accumulation. This ultimately induces H3K27la, which transcriptionally activates PSMD14 and SOX9, forming a loop that maintains GC stemness and facilitates proliferation (89). Similarly, NLRP12 is upregulated in GC and competitively binds TRIM25, blocking TRIM25-HK2 interaction, inhibiting TRIM25-mediated HK2 degradation and markedly enhancing HK2 protein stability. Elevated HK2 increases glycolytic flux and lactate accumulation in GC cells, inducing H3K18la to activate Myc transcription, and promote GC cell proliferation and tumor growth (61). Furthermore, SIRT1 acts as a delactylase for H3K18la. SIRT1 depletion increases H3K18la levels, which transcriptionally activates long noncoding RNA (lncRNA) H19. H19 then upregulates LDHA to enhance glycolysis and lactate production, further inducing H3K18la and forming an 'H19-glycolysis-H3K18la' positive feedback amplification loop that accelerates GC cell proliferation and migration (90).

Histone lactylation also directly activates several classical oncogenic signaling pathways. For example, H3K18la activates the PI3K/AKT pathway by stimulating POM121 transcription, enhancing GC cell proliferation, migration and invasion (91). Similarly, H3K18la promotes VCAM1 transcription, which further upregulates the AKT/mTOR pathway to facilitate GC proliferation, migration and EMT (92). In *Helicobacter pylori*-associated GC, H3K18la exerts comparable oncogenic effects through the HAS2/c-Myc axis (93). Besides H3K18la, H3K9la also directly activates oncogenic signaling to drive GC progression. H3K9la activates TRIM29 transcription. Upregulated TRIM29 blocks ZFP91-mediated

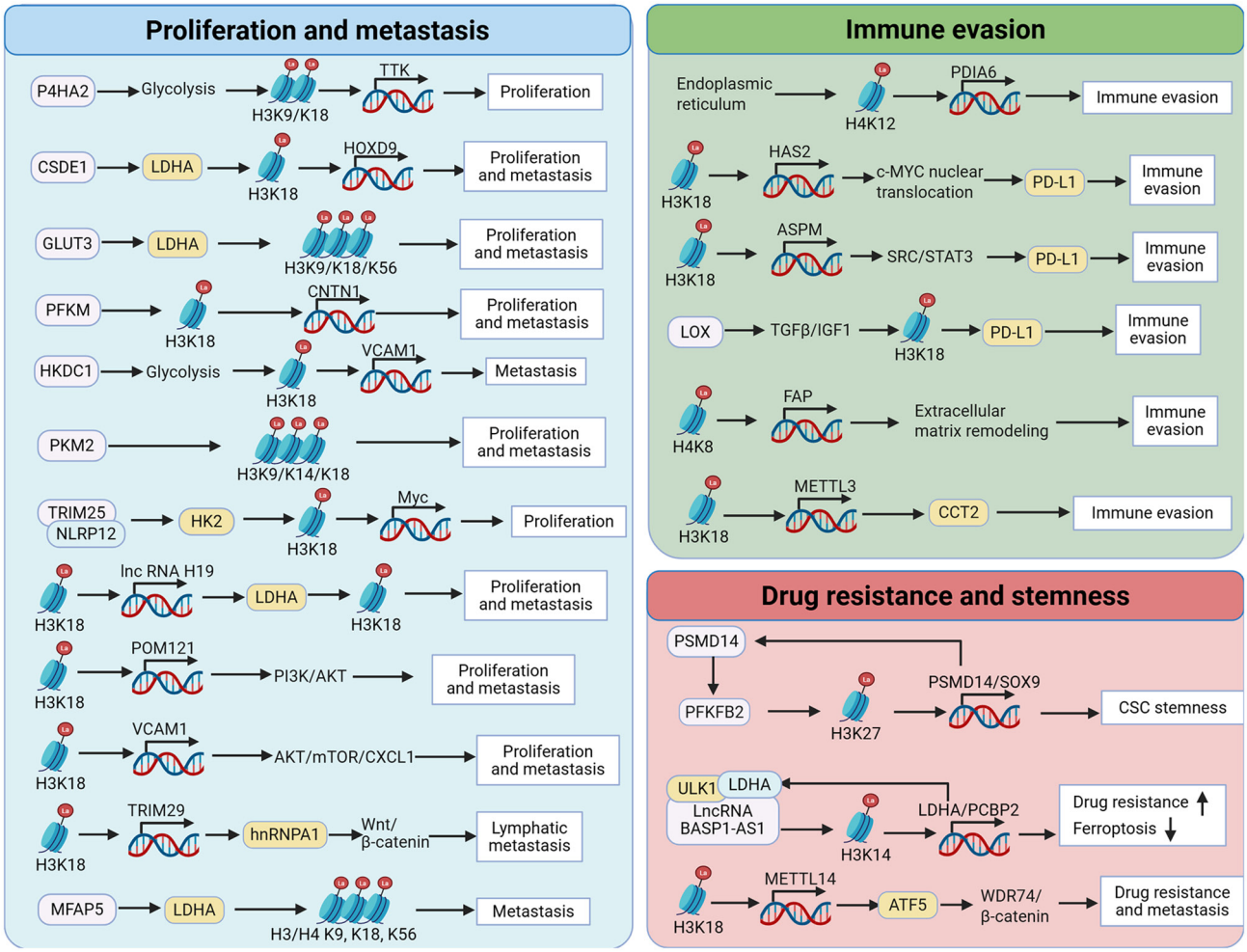

Figure 3. Regulatory mechanisms and biological effects of histone lactylation in gastric cancer. Summary of major histone lactylation sites (such as H3K9la and H3K18la) and their upstream regulatory axes in gastric cancer, which modulate proliferation, metastasis, immune evasion, stemness maintenance and chemoresistance via the transcriptional activation of target genes. CSC, cancer stem cell; GLUT3, glucose transporter 3; LDHA, lactate dehydrogenase A; lncRNA, long noncoding RNA; METTL14, methyltransferase-like 14; PKM2, pyruvate kinase M2.

hnRNPA1 ubiquitination and degradation, thereby activating the Wnt/β-catenin pathway, stimulating VEGF-C secretion, and promoting lymphangiogenesis and lymph node metastasis (94).

Histone lactylation mediates immune escape and TME remodeling in GC. Histone lactylation not only acts directly on GC cells but also participates extensively in the establishment of immune escape by regulating various cellular components in the TME. The following major pathways are involved: i) Upregulation of programmed death-ligand 1 (PD-L1) expression; ii) activation of CAFs; and iii) suppression of $CD8^+$ T-cell function.

At the immune checkpoint regulatory level, histone lactylation transcriptionally activates PD-L1 through multiple signaling axes, representing a core mechanism of immune escape in GC. In *H. pylori*-associated GC, H3K18la promotes PD-L1 expression by activating the HAS2/c-Myc pathway, thereby suppressing the cytotoxicity of $CD8^+$ T cells (93). Meanwhile, CAFs in the TME participate in immune regulation via lactylation. Lactate secreted by CAFs induces H3K18la and activates the ASPM-NCAPG-SRC/STAT3 pathway, further upregulating PD-L1 and impairing T-cell function (95). In addition, lysyl oxidase secreted by CAFs enhances glycolysis and lactate accumulation through the TGF-β/IGF1 axis, enabling H3K18la to directly activate PD-L1 transcription and promote EMT (96).

Histone lactylation also contributes to immune exclusion by remodeling CAFs and the extracellular matrix (ECM). Previous research has shown that AARS1 drives FAP transcription by catalyzing H4K8la, while promoting the expression of collagen synthesis-related genes and activating the ECM receptor interaction pathway. Multicolor immunohistochemistry has suggested that FAP^+ GC mesenchymal stromal cells form a physical barrier around tumor cells in GC tissues, blocking $CD8^+$ T-cell infiltration (97). $MFAP5^+$ CAFs also promote extramural venous invasion in GC via lactylation. Single-cell sequencing has revealed that this subtype gradually increases in primary GC and peritoneal metastases, is associated with worse prognosis, and is enriched in glycolysis, hypoxia and lactylation pathways (98).

Histone lactylation directly attenuates antitumor immunity by inhibiting $CD8^+$ T-cell function. H3K18la upregulates METTL3 expression, and METTL3 enhances CCT2 expression through m^6A modification. Upregulated CCT2 suppresses

Table I. Mechanisms of histone lactylation in gastric cancer.

First author, year	Histone	Kla site	Mechanism	Outcome	(Refs.)
Tu *et al*, 2026	H4	K12	Endoplasmic reticulum stress promotes glycolysis and induces H4K12la in dendritic cells, thereby upregulating PDIA6 expression	Promotes immune evasion	(34)
Zhang *et al*, 2026	H3	K9, K18	P4HA2 upregulates TTK transcription by promoting H3K18 and H3K9 lactylation via glycolysis	Promotes cell proliferation	(53)
Zhao *et al*, 2025	H3	K14	LncRNA BASP1-AS1 promotes glycolysis and H3K14la by forming a complex with ULK1/LDHA, thereby activating the transcription of LDHA and PCBP2	Promotes drug resistance and inhibits ferroptosis	(60)
Zhou *et al*, 2025	H3	K18	NLRP12 competitively binds to TRIM25, inhibiting its ubiquitination-mediated degradation of HK2, thereby promoting glycolysis and H3K18la; H3K18la further activates Myc transcription.	Promotes cell proliferation	(61)
Qian *et al*, 2025	H3	K18	H3K18la upregulates CCT2 m^6A modification by promoting METTL3 transcription, thereby inhibiting Ca^{2+} influx in $CD8^+$ T cells	Promotes immune evasion	(62)
Zhang *et al*, 2025	H3	K18	H3K18la upregulates ATF5 m^6A modification by promoting METTL14 transcription, thereby activating the WDR74/β-catenin axis	Promotes cell proliferation, metastasis and drug resistance	(63)
Zhang *et al*, 2026	H3	K18	CSDE1 promotes glycolysis and lactate production by stabilizing LDHA mRNA, thereby inducing H3K18la and promoting the transcriptional activation of HOXD9	Promotes cell proliferation and migration	(84)
Yang *et al*, 2023	H3	K9, K18, K56	GLUT3 promotes multi-site lactylation of histone H3 by upregulating LDHA	Promotes cell proliferation and metastasis	(85)
Shen *et al*, 2025	H3	K18	PFKM induces H3K18la by promoting lactate production, thereby facilitating the transcriptional activation of CNTN1	Promotes cell proliferation and metastasis	(86)
Jiang *et al*, 2025	H3	K18	HKDC1 promotes H3K18la by enhancing glycolysis and lactate production, thereby activating VCAM1 transcription	Promotes cell proliferation and metastasis	(87)
Wang *et al*, 2026	H3	K9, K14, K18	PKM2 induces lactylation at multiple histone sites by promoting glycolysis	Promotes cell proliferation and metastasis	(88)
Zhao *et al*, 2026	H3	K27	PSMD14 promotes glycolysis and H3K27la by deubiquitinating PFKFB2; H3K27la further activates the transcription of PSMD14 and SOX9	Promotes cell proliferation and stemness	(89)
Tsukihara *et al*, 2025	H3	K18	H3K18la promotes the transcriptional activation of the lncRNA H19, thereby upregulating LDHA and glycolysis, forming a positive feedback loop: 'H3K18la-lncRNA H19-glycolysis-H3K18la'	Promotes cell proliferation and metastasis	(90)
Wang *et al*, 2026	H3	K18	H3K18la activates the PI3K/AKT pathway by promoting POM121 transcription	Promotes cell proliferation and metastasis	(91)

Table I. Continued.

First author, year	Histone	Kla site	Mechanism	Outcome	(Refs.)
Zhao *et al*, 2024	H3	K18	H3K18la upregulates the AKT/mTOR/CXCL1 axis by activating VCAM1 transcription	Promotes cell proliferation and metastasis	(92)
Chen *et al*, 2026	H3	K18	H3K18la promotes the nuclear translocation of c-MYC by activating HAS2 transcription, thereby upregulating PD-L1 expression	Promotes immune evasion	(93)
Hua *et al*, 2026	H3	H3K9la	H3K9la enhances the stability of hnRNPA1 by activating TRIM29 transcription, thereby activating the Wnt/β-catenin pathway and promoting VEGF-C secretion	Promotes lymphatic metastasis	(94)
Zhou *et al*, 2025	H3	K18	Lactate-derived from CAFs promotes the transcriptional activation of ASPM by H3K18la and enhances NCAPG stability, thereby activating the SRC/STAT3/PD-L1 axis	Promotes immune evasion	(95)
Li *et al*, 2024	H3	K18	LOX secreted by CAFs promotes glycolysis and H3K18la by activating the TGFβ/IGF1 axis, thereby activating PD-L1 transcription	Promotes immune evasion and EMT	(96)
Huang *et al*, 2026	H4	K8	H4K8la promotes FAP transcription, thereby promoting ECM remodeling	Promotes immune evasion	(97)
Gao *et al*, 2025	H3/H4	K9, K18, K56	MFAP5 promotes glycolysis by interacting with LDHA, thereby regulating lactylation at multiple histone sites	Promotes metastasis	(98)

CAFs, cancer-associated fibroblasts; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; GLUT3, glucose transporter 3; LDHA, lactate dehydrogenase A; lncRNA, long noncoding RNA; METTL14, methyltransferase-like 14; PKM2, pyruvate kinase M2.

the proliferation, effector molecule expression and cytotoxic activity of $CD8^+$ T cells, thereby promoting immune escape of GC cells (62). ER stress functions through another pathway: ER stress induces H4K12la modification, promotes PDIA6 expression in dendritic cells (DCs), weakens DC immune activity, reduces the activation ratio and cytotoxic factor secretion of $CD8^+$ T cells, and ultimately mediates immune escape in GC (34). These studies demonstrate that histone lactylation coordinately constructs an immunosuppressive TME in GC by regulating tumor cells, CAFs, DCs, $CD8^+$ T cells and other components.

Histone lactylation regulates chemoresistance and stemness in GC. Histone lactylation also participates in chemoresistance and the maintenance of cancer stem cell (CSC) properties in GC. In oxaliplatin-resistant GC, BASP1-AS1 binds and recruits ULK1 and LDHA simultaneously to form the BASP1-AS1/ULK1/LDHA complex, which promotes ULK1-mediated LDHA phosphorylation, enhances LDHA activity and accelerates glycolysis and lactate accumulation. Lactate induces H3K14la to transcriptionally activate LDHA and PCBP2, forming a 'glycolysis-lactate-H3K14la-LDHA' positive feedback loop that ultimately inhibits ferroptosis and confers oxaliplatin resistance in GC cells (60). To maintain GC stemness, H3K18la transcriptionally activates METTL14 expression. METTL14 catalyzes m^6A modification on ATF5 mRNA and promotes its degradation, relieving the ATF5-mediated transcriptional activation of WDR74, thereby suppressing β-catenin nuclear translocation and stemness gene expression (63). In addition, H3K27la contributes to the maintenance of CSC properties in GC via a PSMD14/SOX9 positive feedback loop (89).

Roles and mechanisms of non-histone lactylation in GC. Unlike histone lactylation, non-histone lactylation targets functional proteins directly, including metabolic enzymes, RNA modification enzymes, transcription factors and immune checkpoints. It regulates the malignant progression of GC more directly and diversely by altering enzyme activity, stability, subcellular localization or protein-protein interactions (Fig. 4; Table II). With the development of lactylation proteomics, an increasing number of non-histone substrates have been identified in GC.

Non-histone lactylation regulates proliferation and metastasis in GC. Non-histone lactylation can directly target key metabolic enzymes and core transcription factors, participating in metabolic reprogramming and driving cell proliferation in GC. As a key lactyltransferase, AARS1 translocates into the nucleus upon lactate accumulation and directly catalyzes the lactylation of YAP and TEAD1, enhancing the nuclear retention and transcriptional activity of the YAP-TEAD1 complex.

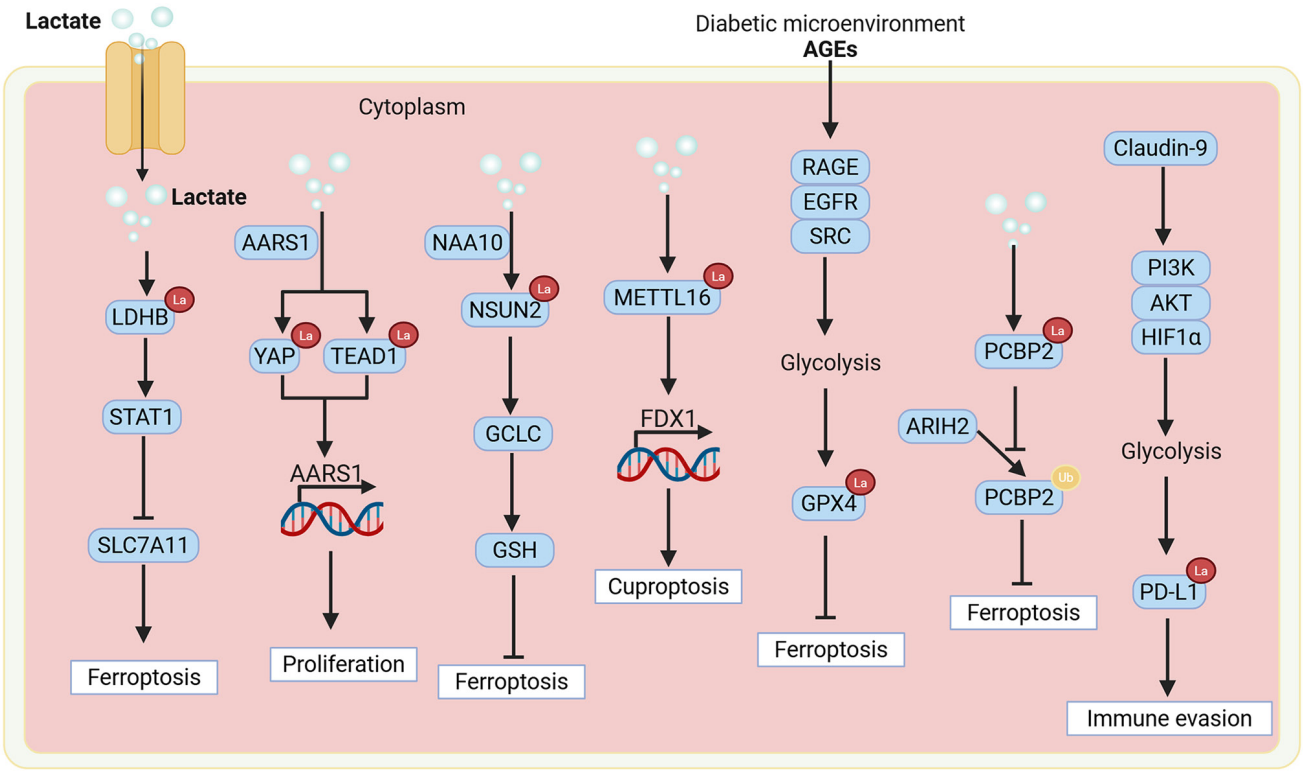

Figure 4. Functional mechanisms of non-histone lactylation in gastric cancer. Non-histone lactylation directly modifies diverse functional proteins including metabolic enzymes, RNA modifiers and immune checkpoint molecules, further regulating gastric cancer proliferation, metastasis, immune escape, ferroptosis/cuproptosis and therapeutic resistance. AARS1, alanyl-tRNA synthetase 1; AGE, advanced glycation end product; GPX4, GSH peroxidase 4; GSH, glutathione; LDHB, lactate dehydrogenase B; METTL16, methyltransferase-like 16; RAGE, receptor for AGEs.

In turn, YAP-TEAD1 transcriptionally activates AARS1, forming a lactate-AARS1-YAP/TEAD1-AARS1 positive feedback loop that continuously drives proliferation and metabolic reprogramming in GC (51). In contrast to the aforementioned oncogenic role, loss of lactylation on LDHB also contributes to the malignant progression of GC. In GC, delactylation at LDHB K58 promotes STAT1 degradation, relieves the transcriptional inhibition of SLC7A11, enhances GSH synthesis and inhibits ferroptosis, ultimately promoting proliferation, invasion and distant metastasis (12). Such opposing effects in GC are primarily determined by the function of lactylated substrate proteins, further studies are required to explore the exact effects of non-histone lactylation on the malignant phenotypes of GC.

Non-histone lactylation regulates immune escape in GC. Previous studies have demonstrated that non-histone lactylation directly modifies immune checkpoint proteins and acts as a key link between metabolic reprogramming and immune escape (99,100). In GC, highly expressed claudin-9 upregulates LDHA expression via the PI3K/AKT/HIF1α axis, enhancing glycolysis and lactate production. Lactate further induces the lactylation of PD-L1 and increases its protein stability, thereby inhibiting $CD8^+$ T-cell function and mediating immune escape (101). This indicates that PD-L1 lactylation is a key molecular event underlying metabolic disorder-driven immune escape in GC, which has research importance.

Non-histone lactylation regulates therapeutic resistance and programmed cell death in GC. Non-histone lactylation plays a core regulatory role in therapeutic resistance and cell fate in GC, and can influence GC therapeutic resistance by modulating ferroptosis and cuproptosis. Notably, several studies have reported that non-histone lactylation mediates chemoresistance by regulating ferroptosis in GC cells. For example, in the context of oxaliplatin resistance, lactate induces the lactylation of PCBP2, inhibits its ubiquitination and degradation, thus stabilizing this protein, and suppresses ferroptosis by maintaining iron homeostasis, thereby enhancing the drug resistance of cancer cells (60). Similarly, delactylation of LDHB inhibits ferroptosis by strengthening GSH synthesis (12). In a diabetic microenvironment, advanced glycation end products promote the lactylation of GPX4 through the EGFR/SRC axis, thus enhancing its stability, and reduce lipid peroxidation, thereby inhibiting ferroptosis in GC cells (102). In addition, lactylation of NSUN2 enhances its m^5C modification activity, upregulates GCLC and promotes GSH synthesis, ultimately conferring a ferroptosis-resistant phenotype in GC cells (54).

Furthermore, non-histone lactylation can suppress GC progression by promoting cuproptosis. Copper stress promotes the lactylation of METTL16, releases its auto-inhibitory conformation, enhances m^6A enzymatic activity and further stabilizes FDX1 to trigger cuproptosis, thereby inhibiting tumor growth. SIRT2 can delactylate METTL16 and reverse this effect, while AARS1/AARS2 promotes its lactylation (56). The bidirectional regulation of GC cell death modes by non-histone lactylation is closely linked to the function of substrate proteins, highlighting the complex role of non-histone lactylation in GC; however, further in-depth

Table II. Mechanisms of non-histone lactylation in gastric cancer.

First author, year	Non-histone	Kla site	Mechanism	Outcome	(Refs.)
Xiao *et al*, 2026	LDHB	K58	LDHB-mediated delactylation promotes the ubiquitination and degradation of STAT1, thereby lifting its inhibition of SLC7A11	Promotes metastasis and resistance to ferroptosis	(12)
Ju *et al*, 2024	YAP/TEAD1	K90/K108	AARS1 catalyzes the lactylation of YAP and TEAD1, thereby promoting YAP nuclear retention, enhancing YAP-TEAD1 complex formation and transcriptional activity; in turn, the YAP-TEAD1 complex activates AARS1 transcription	Promotes cell proliferation	(51)
Niu *et al*, 2025	NSUN2	K508	NAA10 catalyzes the lactylation of NSUN2, thereby enhancing the activity of m^5C methyltransferase, stabilizing GCLC mRNA and promoting GSH synthesis	Inhibits ferroptosis	(54)
Sun *et al*, 2023	METTL16	K229	Lactylation of METTL16 enhances its m^6A methyltransferase activity, thereby stabilizing FDX1 mRNA	Induces cuproptosis	(56)
Zhao *et al*, 2025	PCBP2	K115	Lactylation of PCBP2 blocks its ubiquitination-mediated degradation by ARIH2, thereby enhancing the stability of PCBP2	Promotes drug resistance and inhibits ferroptosis	(60)
Hu *et al*, 2025	PD-L1	-	Claudin-9 enhances glycolysis by activating the PI3K/AKT/HIF1α signaling pathway, thereby inducing lactylation of PD-L1	Promotes immune evasion	(101)
Hu *et al*, 2025	GPX4	-	AGEs promote glycolysis and lactate accumulation by activating the RAGE/EGFR/SRC axis, thereby inducing lactylation of GPX4	Inhibits ferroptosis	(102)

AARS1, alanyl-tRNA synthetase 1; AGE, advanced glycation end product; GPX4, GSH peroxidase 4; GSH, glutathione; LDHB, lactate dehydrogenase B; METTL16, methyltransferase-like 16; RAGE, receptor for AGEs.

investigation is required to elucidate these specific roles and underlying mechanisms.

In summary, non-histone lactylation plays a key role in malignant progression, immune escape and therapeutic resistance of GC by directly modifying metabolic enzymes, RNA modification enzymes and immune checkpoint molecules. This provides new opportunities for anti-GC therapies targeting non-histone lactylation.

Determinants of lactylation in regulating GC progression. Lactylation plays a bidirectional regulatory role in cancer. Although existing evidence generally supports a protumor role for lactylation in GC, it also exhibits tumor-suppressive effects under specific conditions, which are primarily determined by target function and substrate type. The regulatory role of histone lactylation in GC primarily depends on the function of its downstream target genes. For example, H3K18la promotes GC progression by activating the PI3K/AKT pathway through the promotion of POM121 transcription (91), whereas H3K27la enhances GC stemness by activating the transcription of SOX9, a gene associated with tumor stemness (89). For non-histone lactylation, the intrinsic function of the modified substrate protein is the core determinant of the final effect of lactylation. Lactylation of oncogenes typically amplifies malignant phenotypes, whereas lactylation of tumor suppressor proteins may activate tumor-suppressing pathways. For example, YAP/TEAD1 lactylation enhances nuclear retention and transcriptional activity, driving a protumor positive feedback loop (51); by contrast, METTL16 lactylation enhances its m^6A methyltransferase activity, promoting copper-induced cell death by stabilizing FDX1 mRNA, thereby exerting a tumor-suppressive effect (56). Furthermore, the specific cellular metabolic state and TME may also influence the regulatory role of lactylation in GC. Notably, it remains unclear whether temporal-spatial context or differences in tumor stage influence the role of lactylation modification in GC.

5. Application of lactylation-related genes in GC

Lactylation is not only a core mechanism regulating the malignant progression of GC, but its related molecular features also possess clinical translational value. Prognostic risk models constructed based on lactylation-related gene expression profiles have become novel bioinformatics tools for prognostic stratification, survival prediction and even immunotherapy efficacy evaluation in GC, providing new insights for the precise diagnosis and treatment of GC (Fig. 5).

Lactylation-related genes predict the prognosis of GC. Previous studies have constructed prognostic models by integrating lactylation-related genes, and have demonstrated that these models can effectively distinguish risk levels and survival outcomes in patients with GC (103,104). Sun *et al* (105) screened three core genes (namely COL4A1, SLC16A7 and IRAK1) from 322 lactylation-related genes to build a risk model and found that overall survival was notably shorter in the high-risk group. Xu *et al* (106) combined genes associated with macrophage polarization and protein lactylation to establish a two-gene prognostic model and demonstrated that the risk score could act as an independent prognostic factor. Fu *et al* (107) performed lactylome and proteome profiling, identified 127 lactylation-related genes, and constructed four prognostic models, the results of which demonstrated that these models exhibited robust predictive performance. Yang *et al* (108) established a six-gene lactylation scoring system via pathway enrichment and screening, and found that high scores were notably associated with advanced tumor grade, lymph node metastasis and worse prognosis. Collectively, these models demonstrate that lactylation-related gene signatures can serve as stable and effective prognostic biomarkers for GC.

Lactylation-related genes predict immunotherapy response in GC. More clinically valuable, lactylation-related risk models can not only predict survival but also effectively evaluate immunotherapy response, acting as a key bridge linking metabolic characteristics with immunotherapy efficacy. Several studies have indicated that the lactylation score is closely associated with immune escape and immunosuppressive status of the TME. A high lactylation score is usually accompanied by a higher tumor immune dysfunction and exclusion score, suggesting elevated risk of immune escape and lower response rates to immunotherapy such as cytotoxic T lymphocyte-associated protein 4 inhibitors (105,108). Meanwhile, the lactylation score is closely associated with microsatellite instability (MSI) and tumor mutation burden (TMB). Low-score groups tend to have a higher MSI-H and TMB level, predicting improved benefits from immunotherapy (103,108). Regarding the immune microenvironment, the high-risk groups display a notable immunosuppressive phenotype, whereas the low-risk groups show more infiltration of $CD8^+$ T cells, activated $CD4^+$ T cells and M1 macrophages (106). Single-cell sequencing has further revealed that the lactylation score is mainly enriched in stromal cells and directly contributes to the formation of an immunosuppressive microenvironment (104).

In conclusion, prognostic models based on lactylation-related genes can independently predict survival and efficiently evaluate immunotherapy response potential in patients with GC. Combined detection of lactylation score with traditional immune biomarkers is expected to provide a reliable basis for developing more precise immunotherapy strategies for patients with GC.

6. Therapeutic strategies targeting lactylation for GC

Lactylation plays an important driving role in the proliferation, metastasis, immune escape and therapeutic resistance of GC. Thus, targeting lactylation has emerged as a novel direction for precision therapy of GC. Current therapeutic approaches mainly include inhibiting glycolysis and lactate production, regulating key enzymes of lactylation, targeting lactylation with natural products and achieving precise treatment via drug repurposing and nanodelivery systems (Fig. 5; Table III). These strategies synergistically block lactylation-mediated procancer effects through multiple pathways.

Targeting the glycolysis-lactate axis. Lactate serves as the direct substrate for lactylation. Blocking glycolysis and reducing lactate production represents the most upstream and straightforward therapeutic strategy. As a pivotal enzyme for lactate generation, LDHA can be inhibited by oxamate. This agent markedly reduces lactate content and H3K18la levels, suppresses GC cell proliferation and restores $CD8^+$ T-cell function. Combined administration with anti-PD-1 therapy exerts synergistic antitumor effects (93). Low-dose oxamate combined with SRT2104, a SIRT1 agonist, effectively restrains the oncogenic loop associated with lncRNA H19 with limited toxicity (90). In addition, β-alanine and AZD3965, inhibitors of lactylation and MCT1, respectively, downregulate H4K8la, alleviate immune exclusion and improve immunotherapeutic outcomes (97).

Targeting key enzymes of lactylation. The reversible nature of lactylation makes its regulatory enzymes promising therapeutic targets. Activating delactylases and inhibiting lactyltransferases can effectively reverse the oncogenic effects of lactylation. SIRT1 acts as a specific delactylase for H3K18la. Its agonist SRT2104 reduces lactylation levels and restrains tumor progression. Low-dose combination with oxamate improves therapeutic efficacy and alleviates toxic reactions (90). SIRT2 mediates the delactylation of METTL16. Its inhibitor AGK2 strengthens cuproptosis and shows synergistic antitumor effects when combined with elesclomol (56). As a vital lactyltransferase, AARS1 catalyzes the modification of YAP/TEAD1 and H4K8la to drive metabolic reprogramming and immune exclusion, and serves as a valuable potential target (51,97). NAA10 induces NSUN2 lactylation and elevates ferroptosis resistance. Targeting the NAA10-NSUN2 axis helps restore chemosensitivity (54).

Natural products targeting lactylation. Various natural products exert antitumor effects by suppressing glycolysis or lactylation, featuring high safety and diverse targets. For example, saikosaponin D inhibits glycolysis and lactate accumulation by restraining PKM2 activity, thus markedly reducing histone lactylation and malignant behavior in GC cells. It also suppresses tumor growth, and decreases Ki67 expression and global lactylation level in xenograft models (88). Similarly, brusatol inhibits glycolysis and lactylation by

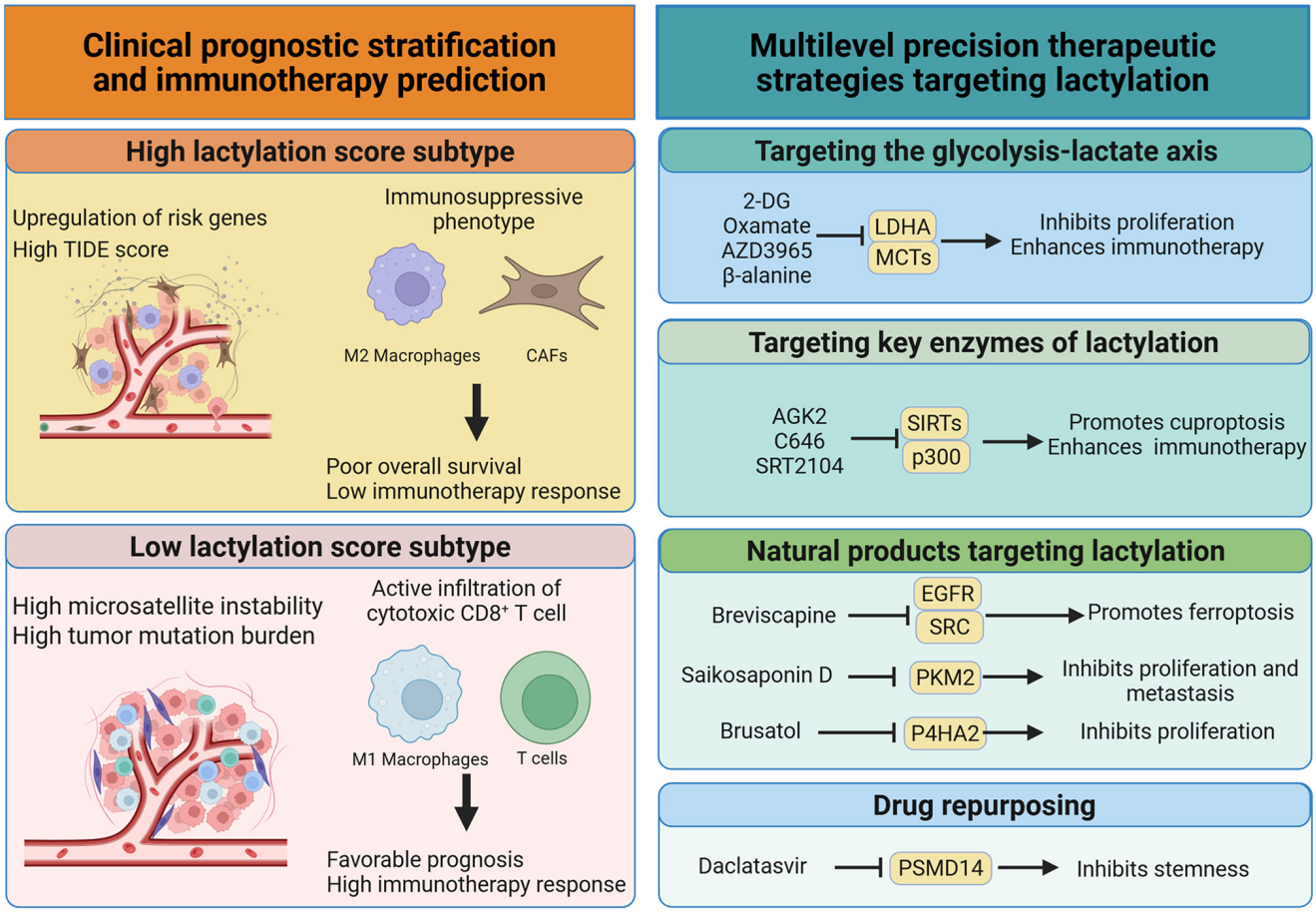

Figure 5. Clinical applications of lactylation in prognostic evaluation and targeted therapy of gastric cancer. Lactylation-related gene signatures construct prognostic models for survival stratification and prediction of immunotherapeutic response. Multiple intervention strategies targeting the glycolysis-lactate axis, lactylation-modifying enzymes, natural compounds and repurposed drugs achieve antitumor effects by suppressing aberrant lactylation. CAFs, cancer-associated fibroblasts; LDHA, lactate dehydrogenase A; MCTs, monocarboxylate transporters; PKM2, pyruvate kinase M2; SIRTs, sirtuins; TIDE, tumor immune dysfunction and exclusion.

promoting P4HA2 degradation and arrests GC cell proliferation. It effectively restrains tumor growth and reduces lactylation *in vivo* (53). Furthermore, breviscapine targets the EGFR/SRC pathway to downregulate LDHA expression and GPX4 lactylation, and specifically triggers ferroptosis in a diabetic-associated GC microenvironment (102). These natural products, which target lactylation, offer novel avenues for developing low-toxic anti-GC drugs.

Drug repurposing and nano-targeted delivery. Drug repurposing and nano-delivery systems provide efficient translational strategies for lactylation targeting. Daclatasvir, a Food and Drug Administration-approved anti-hepatitis C drug, directly binds to PSMD14 and blocks the interaction between PSMD14 and PFKFB2, thereby inhibiting glycolysis and CSC properties. In patient-derived organoid xenograft models, daclatasvir reduces H3K27la level and suppresses tumor growth (89). Nano-targeted delivery systems serve as novel tools for precise lactylation modulation. In previous research, erythrocyte membrane-camouflaged vesicles modified with anti-CD8a antibody were constructed to deliver the p300 inhibitor C646 into $CD8^+$ T cells. This nanoplatform efficiently lowers H3K18la, restores the cytotoxic activity of $CD8^+$ T cells and inhibits tumor progression (76).

In summary, a multi-level therapeutic system targeting lactylation has been established, including upstream metabolic blockade, modifying enzyme regulation, natural product intervention and precise delivery systems. Combination therapy presents the prominent advantages of high efficacy and low toxicity. However, numerous strategies remain in the preclinical stage. Drugs with high site specificity remain insufficient, and cross-regulatory mechanisms between lactylation and other acylation modifications need further exploration. With advances in epigenetic editing technology and potent inhibitors, lactylation-targeted therapy is expected to become a vital novel strategy for precise diagnosis and treatment of GC.

7. Conclusion and prospects

As a novel protein PTM driven by the glycolytic metabolite lactate, lactylation has been established as an important hub connecting metabolic reprogramming and epigenetic regulation in GC. Abnormal intensification of the Warburg effect leads to enhanced lactate accumulation, which functions as an epigenetic modifier to induce histone and non-histone lactylation, thereby modulating proliferation, metastasis, immune escape and therapeutic resistance. Clinically, lactylation-related risk models have shown potential for

Table III. Therapeutic strategies targeting lactylation for gastric cancer.

First author, year	Drug	Category	Mechanism	Outcome	(Refs.)
Zhang *et al*, 2026	Brusatol	Natural compound	By specifically binding to P4HA2 and promoting its degradation, it inhibits glycolysis and lactate production, thereby downregulating H3K9la and H3K18la levels	Inhibits the proliferation of cancer cells	(53)
Sun *et al*, 2023	AGK2	SIRT inhibitor	Inhibits SIRT2 activity, thereby upregulating METTL16 lactylation levels	Promotes cuproptosis	(56)
Xiang *et al*, 2026	C646	p300 inhibitor	Inhibits p300 activity, thereby suppressing H3K18la	Enhances antitumor immunity	(76)
Hu *et al*, 2025	Breviscapine	Natural compound	Targets the EGFR/SRC axis to downregulate LDHA expression and lactate production, thereby reducing GPX4 lactylation levels	Promotes ferroptosis and inhibits the proliferation of cancer cells	(102)
Wang *et al*, 2026	Saikosaponin D	Natural compound	Downregulates PKM2 expression, inhibits glycolysis and lactate production, thereby downregulating H3K9la, H3K14la and H3K18la	Inhibits the proliferation and metastasis of cancer cells	(88)
Zhao *et al*, 2026	Daclatasvir	Anti-hepatitis C drug	Inhibits the activity of PSMD14 to increase ubiquitination and degradation of PFKFB2, thereby suppressing glycolysis and downregulating the level of H3K27la	Inhibits stemness	(89)
Tsukihara *et al*, 2025	SRT2104	SIRT agonist	Enhances the activity of the deacetylase SIRT1, thereby inhibiting H3K18la	Inhibits cancer cell proliferation and migration	(90)
Tsukihara *et al*, 2025	Oxamate/2-DG	Glycolysis inhibitor	Inhibits LDHA activity and reduces histone lactylation levels	Inhibits the proliferation of cancer cells and enhances anti-tumor immunity	(90)
Huang *et al*, 2026	AZD3965	MCT1 inhibitor	Inhibits MCT1 and reduces intracellular lactate accumulation, thereby lowering H4K8la levels	Enhances anti-tumor immunity	(97)
Huang *et al*, 2026	β-alanine	Lactylation inhibitor	Competitive inhibition of lactylation modification to reduce H4K8la levels	Enhances anti-tumor immunity	(97)

GPX4, glutathione peroxidase 4; LDH, lactate dehydrogenase; MCT1, monocarboxylate transporters 1; METTL16, methyltransferase-like 16; PKM2, pyruvate kinase M2; SIRT, sirtuin.

prognostic stratification and prediction of immunotherapy response. Therapeutically, multi-level interventions targeting the glycolysis-lactate axis, lactylation-modifying enzymes and downstream effector molecules have been proposed. However, the majority of strategies remain in the preclinical stage.

Existing research has preliminarily elucidated the molecular mechanisms by which lactylation contributes to the malignant progression of GC; however, numerous technical limitations and gaps in clinical translation remain in this field. First, the majority of previous studies indirectly alter lactylation levels by systemically intervening in lactate levels or globally regulating modifying enzymes, while lacking tools for precise editing of individual lysine sites, making it difficult to isolate the independent functions of different Kla sites. Future research could involve constructing a dCas9-AARS/SIRT fusion site-specific editing vector to precisely manipulate

modifications at specific sites, thereby elucidating the causal effects of each modification on GC proliferation and immune evasion (109). Second, existing batch omics data cannot distinguish differences in lactylation expression among tumor epithelium, CAFs and infiltrating immune cells, thus lacking *in situ* spatial information. In the future, single-cell sequencing and spatial modification proteomics could be integrated to map the distribution of lactylation in the GC microenvironment and to analyze the interactive networks of metabolic modifications among various cell types. Third, previous research on lactylation biomarkers has primarily focused on advanced GC, with insufficient exploration of precancerous lesions such as atrophic gastritis and intestinal metaplasia. The dynamic changes in lactate levels within the Correa carcinogenesis pathway remain unclear. In future studies, clinical samples spanning from precancerous to cancerous stages could be collected longitudinally to identify early-stage risk biomarkers for GC. Fourth, current lactic acid-modulating therapeutic agents are primarily broad-spectrum metabolic inhibitors and natural products. Highly selective small molecules targeting AARS1 and SIRT2 remain scarce, and there is a lack of efficacy validation in GC organoids and *in situ* models. Future research could focus on screening for enzyme-specific inhibitors and evaluating the synergistic antitumor effects of drug combinations with radiotherapy and chemotherapy using patient-derived models. Conducting research along these lines will help refine the metabolic epigenetic regulatory network of GC and advance the clinical application of lactate-related biomarkers and targeted therapies.

In summary, as a key node at the intersection of metabolism and epigenetics, lactylation has potential to translate from basic mechanisms to clinical diagnosis and treatment. With sustained breakthroughs of site-specific tools, clinical verification and targeted drugs, lactylation may have a role in the precise diagnosis, prognostic evaluation and targeted therapy of GC, and could provide important strategies to improve clinical outcomes in patients with GC.

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Authors' contributions

YF and XL conceived the present study. YF, PC, YG, YL and XL edited and revised the manuscript. All authors read and approved the final 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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