Dual roles of lactylation modification in gastric cancer: Crosstalk between metabolic reprogramming and epigenetic regulation (Review)

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Abstract. Gastric cancer (GC) is among the most prevalent malignant tumors worldwide, and its occurrence and progression are closely associated with metabolic abnormalities and remodeling of the tumor microenvironment. As an emerging metabolism-related post-translational modification, lactylation acts as a central hub connecting metabolic reprogramming and epigenetic regulation in tumor cells. The present review systematically describes the reprogramming features of lactate metabolism in the GC microenvironment; dissects the enzymatic system and molecular characteristics of lactylation; and reveals a bidirectional positive feedback loop in which histone H3 lysine 18 lactylation (H3K18la) promotes lactate production by upregulating glycolytic genes, and lactate accumulation, in turn, enhances H3K18la levels. A three-dimensional regulatory network of 'metabolic reprogramming-epigenetic regulation-immune microenvironment remodeling' is thereby established in GC. The present review also reveals the clinical value of lactylation as a prognostic biomarker for GC, proposes combination therapeutic strategies targeting lactylation, and provides a theoretical basis and translational direction for the precise diagnosis and treatment of GC.

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Abbreviations: AARS1, alanyl-tRNA synthetase 1; FAP, fibroblast activation protein; FASN, fatty acid synthase; GC, gastric cancer; GCLC, glutamate-cysteine ligase catalytic subunit; GLS, glutaminase; GLUT1, glucose transporter 1; HBO1, histone acetyltransferase binding to ORC1; HDAC, histone deacetylase; HGLRG, hypoxia-glycolysis-lactylation-related genes; HK2, hexokinase 2; Kla, lysine lactylation; LDHA, lactate dehydrogenase A; MCT1, monocarboxylate transporter 1; NSUN2, NOP2/Sun RNA methyltransferase 2; PKM2, pyruvate kinase M2; PLOD2, prolyl 3-hydroxylase domain-containing protein 2; SREBP-1, sterol regulatory element-binding protein-1; TCA, tricarboxylic acid; TIME, tumor immune microenvironment; TME, tumor microenvironment

Key words: gastric cancer, lactylation modification, metabolic reprogramming, epigenetic regulation

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1. Introduction

Gastric cancer (GC) is one of the most common malignant tumors of the digestive system, and its high incidence and mortality pose severe challenges to global public health (1,2). In 2020, GC accounted for ~1.09 million new cases and 770,000 deaths worldwide, ranking 5th and 3rd in terms of global incidence and mortality among malignant tumors, respectively (3). Asia has the highest global burden of GC. By 2040, the number of new cases and deaths from GC in Asia is predicted to increase by 72.20 and 75.90%, respectively, compared with current levels (4), leading to increasingly intense pressure on disease prevention and control. Despite the continuous optimization of the three-level prevention system and comprehensive treatment regimens for

GC, traditional surgery, chemotherapy, and targeted therapy still struggle to overcome the bottleneck of drug resistance and recurrence owing to the complexity of the tumor microenvironment (TME) (5-9). The 5-year survival rate of patients with advanced GC remains <10%, highlighting the urgent need to explore novel molecular mechanisms and therapeutic targets.

The Warburg effect, in which tumor cells preferentially generate ATP through glycolysis and accumulate large amounts of lactate even under aerobic conditions, is a core characteristic of tumor cells (10). Lactate has long been considered a metabolic waste product of glycolysis. It was not until 2019 that Zhang *et al* (11) first confirmed that lactate can be converted into lactyl-CoA, which serves as an acyl donor in histone lysine lactylation (Kla) modification and directly regulates gene expression, completely subverting the traditional understanding of the function of lactate. Subsequent research has confirmed that lactylation modification is common in histones and non-histones and plays a key regulatory role in tumor metabolic reprogramming, epigenetic disorders, and immune microenvironment remodeling (12).

In recent years, the regulatory role of lactylation modification in the occurrence and development of GC has attracted increasing research attention. Yang *et al* (13) identified >2,000 Kla sites in human gastric adenocarcinoma cell lines through mass spectrometry analysis, spanning functional groups such as metabolic enzymes, transcription factors, and cytoskeletal proteins, and confirmed the widespread existence of this modification in GC cells. Mechanistic studies have shown that as a core metabolic product of glycolytic reprogramming, lactate shapes an immunosuppressive microenvironment by regulating the polarization of tumor-associated macrophages and the function of T cells (14,15). Furthermore, lactate also competes synergistically with classical epigenetic modifications such as histone acetylation and methylation, creating a 'metabolism-epigenetics' interactive regulatory network that participates in the malignant progression of GC (16).

Nonetheless, several core scientific issues merit urgent attention: First, the synergistic regulatory mechanism by which lactylation modification drives metabolic reprogramming and epigenetic disorders in GC remains unclear; second, the temporal relationship and synergistic effect of histone and non-histone lactylation in the progression of GC have not been analyzed; and third, a consensus on the clinical transformation value of lactylation modification, particularly in its application as a diagnostic biomarker and potential therapeutic target for GC, remains lacking. These issues have severely restricted the in-depth development and clinical translation of this research field.

The present review systematically integrates the latest research progress in the field of GC lactylation modification, reconstructs the metabolism-epigenetics-immunity three-dimensional regulatory network, discusses the core controversies in the field, and clarifies the clinical transformation strategy of lactylation modification. Overall, the review aims to inspire novel strategies and directions for the precise diagnosis and treatment of GC.

2. Role of lactate in metabolic reprogramming

GC cells remodel their energy and biosynthetic pathways through metabolic reprogramming. Coordinated dysregulation of glycolysis, glutamine metabolism, and lipid metabolism is the core driver of massive lactate production and accumulation (17), which provides the metabolic basis for lactylation.

Activation of the glycolytic pathway: The primary source of lactate production. A hallmark of metabolic reprogramming in GC cells is the canonical Warburg effect, whereby tumor cells preferentially rely on glycolysis for ATP production even under aerobic conditions, accompanied by the suppression of mitochondrial oxidative phosphorylation. This metabolic phenotype ultimately drives robust intracellular lactate production and accumulation (18-20) (Fig. 1). In GC cells, hypoxia-inducible factor 1α and c-Myc serve as the core transcriptional regulators driving the sustained activation of the glycolytic pathway. Both factors transcriptionally upregulate key glycolytic molecules, including glucose transporter 1 (GLUT1, encoded by SLC2A1), hexokinase 2 (HK2), pyruvate kinase M2 (PKM2), and lactate dehydrogenase A (LDHA), which markedly enhance cellular glucose uptake and glycolytic flux (21). Among these, upregulated expression of GLUT1 significantly augments transmembrane glucose transport, providing sufficient substrates for glycolytic reactions (22). Intracellular glucose is first catalyzed by HK2 to generate glucose-6-phosphate, which is then converted to pyruvate via a cascade of sequential enzymatic reactions. As the terminal rate-limiting enzyme of the glycolytic pathway, PKM2 acts as a core modulator of glycolytic flux (23).

Pyruvate derived from glycolysis is catalyzed by LDHA and ultimately reduced to lactate, coupled with the oxidation of NADH to NAD^+. This process completes the regeneration of coenzymes required for the glycolytic cycle, thus ensuring sustained operation of the pathway (24). Transmembrane lactate transport is mainly regulated by two members of the monocarboxylate transporter (MCT) family: MCT1 and MCT4 (25,26). MCT4 is abundantly expressed in the plasma membrane of GC cells, and effluxes excess intracellular lactate into the TME via a monocarboxylate-proton co-transport mechanism. By contrast, MCT1 primarily mediates the uptake of lactate from the TME into cells to support cellular oxidative metabolism (27-29). Together, these two transporters mediate the intracellular-extracellular lactate cycle, which ultimately leads to massive lactate accumulation and the formation of a characteristic acidic TME of GC (30).

Glutamine metabolism: An amplifier of lactate production. Glutaminolysis is another hallmark of GC metabolic reprogramming (Fig. 2). Glutaminase (GLS) catalyzes the conversion of glutamine to glutamate, which is further metabolized to α-ketoglutarate for entry into the tricarboxylic acid (TCA) cycle. This process provides critical metabolic precursors that support ATP generation and macromolecule biosynthesis in tumor cells (31). GLS is abundantly expressed in GC tissues (32,33), and its dysregulation synergistically drives lactate accumulation via two distinct pathways. First, by replenishing TCA cycle intermediates, GLS reduces the mitochondrial oxidative catabolism of pyruvate, thereby shunting pyruvate toward lactate production (34). Second, glutamine is an essential nitrogen source for nucleotide biosynthesis (35). Aspartate deficiency during glutamine metabolism induces the expression of the glutamine transporter alanine-serine-cysteine

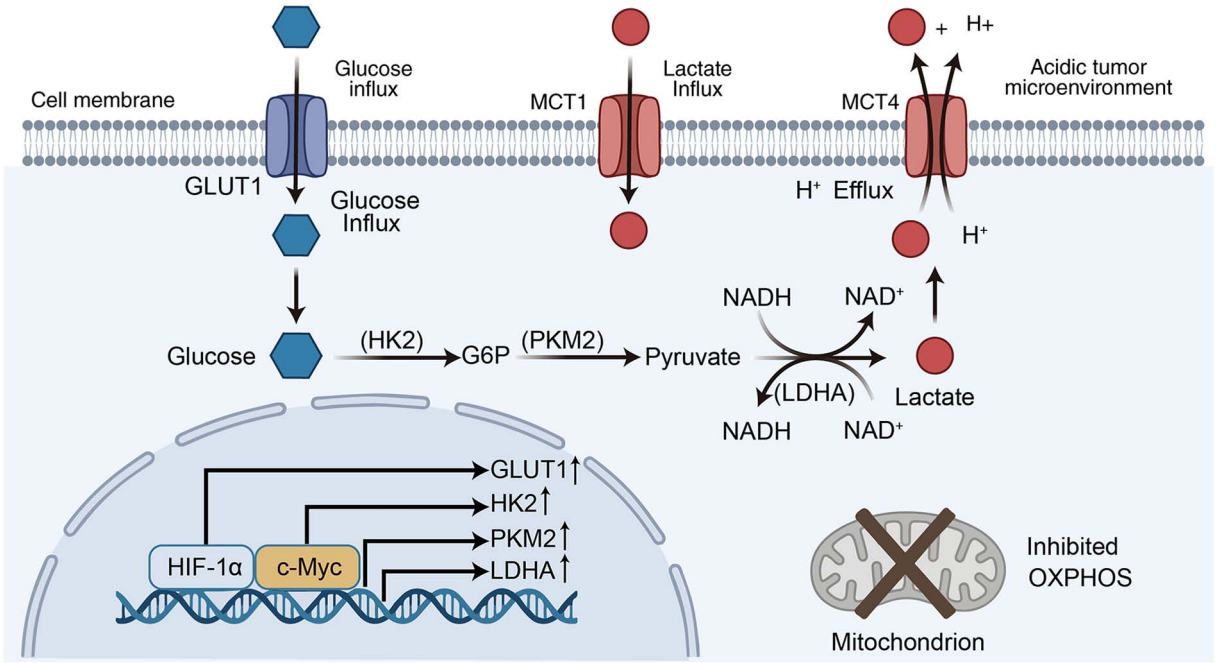

Figure 1. Glycolytic pathway-mediated lactate production and acidic tumor microenvironment formation in gastric cancer cells. GLUT1, glucose transporter 1; HK2, hexokinase 2; G6P, glucose-6-phosphate; PKM2, pyruvate kinase M2; LDHA, lactate dehydrogenase A; MCT1, monocarboxylate transporter 1; MCT4, monocarboxylate transporter 4; HIF-1α, hypoxia-inducible factor 1 α; c-Myc, cellular myelocytomatosis oncogene; NADH, nicotinamide adenine dinucleotide (reduced form); NAD^+, nicotinamide adenine dinucleotide (oxidized form); OXPHOS, oxidative phosphorylation.

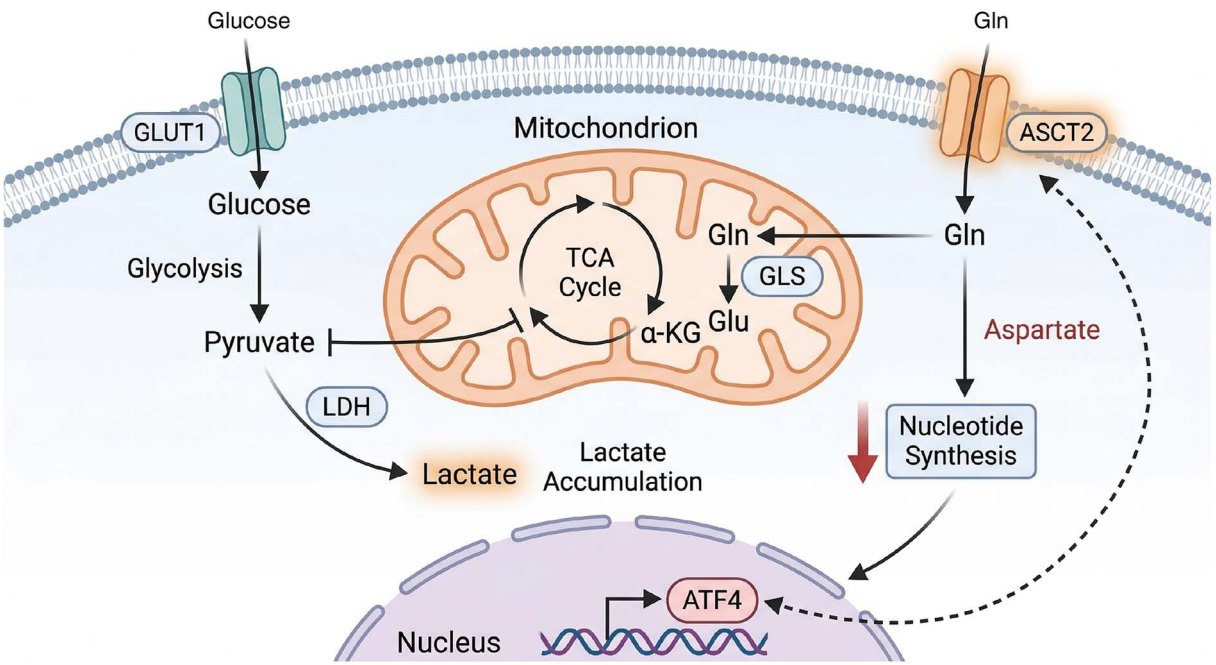

Figure 2. Glutamine metabolism reprogramming mediates lactate accumulation in gastric cancer cells. GLUT1, glucose transporter 1; GIn, glutamine; Glu, glutamate; ASCT2, alanine-serine-cysteine transporter 2; GLS, glutaminase; TCA, tricarboxylic acid cycle; LDH, lactate dehydrogenase; ATF4, activating transcription factor 4.

transporter 2 by activating transcription factor 4 (36), thus forming a positive metabolic feedback loop that further augments the Warburg effect and promotes lactate production. Inhibition of GLS activity significantly reduces lactate production in GC cells while concomitantly suppressing tumor cell proliferation and reversing the chemoresistant phenotype (37).

Lipid metabolic reprogramming: Maintenance of lactate metabolic homeostasis. In terms of fatty acid metabolism, GC cells employ a sterol regulatory element-binding protein-1 (SREBP-1)-mediated transcriptional program to activate enzymes such as fatty acid synthase (FASN) and acetyl-CoA carboxylase, converting acetyl-CoA into long-chain fatty

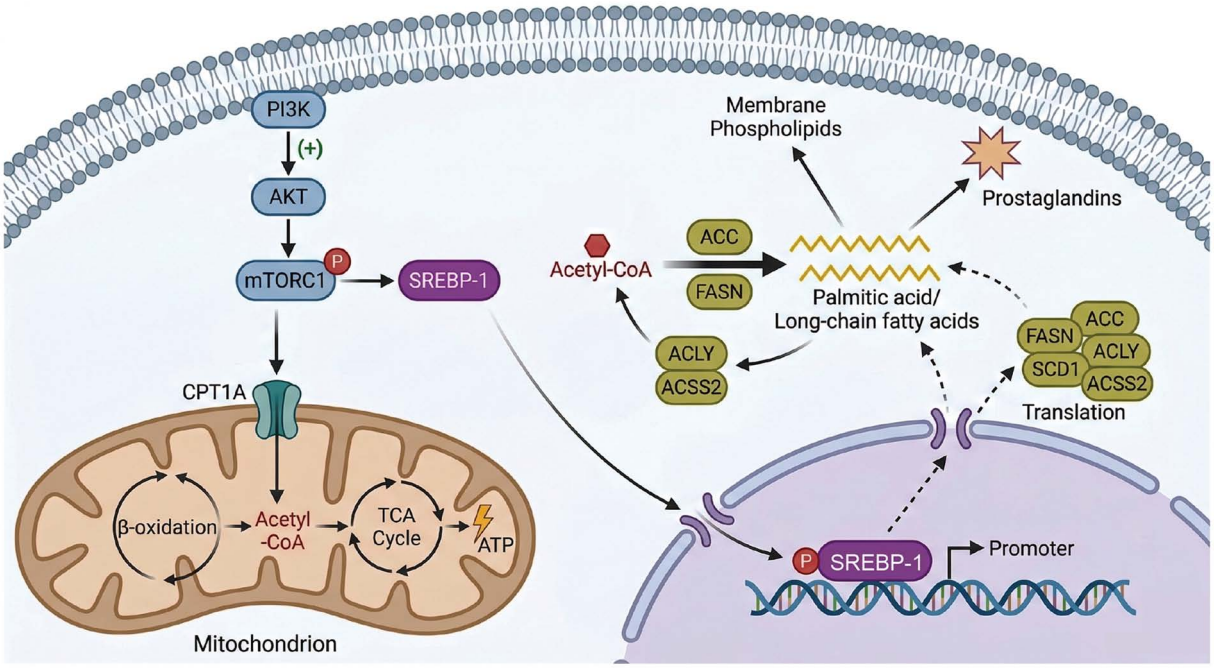

Figure 3. Lipid metabolic reprogramming in gastric cancer cells. PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTORC1, mammalian target of rapamycin complex 1; SREBP-1, sterol regulatory element-binding protein 1; CPT1A, carnitine palmitoyltransferase 1A; TCA, tricarboxylic acid cycle; ATP, adenosine triphosphate; Acetyl-CoA, acetyl coenzyme A; ACLY, ATP citrate lyase; ACSS2, acyl-CoA synthetase short-chain family member 2; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; SCD1, stearoyl-CoA desaturase 1.

acids for the synthesis of membrane phospholipids and signaling molecules (38). This process is regulated by the PI3K/AKT/mTOR pathway: mTORC1 phosphorylation promotes the nuclear translocation of SREBP-1 and enhances the expression of genes associated with fatty acid synthesis, including *FASN*, stearoyl-CoA desaturase 1, and ATP citrate lyase (39). As a transcriptional hub, SREBP-1 directly binds to the promoters of ATP citrate lyase and acyl-CoA synthetase short-chain family member 2, systematically regulating lipid metabolism at the transcriptional level (40). Concurrently, carnitine palmitoyl transferase 1A mediates mitochondrial β-oxidation of long-chain fatty acids, breaking them down into acetyl-CoA to replenish the TCA cycle and maintain energy metabolism in tumor cells (41). This metabolic flexibility between synthesis and catabolism provides membrane structural materials for GC cell proliferation and supports cell survival through energy reserves, thus representing a critical feature of metabolic reprogramming in the GC microenvironment (Fig. 3).

The synergistic remodeling of glycolysis and glutamine and fatty acid metabolism provides an energy and material basis for GC cells. Lactate, the end product of glycolysis, is not only involved in microenvironment regulation but also mediates lactylation as a new mode of epigenetic regulation, emerging as a bridge connecting metabolic reprogramming and gene expression networks.

3. Enzymatic system of lactylation modification

Protein lactylation is primarily categorized into two classes, histone lactylation and non-histone lactylation, which represent markedly divergent modes of functional regulation. Histone lactylation governs target gene transcription by remodeling the spatial conformation of chromatin, whereas non-histone lactylation mostly exerts direct effects on the activity, localization, and interaction of target proteins. Currently, the mechanism underlying lactylation remains controversial and is generally divided into two models: Enzyme-dependent lactylation, and non-enzymatic spontaneous lactylation induced by a high-lactate microenvironment (42) (Fig. 4). Both models offer critical research breakthroughs in deciphering the molecular mechanisms underlying lactylation.

Writer enzymes of lactylation modification. Writer enzymes are core molecules that catalyze the conjugation of lactyl groups to lysine residues of target proteins and initiate the lactylation modification process. Notably, some of the currently identified lactylation-writer enzymes share an enzymatic system with acetylation modifications, which is an important research focus in this field.

p300, a member of the histone acetyltransferase family, was the first enzyme identified to mediate histone lactylation (11). It possesses dual catalytic activity as both an acetyltransferase and lactyltransferase, representing a key molecule for the overlapping enzymatic systems of lactylation and acetylation. This discovery once sparked academic controversy over whether lactylation is merely a concomitant byproduct of acetylation. As a pivotal writer enzyme for lactylation, p300 can specifically transfer lactyl groups to lysine residues of histones, such as histone H3 lysine (H3K9) and histone H3 lysine 18 (H3K18) (43); mediate chromatin structural remodeling by altering the binding affinity between histones and DNA; and subsequently activate the transcriptional expression of downstream target genes (44), thereby serving as a

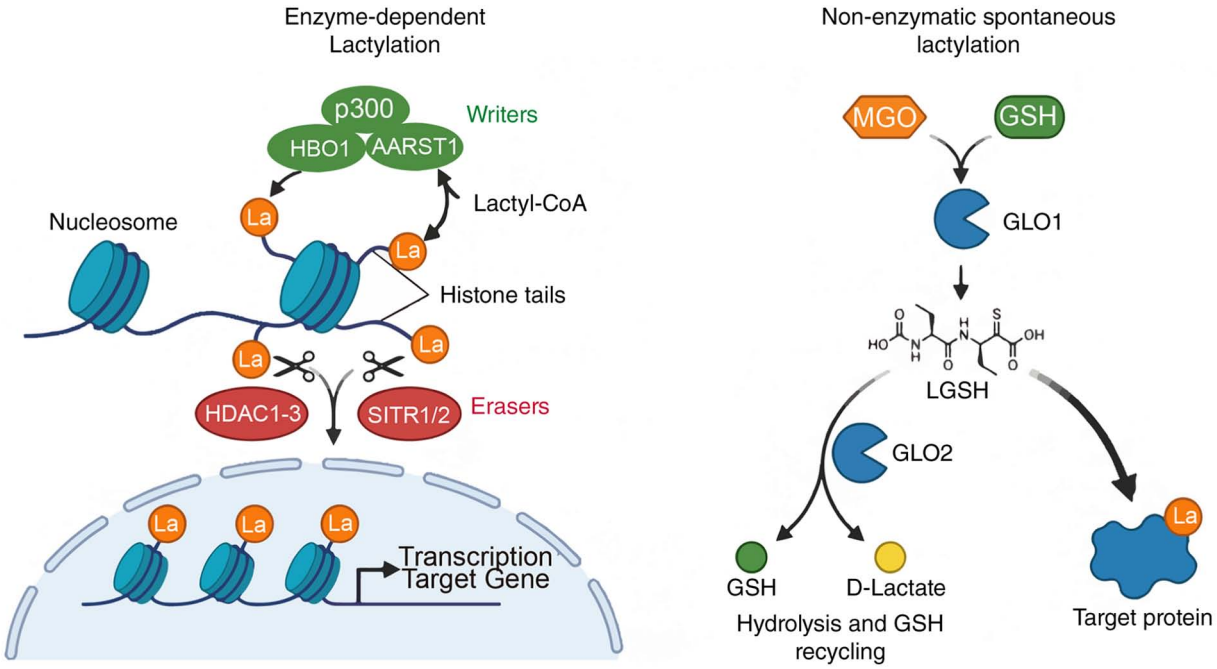

Figure 4. Enzyme-dependent and non-enzymatic spontaneous regulatory mechanisms of lactylation modification. Lactyl-CoA, lactyl-coenzyme A; p300, E1A-associated protein p300; HBO1, histone acetyltransferase binding to ORC1; AARS1, alanyl-tRNA synthetase 1; La, lactylation; HDAC1-3, histone deacetylase 1-3; SIRT1/2, sirtuin 1/2; MGO, methylglyoxal; GSH, glutathione; GLO1, glyoxalase 1; GLO2, glyoxalase 2; LGSH, S-D-lactoylglutathione.

critical molecular hub connecting cellular metabolic signals to epigenetic regulation.

However, lactylation and acetylation at the same site are not functionally redundant. Instead, they compete for substrates and exhibit mutually exclusive modification sites, leading to distinct transcriptional outputs. Acetylation neutralizes the positive charge of lysine via a 2-carbon group, achieving broad-spectrum chromatin relaxation (45); By contrast, the 3-carbon group of lactylation carries a hydroxyl moiety, which not only neutralizes charge but also confers greater steric hindrance and hydrophobicity, specifically remodeling the chromatin conformation at the promoter regions of target genes (11). Both modifications also differ in their specific reader proteins: Acetylation is recognized by bromodomain containing (BRD)2 and BRD4 (46) to regulate housekeeping genes associated with cellular homeostasis, whereas lactylation is specifically bound by double PHD fingers 2 (47). In the high-lactate microenvironment of GC, p300 preferentially catalyzes lactylation (13), which precisely activates glycolytic reprogramming and drives the malignant phenotype of GC, showing a sharp divergence from the broad-spectrum transcriptional output of acetylation.

Histone acetyltransferase binding to ORC1 (HBO1), a canonical histone acetyltransferase of the MYST family, classically functions to catalyze acetylation at histone sites including histone H4 lysine 16 and histone H3 lysine 14, thereby regulating chromatin structure and gene transcription (48,49). HBO1 also exhibits novel lysine lactyltransferase activity and can specifically catalyze histone lactylation at the H3K9 site (50), endowing it with new functional implications in metabolically-dependent epigenetic regulation. Of particular importance, HBO1 is abundantly expressed in GC tissues (51), and its overexpression is negatively correlated with the 5-year survival rate of patients with GC (52), suggesting that it may contribute to the malignant progression of GC by mediating histone lactylation and exerting a non-negligible impact on patient prognosis. Using stable isotope labeling with amino acids in cell culture-based quantitative proteomics, researchers further identified 95 endogenous Kla sites regulated by HBO1, among which histone-related modification sites account for 32%, including key sites such as H3K9 lactylation and histone H4 lysine 5 lactylation. These results directly validated the core writer enzyme function of HBO1 in histone lactylation (50).

Alanyl-tRNA synthetase 1 (AARS1) is an enzyme involved in lactylation. Unlike p300 and HBO1, AARS1 does not depend on canonical lactyl-CoA as a lactyl group donor. Instead, it directly binds to lactate and catalyzes the formation of a lactate-AMP intermediate, thereby covalently transferring lactyl groups to lysine residues of target proteins to achieve lactylation (53). This discovery expands the molecular framework underlying lactylation modifications.

Eraser enzymes of lactylation modification. Eraser enzymes are core molecules that specifically remove lactyl groups from the lysine residues of target proteins and reverse the lactylation process. They maintain the dynamic homeostasis of intracellular lactylation by negatively regulating excess lactylation (54,55). Histone deacetylase (HDAC)1-3 isoforms have been validated as specific eraser enzymes for lactylation (56). They selectively recognize lactylated lysine residues and precisely remove lactyl groups, thereby mediating the targeted regulation of lactylation. In addition, sirtuin (SIRT)1 and SIRT2 have also been verified to possess lactylation erasure activity (57). In GC, these two enzymes suppress the malignant phenotype and progression of tumor

cells by specifically reducing the levels of H3K18 lactylation (H3K18la) modification (58).

Enzyme-dependent and non-enzymatic spontaneous lactylation. There is an ongoing scientific controversy with regard to the exact mechanism by which lactylation modifications occur; the debate primarily centers on whether enzyme-dependent or non-enzymatic spontaneous lactylation processes are involved (59). Enzyme-dependent lactylation is a well-validated core regulatory mechanism in GC research. This process relies on the catalysis of writer and eraser enzymes and is characterized by site specificity and regulability (59,60).

In contrast to enzymatic lactylation, non-enzymatic lactylation originates from methylglyoxal (MGO), a byproduct of glycolysis (60), and is primarily mediated by the glyoxalase pathway (61). The intracellular concentration balance of MGO is maintained by the glyoxalase cycle, which requires the coordinated action of glyoxalase 1 (GLO1) and glyoxalase 2 (GLO2). GLO1 first catalyzes the isomerization of the hemithioacetal formed by glutathione (GSH) and MGO to generate S-D-lactoylglutathione (LGSH). GLO2 then hydrolyzes LGSH to recycle GSH and produce D-lactate (62). LGSH covalently attaches lactoyl groups to protein lysine residues via non-enzymatic acyl transfer to form lactoyl-lysine modifications, establishing a link between glycolytic by-products and protein post-translational modifications, in which GLO2 plays a major regulatory role (63,64).

Although the basic regulatory mechanism of non-enzymatic lactylation has been preliminarily elucidated, there is no direct *in vivo* experimental evidence confirming the existence of functional non-enzymatic lactylation in GC tissues. Furthermore, it remains to be verified whether non-enzymatic and enzyme-dependent lactylation act synergistically to enhance the pro-tumor effects of lactylation, or competitively occupy modification sites to antagonize the normal regulation of enzyme-dependent lactylation during GC tumorigenesis and progression.

4. Lactylation drives remodeling of the GC tumor microenvironment

Remodeling of the metabolic microenvironment. Increasing evidence over recent years has established that lactylation is not merely a passive byproduct of metabolic reprogramming but a critical nexus bridging cellular energy metabolism and epigenetic regulation. Lactylation modulates the activity of the glycolytic pathway at two fundamental levels, namely epigenetic transcriptional control and protein post-translational modification, thereby driving an epigenomic-metabolic cooperative regulatory circuit that represents a core mechanism sustaining the persistent activation of aerobic glycolysis in GC cells (65).

Lactylation marks have been found to be enriched in the promoter regions of key glycolytic genes, including *GLUT1, HK2,* and *LDHA*. At these loci, lactylation upregulates target gene transcription by remodeling chromatin accessibility, thereby directly activating the glycolytic cascade. Specifically, lactylation of LDHA at lysine 5 increases the catalytic efficiency of pyruvate-to-lactate conversion by 40% via an allosteric effect, while potently inhibiting the reverse reaction to maintain lactate homeostasis (66). Lactylation of HK2 at lysine 382 enhances its interaction with voltage-dependent anion channel 1, thereby directing >80% of the glucose-derived carbon flux into the glycolytic pathway (67). Furthermore, the lactylation of PKM2 at lysine 433 promotes its nuclear translocation, which in turn activates c-Myc expression via histone H3 phosphorylation. This modification leads to a 25% increase in the proportion of cells in the S phase of the cell cycle, achieving cross-functional regulation of this metabolic enzyme beyond its canonical catalytic role (68).

Clinical studies have validated the regulatory role of lactylation. Specifically, GC tissues exhibit significantly higher expression of LDHA mRNA and lactate content than paired adjacent non-tumor tissues (69). H3K18la expression was shown to be positively correlated with the expression of LDHA and HK2, and patients with concurrently high expression of both Nijmegen breakage syndrome protein 1 K388 lactylation and LDHA had a significantly poorer overall survival (70).

In addition to its core regulatory function in the glycolytic pathway, lactylation acts via alternative mechanisms to cooperatively sustain the survival and proliferation of GC cells. Lactylation of NOP2/Sun RNA methyltransferase 2 (NSUN2) at lysine 508 (K508) enhances its enzymatic activity and preserves the stability of the 5-methylcytosine (m5C) modification of glutamate-cysteine ligase catalytic subunit (GCLC) mRNA, thereby augmenting the antioxidant capacity of tumor cells (71). Under copper stress, the lactylation of methyltransferase-like 16 at lysine 229 triggers cuproptosis, a process that is potently inhibited by SIRT2. Accordingly, combined treatment with copper ionophores and SIRT2 inhibitors synergistically induces apoptosis of GC cells (72). As a *bona fide* lactate transferase, AARS1 senses intracellular lactate concentrations and subsequently translocates to the nucleus, where it activates the Yes-associated protein-TEA domain transcription factor complex through lactylation, and in turn forms a positive feedback loop with the Hippo pathway to continuously amplify the oncogenic effects of glycolysis (73).

The regulatory mechanisms of the aforementioned metabolic microenvironment demonstrate that histone lactylation and non-histone lactylation do not function independently. Following a sequential pattern where histone lactylation initiates metabolic reprogramming and non-histone lactylation sustains and amplifies malignant phenotypes, they form a synergistic regulatory network by sharing metabolic substrates and responding to lactate concentration gradients in a graded manner, thus serving as the core regulatory axis driving the malignant progression of GC.

Remodeling of the immune microenvironment. Histone lactylation is a pivotal driver of lactate-mediated remodeling of the GC tumor immune microenvironment (TIME). Among the identified histone lactylation sites, H3K18la is the most extensively characterized to date, and its pro-tumor and immunomodulatory effects are mediated primarily via two major mechanisms. H3K18la directly targets and activates the transcription of vascular cell adhesion molecule 1, thereby enhancing the intrinsic malignant phenotype of GC cells via the AKT/mTOR signaling pathway. Second, H3K18la upregulates the expression of the chemokine C-X-C motif chemokine ligand 1 to recruit GC-associated mesenchymal

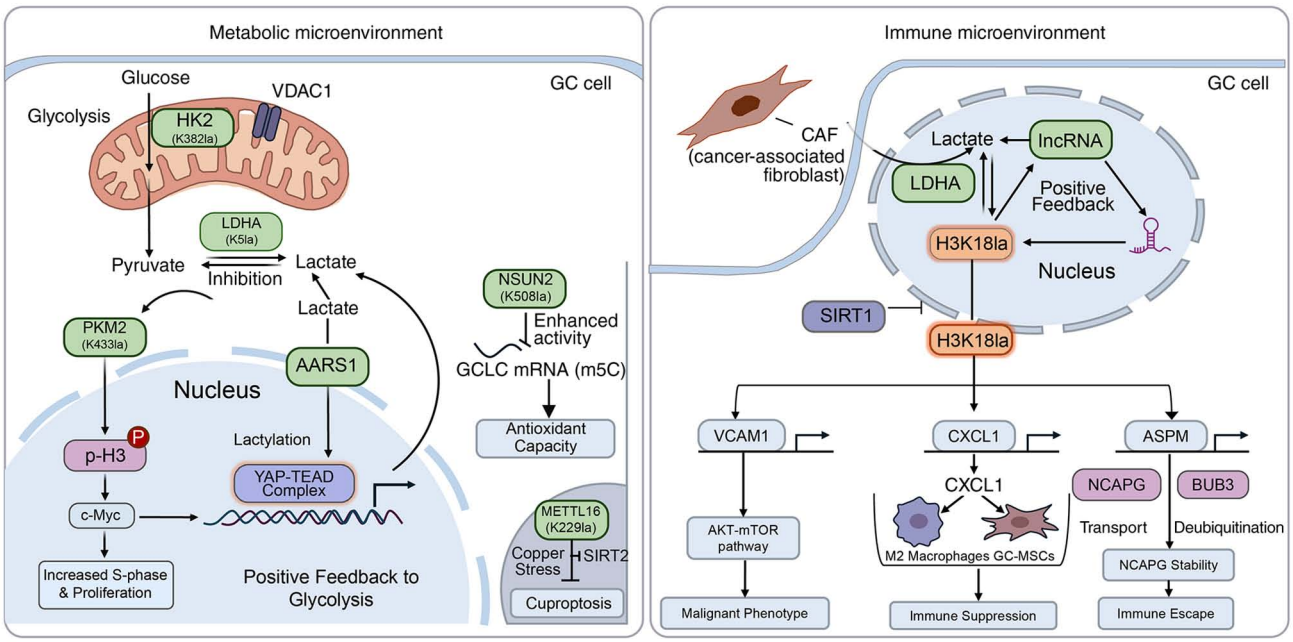

Figure 5. Lactylation modification regulates the functional network of metabolic and immune microenvironment remodeling in gastric cancer. GC, gastric cancer; HK2, hexokinase 2; la, lactylation (lysine lactylation, Kla); LDHA, lactate dehydrogenase A; PKM2, pyruvate kinase M2; VDAC1, voltage-dependent anion channel 1; AARS1, alanyl-tRNA synthetase 1; YAP, Yes-associated protein; TEAD, TEA domain transcription factor; c-Myc, cellular myelocytomatosis oncogene; p-H3, phosphorylated histone H3; NSUN2, NOP2/Sun RNA methyltransferase 2; GCLC, glutamate-cysteine ligase catalytic subunit; m5C, 5-methylcytosine; METTL16, methyltransferase-like 16; SIRT2, sirtuin 2; CAF, cancer-associated fibroblast; lncRNA, long non-coding RNA; H3K18la, histone H3 lysine 18 lactylation; SIRT1, sirtuin 1; VCAM1, vascular cell adhesion molecule 1; AKT, protein kinase B; mTOR, mammalian target of rapamycin; CXCL1, C-X-C motif chemokine ligand 1; GC-MSCs, gastric cancer mesenchymal stem cells; ASPM, abnormal spindle-like microcephaly-associated protein; NCAPG, non-SMC condensin I complex subunit G; BUB3, budding uninhibited by benzimidazoles 3.

stem cells and M2-polarized tumor-associated macrophages to the TME, which further amplifies the immunosuppressive effect (74). Furthermore, as a major source of lactate in the TME, cancer-associated fibroblasts secrete high levels of lactate that specifically induce H3K18la in GC cells, thereby regulating and activating the expression of its downstream target gene assembly factor for spindle microtubules (ASPM). ASPM directly binds to the non-SMC condensin 1 complex subunit G (NCAPG) protein to promote its nucleocytoplasmic translocation and enhances the BUB3-mediated deubiquitination of NCAPG, which markedly increases the stability and expression of NCAPG and ultimately mediates the immune evasion of GC cells (75).

At the regulatory circuit level, the histone delactylase SIRT1 negatively regulates the transcription of long noncoding RNA H19 by specifically erasing H3K18la marks. In turn, H19 forms a positive feedback regulatory loop with LDHA, the key rate-limiting enzyme for lactate production, and H3K18la, which sustainably amplifies the pro-tumor effects and immune microenvironment remodeling mediated by histone lactylation (58). Single-cell RNA sequencing analysis of human gastric cardia adenocarcinoma tissues has revealed that elevated H3K18la modification levels are associated with impaired $CD8^+$ T-cell function (76), providing clinical evidence supporting the critical role of histone lactylation in GC progression and TIME regulation. By contrast, the specific biological roles and underlying molecular mechanisms of non-histone lactylation in the remodeling of the GC immune microenvironment remain poorly defined and warrant further in-depth investigation (Fig. 5).

5. Construction of lactylation gene models and therapeutic strategies for GC

Exploration of lactylation-associated gene models in GC. Lactylation influences tumor cell proliferation, invasion, and immune escape by connecting energy metabolism and epigenetic regulation. However, the mechanisms by which lactylation-related genes integrate metabolic features, drug responsiveness, and immune infiltration patterns remain to be elucidated. Recent studies on the lactylation regulatory network in GC have provided newer insights into disease prediction and therapy (Table I).

Zhang *et al* (77) developed a predictive model based on 'hypoxia-glycolysis-lactylation-related genes (HGLRG)'. By integrating bulk and single-cell RNA sequencing data from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus databases, they identified a prognostic signature comprising 13 genes, including *CP*, biglycan (*BGN*), *DUSP1*, *SERPINE1*, and *CLDN9*. Functional correlation analysis has revealed that *BGN* expression was significantly associated with amino acid and lipid metabolites, suggesting a critical role in metabolic reprogramming. Immunophenotypic analysis has further indicated that the HGLRG signature was correlated with M1 macrophage and $CD8^+$ T-cell infiltration, providing a theoretical basis for combined therapeutic strategies targeting metabolic pathways and the immune microenvironment (77).

Yin *et al* (78) analyzed lactylation-related and mitochondrial function genes in stomach adenocarcinoma based on multi-omics data and observed significant prothymosin α (*PTMA*) overexpression in cancer tissues. Knockdown of

Table I. Lactylation-related gene models and novel therapeutic srategies for gastric cancer.

Key models/strategies	Targets	Clinical value	(Refs.)
HGLRG prognostic model	CP, BGN, DUSP1, SERPINE1, CLDN9, PAK2, TP53, HK3, PAXIP1, NUP50, EFNA3, ESRRB and OGT	It can be applied to identify immunotherapy-eligible favorable populations.	(77)
PTMA gene integrated analysis	PTMA	Provides a new target for targeting the mitochondrial-lactylation axis.	(78)
Lactylation score system	VCAN, PLOD2, NUP50, HBB, STC1, EFNA3	The lactylation score can be used as a predictive indicator for malignant progression and response to immunotherapy.	(79-81)
NSUN2 lactylation nlockade	NAA10, NSUN2, GCLC	Provides a combined treatment strategy of ferroptosis induction + lactylation intervention.	(71)
CB-839 nanodelivery system (IRCB@M)	CB-839, IR-780	Provides a new carrier for combined metabolic-oxidative stress therapy.	(82)
MCT1 inhibitor (AZD3965)	MCT1, AZD3965, FAP, PD-L1, MACC1	Provides a new combined treatment strategy of metabolic regulation + immune remodeling.	(83)

HGLRG, hypoxia-glycolysis-lactylation-related genes; GC, gastric cancer; CP, citrin; BGN, biglycan; DUSP1, dual specificity phosphatase 1; SERPINE1, serpin family E member 1; CLDN9, claudin 9; PAK2, p21-activated kinase 2; TP53, tumor protein p53; HK3, hexokinase 3; PAXIP1, PAX interacting protein 1; NUP50, nucleoporin 50; EFNA3, ephrin A3; ESRRB, estrogen related receptor β; OGT, O-linked N-acetylglucosamine transferase; PTMA, prothymosin α; VCAN, versican; PLOD2, procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2; HBB, hemoglobin subunit β; STC1, stanniocalcin 1; NSUN2, NOP2/Sun RNA methyltransferase 2; NAA10, N-α-acetyltransferase 10; GCLC, glutamate-cysteine ligase catalytic subunit; CB-839, glutaminase inhibitor CB-839; IR-780, near-infrared fluorescent dye IR-780; IRCB@M, CB-839-IR-780 nanodelivery system; MCT1, monocarboxylate transporter 1; AZD3965, MCT1 inhibitor AZD3965; FAP, fibroblast activation protein; PD-L1, programmed death-ligand 1; MACC1, metastasis-associated in colon cancer 1.

PTMA inhibited gastric cell proliferation, migration, and invasion while inducing apoptosis, revealing its oncogenic role in regulating mitochondrial function and metabolic reprogramming (78).

Yang *et al* (79) screened six core lactylation-related genes from a Gene Set Enrichment Analysis database and developed a GC lactylation scoring model. In a multi-cohort analysis, they observed that the lactylation score was correlated with the overall survival, tumor progression, and response to immunotherapy of the patient. High-scoring populations exhibited a higher risk of immune escape. Mechanistically, LDHA inhibitors suppress malignant tumor phenotypes by down-regulating the expression of lactylation-related genes such as prolyl 3-hydroxylase domain-containing protein 2 (*PLOD2*) and glucose transporter type 3 (*GLUT3*) (79). Clinical studies have further substantiated that an increased expression of *PLOD2* and *GLUT3* is closely associated with tumor invasion, metastasis, and poor prognosis (80,81).

The prevailing TCGA molecular classification system for GC is primarily based on genomic and epigenomic features. By contrast, the aforementioned lactylation-related gene signature and its corresponding scoring model have enabled an integrated characterization of cancer metabolic reprogramming, heterogeneity of the TIME, and therapeutic response profiles. Thus, this model addresses critical unmet gaps in the TCGA classification system with respect to the prediction of metabolic phenotypes, the immunosuppressive TME, and immunotherapeutic response, and ultimately provides a more robust and precise stratification framework for the genomically stable (GS) and chromosomal unstability (CIN) subtypes of GC, which are characterized by pronounced prognostic heterogeneity.

The lactylation-related gene signatures and scoring models can further integrate information on tumor metabolic reprogramming, immune microenvironment heterogeneity, and therapeutic responses. They complement the predictive blind spots of the GC molecular classification system of TCGA with regard to metabolic phenotypes, immunosuppressive microenvironments, and immunotherapy response, and can provide more precise stratification criteria for GS- and CIN-type GC, which display marked prognostic heterogeneity.

Novel strategies targeting the 'metabolism-immunity' axis via lactylation modification in GC. Lactate accumulation in the TME drives metabolic reprogramming and epigenetic remodeling in GC by promoting histone and non-histone lactylation. Interventions targeting the upstream and downstream pathways of lactylation demonstrate antitumor potential through metabolic regulation and immune microenvironment remodeling.

In the acidic TME, N-α-acetyltransferase 10 (NAA10)-mediated K508 lactylation of NSUN2 activates its enzymatic activity, promoting m5C methylation and the stability of GCLC mRNA, enhancing glutathione synthesis to inhibit lipid peroxidation, and inducing doxorubicin resistance. Targeted blockade of NSUN2 lactylation disrupts drug resistance, restores sensitivity to ferroptosis-inducing drugs, and enhances chemotherapeutic efficacy (71).

The cancer cell membrane-camouflaged nanodelivery system IRCB@M was developed based on the glutaminolysis inhibitor CB-839 to allow co-delivery of CB-839 and photosensitizer IR-780 via homologous targeting. CB-839 suppresses the glutamine-dependent antioxidant defense system and reduces nicotinamide adenine dinucleotide phosphate and GSH levels, while markedly enhancing the apoptotic effect of photodynamic therapy in tumor cells, thus achieving coordinated regulation of tumor energy metabolism and redox homeostasis (82).

Regarding the remodeling of the TIME and metastasis inhibition, MCT1 acts as a key target for reversing immunosuppression in GC. The MCT1 inhibitor AZD3965 not only suppresses the abnormal expression of the pro-fibrotic factor fibroblast activation protein (FAP) in mesenchymal stromal cells, which attenuates stromal fibrosis and tumor-promoting proliferation, but also downregulates the expression of programmed death-ligand 1 (PD-L1) in tumor cells and the metastasis-related gene *MACC1*. It simultaneously relieves immune evasion and blocks invasion and metastasis, thereby restraining the malignant progression of GC via dual pathways (83).

6. Conclusion and prospects

The present review examined the role of lactylation modifications in metabolic reprogramming, epigenetic regulation, and TME remodeling in GC, and presents two main conclusions. First, a bidirectional positive feedback loop of metabolism, epigenetics, and immunity mediated by lactylation is involved in the malignant progression of GC. The core characteristic of this loop is a bidirectional positive feedback cycle in which H3K18la promotes lactate production by upregulating glycolytic genes, while lactate accumulation in turn elevates H3K18la levels, which also distinguishes lactylation from other acylation modifications. Molecules related to this loop can be used as novel biomarkers for prognostic stratification and prediction of therapeutic response in gastric cancer, making up for the deficiencies of the existing TCGA molecular classification of GC in predicting metabolic phenotypes and immunotherapeutic response. Second, MCT1, LDHA, and HDAC1-3 are targets with well-defined clinical translation potential in the field of lactylation research. Among them, the MCT1 inhibitor AZD3965 is backed by cross-cancer clinical research data, which provides a rationale for the development of combination therapeutic regimens for GC. The systematic regulatory framework established in this review provides a comprehensive theoretical reference for subsequent studies on lactylation in GC.

Although research on lactylation in GC has made marked advances, there remains extensive room for further exploration of underlying mechanisms and eventual clinical translation. Future studies should address the complexity of lactylation regulation from the perspective of mechanistic dissection and technological innovation. At the basic research level, single-cell sequencing and spatial multi-omics technologies can be integrated to decipher the cellular heterogeneity and spatiotemporal distribution characteristics of lactylation across different molecular subtypes of GC, and to elucidate the regulatory effect of lactate shuttling between cancer stem cells, stromal cells, and immune cells on lactylation modification. Research has identified >2,000 Kla sites in GC cells; however, the functions of fewer than 10 non-histone sites have been systematically validated. Subsequent studies should perform quantitative lactylomics using clinical GC tissues to screen for specific non-histone lactylation sites associated with clinicopathological features, dissect the effect of this modification on the activity of target proteins, and clarify the substrate selection mechanisms of writer enzymes such as p300 and HBO1. Substrate competition, site preference, and regulatory patterns of enzymatic and non-enzymatic lactylation in the hyperlactated TME of GC should also be elucidated.

With regard to clinical translation, efforts should focus on synergistic breakthroughs in immunometabolic checkpoints and targeted precision medicine. Mathematical models integrating modification status, immune function, and therapeutic response should be constructed for lactylation-regulated immune molecules such as PD-L1 and FAP. Screening of lactylation-dependent key immune nodes (including the G protein-coupled receptor 81/regulatory T cell axis) using gene editing technologies could lead to combination treatment regimens including a lactylation inhibitor and a bispecific antibody to overcome immune resistance bottlenecks. Additionally, by leveraging the circadian rhythm and pH-dependent characteristics of lactylation modifications, smart delivery systems that are responsive to the TME (such as pH-sensitive nanoparticles) can minimize toxicity to normal tissues and maximize the targeted inhibition of tumor proliferation. This approach expands the therapeutic window and overcomes metabolism-related side effects.

Further progress in these directions calls for multi-technological and cross-disciplinary collaboration and expertise to drive innovation strategies from mechanistic interpretation to precision medicine. This may pioneer a new frontier in GC prevention and treatment via metabolic-epigenetic regulation.

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Availability of data and materials

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Authors' contributions

YX and WW conceived the review, designed its scope and structure, and prepared the original draft of the manuscript. YZ prepared the schematic diagrams and figures included in the review. YF conducted structured literature searches and related investigation. WD and JY critically synthesized and interpreted the research findings, and completed the review

and editing of the entire manuscript. All authors have read and agreed to the published 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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