Clinical implications of lactylation modification in digestive system tumors (Review)

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Abstract. Lactylation, a novel post-translational modification, has emerged as a critical mechanistic link between metabolic reprogramming and epigenetic regulation in cancer. The present review aimed to synthesize emerging evidence on the role of lysine lactylation in the pathogenesis and progression of major digestive system malignancies, including esophageal, gastric, colorectal, hepatocellular and pancreatic cancer. The molecular mechanisms through which lactate-derived lactylation modifies histone and non-histone proteins are described, which thereby regulate key oncogenic processes such as metabolic adaptation, cancer stemness maintenance, epithelial-mesenchymal transition, immunosuppressive tumor microenvironment remodeling, angiogenesis, perineural invasion and therapeutic resistance. The translational potential of targeting the lactylation axis by inhibiting lactate production, blocking lactate transport or directly modulating lactylation-related enzymes are explored, and the development of lactylation-based prognostic models and their implications for innovative combination strategies to overcome treatment resistance are also highlighted. The present review highlights lactylation as a pivotal regulator in digestive oncology and a promising target for novel diagnostic and therapeutic strategies.

Contents

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1. Introduction

Malignant tumors of the digestive system, including esophageal cancer (EC), gastric cancer (GC), colorectal cancer (CRC) and pancreatic cancer (PC), are among the most prevalent worldwide. Notable variations exist in cancer epidemiology across countries and regions. According to GLOBOCAN 2022 data, CRC ranks third in incidence and second in mortality globally. Although the incidence of CRC is higher in developed countries, its prevalence has been increasing annually in developing countries, particularly among younger populations (1). Established risk factors include alcohol consumption, smoking, intake of red or processed meat and excess body fat (2). Additionally, liver cancer and GC account for a considerable proportion of gastrointestinal malignancies. Hepatocellular carcinoma (HCC) occurs predominantly in Asia and Northern Africa, with major risk factors including metabolic diseases and viral hepatitis (3). GC occurs predominantly in Eastern Asia, Eastern Europe and South Central Asia, where the incidence is generally higher in males compared with females (1).

The Warburg effect, a hallmark of cancer, is characterized by a preference for glycolytic energy production even under aerobic conditions. Lactate, a metabolic byproduct of glycolysis, supports cellular growth and metabolism and functions as a signaling molecule involved in the regulation of signaling pathways. In tumors, lactate contributes to the formation of an acidic tumor microenvironment (TME) and facilitates immune evasion, playing a crucial role in tumor progression.

As key regulators of cellular processes, post-translational modifications (PTMs) serve as critical mediators of tumor progression. Common PTMs include acetylation (4), ubiquitination (5), methylation (6), phosphorylation (7) and glycosylation of amino acid residues. In 2019, Zhang *et al* (8) discovered a novel epigenetic modification termed lysine lactylation (Kla), a PTM occurring on lysine residues. A recent study revealed that lactylation is associated with the development and progression of multiple malignancies such as CRC, HCC and lung cancer. For example, lactylation

has been implicated in cisplatin resistance in bladder cancer (9). In cancer, lactylation promotes tumor progression by modifying histones and non-histone proteins, which influences metabolic reprogramming, gene expression and the TME. Emerging evidence also suggests that lactylation participates tumor drug resistance and autophagy. Recent systematic reviews have established the fundamental role of lactylation in digestive system tumors, elucidating its core mechanisms in metabolic reprogramming and TME remodeling. Relevant studies have provided in-depth investigations into the molecular mechanisms and the interplay between histone and non-histone lactylation, as well as focusing on diagnostic biomarkers and therapeutic targets for gastrointestinal cancer from a clinical perspective (10). Building upon this foundation, the present review systematically integrated histone and non-histone lactylation mechanisms to construct a unified framework of metabolic-epigenetic crosstalk in tumor progression, and summarized advances in related pharmacological research (10,11). Furthermore, the application of machine learning techniques for lactylation site prediction and patient stratification is discussed, the limitations of current research are examined, and the combination of lactylation-targeted therapies with conventional treatments and immunotherapy are explored, thereby proposing potential directions for future lactylation research.

2. Lactate and lactylation

Lactate production and function. Within the TME, lactate production mainly occurs through two distinct metabolic pathways. The first pathway involves lactate generation via glycolysis. In tumor cells, glucose is transported into the cells through glucose transporters GLUT 1 or GLUT3, where it is subsequently metabolized through glycolysis to generate pyruvate. Pyruvate is subsequently converted to lactate via a reaction catalyzed by lactate dehydrogenase (LDH) (12). The second pathway involves lactate production derived from glutamine metabolism (13). In this route, intracellular glutamine is first converted to glutamate by glutaminase. Glutamate is then further metabolized into α-ketoglutarate via enzymatic reactions mediated by glutamate dehydrogenase and related enzymes, after which it enters the tricarboxylic acid (TCA) cycle. Within the TCA cycle, glutamine-derived metabolites are ultimately converted into malate, which is subsequently transported out of the mitochondria. Cytosolic malate is then metabolized to generates pyruvate and NADPH. The resulting pyruvate is further converted into lactate through LDH-mediated catalysis.

Furthermore, lactate is transported across the cell membrane monocarboxylate transporters (MCTs), with MCT1 and MCT4 serving predominant roles in tumor lactate shuttling. MCT1 mediates bidirectional lactate transport in an environment-dependent manner. Under the conditions of high oxygen availability or elevated extracellular lactate concentrations, MCT1 primarily facilitates lactate influx into tumor cells. Conversely, when intracellular lactate accumulates, MCT1 facilitates lactate efflux. By contrast, MCT4 functions predominantly as a lactate exporter. Lactate exchange between cells via MCTs alleviates intracellular acidosis resulting from caused enhanced tumor glycolysis, while simultaneously enabling tumor cells to reutilize imported lactate as an alternative metabolic fuel. This dynamic shuttle system also contributes to the establishment and maintenance of an acidic TME. MCT1 expression is primarily promoted by oncogenic signals such as MYC, and is favored under oxygen-rich conditions, whereas MCT4 is a direct transcriptional target of HIF-1α and is strongly induced under hypoxia (14,15). The coordinated activity of MCT1 and MCT4 enhances the metabolic flexibility and adaptability of tumors (16). Given their central roles in tumor metabolism and progression, MCT1 and MCT4 represent promising therapeutic targets in cancer treatment.

Lactate contributes to cellular energy metabolism. In addition to being oxidized through the TCA cycle to generate energy, lactate serves as a metabolic substrate for neighboring cells within the TME via the lactate shuttle. Through MCT-mediated transport, lactate is transferred to adjacent cancer-associated fibroblasts (CAFs) and tumor cells, where it supports oxidative phosphorylation (OXPHOS) and sustains the high bioenergetic demands of rapidly proliferating malignancies (17). In addition to meeting bioenergetic demands, lactate serves a critical role in regulating cellular redox homeostasis. Lactate metabolism is tightly coupled to NADH and NADPH dynamics, as its production and utilization influence the balance of these key redox cofactors. NADH and NADPH supply reducing equivalents to antioxidant systems, thereby maintaining their intracellular redox stability. Within the hypoxic TME, excessive reactive oxygen species are generated, promoting DNA damage and activating the DNA damage response. DNA repair processes consume substantial amounts of nuclear NAD^+, which partially serves to replenish NAD^+ pools through redox cycling, helping to maintain the NADH/NAD^+ balance required for genomic stability (13). In parallel, elevated NADPH levels support antioxidant defenses and biosynthetic pathways, thereby sustaining redox balance and facilitating the rapid proliferation of cancer cells (18). Beyond its metabolic functions, lactate also acts as a signaling molecule that modulates tumor-associated pathways. Within the TME, macrophages take up extracellular lactate, which activates mTORC1 signaling. This event suppresses the nuclear translocation of transcription factor EB (TFEB), resulting in reduced expression of ATP6V0d2. This cascade promotes the stabilization and accumulation of HIF-2α, ultimately enhancing VEGF secretion and promoting tumor angiogenesis (19). Lactate contributes to the formation of an acidic TME and exerts immunosuppressive effects. Elevated lactate levels impair T-cell function (20) and promote the expansion of regulatory T cells (Tregs), facilitating tumor immune evasion (20-24). Furthermore, lactate enhances the polarization of tumor-associated macrophages (TAMs) toward an M2-like immunosuppressive phenotype, further reinforcing an immune-suppressive TME. Lactate can promote the secretion of High Mobility Group Box 1 by macrophages and induce their M2 polarization. It also activates the ERK, epithelial-mesenchymal transition (EMT) and Wnt signaling pathways in cancer cells, forming a positive feedback loop that facilitates the progression of CRC (25).

Lactylation. Lactylation involves the covalent modification of lysine residues on both histone and non-histone proteins. Lactic acid exists as two stereoisomers: L-lactate and D-lactate; lactylation is primarily associated with L-lactate. This modification can be processed through both enzymatic and non-enzymatic pathways. In the enzymatic route, lactate is converted into lactyl-CoA within the nucleus by L-lactate-CoA synthetases, including acetyl-CoA synthetase 2 (ACSS2) or GTP-specific succinyl-CoA (GTPSCS) (26). Initially, GTPSCS can be transported into the nucleus, where it catalyzes the conversion of L-lactate and coenzyme A into lactyl-CoA, thereby promoting histone lactylation and glioma development (27). Meanwhile, ACSS2 has been confirmed to function as a lactyl-CoA synthetase. Upon EGFR activation and ERK-mediated phosphorylation, ACSS2 translocates to the nucleus, where it converts lactate into lactyl-CoA, thereby participating in histone lactylation and promoting tumor progression (26). Lactate is converted into lactyl-CoA, which then serves as a donor for the enzymatic transfer of the lactoyl group onto lysine residues of histone proteins in the nucleus (8). The processes of histone acetylation and gene expression require the coordinated action of 'writing', 'erasing' and 'reading' enzymes. Enzymes such as p300/E1A binding protein p300/CREB-binding protein (CBP), lysine acetyltransferase 2A (GCN5) and lysine acetyltransferase 7 act as lactyl transferases, adding lactyl groups to proteins via covalent bonds. Class I histone deacetylases (HDAC1-3) and class III deacetylases (SIRT1-3) serve as erasers, participating in hydrolysis to remove lactyl groups from lysine residues on proteins. Lactylation readers specifically recognize and bind to lactylated sites, translating these modifications into specific gene expression programs or cellular functions (28). For example, Zhai *et al* (29) discovered that double PHD fingers 2 (DPF2) specifically recognizes the H3K14la modification site through its DPF domain, in which the D274 residue forms a hydrogen bond with the lactyl group. The DPF2-H3K14la interaction drives oncogene transcription and tumor cell proliferation. Outside the nucleus, lactate can also be metabolized by aminoacyl-tRNA synthetases (AARS) to generate lactyl-AMP, which subsequently transfers the lactoyl group to lysine residues on non-histone proteins (30-32). L-lactate-mediated modifications are closely associated with epigenetic reprogramming related to cellular metabolic states, hypoxia and the Warburg effect, serving important roles in transcriptional regulation, macrophage polarization and tumor progression. In addition to these enzymatic pathways, a non-enzymatic route exists, primarily mediated by glutathione. D-lactylation is primarily mediated by non-enzymatic pathways. The glycolytic byproduct methylglyoxal is processed by the glyoxalase system to form lactoylglutathione, which acts as a lactoyl donor. Through non-enzymatic acyl transfer reactions, the lactoyl group can be covalently attached to lysine residues, expanding the scope of protein lactylation. D-lactylation has been reported to regulate metabolic flux through the inhibition of glycolytic enzyme activity (33). D-lactate is also derived from intestinal bacteria, and upon entering host cells, bacteria-derived D-lactate may influence host protein function via D-lactylation modification. Notably, Zalambani *et al* (34) found that D-lactate induces alterations in host cell histone lactylation, and these changes are associated with enhanced resistance to infection. Although research regarding D-lactate-mediated non-histone lactylation remains limited, it has been demonstrated that D-lactate derived from endogenous metabolism inhibits NF-κB activity by modifying the K310 residue of RelA (p65) in macrophages regulates inflammatory cytokines such as TNF-α, IL-6 and IL-10, and promotes their transition toward a pro-repair state (Fig. 1) (35).

Roles of lactylation. While lysine lactylation occurs on both histone and non-histone proteins through similar mechanisms, their underlying mechanisms differ in key aspects. Structural constraints within the nucleus limit the number of lactylation (Kla) sites on histones, resulting in far fewer modified residues compared with non-histone proteins. Supporting this, a global lactylome analysis by Yang *et al* (36) in a hepatitis B virus-associated HCC cohort identified 9,275 Kla sites through integrated proteomic profiling. Of these, 9,256 sites were mapped to non-histone proteins. Regarding lactylation pathways, histone lactylation primarily occurs via L-lactate-induced enzymatic reactions, whereas non-histone lactylation can proceed through both enzymatic and non-enzymatic mechanisms (37). Their biological effects also differ; histone Kla primarily modulates global gene transcription by altering chromatin structure, while non-histone lactylation mainly regulates cellular processes dynamically by modifying protein charge and conformation (38). In lactylation research, studies on histone lactylation are relatively well-established (39,40). In digestive system tumors, including GC and EC, lactylation at specific sites such as H3K18 and H3K9 has been extensively characterized (11). This modification primarily influences the expression of target genes through chromatin remodeling. To further elucidate these mechanisms, the present review summarized recently reported lactylation regulatory axes (41-43). The common and specific lactylation mechanisms in digestive cancer are summarized in the supplementary tables (Tables SI and SII). The effects of histone lactylation on tumor cells are primarily observed in the following processes. First, by metabolic reprogramming and the establishment of a positive feedback loop. For example, in the shared mechanisms of digestive cancer, H3K18la in HCC promotes the transcription of Y-box binding protein 1 (YBX1). Elevated YBX1 levels, in turn, further enhance the expression of glycolytic genes and lactate production, forming a YBX1-glycolysis-H3K18la positive feedback loop that accelerates HCC progression (44). Enrichment of H3K18la at gene promoters activates the transcription of mitotic checkpoint regulators dual specificity protein kinase TTK (TTK) and BUB1 mitotic checkpoint serine/threonine kinase B (BUB1B), upregulates p300 expression and further enhances glycolysis. Simultaneously, H3K18la induces phosphorylation of TTK at Y239, which activates lactate dehydrogenase A (LDHA), reinforcing glycolytic flux. The resulting lactate further reinforces histone lactylation, establishing a glycolysis-H3K18la-TTK/BUB1B positive feedback loop that accelerates tumor progression (Table SI) (45). Second, by remodeling of the immune

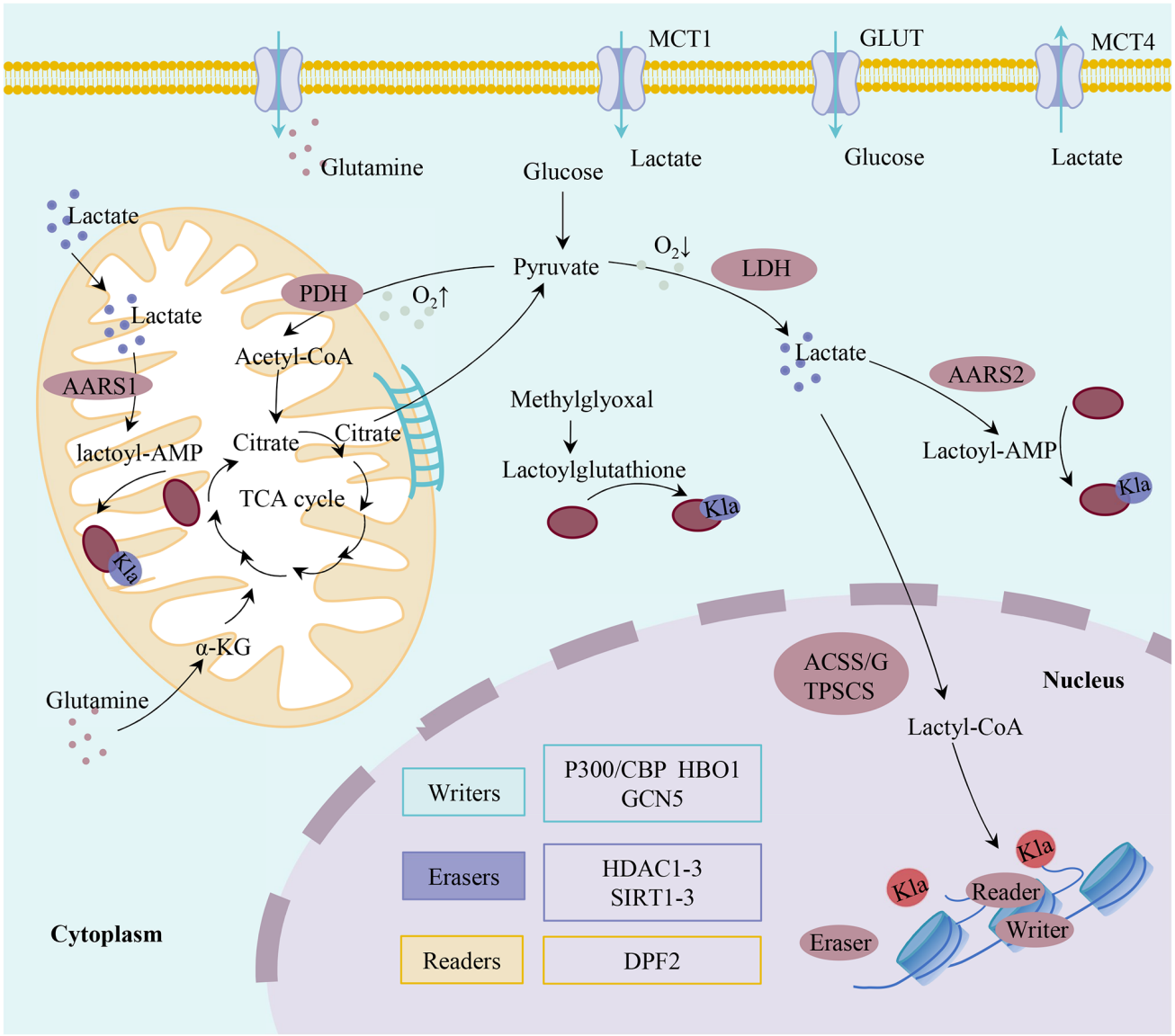

Figure 1. Lactate production, transport, and the mechanism of lactylation. Meanwhile, pyruvate generated from glucose through anaerobic glycolysis, as well as pyruvate derived from the citrate cleavage pathway, is converted to lactate under hypoxic conditions. Lactate can be translocated into the nucleus, where it is converted to lactyl-CoA through catalysis by ACSS2 or GTPSCS. With the involvement of writer and eraser enzymes, lactyl-CoA participates in histone lactylation and delactylation. Subsequently, with the assistance of reader enzymes, gene expression can be regulated. Additionally, lactate can directly participate in non-histone lactylation through catalysis by AARS. Furthermore, methylglyoxal is metabolized to lactoylglutathione, which serves as a lactyl donor, covalently linking lactyl groups to lysine residues on proteins via non-enzymatic acyl transfer reactions. MCT, membrane by monocarboxylate transporter; GLUT, glucose transporter; AARS1, aminoacyl-tRNA synthetases 1; AARS2, aminoacyl-tRNA synthetases 2; PDH, pyruvate dehydrogenase complex; LDH, lactate dehydrogenase; Kla, lysine lactylation; ACSS2, acetyl-CoA synthetase 2; HDAC, histone deacetylase; SIRT, sirtuin; GTPSCS, GTP-specific succinyl-CoA; DPF2, double PHD fingers 2; GCN5, lysine acetyltransferase 2A; CBP, CREB-binding protein; α-KG, α-ketoglutarate; Co-A; coenzyme A; HBO1, histone acetyltransferase binding to ORC1.

microenvironment. The TME consists of a complex cellular network and structural framework surrounding malignant cells. In addition to cancer cells, the TME comprises peritumoral vasculature, the extracellular matrix, non-malignant cellular components such as immune cells and CAFs and signaling molecules including cytokines and growth factors (46). In the shared mechanisms of digestive cancer, H3K9la in EC modulates *LAMC2* expression, activates vascular endothelial growth factor A (VEGFA), promotes tumor-associated angiogenesis and reshapes the immune microenvironment (47). Beyond direct gene regulation, histone lactylation influences immune cell function. In CRC, elevated H3K9la enhances PKM2 expression, acidifying the TME, which suppresses natural killer (NK) and $CD8^+$ T cell activity while promoting M2-like macrophage polarization (Table SI) (48). In GC, H3K18la impairs T cell function by upregulating METTL3 and directly promoting programmed death-ligand 1 (PD-L1) transcription (49). Additionally, histone lactylation can modulate the TME by regulating immunosuppressive factors or chemokines. For example, in GC, H3K18la promotes vascular cell adhesion molecule-1 transcription, activates the AKT-mTOR pathway, facilitates EMT, recruits C-X-C motif chemokine ligand 1 (CXCL1), and enhances infiltration of gastric-derived mesenchymal

stem cells and M2 macrophages (50). Third, effects of histone lactylation on tumor cells are mediated by their contribution to tumor cell drug resistance. H3K18la and H3K9la enhance drug resistance primarily by enhancing autophagy, promoting DNA repair and increasing antioxidant capacity. In PC, H3K18la activates autophagy by stabilizing the mRNA of TNF receptor-associated factor 6 (TRAF6) and aldehyde dehydrogenase 1 family member A3 in an m^6A-dependent manner (51). In HCC, H3K18la upregulates the deubiquitinase USP34, enhancing DNA damage repair and promoting resistance to genotoxic agents such as cisplatin (52). Furthermore, H3K18la promotes the transcription of the E3 ubiquitin ligase HECTD2, which increases the ubiquitination and degradation of Kelch-like ECH-associated protein 1 ubiquitination and degradation, thereby activating ECH-associated protein 1, which activates the NRF2 antioxidant pathway. This enhances resistance to oxidative damage induced by drugs such as lenvatinib (53).

With advances in non-histone lactylation research, its functional roles in digestive system tumors have become increasingly apparent. As an emerging PTM, non-histone lactylation dynamically regulates enzyme activity, protein stability, interaction networks and DNA-binding capacity, while coordinating with other PTMs to form intricate signaling networks (54). Collectively, these modifications profoundly influence cellular behavior.

Key roles of non-histone lactylation in digestive system tumors. i) Direct regulation of signaling pathways. Non-histone lactylation modifies critical nodal proteins in pathways such as Wnt and Hippo, including Axin1 and β-catenin. These modifications enhance protein stability, sustaining pathway activation and promoting tumor proliferation, stemness and invasion (Table SI) (55,56).

ii) Promoting metabolic reprogramming. Lactylation of metabolic enzymes, such as aldo-keto reductase family 1 member B10 and malic enzyme 2 in HCC and CRC, enhances glycolytic flux and maintains redox homeostasis, establishing a self-amplifying metabolic loop that supplies energy and biosynthetic precursors for tumor growth (18,57).

iii) Regulating protein synthesis and stability. Lactylation of translation elongation factors, including eEF2 and eEF1A2 in CRC, improves the efficiency and fidelity of protein synthesis. By linking upstream metabolic signals to downstream cellular pathways, non-histone lactylation modulates transcription, translation and protein turnover (58). For example, β-catenin lactylation under hypoxic, lactate-rich conditions stabilizes the protein, activates Wnt signaling, and enhances proliferation and stemness in CRC cells (56).

iv) Enhancing therapeutic resistance. Lactylation of proteins such as MRE11 homolog, double-strand break repair nuclease (MRE11), insulin like growth factor 2 mRNA binding protein 3 (IGF2BP3) and FOXO3 promotes drug resistance through multiple mechanisms, including enhanced DNA repair, activation of antioxidant pathways (such as NRF2), and autophagy, often facilitated by increased binding to DNA and mRNA (59-61).

v) Participating in immune evasion and invasion. Non-histone lactylation can directly modify immune-related proteins such as PD-L1, suppressing immune cell function and remodeling the TME. It also activates invasion-related transcriptional programs, including EMT, thereby enhancing tumor invasiveness (62).

3. Molecular mechanisms of tumor lactylation

Esophageal carcinoma. Esophageal carcinoma, one of the most aggressive malignancies (63), is primarily classified into two subtypes: Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (64). ESCC accounts for ~90% of global cases, with the highest incidence observed in East Asia (65). In 2022, there were an estimated 511,000 new EC cases and 445,000 related deaths worldwide (1). EC is characterized by high aggressiveness, poor prognosis and a low 5-year survival rate (66). Major risk factors for ESCC include smoking and alcohol consumption. Current clinical management relies on multimodal therapeutic approaches, including surgery, chemotherapy and radiotherapy (67,68).

Lactylation contributes to tumor metabolic reprogramming (69); rapid tumor growth creates a hypoxic TME, promoting cancer cells to rely on glycolysis for energy production, a phenomenon known as the Warburg effect. In digestive system tumors, lactylation serves a key role in this metabolic shift. Serine hydroxy methyltransferase 2 (SHMT2), which catalyzes one-carbon units are critical for tumor growth, undergoes enhanced lactylation under hypoxic conditions (70). This modification increases SHMT2 stability and upregulates methylenetetrahydrofolate dehydrogenase 1-like expression, thereby promoting glycolysis, stemness and migration in EC (71). Lactylation modulates signaling pathways to enhance tumor progression. lactylation of Axin1 at lysine 147 in the Axin1/Wnt/β-catenin pathway promotes its ubiquitination and degradation. The resulting activation of Wnt/β-catenin signaling enhances glycolysis and stem cell-like properties, contributing to tumor growth in multiple types of cancer, including EC and bladder cancer (71,72). Strategies targeting Axin1, such as overexpression or K147 mutation combined with glycolysis inhibition (for example, with 2-deoxy-D-glucose), represent potential therapeutic approaches for EC. Overall, lactylation coordinates metabolism, epigenetics and signaling networks to enhance tumor development. Consequently, targeting lactylation offers a promising therapeutic strategy to suppress tumor progression.

GC. GC has the highest incidence among gastrointestinal malignancies and is one of the most prevalent types of cancer globally (1,73,74). According to global cancer epidemiological surveys, GC exhibits the highest incidence in East Asia (74). In Europe, the number of GC cases has been increasing annually and is projected to reach 174,000 cases by 2050 (74,75). Its current management primarily involves surgical intervention and chemotherapy. However, because early-stage GC often presents with non-specific clinical manifestations, delayed diagnosis is common and leads to poor prognosis. Patients with GC have a high risk of distant metastasis and local recurrence (1,76,77). Its pathogenesis is primarily associated with modifiable risk factors including poor dietary habits and *Helicobacter pylo*ri infection (78).

Lactylation serves an important role in the metabolism-epigenetics axis. Metabolomic analyses have shown that aerobic glycolysis is upregulated in GC to meet the

increased demands of tumor cell proliferation, leading to lactate accumulation and formation of an acidic TME (79). Under conditions of lactate accumulation, lactylation activates oncogenic transcriptional programs by modifying histones and non-histone proteins. Increased intracellular lactate levels, promote nuclear translocation of AARS1 via its conserved nuclear localization signal, where it catalyzes lactylation of the transcriptional coactivator YAP1 (YAP) at lysine 90 and the TEA domain transcription factor 1 at lysine 108. These modifications promote GC proliferation and upregulate AARS1 expression, forming a positive AARS1-YAP-TEAD feedback loop (30). Furthermore, lactate accumulation confers resistance to apoptosis by increasing protein stability through lactylation. Intracellular copper accumulation induces cell death (80); elevated copper levels in tumor cells enhance interactions between latent lactyltransferases AARS1/AARS2 and METTL16, promoting METTL16 lactylation at K229 (81). METTL16 stabilizes ferredoxin 1 (FDX1) mRNA through m^6A modification, which promotes FDX1 protein expression. Acting as a copper reductase, FDX1converts Cu^{2+} to toxic Cu^{+}, triggering lipoylation of dihydrolipoamide S-acetyltransferase (DLAT) and ultimately inducing cuproptosis (82). Lactylation also inhibits ferroptosis by stabilizing poly(rC)-binding protein 2 (PCBP2). In GC, lactate generated through metabolic reprogramming induces lactylation of PCBP2 at lysine 115 and histone H3 at lysine 14. This modification stabilizes PCBP2 and upregulates the transcription of *LDHA* and *PCBP2*. This positive feedback loop suppresses ferroptosis and sustains drug resistance (83).

CRC. CRC, a highly prevalent malignancy, represents a notable global health burden (1,84). According to the GLOBOCAN data, CRC accounts for approximately one-tenth of global cancer cases and cancer-related deaths (1). The highest incidence rates are observed in Europe and Australia (1), and CRC is the second leading cause of cancer-related death in the United States (1,2). Current therapeutic strategies for CRC primarily involve surgical resection combined with radiation therapy, chemotherapy and targeted therapies (85,86). CRC pathogenesis is enhanced by genetic alterations and modifiable risk factors, including physical inactivity, obesity, tobacco use, alcohol consumption and suboptimal dietary habits (87). Early-stage CRC demonstrates a favorable prognosis, with 5-year survival rates >90% (88). By contrast, advanced-stage disease is associated with poorer clinical outcomes and substantially reduced 5-year survival rates (89).

Lactylation contributes to drug resistance in CRC through multifaceted mechanisms. It enhances homologous recombination repair in tumor cells, thereby increasing genomic stability and resistance to DNA-damaging agents. Specifically, MRE11 lactylation at lysine 673 (K673) enhances its DNA-binding affinity, promotes homologous recombination repair and increases drug resistance (90). Furthermore, DNA damage activates ataxia-telangiectasia mutated (ATM), which phosphorylates GCN5. GCN5 then catalyzes lactylation of XRCC4-like factor (XLF) at lysine 288, which facilitates XLF recruitment to DNA damage sites and enhances the efficiency of non-homologous end joining repair, ultimately resulting in chemoresistance (91). Lactylation also promotes drug resistance by regulating transcriptional programs and cancer stemness pathways through the establishment of sustained positive feedback loops. For example, lactylation of the RNA methyltransferase NOP2/Sun RNA methyltransferase 2 and nucleolar protein 6 (NOL6) forms a metabolism-epigenetics positive feedback loop via m^6C modification and glycolysis, as well as a transcriptional feedback loop by the NOL6-Y1-c-Myc axis. These loops continuously promote malignant progression in CRC (92,93). In lactate-rich environments, lactylation of β-catenin increases its protein stability, activates Wnt signaling and promotes CRC cell proliferation and stemness (56). Lactylation confers drug resistance by inhibiting apoptosis; it directly modifies HDAC1 at lysine 412 and is accompanied by epigenetic regulation via histone H4K12la. These modifications collectively suppress ferroptosis, thereby promoting chemoresistance (94). Furthermore, the immune microenvironment serves a role in CRC drug resistance. Lactate derived from CAFs promotes anthrax toxin receptor 1 (ANTXR1) transcription via histone lactylation and induces lactylation of the ANTXR1 protein at lysine 453. This dual lactylation activates the RhoC/ROCK1/SMAD5 signaling pathway in CRC, enhances cancer stemness and directly leads to chemotherapy resistance (95). Simultaneously, TME-mediated suppression of retinoic acid receptor γ in macrophages activates TRAF6 expression, leading to NF-κB pathway activation, increased interleukin-6 production and subsequent STAT3 signaling. These changes impair macrophage antitumor activity, promote a protumor phenotype and contribute to CRC drug resistance (96). Collectively, lactylation serves as a mechanistic bridge linking lactate metabolism to malignant phenotypes, including immunosuppression and drug resistance. Therefore, targeting the lactylation network offers a promising strategy for reversing tumor immunosuppression and overcoming therapy resistance.

HCC. Liver cancer is the third leading cause of cancer-related mortality globally (97). Primary liver malignancies are predominantly classified as HCC and cholangiocarcinoma, with HCC being the most common subtype (1). HCC has a high propensity for metastasis and is associated with poor clinical prognosis. Current therapeutic modalities include surgical resection, radiotherapy, chemotherapy and molecularly targeted therapies (98). The predominant risk factor is chronic infection with the hepatitis B or C virus, with additional contributions from aflatoxin exposure, obesity and chronic alcohol consumption.

Lactylation promotes HCC progression through multiple mechanisms, including accelerating cell-cycle progression, interfering with key signaling pathways, enhancing cancer stemness and promoting drug resistance. Fundamentally, lactylation directly accelerates cell cycle progression to promote tumor proliferation. Lactylation of Xklp2 inhibits binding of protein phosphatase 1 to Aurora kinase A (AURKA), thereby maintaining phosphorylation of AURKA at threonine 288, which facilitates cell cycle progression and promotes tumor development (99). Beyond proliferative signaling, lactylation interferes with tumor-suppressive signaling pathways to promote cell survival. Histone H2B lysine 58 lactylation directly binds to the promoter N-Myc downstream-regulated gene 1 (NDRG1), activating its transcription and suppressing the GSK-3β-p53 pathway, which blocks senescence-associated

signaling (100). Lactylation also regulates immune cells within the TME. Lactate-mediated lactylation of moesin enhances TGF-β/SMAD3 signaling, promoting differentiation of immunosuppressive Tregs and facilitating tumor immune escape (24). In macrophages, lactate-induced histone lactylation increases nuclear protein 1 expression, which inhibits ERK/JNK signaling, induces M2 polarization and upregulates PD-L1 expression. Ultimately, these changes lead to the exhaustion of $CD8^+$ T cells (101). Lactylation further maintains HCC stemness through direct epigenetic regulation and modulation of key transcriptional regulators. Clinical analysis has shown that tumors with elevated H3K56la exhibit increased proliferative activity. H3K56la directly activates the promoter of the stemness-associated gene OCT4, thereby increasing stemness in HCC (102). Under hypoxic and lactate-rich conditions, lactylation of transcription factors such as YAP and Twist family BHLH transcription factor 1 stabilizes the proteins, promotes their activation and nuclear translocation, and synergistically promotes proliferation, invasion and stemness maintenance (103,104). In addition, lactylation can alter the nuclear localization of ABCF1, activating the lysine demethylase 3A (KDM3A)-HIF1α signaling axis. HIF1α further promotes glycolysis and lactate production, establishing a lactate-ABCF1 lactylation-HIF1α positive feedback loop that further amplifies tumor malignancy (105). Lactylation also enhances drug resistance in HCC via epigenetic regulation and protein PTMs. H3K14la activates the NEDD4-PTEN-PI3K/Akt/mTOR signaling axis, forming a glycolysis-driven positive feedback loop that promotes tumor survival and proliferation (106). In parallel, protein lactylation (such as peroxiredoxin 1 and IGF2BP3) suppresses ferroptosis by activating the NRF2 antioxidant pathway or upregulating FSP1 expression. These mechanisms confer resistance to local therapies and targeted drugs, such as regorafenib and lenvatinib (60,107).

PC. Pancreatic ductal adenocarcinoma (PDAC) is among the most lethal malignancies, ranking sixth globally in cancer-related deaths (1). Owing to its high aggressiveness, rapid progression and non-specific early symptoms, prognosis remains poor, with a 5-year survival rate of ~10% (108). For patients diagnosed at an early stage, surgical resection is currently the primary clinical treatment. Owing to the TME of PC, chemotherapy and immunotherapy often exhibit limited effectiveness (109).

Lactylation contributes to malignant progression through multiple dimensions, including metabolic reprogramming, regulation of oncogenic signaling pathways and formation of an immunosuppressive microenvironment. In the hypoxic and poorly vascularized TME of PDAC, lactate enhances the stability of nucleolar and spindle-associated protein 1 (NUSAP1) via lactylation. Lactylated NUSAP1 forms a complex with c-Myc and HIF-1α, which upregulates the key glycolytic enzyme LDHA, thereby increasing lactate production. This process establishes a NUSAP1-LDHA-glycolysis-lactate positive feedback loop that sustains glycolysis and lactate generation (110). Simultaneously, lactate acts as a signaling molecule and mediates upstream-downstream signal transduction via lactylation. In response to upstream signals such as hypoxia, calcium signaling or specific gene deficiencies, lactate induces lactylation of key regulators, including NMNAT1 and Snail1. These modifications activate downstream survival pathways, including the NAD^+/Sirt1 signaling axis. These interconnected pathways form a positive feedback network that promotes malignant progression (13,111). Lactylation also promotes tumor progression by shaping an immunosuppressive TME and facilitating drug resistance. It mediates the functional conversion of immune cells, leading to immunotherapy failure. For example, in macrophages, K63 lactylation of the endosulfine α protein inhibits PP2A, resulting in sustained STAT3 activation. Consequently, it transcriptionally upregulates C-C motif chemokine ligand 2 to recruit TAMs and ultimately causes resistance to immune checkpoint blockage (112). Liu *et al* (113) found that upregulated CCCTC-binding factor epigenetically upregulates the m^6A reader IGF2BP2, which promotes macrophage M2 polarization by stabilizing colony stimulating factor 1 mRNA. Collectively, these processes contribute to the establishment of an immunosuppressive microenvironment. Furthermore, lactylation cooperates with ubiquitination to stabilize the transcription factor TFEB by inhibiting its degradation and directly activates the transcription factor FOXO3, enhancing its transcriptional activity. These coordinated actions upregulate autophagy- and lysosome-related genes, resulting in sustained autophagy activation, further promoting tumor progression (61,114).

4. Clinical drug research

Targeting lactate. i) Targeting lactate-producing metabolism. LDH, a key enzyme in lactate production, can be inhibited to reduce lactate generation. Inhibiting LDH can impair intracellular redox balance and cellular metabolism, thereby suppressing tumor growth (115,116). In digestive system tumors, a phase I/II study (NCT00561197) evaluating AT-101 plus standard chemoradiotherapy [docetaxel, fluorouracil (FU) and radiotherapy] for locally advanced gastroesophageal cancer reported increased clinical response rates; however, challenges related to adverse effects and limited durability of efficacy remain unresolved (117). LDHA inhibitors, including GNE-140, NHI-Glc-2, oxamate and NCI-006, can affect tumor cell metabolism and may be used in combination with other drugs, showing potential clinical applicability (118-120). Currently, multitarget strategies against LDH are under investigation. The LDH proteolysis-targeting chimera degrader MS6105 induces a time- and ubiquitin-proteasome-dependent degradation of LDHA and LDHB, significantly inhibits PC cell growth and demonstrates favorable *in vivo* bioavailability in mouse models, thus showing potential as a novel cancer therapeutic strategy (121). Additionally, the dual LDH inhibitor NCI-006 rapidly inhibits tumor glycolysis and induces metabolic reprogramming, as confirmed by hyperpolarized real-time magnetic resonance imaging (MRI). When combined with mitochondrial complex I, NCI-006 inhibitors significantly enhance antitumor efficacy and prolongs survival in mouse models of PC, demonstrating the translational potential of combination strategies targeting tumor metabolic plasticity (122). However, these drugs have certain limitations. For agents evaluated *in vivo*, such as GNE-140 and MS6105, notable challenges include unfavorable pharmacokinetic properties and inconsistent pharmacodynamic effects, whereas

tumor metabolic plasticity may readily promote drug resistance. In a preclinical study, GNE-140 exhibited unfavorable pharmacokinetic properties. Specifically, it demonstrated non-linear pharmacokinetics, meaning that as the dose increased, the drug concentration in the body did not increase proportionally, likely due to the saturation of metabolic or excretory pathways. This non-linearity, combined with low excretion and high plasma protein binding, led to unpredictable drug exposure *in vivo*. As a consequence of this unpredictable exposure, GNE-140 produced inconsistent pharmacodynamic effects; although the drug engaged its target, the biological outcome deviated from expectations. Instead of inducing cell death, it only induced reversible cell cycle arrest (a cytostatic effect), leaving tumor cells viable and prone to developing resistance (123). For compounds in early-stage development, including oxamate and NHI-Glc-2, insufficient *in vivo* validation limits assessment of their clinical translational potential. In addition to LDH, PKM2 and HK2 are key rate-limiting enzymes in glycolysis and are highly expressed in various malignancies such as breast cancer, lung cancer and HCC. Studies of natural compounds have shown that agents exert exhibit inhibitory effects on PKM2. In mouse models of liver cancer, shikonin inhibits tumor growth and induces cell death by suppressing the chymotrypsin-like activity of the proteasome (124). Furthermore, tannic acid, apigenin and kaempferol directly or indirectly inhibit PKM2, thereby suppressing CRC cell proliferation and glucose metabolism, and reversing resistance to 5-FU. These findings provide mechanistic insights and translational rationale for metabolism-based therapeutic strategies in CRC (125-127). Dual inhibitors targeting PKM2 and HK2 have also been developed. Dauricine suppresses HK2 and PKM2 by upregulating miR-199a expression in HCC cells. In a subcutaneous HCC xenograft nude mouse model, co-administration of Dauricine with sorafenib significantly suppressed tumor growth compared with sorafenib monotherapy, confirming the *in vivo* chemosensitization effect of Dauricine (128). However, these natural antitumor products remain at the preclinical stage, with pharmacokinetic limitations, poor bioavailability and instability representing considerable barriers to clinical translation. Furthermore, glutamine metabolism serves as a critical energy source for tumor cells, making glutaminase a potential therapeutic target in digestive system tumors. In a phase I/II clinical trial (NCT03263429), CB-839 combined with an RGFR monoclonal antibody and chemotherapy demonstrated feasibility and preliminary activity in refractory CRC. However, larger phase II studies are required to confirm its efficacy and safety, and explore predictive biomarkers (129). Newly developed thiazolidine-2,4-dione derivatives exhibit high selectivity for Glutaminase 1, although related research remains at an early stage (130). Furthermore, glutaminase inhibitors can be combined with other targeted drugs. For example, combined treatment with BPTES and an acetyl-CoA carboxylase inhibitor effectively suppresses PC cells by targeting fatty acid synthesis and glutaminolysis (131). Similarly, combined treatment with shikonin and BPTES significantly inhibited tumor growth in mouse models, demonstrating the *in vivo* efficacy of this strategy (132). Lactate oxidase (LOX) also represents a potential treatment option for reducing intratumoral lactate levels and altering the TME through H_2O_2 generation. Lactate-targeting LOX delivery systems can respond to TME characteristics, degrade lactate and synergize with treatments such as chemotherapy to enhance therapeutic efficacy and reduce toxicity. These approaches may represent a promising direction for next-generation precision cancer therapy (133,134). However, both LOX-based combination strategies and LOX delivery systems remain in early stages of development, and their effects on tumor metabolic reprogramming require further elucidation (Table I).

ii) Targeting transporters. In various tumor types such as EC, GLUT expression levels are associated with tumor malignancy (135); several GLUT inhibitors are currently under investigation. BAY-876, a highly selective GLUT1 inhibitor, has demonstrated significant inhibitory effects in mouse models without apparent toxicity (136). Furthermore, selective serotonin reuptake inhibitors exhibit synergistic antitumor effects when combined with anti-PD-1 therapy (137). GLUT inhibitors can also be used in combination with other drugs to reduce drug resistance. WZB117 increases the sensitivity of 5-FU-resistant tumors, thus offering a further option for 5-FU-resistant CRC (138). Quercetin competitively inhibit GLUT1-mediated glucose uptake, induces apoptosis, suppresses metabolic activity in liver cancer and cholangiocarcinoma cell lines, and exerts synergistic anticancer effects when combined with sorafenib (139). However, critical issues related to GLUT1 inhibitors, such as mechanisms of action, drug resistance development and drug safety, remain to be further elucidated. Beyond GLUT1, the GLUT4 inhibitor riluzole has entered phase I clinical trials (NCT04761614). A phase I clinical trial indicate that riluzole and bevacizumab is well-tolerated in patients with drug-resistant metastatic CRC, with a high disease control rate and certain clinical activity (140). Similar results from the NCT04761614 study demonstrated that the combination of riluzole, mFOLFOX6 and bevacizumab was well-tolerated and exhibited efficacy activity in treatment-resistant patients with metastatic CRC (141). The GLUT5 inhibitor MSNBA selectively inhibits CRC cell proliferation with minimal impact on normal cells, demonstrating a favorable therapeutic window (142). Currently, GLUT inhibitor monotherapy exhibits limited efficacy and remains in early development. Future efforts should prioritize the development of highly selective inhibitors and rational combination strategies with chemotherapy, targeted therapy and immunotherapy. MCT inhibitors cannot effectively block lactate production as intracellular lactate accumulation can generate a compensatory, promoting force that offsets reduced membrane permeability and maintains lactate flux. Nevertheless, MCT inhibitors may exert anti-cancer effects through cytotoxicity, off-target effects or intracellular lactate accumulation (143). Concurrently, it has been reported that combined treatment with the small molecule inhibitors FX11 (targeting LDHA) and AR-C155858 (an MCT1 inhibitor) reduces tumor cell proliferation *in vitro* by targeting LDHA and MCT1, suggesting their potential as metabolic targets for cancer therapies (144). Flavonoids such as silibinin inhibit MCT1, leading to lactate accumulation and induction of tumor cell death in human colon cancer cells (145). To address challenges associated with MCT inhibitor delivery, Rincon-Torroella *et al* (146) developed a microencapsulated 3-Bromopyruvate formulation, which enables precise delivery

Table I. Drugs targeting lactate production and related metabolic enzymes.

Drug	Target	Clinical development stage	Cancer type	Mechanism	Findings and limitations	(Refs.)
AT-101 and its derivative	LDHA	Phase I/II clinical trial (NCT00561197)	PC	Lactate anabolism	A small-scale trial achieved a high response rate; however, evidence remains preliminary due to the small sample size, non-randomized design and premature termination of the study.	(117)
GNE-140	LDHA	Preclinical	PC	Lactate anabolism	Potently inhibits LDHA with efficacy dependent on tumor glycolytic dependence. Resistance mechanisms are well-characterised and may be overcome by combination therapy, but short *in vivo* exposure and transient metabolic effects, coupled with robust tumor metabolic plasticity, limit clinical application.	(118)
NHI-Glc-2	LDHA	Preclinical	PC	Lactate anabolism	Effectively inhibits glycolysis and mitochondrial respiration in pancreatic cancer cells, disrupting energy metabolism but limited to *in vitro* cell experiments.	(119)
Oxamate	LDHA/B	Preclinical	GC	Lactate anabolism	Inhibiting glycolysis while promoting autophagy may enhance efficacy when combined with autophagy inhibitors; however, the mechanism remains poorly understood and lacks *in vivo* validation.	(120)
MS6105	LDHA/B	Preclinical	PC	Lactate anabolism	Exhibits favorable pharmacokinetic properties *in vivo*, but its efficacy in inhibiting cancer cell proliferation is significantly weaker compared with its protein degradation capacity.	(121)
NCI-006	PKM2	Preclinical	PC	Lactate anabolism	Hyperpolarized magnetic resonance spectroscopic imaging reveals the mechanism of drug resistance through metabolic reprogramming, proposing a combined strategy of lactate dehydrogenase inhibitor plus mitochondrial complex I inhibitors. However, challenges include lack of efficacy in oral administration, narrow therapeutic window, hemolytic risk and unknown efficacy in humans.	(120,122)
Shikonin	PKM2	Preclinical	HCC, CCA, PDAC	Lactate anabolism	Induces accumulation of pro-apoptotic proteins, demonstrating antitumor activity *in vitro* and *in vivo*, primarily in preclinical models; however, efficacy and safety of the single component remain unclear.	(124)
Tannic acid	PKM2	Preclinical	CRC	Lactate anabolism	Inhibits metabolic activity but lacks *in vivo* testing and exhibits low bioavailability.	(125)

Table I. Continued.

Drug	Target	Clinical development stage	Cancer type	Mechanism	Findings and limitations	(Refs.)
Apigenin	PKM2	Preclinical	CRC	Lactate anabolism	Directly binds and allosterically inhibits PKM2 to suppress glycolysis, but lacks *in vivo* experimental validation.	(126)
Kaempferol	PKM2/ HK2	Preclinical	CRC	Lactate anabolism	Inhibiting glycolysis and reversing 5-FU resistance in CRC remains in the preclinical stage; natural products exhibit complex compositions and unclear pharmacokinetics.	(127)
Dauricine	GLS1	Preclinical	HCC	Lactate anabolism	Reversing the metabolic phenotype of liver cancer enhances chemotherapy sensitivity, but this remains confined to preclinical studies with unknown safety profile.	(128)
CB-839	GLS	Phase I/II clinical trial (NCT03263429)	CRC	Glutamine metabolism	In a phase I trial, CB-839 plus panitumumab and irinotecan was tolerable and showed preliminary activity (partial response 14%, stable disease 71%), though limited by small sample size.	(129)
Thiazolidine-2,4-diones	GLS1	Preclinical	PC	Glutamine metabolism	Demonstrates anti-tumor activity *in vitro* and *in vivo* but is at an early preclinical stage; efficacy and safety data are insufficient.	(130)
BPTES	GLS1	Preclinical	GC	Glutamine metabolism	Provides a preclinical rationale for metabolic combination therapy, but requires more specific tool compounds, deeper mechanistic studies, and clinical trial validation.	(131,132)
Lox	Lactate	Preclinical	HCC	Lactate catabolism	Reverses immunosuppression by depleting lactate and synergizes with multiple therapies, but further studies on materials, safety and mechanisms are lacking.	(133,134)

LDHA, lactate dehydrogenase A; LDHB, lactate dehydrogenase B; PKM, pyruvate kinase M; GLS, glutaminase; LOX, Lactate oxidase; PC, pancreatic cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; PDAC, Pancreatic ductal adenocarcinoma; 5-FU, 5-Fluorouracil.

to PC, improves drug delivery efficiency, reduces toxicity associated with MCT1 inhibitors and represents a potential therapy for patients with PDAC (146). Beyond MCT1, MCT4 inhibitors also show promise in digestive system tumors. In mouse models of HCC, the MCT4 inhibitor VB124 alleviates TME acidosis, enhances CXCL9and CXCL10 secretion and promotes $CD8^+$ T-cell infiltration by targeting MCT4, thereby synergizing with anti-PD-1 immunotherapy to suppress tumor growth and improve prognosis (147). Recently, dual MCT inhibitors have also been under investigation due to the issue of drug resistance associated with single-agent MCT inhibitors that has been confirmed in multiple preclinical models (147,148). For instance, in lymphoma and CRC xenograft models treated with the MCT1 inhibitor AZD3965, relapse was frequently observed. Mechanistic analysis revealed an upregulation of MCT4 expression in resistant tumors, enabling cancer cells to maintain lactate efflux despite MCT1 inhibition (149). Dual MCT1/MCT4 inhibitors can overcome compensatory mechanisms and improve drug resistance, and can also be combined with other chemotherapeutic agents to enhance their therapeutic efficacy. Syrosingopine, dual MCT1/MCT4 inhibitor, suppresses tumor growth by impairing NAD^+ regeneration, interrupting glycolysis, and depleting ATP when used in combination with metformin (150). Wu *et al* (151) developed a novel nano-platform based on hollow Fe_3O_4 nanozymes co-loaded with syrosingopine and LOX, which integrated tumor metabolic regulation with antitumor immunity activation to achieve multimechanistic synergistic therapy. Additionally, 7-aminocarboxycoumarins selectively inhibit lactate influx, suppress tumor growth and reduce drug resistance by the functional cycle of MCT1 and MCT4 transporters, while demonstrating synergistic effects with drugs such as cisplatin (152). Currently, progress research on MCT inhibitors has been limited, primarily because of tumor metabolic plasticity leading to drug resistance, target-related toxicity and insufficient selectivity. In addition to the issue of drug resistance associated with single-agent inhibitors as aforementioned, target-related toxicity has emerged as a notable hurdle in clinical translation. In a phase I clinical trial (NCT01791595) evaluating AZD3965 in patients with advanced solid tumors, dose-limiting toxicities were observed, including reversible visual disturbances and QTc interval prolongation (153). However, insufficient selectivity further limits their application. Due to the existence of MCT isoenzymes, data suggest that the selectivity of various MCT inhibitors, such as BAY-8002 and AZD3965, for MCT1 vs. MCT2 is inadequate (154,155). Future efforts should focus on developing safer dual inhibitors, advancing combination therapies based on validated mechanisms, and applying precision medicine approaches for targeted drug delivery (Table II).

Targeting lactylation. Furthermore, direct targeting of lactylation is feasible as a therapeutic strategy for digestive system cancers. In tumors such as EC and PC, lactylation of histone and non-histone proteins is associated with tumor malignancy (156,157). Demethylzeylasteral (DML) inhibits tumorigenicity induced by liver cancer stem cells by suppressing H3K9la and H3K56la (158). However, studies on the role of DML in H3 lactylation remain incomplete, lacking mass spectrometry analysis, ChIP-qPCR analyses to validate the direct regulatory relationship between H3 lactylation and target genes, and exclusion of potential effects mediated by lactylation of other proteins. Further research on DML is thus warranted (159). Similarly, the unsaturated fatty acid royal jelly acid inhibits HCC progression by inhibiting glycolysis and reducing histone lactylation at H3K9la and H3K14la sites (160). However, similar to DML, limitations related to incomplete validation and coverage of downstream mechanisms which warrant further investigation. Additionally, CREB-binding protein acetyltransferase undergoes ATM-dependent phosphorylation following DNA damage and catalyzes lactylation of MRE11 at lysine 673 (90). The cell-penetrating peptide K673-pe, developed by Chen *et al* (90), competitively binds to CBP or disrupts the CBP-MRE11 interaction by mimicking the local sequence surrounding the MRE11 K673 site, thereby inhibiting CBP-mediated lactylation modification of MRE11. The therapeutic efficacy of K673-pe combined with chemotherapeutic agents such as olaparib and cisplatin has been demonstrated across various preclinical models, including cell lines, patient-derived organoids and patient-derived xenograft models (90,161). However, the *in vivo* stability of K673-pe and its pharmacokinetics remain insufficiently studied. Future research may focus on developing small-molecule inhibitors based on this peptide structure or exploring its integration with other treatment modalities, including immunotherapy. β-Alanine, owing to its high structural similarity to lactate, can competitively occupy the lactate-binding pocket of AARS1 and inhibit the formation of the lactate, AMP intermediate, thereby globally suppressing lysine lactylation. Furthermore, β-alanine specifically inhibits lactylation at K120 and K139 sites of p53, residues located within the DNA-binding domain of p53. Inhibition of their lactylation enhances p53 transcriptional activity and restores its tumor-suppressive function to inhibit tumor progression. β-alanine may represent a combination therapy strategy targeting p53-mutant tumors; however, toxicity concerns and clinical validation remain limited to preclinical studies (32). MG149, a histone acetyltransferase inhibitor, also suppresses the lactyltransferase activity of KAT8. By targeting the MYST domain of KAT8, MG149 dose-dependently reduces cellular global lactylation levels without affecting intracellular lactate levels. Concurrently, MG149 inhibits KAT8's lactyltransferase activity while preserving its acetyltransferase function. Through KAT8 inhibition, MG149 significantly decreases eEF1A2 lactylation levels, thereby suppressing cellular translation and protein synthesis (162). Although MG149 has demonstrated efficacy in cell and mouse models, its initial development as an acetyltransferase inhibitor raises concerns regarding off-target effects, and limitations related to the scope of action and pharmacokinetic parameters remain unresolved (162). While MG149 has been instrumental in validating KAT8 as a lactyltransferase, its utility is limited by off-target effects (162). A study by de Talhouët *et al* (163) demonstrated that MG149 induces mitochondrial depolarization while paradoxically inhibiting PINK1-dependent mitophagy initiation. In a physiological context, depolarization should activate PINK1 accumulation and subsequent mitophagy. However, the observation that MG149 induces mitochondrial depolarization while simultaneously inhibiting the initiation of PINK1-dependent mitophagy presents a paradoxical pharmacological profile. This disconnect, characterized by the failure of mitochondrial

Table II. Targeting transporters associated with lactate metabolism.

Drug	Target	Clinical development stage	Cancer type	Mechanism	Findings and limitations	(Refs.)
BAY-876	GLUT1	Preclinical	CRC	Glucose transport	Effectively inhibits CRC proliferation both *in vitro* and *in vivo*. However, preclinical studies lack human data; mechanisms and resistance require further investigation.	(136)
Citalopram	GLUT1	Preclinical	HCC	Glucose transport	Combination immunotherapy suppresses hepatocellular carcinoma, but the specificity and universality of different drugs require further validation.	(137)
WZB117	GLUT1	Preclinical	CRC	Glucose transport	Reversal of 5-FU resistance in CRC induced by GLUT1 overexpression, but only at the cellular level	(138)
Quercetin	GLUT4	Preclinical	HCC	Glucose transport	Inhibits HCC *in vitro* and exhibits synergistic effects with sorafenib, though this is limited to cellular studies.	(139)
Riluzole	metabotropic glutamate receptor 3	Phase I clinical trial (NCT04761614)	CRC	Glutamate metabolism	Phase I clinical trials demonstrated high disease control rates, but these were single-arm, small-sample phase I trials.	(140,141)
MSNBA analogues	MCT1	Preclinical	CRC	Glucose transport	MSNBA analogues selectively inhibit the viability of CRC, but this has only been demonstrated *in vitro* with a small sample size and limited to mRNA detection. The underlying mechanism and potential for drug resistance require further investigation.	(142)
AR-C155858	MCT1	Preclinical	CRC	Lactate excretion	Combination with LDHA effectively inhibits CRC, but only in preclinical studies.	(143)
Silibinin	MCT1	Preclinical	CRC	Lactate excretion	Silibinin are competitive inhibitors of MCT1, suggesting a risk of drug-food interactions. However, this conclusion is based solely on *in vitro* cellular experiments and does not elucidate the underlying molecular mechanisms or the reasons for differences in activity among similar compounds.	(145)
ME3BP-7	MCT4	Preclinical	PDAC	Lactate excretion	Effectively inhibits tumor growth and metastasis in an *in situ* pancreatic cancer model, but is limited to preclinical studies.	(146)
VB124	MCT1/4	Preclinical	HCC	Lactate excretion	VB124 can alleviate the TME acidification and increase CXCL9/CXCL10 secretion by inhibiting MCT4, thereby enhancing CD8+ T-cell infiltration and the efficacy of anti-PD-1 immunotherapy. However, these conclusions are primarily based on mouse models and retrospective patient sample analyses; the specific molecular mechanisms and their potential for clinical translation still require further validation.	(147)

Table II. Continued.

Drug	Target	Clinical development stage	Cancer type	Mechanism	Findings and limitations	(Refs.)
Syrosingopine	MCT1/4	Preclinical	HCC	Lactate excretion	Exhibits a synergistic lethal effect on cancer cells when combined with metformin; however, this is limited to preclinical studies.	(150,151)
7ACC	MCT1/4	Preclinical	CRC	Lactate excretion	Inhibiting MCT-mediated lactate influx demonstrates efficacy in multiple tumor models but remains confined to preclinical studies.	(152)

GLUT, glucose transporter; MCT, monocarboxylate transporter; 7ACC, 7-aminocarboxycoumarin; CRC, colorectal cancer; HCC, hepatocellular carcinoma; PDAC, pancreatic ductal adenocarcinoma; MSBNA, N-[4-(methylsulfonyl)-2-nitrophenyl]-1,3-benzodioxol-5-amine.

depolarization to trigger the expected PINK1-dependent mitophagy, indicates the presence of off-target interactions that transcend KAT5/8 inhibition. Although MG149 effectively inhibits KAT8-mediated eEF1A2 lactylation, its pleiotropic effects underscore the need for more selective inhibitors targeting the lactyltransferase function of KAT8. Combining lactylation inhibitors with other drugs can produce synergistic antitumor effects. HDAC inhibitors, such as vorinostat and trichostatin A, specifically reduce lactylation modification at the K412 site of HDAC1 protein, impairing its transcriptional repression function. This leads to elevated H3K27 acetylation levels in the promoter regions of *FTO* and *ALKBH5*. Enhanced expression of *FTO* and *ALKBH5* removes m6A modifications from FSP1 mRNA, decreasing its stability and expression and thereby promoting ferroptosis in tumor cells (164). The NCT00537121 clinical trial has established the safety profile and optimal dosing of vorinostat combined with irinotecan, FU and leucovorin for treating patients with advanced upper gastrointestinal cancer. SIRT2, which also functions as an HDAC, has been studied in combination therapy (164). Combined treatment with the SIRT2 inhibitor AGK2 and copper ionophore elesclomol stabilizes METTL16-K229 lactylation by inhibiting SIRT2-mediated delactylation. Concurrently, copper stress induced by elesclomol-mediated copper influx promotes AARS1/2-mediated lactylation modification of METTL16. Through m^6A modification of FDX1 mRNA, METTL16 upregulates FDX1 protein expression, enhances DLAT lipoylation and accelerates cellular cuproptosis (82). Additionally, lactylation at the K430 site of the ABCF1 protein promotes its nuclear translocation and binding to the KDM3A promoter, activating the KDM3A-H3K9me2-HIF1A signaling axis and fueling HCC growth and lung metastasis. Using target structure analysis and virtual screening, Hong *et al* (105) reported that Tubuloside A inhibits the lactate-ABCF1 lactylation-HIF1α feedback loop by suppressing ABCF1 lactylation. In the BALB/c nude mouse model, it suppressed tumor metastasis without exhibiting significant toxicity. Nevertheless, clinical research on AGK2 and Tubuloside A is at an early stage, and further investigation is required into their regulatory mechanisms and toxicity profiles. Integrating lactylation-targeting strategies with existing therapeutic regimens offers additional avenues for overcoming drug resistance and enhancing treatment efficacy in gastrointestinal cancer. By targeting lactate or its transporters, tumor metabolism can be disrupted, thereby sensitizing cancer cells to conventional chemotherapy. Furthermore, combining lactylase and delactylase inhibitors with chemotherapy, SIRT inhibitors and emerging agents such as copper ionophores has shown promise in preclinical studies as aforementioned. In summary, the combination of lactylation modulators with chemotherapy, targeted therapy and immunotherapy constitutes a multidimensional therapeutic strategy with significant translational potential for improving the prognosis of patients with gastrointestinal malignancies (Table III).

5. Future perspectives and challenges

Controversies and technical limitations in the field of lactylation. Current research on lactylation is subject to numerous limitations. First, regarding its mechanism of action,

Table III. Drugs targeting lactylation.

Drug	Clinical development stage	Cancer type	Mechanism	Findings and limitations	(Refs.)
DML	Preclinical	HCC	Histone modification	DML may exert its anti-HCC effects by inhibiting the lactate-lactylation axis; however, the specific contribution of H3 lactylation has not yet been validated.	(159,160)
RJA	Preclinical	HCC	Histone modification	RJA specifically inhibits histone lactylation by reducing lactate levels; however, the study did not assess other key lactylation sites or elucidate the downstream transcriptional regulatory mechanisms, and lacks evidence for clinical translation.	(161)
K673-pe	Preclinical	CRC	Non-histone modification	K673-pe has been shown to impair homologous recombination repair by specifically inhibiting lactylation of DNA repair proteins; however, its structural mechanism of action remains unclear, and studies on drug stability and pharmacokinetics are lacking.	(90)
β-alanine	Preclinical	CRC	Non-histone modification	β-alanine restores the tumor-suppressing function of p53 by competitively inhibiting AARS1, but its long-term safety and clinical efficacy require further validation.	(32)
MG149	Preclinical	CRC	Non-histone modification	MG149 blocks tumor-associated lactylation by inhibiting the lactyl transferase activity of KAT8, but as a non-specific acyltransferase inhibitor, it carries off-target risks and has limited preclinical data.	(163,164)
Vorinostat	Phase I clinical trial (NCT00537121)	CRC	Non-histone modification	HDAC inhibitors effectively sensitize tumor cells to ferroptosis, but exhibit dose-dependent toxicity when used as monotherapy.	(165)
AGK2	Preclinical	GC	Non-histone modification	The combination of AGK2 with copper-containing drugs significantly enhances the therapeutic efficacy against GC; however, its clinical efficacy and safety have not yet been fully validated in humans.	(82)
Tubuloside A	Preclinical	HCC	Non-histone modification	Tubuloside A has been found in preclinical studies to combat HCC by targeting and inhibiting the ABCF1-K430la protein, but its efficacy and safety still require validation through clinical trials.	(105)

DML, Demethylzeylasteral; RJA, royal jelly acid; SAHA, vorinostat; CRC, colorectal cancer; HCC, hepatocellular carcinoma; GC, gastric cancer.

lactylation exhibits cross-interference with other PTMs. For instance, lactylation and acetylation share similarities in metabolic pathways, catalytic enzymes and target sites. The histone acetyltransferase p300/CBP catalyzes acetylation and histone lactylation. The acetylation donor acetyl-CoA and the lactylation donor lactate-CoA are indirectly regulated by cellular conditions, particularly oxygen availability and oncogenic signaling. Specificity is achieved through competition for the same modification site (165). Furthermore, lactylation interacts with ubiquitination; lactylation directly regulates gene expression, thereby influencing components of the ubiquitination system (165). For example, in ocular melanoma, elevated histone lactylation levels promote the expression of the oncogene YTHDF2. As an m^6A reader protein, it promotes degradation of mRNAs such as TP53, thereby activating downstream ubiquitin-proteasome-mediated proteolysis (28). However, the regulatory networks underlying these interactions require further elucidation. Second, the specificity and substrate recognition of lactyltransferases remain insufficiently characterized. Current research on lactylating enzymes is still limited, and the enzymatic properties of proteins such as p300 and AARS1 have not yet been sufficiently defined. Further investigation into lactylation substrates is warranted because of their broad range. The development of cyclic immonium ion diagnostic and YnLac technologies hold promise for filling these gaps. High-precision mass spectrometry techniques, exemplified by cyclic immonium ion diagnostics, can further expand the lactoylated substrate family (166). YnLac is an alkynyl-functionalized chemical reporter metabolically incorporated into lactylated proteins for fluorescence detection and proteomic identification. YnLac technology enables the discovery of novel substrates and the investigation of dynamic regulation (167). Furthermore, Zhai *et al* (29) recently identified the first reader protein for histone lactylation, which specifically recognizes this modification and mediates transcriptional programs and biological outcomes distinct from those induced by acetylation, which may promote further in-depth research on the lactylation mechanism. However, research on histone lactylation reader proteins in gastrointestinal tumors remains scarce. Additionally, although the abundance of lactyl-CoA *in vivo* is primarily correlated with lactate levels, research on lactyl-CoA synthetases remains limited (168). Non-enzymatic lactylation primarily occurs as a passive response to metabolic states characterized by high lactate levels or accumulation of metabolic intermediates, whereas enzymatic lactylation represents a precise and regulated modification of specific substrate sites (26). However, quantitative assessments of their respective contributions to tumor biology remain insufficient. Additionally, technical limitations constrain the detection of lactylation. Current approaches rely largely on mass spectrometry, which has limited sensitivity. Furthermore, specific detection tools for lactylation are lacking, and high-affinity antibodies remain scarce (169). Development of chemical probes targeting lactylation may improve the understanding of lactylation-mediated signal transduction dynamics.

Treatment. Although various inhibitors of lactate metabolism and lactylation have been developed, which have demonstrated the potential of combining lactate- and lactylation-targeted strategies with immunotherapy to overcome tumor drug resistance, drug development faces several challenges. Lactate production and lactylation are ubiquitous biological processes that occur across various tissues (168). Therefore, high drug specificity is required to minimize toxicity and adverse effects. Additionally, the crosstalk between lactylation and other PTMs necessitates consideration of off-target effects during drug development. For example, enzymes such as p300 catalyze lactylation and acetylation; therefore, lactylation inhibitor development must evaluate the potential disruption of normal acetylation. Furthermore, developing novel drug delivery systems for targeted therapy represents a key future direction. As such, a PLGA-PEG nanoparticle-based drug delivery system developed by Paulino da Silva Filho *et al* (170) demonstrated enhanced drug safety with increased cellular uptake. Nanodelivery systems may advance tumor treatment by enabling targeted delivery of lactylation inhibitors in combination with chemotherapeutic and immunotherapeutic agents. With the advancement of therapeutic technologies, the development of non-invasive imaging techniques to visualize lactate metabolism and lactylation dynamics *in vivo* holds promise for advancing theranostic paradigms. Hyperpolarized ^{13}C MRI and deuterium metabolic imaging have enabled real-time spatiotemporal monitoring of lactate flux and utilization within tumors. These techniques serve as reliable tools for directly assessing the pharmacodynamics of lactate- and lactylation-targeted inhibitors, while also predicting patient responses to targeted therapies (171,172). Furthermore, by visualizing tumor metabolic heterogeneity, such imaging approaches can guide patient stratification, enabling precise identification of those most likely to benefit from lactylation-targeted therapies while sparing non-responders from unnecessary toxicity. Consequently, the convergence of advanced nanodelivery systems and metabolic imaging technologies holds promise for realizing theranostic paradigms.

Biomarkers and the establishment of prognostic models. Lactylation has demonstrated potential as a prognostic and predictive biomarker across various tumors. Lactate-related gene signatures have been used to establish risk assessment models for several types of cancer, including GC, PC and CRC. A lactylation-related prognostic model developed by Sun *et al* (173) for GC demonstrated significant predictive value for patient outcomes. Specifically, the model, based on three lactylation-related genes (COL4A1, SLC16A7 and IRAK1), stratified GC patients into high- and low-risk groups, with the high-risk group exhibiting significantly worse overall survival (OS). Regarding molecular and immune features, the model revealed that the high-risk group was characterized by elevated stromal and immune scores, increased infiltration of M2-type macrophages, and activation of oncogenic pathways including WNT, VEGF and TGF-β signaling. In terms of therapeutic response, the low-risk group showed higher tumor mutational burden and microsatellite instability, along with lower Tumor Immune Dysfunction and Exclusion (TIDE) scores, indicating a greater likelihood of benefiting from immune checkpoint inhibitor therapy. Furthermore, experimental validation demonstrated that SLC16A7 knockdown in GC cells reduced PD-L1 expression and enhanced T cell-mediated tumor cell killing, suggesting potential implications for chemotherapy

and immunotherapy responses. In addition, integrating multi-omics data with machine learning applied to lactylation-related genes can establish molecular biomarkers and prognostic predictions. Through multiomics integration, spanning clinical phenotype stratification, systematic screening, mechanistic exploration and target validation, a regulatory network of lactylation in the progression of lower digestive system tumors can be constructed. Additionally, analysis of lactylation-related multi-omics datasets using feature engineering and algorithmic modeling enables the identification of lactylation-related biological patterns and the construction of clinically predictive models. Hua and Li (174) integrated multi-omics data with machine learning approaches to construct a prognostic model for lung adenocarcinoma based on nine lactylation-related genes. This model stratified patients into high-risk and low-risk groups; patients in the high-risk group exhibited more advanced TNM stages, higher rates of recurrence and metastasis and significantly poorer OS. Regarding immunotherapy response, the low-risk group demonstrated higher tumor immune activity, more abundant immune cell infiltration in the TME, and TIDE algorithm predictions indicated an improved response to immunotherapy. These findings suggest that this model not only facilitates prognostic assessment but also provides predictive value for immunotherapy efficacy (174). These advances pave the way for the lactate-related oncology field to move toward personalized therapy.

In the future, several critical challenges must be addressed to translate these foundational discoveries into clinical practice. First, while existing prognostic models have demonstrated utility in retrospective cohorts, prospective, multicenter clinical studies are urgently needed to validate their generalizability across diverse patient populations and clinical settings. Second, the translation of lactylation-related biomarkers into clinically applicable detection methods requires the development of highly specific antibodies and standardized assays capable of reliably quantifying lactylation modifications in patient samples. Finally, the identification of distinct lactate-related tumor subtypes provides a rationale for subtype-guided targeted therapies, which necessitates the development of small-molecule inhibitors or biological therapies that selectively target lactylation regulators, followed by rigorous evaluation in well-designed clinical trials. In summary, this review concludes the molecular mechanisms of lactate and lactylation in digestive system tumors. It further summarizes current progress in developing drugs targeting lactate and lactylation and discusses limitations of lactylation research. Moreover, advances in lactylation-based prognostic model construction and combination therapy may support more precise treatment strategies and prognostic assessment for digestive system tumors.

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Availability of data and materials

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Authors' contributions

LP was responsible for the study conceptualization, literature investigation and writing the original draft, including visualization. FL critically reviewed and edited the manuscript, and provided supervision. WY contributed to the conception and design of the review, critically revised the manuscript for important intellectual content, acquired funding and gave final approval of the manuscript. Data authentication is not applicable. All authors reviewed and approved the final version.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, the authors used ChatGPT (GPT-4o) [https://chatgpt.com] to improve the readability and language of the manuscript. The authors reviewed and edited the content as necessary, and take full responsibility for the final content of the present manuscript.

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