Lactate and lactylation in gastrointestinal cancer: Current progress and perspectives (Review)

YUFEN HE[1*], YAXI HUANG[1*], PENG PENG[1], QI YAN[1] and LIDAN RAN[2]

[1]Department of Gastroenterology and Hepatology, Chongqing University Central Hospital, Chongqing Emergency Medical Center, Chongqing Key Laboratory of Emergency Medicine, Chongqing 400014, P.R. China; [2]Department of Intensive Care Unit, Chongqing University Central Hospital, Chongqing Emergency Medical Center, Chongqing Key Laboratory of Emergency Medicine, Chongqing 400014, P.R. China

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Abstract. Gastrointestinal (GI) cancers, which have notable incidence and mortality, are impacted by metabolic reprogramming, especially the increased production and accumulation of lactate. Lactylation, a post-translational modification driven by lactate, is a crucial regulator of gene expression and cellular function in GI cancer. The present review aimed to examine advancements in understanding lactate and lactylation in GI cancer. The mechanisms of lactate production, its influence on the tumor microenvironment and the clinical implications of lactate levels as potential biomarkers were explored. Furthermore, lactylation was investigated, including its biochemical foundation, primary targets and functional outcomes. The present review underscored potential therapeutic strategies targeting lactate metabolism and lactylation. Challenges and future directions emphasize the potential of lactate and lactylation as innovative therapeutic targets in GI cancer to improve clinical outcomes.

Correspondence to: Dr Qi Yan, Department of Gastroenterology and Hepatology, Chongqing University Central Hospital, Chongqing Emergency Medical Center, Chongqing Key Laboratory of Emergency Medicine, 1 Health Road, Yuzhong, Chongqing 400014, P.R. China
E-mail: qiyan_chongqing@163.com

Dr Lidan Ran, Department of Intensive Care Unit, Chongqing University Central Hospital, Chongqing Emergency Medical Center, Chongqing Key Laboratory of Emergency Medicine, 1 Health Road, Yuzhong, Chongqing 400014, P.R. China
E-mail: 759035864@qq.com

*Contributed equally

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Contents

1. Introduction

Gastrointestinal (GI) cancers represent more than 25% of all cancer incidence and 35% of cancer-related mortality globally (1). These malignancies include colorectal cancer (CRC) (2), gastric (3), esophageal (4) and pancreatic cancer (5), each contributing notably to morbidity and mortality worldwide. Despite advancements in diagnosis and treatment, prognosis for patients with GI cancer remains poor, primarily due to late-stage detection and the aggressive nature of these tumors. Understanding the molecular mechanisms underlying GI cancer progression is key for developing more effective therapeutic strategies.

A hallmark of cancer metabolism is the Warburg effect, characterized by increased glycolysis and lactate production even in the presence of oxygen (6,7). This metabolic reprogramming supports rapid cell proliferation and creates an acidic tumor microenvironment (TME) that promotes invasion, metastasis and immune evasion. Lactate, traditionally viewed as a metabolic waste product, has emerged as a key player in cancer biology, serving as both a signaling molecule and an energy source (7). Lactate influences various aspects of tumor progression by modifying the TME, promoting immune evasion and enhancing cancer cell survival and metastasis (8-10).

Recent advances have identified lactylation, a post-translational modification driven by lactate, as a key regulatory mechanism linking cellular metabolism with gene expression (8,11). Histone lactylation, in particular, has emerged as a key process influencing chromatin structure and function, thereby affecting gene transcription (8). This modification

underscores the intricate interplay between metabolism and epigenetics, highlighting the potential for novel therapeutic targets in cancer treatment (11).

Lactate and lactylation modulate various cellular processes, including inflammation, immune response and proliferation (12). In GI cancers, these modifications are hypothesized to contribute to tumor development and progression (13). Elucidating the mechanisms underlying lactate production and lactylation may identify new biomarkers for early detection and prognosis, as well as novel therapeutic strategies to disrupt these metabolic and epigenetic pathways.

The present review aimed to provide a comprehensive overview of current progress in understanding lactate and lactylation in GI cancers, the biochemical basis of these processes, impact on the TME and their clinical relevance. The present review highlights the potential of targeting lactate metabolism and lactylation as innovative approaches for treating GI cancer.

2. Lactate metabolism in GI cancer

Glycolysis and the Warburg effect. Cancer cells possess unique metabolic traits distinct from normal cells, notably the Warburg effect (14,15). This phenomenon involves cancer cells preferring energy production via glycolysis followed by lactate fermentation in cytosol, despite sufficient oxygen for oxidative phosphorylation. This metabolic shift facilitates rapid proliferation of tumor cells and notably alters the TME. The excess lactate produced is exported, leading to acidification of the TME, which degrades the extracellular matrix and promotes tumor invasion and metastasis. Additionally, the acidic environment suppresses immune cell function, helping cancer cells evade the immune system. This shift also supports biosynthetic processes essential for rapid cancer cell proliferation (7). Typically, cells generate ATP through oxidative phosphorylation in mitochondria, producing up to 36 ATP/glucose molecule. Conversely, glycolysis in cytoplasm yields only 2 ATP/glucose molecule but occurs at a much faster rate, enabling rapid ATP production. Cancer cells enhance glycolysis through various mechanisms. Tumor cells often show elevated levels of glycolytic enzymes such as hexokinase, phosphofructokinase and pyruvate kinase, facilitating glucose to pyruvate conversion and promoting glycolytic flux (8). Oncogenes such as MYC and RAS upregulate glycolysis, while tumor suppressors such as p53, which typically inhibit glycolysis, are frequently mutated or inactivated in cancer. Hypoxic conditions within tumors stabilize hypoxia-inducible factor (HIF)-1, which activates genes involved in glycolysis, including glucose transporter 1 and glycolytic enzymes. HIF-1 also induces lactate dehydrogenase (LDH) expression, converting pyruvate to lactate (12). The Warburg effect notably influences tumor progression. Elevated glycolytic activity leads to high lactate production, exported via monocarboxylate transporters (MCTs), contributing to acidification of the TME (10). The acidic environment promotes tumor invasion and metastasis by degrading extracellular matrix and inhibiting immune cell function while selecting aggressive, apoptosis-resistant cancer cells. Additionally, glycolysis intermediaries support biosynthetic pathways essential for the synthesis of nucleotides, amino acids and lipids required by rapidly proliferating cancer cells (16). Non-malignant cells, such as tumor-associated macrophages (TAMs) and cancer-associated fibroblasts, also contribute to lactate accumulation in the TME through the reverse Warburg effect (16). Hypoxic tumor cells secrete lactate, which normoxic tumor cells take up, facilitating glucose diffusion towards hypoxic cells. This lactate-based metabolic symbiosis supports both hypoxic and normoxic cancer cells (11). Studies indicate lactate concentration is associated with cancer grade and prognosis (17,18). Isotope tracer measurements reveal rapid lactate exchange between tumors and circulation, with tumors converting pyruvate to lactate faster than adjacent benign tissue (17,18).

In GI cancers, including CRC, gastric, esophageal and pancreatic cancers, the Warburg effect is prominent. These tumors exhibit high glycolytic rates and elevated lactate levels, which are associated with poor prognosis and therapy resistance (6). Targeting glycolysis and its regulatory pathways offers a promising therapeutic strategy for GI cancer. Inhibitors of key glycolytic enzymes, lactate transporters and HIF-1 are under investigation for their potential to disrupt metabolic adaptability of cancer cells and enhance treatment outcomes (8). Recent studies have also underscored the role of glycolysis in modulating the immune response within the TME (12,19). For example, lactate inhibits cytolytic functions of cytotoxic T cells and natural killer (NK) cells by reducing the production of key molecules such as perforin, granzyme and IFN-γ, and by downregulating signaling pathways such as nuclear factor of activated T cells and Peroxisome proliferator-activated receptor (PPARγ), ultimately facilitating tumor immune evasion (19). Understanding the interaction between cancer metabolism and immune regulation is key for developing effective immunotherapies. In summary, the Warburg effect is a key aspect of cancer metabolism that promotes tumor cell proliferation, survival and invasiveness. Elucidating the molecular mechanisms of this metabolic reprogramming may identify novel therapeutic targets for combating GI cancers.

Lactate transport and accumulation. Lactagenesis, or augmented lactate production, has been proposed as an explanation for the Warburg effect that drives carcinogenesis. This process encompasses five steps: Enhanced glucose uptake, increased expression and activity of glycolytic enzymes, decreased mitochondrial function, elevated lactate generation, accumulation and release and upregulation of MCT1/4 for accelerated lactate shuttling (Fig. 1) (20).

Lactate, a byproduct of the Warburg effect, serves a pivotal role in the metabolic reprogramming of cancer cells. Its accumulation in the TME, facilitated by specialized transporters, notably impacts tumor progression, immune evasion and metastasis. Understanding lactate transport and accumulation mechanisms may provide potential therapeutic targets for GI cancer (19). Lactate crosses the cell membrane via MCTs, a family of proton-linked transporters mediating bidirectional transfer of lactate and other MCs, such as pyruvate and ketone bodies. The primary MCTs involved in cancer cell lactate transport are MCT1 and MCT4. MCT1 is widely expressed by various tissues, including skeletal muscle, heart, brain, liver, and endothelial cells (21). It plays a crucial role in facilitating lactate uptake and export depending on the metabolic needs of the cell and the tissue environment. In tumor cells, MCT1 imports lactate to support oxidative metabolism and prevent

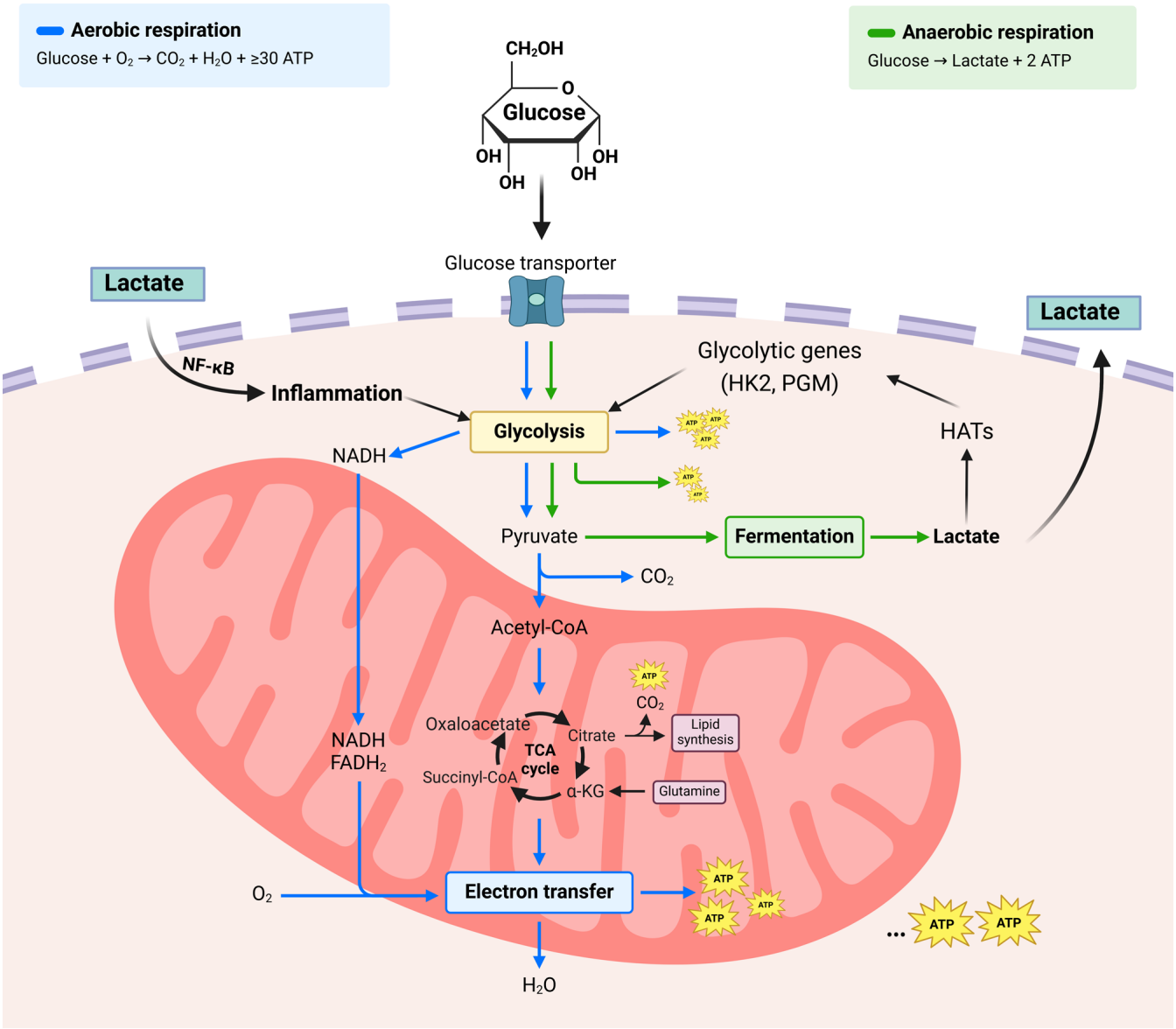

Figure 1. Metabolic pathway of lactate in cells. Glucose is taken up by cells and converted to pyruvate through glycolysis. Pyruvate can enter the mitochondria for aerobic respiration, producing ATP through the TCA cycle and electron transfer chain. Alternatively, under anaerobic conditions, pyruvate is converted into lactate through fermentation, which accumulates and can signal inflammatory pathways like NF-κB. Lactate production and release are regulated by glycolytic gene expression and affect cellular energy homeostasis, supporting various cellular functions. HK2, hexokinase2; PGM, Phosphoglucomutase; HAT, histone acetyltransferases; TCA, Tricarboxylic acid cycle.

toxic intracellular lactate accumulation (21). MCT4 primarily exports lactate and is upregulated in highly glycolytic cells, such as those in the hypoxic tumor core (21). This transporter maintains intracellular pH by removing excess lactate, thereby supporting continuous glycolytic activity. Several factors, including HIF-1 and c-Myc, regulate MCT1 and MCT4 expression. HIF-1, stabilized under hypoxic conditions, upregulates glycolytic enzymes and lactate transporters to adapt to low-oxygen environments (22).

Elevated glycolytic activity in cancer cells leads to excessive lactate production, which is exported into the TME via MCTs. This lactate export, coupled with proton co-transport, acidifies the extracellular space, creating a low-pH environment that promotes tumor invasion and metastasis (21). Acidification activates proteolytic enzymes that degrade the extracellular matrix and select for more aggressive cancer cell phenotypes (23). Lactate accumulation in the TME also inhibits immune cells, including cytotoxic T and NK cells, by suppressing cytokine production and decreasing their cytolytic activity, thus enabling tumor cells to evade immune surveillance (24). Additionally, lactate acts as a signaling molecule promoting angiogenesis by inducing vascular endothelial growth factor (VEGF) expression, facilitating novel blood vessel formation and providing the tumor with increased oxygen and nutrient supply, thereby supporting continued tumor growth (8).

3. Mechanisms and roles of lactylation in cancer

Discovery and mechanism of lactylation. Lactylation, first identified as a post-translational modification by Zhang *et al* (25), involves addition of lactate molecules to lysine residues on

histones, termed histone lactylation. This followed an investigation into the non-metabolic functions of lactate, revealing its role beyond traditional metabolic contexts (25). Advanced mass spectrometry techniques have facilitated the precise detection and characterization of histone lactylation, showing its occurrence under both normoxic and hypoxic conditions, indicating its potential relevance in numerous physiological and pathological contexts, including cancer (26). Protein lactylation, especially histone lactylation, involves covalent attachment of lactate to the ε-amino group of lysine residues. This process is similar to other acylation modifications such as acetylation and methylation, but uniquely uses lactate as the modifying group. The lactylation begins with lactate production, where the Warburg effect in cancer cells increases lactate production via glycolysis, with pyruvate reduced to lactate by LDH (27). For lactylation to occur, lactate must be activated, potentially due to the formation of lactyl-CoA, a high-energy intermediary that donates the lactate moiety to target proteins. The exact enzymatic pathways and cofactors involved in this activation remain under investigation (8). The transfer of lactate to lysine residues on histones and other proteins is hypothesized to be facilitated by specific enzymes, though definitive lactyltransferases have not yet been identified. It is hypothesized that enzymes with acyltransferase activity may catalyze this process (8). Potential candidates include histone acetyltransferases (HATs), which catalyze addition of acetyl groups to histones, although direct evidence linking HATs to lactylation is lacking. Sirtuins, a family of NAD^+-dependent deacetylases, may serve a role in reversing lactylation, similar to their role in deacetylation; understanding the interplay between lactylation and deacetylation may reveal more about the regulatory mechanisms underlying lactylation (28,29). The involvement of cofactors such as NAD^+ and acetyl-CoA analogs such as lactyl-CoA suggests a complex regulatory network, potentially influencing the availability and activity of lactylation enzymes. In GI cancers, lactylation represents a crucial regulatory mechanism linking metabolic reprogramming to gene expression (30,31).

Similar to other epigenetic modifications such as methylation and acetylation, lactylation is regulated by writers (enzymes that add lactyl groups), erasers (enzymes that remove lactyl groups) and readers (proteins that recognize lactylation and mediate its effects) (32). Lactyl-CoA, detected in mammalian cells by liquid chromatography mass spectrometry, serves as the substrate for enzymatic lactylation, while lactyl-glutathione participates in non-enzymatic lactylation (33). The enzyme p300 has been identified as a lactylation writer and may share functions with other epigenetic modifiers, indicating potential overlaps in enzymatic regulation of different epigenetic markers (34).

Histone lactylation and gene expression. Histone lactylation, a key post-translational modification, affects chromatin structure and function by loosening chromatin, thereby facilitating transcription of genes involved in tumor progression, invasion, and immune evasion (35). This modification links cellular metabolism to gene regulation by adding lactate molecules to lysine residues on histones, influencing chromatin dynamics and gene expression (36). Metabolic shifts in cancer cells directly impact the epigenetic landscape and drive tumor progression. By altering the chemical properties of histone proteins, histone lactylation modulates the interactions between histones and DNA, as well as the binding of regulatory proteins to chromatin (37). Understanding the precise molecular mechanisms of lactylation is key for developing targeted therapies aimed at disrupting this modification to hinder cancer progression. Neutralizing the positive charge of histones via lactylation reduces their affinity for negatively charged DNA, resulting in a more relaxed chromatin structure that facilitates transcriptional activation (25).

Histone lactylation activates transcription of genes involved in metabolic processes, immune responses and cell stress pathways (38-40). Research has shown that lactylation induces transcriptional activation in response to metabolic changes within cells (41). In cancer cells, histone lactylation upregulates genes associated with glycolysis and other metabolic pathways, ensuring metabolic needs of rapidly proliferating tumor cells are met, thereby promoting sustained proliferation and survival. Additionally, lactylation regulates immune response genes (42,43). For example, in macrophages, histone lactylation activates genes involved in the anti-inflammatory response, highlighting its potential role in modulating the tumor immune landscape (40).

Under cellular stress conditions such as hypoxia, lactylation activates stress response genes, aiding cells in adapting to adverse conditions, which is key in the TME where cancer cells are subject to fluctuating oxygen and nutrient levels. Identifying specific genes and pathways regulated by histone lactylation is an area of active research, such as mapping lactylation sites across the genome and associating them with changes in gene expression (44,45). Techniques such as chromatin immunoprecipitation followed by sequencing have identified that lactylation is enriched at promoters and enhancers of actively transcribed genes (46,47).

Functional studies have demonstrated that genes regulated by lactylation participate in key cellular processes, including cell cycle regulation, apoptosis and DNA repair (48,49). For example, lactylation of histone H3 at lysine 18 (H3K18la) activates genes associated with cell proliferation and survival (48,49). Understanding the mechanisms and consequences of histone lactylation provides insights into the metabolic-epigenetic interplay in cancer and may reveal novel therapeutic targets. By modulating chromatin structure and function, lactylation activates genes that drive tumor progression, immune evasion and adaptation to stress.

Impact on the TME. Cancer cells export lactate and protons via MCTs, mainly MCT1 and MCT4, thereby lowering the extracellular pH and creating an acidic environment (50-52). This acidification activates proteolytic enzymes such as MMPs, which degrade the extracellular matrix and facilitate tumor cell invasion. Additionally, acidic pH enhances cancer cell migration and invasion by inducing epithelial-mesenchymal transition (EMT), increasing cell motility (53,54).

Reprogrammed metabolism, a hallmark of cancer, links lactylation and cell metabolism (55,56). Histone lactylation connects metabolic reprogramming with abnormal gene expression in cancer cells. Metabolic changes alter lactate levels, reshaping the histone lactylation landscape and transcriptomic profile to adapt to metabolic reprogramming (57). In non-small cell lung cancer, lactate modulates metabolism

by altering the expression of glycolytic and tricarboxylic acid cycle enzymes through promoter histone lactylation. Histone lactylation is associated with arginase (Arg)1 expression in TAMs and enhances VEGFA transcription during TAM polarization (55).

Immunosuppressive effects of lactylation. In addition to serving as an intermediate metabolite in energy and biosynthetic pathways, lactate accumulates during local inflammation, linking it to tumor-associated inflammation, a hallmark of cancer (19). Macrophages, key for regulating immune response and maintaining tissue homeostasis, exhibit plasticity modulated by epigenetic dynamics during inflammation (58). Macrophages exist in two types: Proinflammatory M1 and immune regulatory M2. The transition from M1 to M2 is vital for restoring immune homeostasis. B cell adapter for PI3K facilitates this transition by elevating lactate production, enhancing histone lactylation and upregulating genes such as Forkhead box protein O1 and glycogen synthase kinase-3β (GSK3β) (59). Lactate-derived histone lactylation induces expression of homeostatic genes such as Arg1, which is highly expressed by immunosuppressive myeloid-derived suppressor cells and TAMs during the macrophage transition from M1 to M2 (60). Lysine lactylation is considered a consequence rather than a cause of macrophage activation, consistent with Arg1-dependent metabolic rewiring during inflammation (60). TAMs exhibit an M1 phenotype with anti-tumor activity at tumor initiation but shift to an M2 phenotype during cancer progression (61). Lactate mediates immunosuppressive effects of efferocytosis under hypoxia by inducing anti-inflammatory genes (62). While high lactate and low pH in inflamed tissues under hypoxia can aid pathogen clearance by confining T cells to the inflammatory site, this is detrimental during tumor-associated inflammation, suppressing cytolytic function of $CD8^+$ T cells and inducing the T helper 17 phenotype in $CD4^+$ T cells (63). Under hypoxia, lactate mediates immunosuppressive effects by inducing expression of anti-inflammatory genes (58,63).

Lactate accumulation in the TME impairs the immune response, facilitating tumor immune evasion. Elevated lactate levels inhibit cytotoxic T and NK cells (36,64) by impairing cytokine production, such as IFN-γ, essential for anti-tumor activity. Additionally, lactate decreases the proliferation and activity of these immune cells, weakening their ability to target and eliminate cancer cells. The acidic environment created by lactate further suppresses immune function by inducing mitochondrial stress and apoptosis in NK cells, particularly in liver-resident NK cells in colorectal liver metastasis (65,66).

Lactate promotes differentiation and activity of regulatory T cells (Tregs), which suppress the immune response against tumors (67,68). Tregs in the TME inhibit cytotoxic immune cells, aiding tumor immune evasion. Lactate-induced Tregs produce anti-inflammatory cytokines and inhibit effector T and NK cells, creating an immunosuppressive environment that fosters tumor growth and progression (69).

In summary, lactate in the TME modulates the immune response by inhibiting key immune cells and promoting immunosuppressive Tregs. These effects enhance the immune evasion of tumors, underscoring the potential of targeting lactate metabolism as a therapeutic strategy in GI cancers.

4. Lactate and lactylation in GI cancer

Lactate accumulation in GI tumors. The accumulation of lactate in GI tumors is a hallmark of the altered metabolic state of cancer cells. There are elevated lactate levels in various types of GI cancer, including CRC (70), gastric (71-73) and pancreatic (74) cancers. This elevation is primarily due to the Warburg effect (13).

Advanced techniques have quantified lactate levels in tumors, enhancing the understanding of lactate metabolism in cancer. Proton magnetic resonance spectroscopy is a non-invasive imaging technique widely used to measure lactate concentration *in vivo* (16,75), allowing real-time monitoring of metabolic changes in tumors. LC-MS (76) precisely quantifies lactate levels in tumor tissue and blood samples with high sensitivity and specificity.

Clinical studies consistently show significantly elevated lactate levels in GI tumors compared with normal tissues (70,71,71). For example, patients with CRC have lactate concentrations in tumor tissue several fold higher than in adjacent non-tumorous tissues. Similar findings in gastric and pancreatic cancer show an association between high lactate levels with advanced disease stage and poor prognosis (71,74), underscoring lactate as a biomarker for tumor aggressiveness and potential therapeutic target.

Lactate accumulation in GI tumors influences tumor progression, invasion and therapy resistance. Further research into the mechanisms of lactate accumulation and its effects on the TME may advance the understanding of GI cancer biology and improve clinical outcomes.

Lactylation in GI cancer progression. Lactylation connects cellular metabolism to gene expression, affecting tumor development, invasion and metastasis.

Lactylation notably impacts tumor growth by activating genes involved in cell proliferation and survival. For example, H3K18la upregulates genes that enhance glycolysis and other metabolic pathways essential for rapidly dividing cancer cells. By boosting expression of these genes, lactylation meets the metabolic demands of tumor cells, supporting sustained tumor growth and expansion. Aberrant lactate production facilitates cancer hallmarks such as uncontrolled growth and resistance to cell death. For example, eliminating tumor-produced lactate by deleting MCT1 in lung cancer cells halts tumor growth (77). Similarly, inhibiting MCT1 or MCT4 stops proliferation of leukemia cells, and selective inhibition of MCT4 impedes invasive bladder cancer cell proliferation (78-80). Additionally, cancer-produced lactate activates G-protein-coupled receptor 81, with its deletion arresting breast cancer tumor growth *in vitro* and *in vivo*, underscoring the role of lactate in cancer proliferation (81,82).

Lactylation also enhances the invasive and metastatic potential of GI cancers. Histone lactylation activates genes encoding MMPs and other enzymes that degrade the extracellular matrix, facilitating tumor cell invasion into surrounding tissue and the establishment of metastases in distant organs (83). Additionally, lactylation-induced gene expression changes promote EMT, enabling cancer cells to acquire migratory and invasive capability (84-86).

By modulating the expression of genes involved in immune regulation, lactylation helps cancer cells evade immune surveillance (36). For example, lactylation suppresses pro-inflammatory cytokines and enhances anti-inflammatory factors, creating an immunosuppressive TME (84). This environment inhibits the activity of immune cells, such as cytotoxic T and NK cells, allowing tumor cells to proliferate unchecked (86).

Key proteins and pathways modified by lactylation in gastrointestinal GI cancers impact tumor behavior and progression (87,88). Lactylation enhances HIF-1 stability and activity, promoting angiogenesis, glycolysis and cell survival under hypoxic conditions common in tumors (89). This stabilization activates genes that support tumor growth and adaptation to low-oxygen environments (90). Similarly, lactylation modifies NF-κB, a transcription factor key for in inflammation and cell survival pathways. Lactylation increases NF-κB transcriptional activity, upregulating genes involved in inflammation, cell proliferation and resistance to apoptosis, thus aiding tumor progression (91,92). Histone lactylation, particularly at markers such as H3K18la, influences cancer progression by activating genes that drive EMT, immune evasion and tumor aggressiveness (92). By modulating these critical pathways, lactylation facilitates the complex network of gene regulation enabling GI tumors to grow, invade and resist therapeutic intervention.

Understanding lactylation mechanisms and effects in GI cancer is essential for developing targeted therapy to disrupt this modification and improve patient outcomes (Table I).

Differential mechanisms of lactylation in GI tumor subtypes. Lactylation serves distinct regulatory roles in various types of GI cancer, including gastric, CRC and pancreatic cancers, through different molecular pathways. In gastric cancer, lactylation primarily affects glycolysis and mitochondrial function by enhancing activity of key metabolic enzymes such as LDH-A, which increases glycolytic flux. This metabolic reprogramming leads to rapid cellular proliferation and migration, as well as upregulation of oncogenic and cell cycle-related genes, contributing to tumor aggressiveness and resistance to apoptosis (83). Additionally, lactylation can regulate mitochondrial dynamics and energy production, supporting the highly proliferative nature of gastric cancer cells (93). In CRC, lactylation plays a critical role in shaping the TME by modulating immune cell function. High levels of lactylation are associated with increased recruitment of Tregs and suppression of cytotoxic T cells, leading to immune evasion and poor prognosis (94,95). Furthermore, lactylation has been shown to promote chemoresistance in CRC by regulating genes involved in drug metabolism and efflux pathways (93). Recent studies have identified a panel of lactylation-associated genes associated with poor survival outcomes that may serve as potential prognostic markers (95,96). Targeting these lactylation-related pathways may overcome therapeutic resistance and improve patient outcomes. In pancreatic cancer, lactylation impacts stromal interactions and extracellular matrix remodeling. By activating cancer-associated fibroblasts, lactylation enhances production of extracellular matrix proteins, leading to a dense, fibrotic stroma that is characteristic of pancreatic tumors. This stromal barrier not only impedes drug delivery but also creates an immunosuppressive environment that shields the tumor from immune surveillance (36,96). Additionally, lactylation modulates key signaling pathways such as HIF-1α and TGF-β, further promoting fibrosis, tumor growth and metastasis (96).

5. Therapeutic implications

Targeting lactate metabolism. Targeting lactate metabolism offers a promising therapeutic strategy for GI cancer due to its role in tumor progression and immune evasion. Various approaches aim to disrupt lactate production and transport, thereby altering the TME and enhancing the efficacy of existing treatments.

Inhibitors of glycolytic enzymes. One approach involves inhibiting key glycolytic enzymes to reduce lactate production. Agents targeting enzymes such as hexokinase, phosphofructokinase and LDH have shown potential in preclinical studies (97-100). For example, LDH inhibitors decrease lactate levels, leading to reduced tumor growth and improved chemotherapy response. Inhibitors such as oxamate (97,98), which targets LDH-A, have demonstrated effectiveness in preclinical models by decreasing lactate production and promoting immune activation within the TME (99). Additionally, targeting pyruvate dehydrogenase kinase, which regulates conversion of pyruvate to lactate, has shown efficacy in reducing lactate production and tumor cell proliferation (100).

MCT inhibitors. Another strategy involves blocking lactate export from cancer cells by inhibiting MCTs, particularly MCT1 and MCT4 (101). MCT inhibitors prevent the acidification of the TME, enhancing immune cell function and reducing tumor invasion. AZD3965, an MCT1 inhibitor, has shown promise in clinical trials, demonstrating potential to disrupt lactate transport and improve treatment outcomes in various types of cancer (102-104). MCT4 facilitates efflux of lactic acid from glycolytic cancer cells (105). Knocking down or silencing MCT4 leads to cytoplasmic acidification and subsequent tumor cell death. MCT4 is predominantly expressed in hypoxic regions of rapidly proliferating tumors, making it a promising therapeutic target. Although existing drugs aimed at MCT4 lack specificity, further investigation into their potential effectiveness in cancer therapy is needed (106,107). Additionally, localization and stability of MCT1 and MCT4 at the plasma membrane are regulated by CD147. Targeting CD147 could be a novel strategy to inhibit both transporters. AC-73, a dimerized and humanized anti-CD147 antibody, has demonstrated antitumor activity in preclinical study (108). In summary, inhibiting lactic acid transporters MCT1 and MCT4, along with their chaperones, may have antitumor potential. However, clinical data supporting these findings are currently lacking (108). Blocking MCT1 and MCT4 normalizes the pH of the TME, thereby enhancing immune responses and reducing metastatic potential.

Combination therapy. Combining lactate metabolism inhibitors with other therapeutic modalities, such as immunotherapy and conventional chemotherapy, has been researched (109-111). For example, combining LDH inhibitors with immune checkpoint inhibitors has shown synergistic effects, enhancing anti-tumor immune responses by reversing lactate-induced immunosuppression. This multi-faceted approach targets various aspects of tumor biology, potentially

Table I. Mechanisms of lactylation in gastrointestinal tumors.

Cancer	Proteins modified by lactylation	Affected genes/pathways	Role of lactylation	(Refs.)
Colorectal	β-catenin	Wnt/β-catenin	Promotes cell proliferation and stemness	(121)
	H3K18	Autophagy	Promotes resistance to bevacizumab by enhancing autophagy.	(70)
Gastric	METTL16	FDX1	Enhances cuproptosis sensitivity	(71)
	-	GLUT3	Promotes lactylation modification by regulating LDHA	(83)
Esophageal	H3K9	LAMC2	Promotes LAMC2 expression, enhancing cell proliferation under hypoxia	(122)
Pancreatic	H3K18	METTL3	Promotes immunosuppression of tumor-infiltrating myeloid cells	(42)

GLUT3, glucose transporter 3; LDHA, lactate dehydrogenase A; LAMC2, laminin Subunit γ2; FDX, ferredoxin; METTL, methyltransferase-like proteins.

improving patient outcomes (112-114). Combination therapy can enhance the efficacy of therapies such as chimeric antigen receptor T cell therapy by decreasing lactate-induced immunosuppression (108,115). In summary, targeting lactate metabolism using glycolytic enzyme and MCT inhibitors and combination therapies shows promise for treating GI cancers. These strategies aim to disrupt the lactate-driven metabolic reprogramming and immune evasion mechanisms that tumors exploit, enhancing the overall effectiveness of cancer therapy. Further research and clinical trials are essential to validate these approaches and translate them into effective treatments. Inhibitors of LDH and MCTs are still in early-phase clinical trials, with mixed results regarding efficacy and safety (108,109). Challenges include potential off-target effects, limited tumor specificity and TME complexity, which may reduce treatment effectiveness. Furthermore, the metabolic flexibility of cancer cells may enable resistance to these therapies. Addressing these issues requires comprehensive clinical studies, better biomarkers for patient selection and combination therapies to overcome resistance and enhance therapeutic outcomes.

Inhibiting lactylation. Inhibiting lactylation is a therapeutic approach in GI cancers due to its role in regulating gene expression and promoting tumor progression (116-120).

Histone deacetylase (HDAC) inhibitors. HDAC inhibitors, which can also affect histone lactylation, have been explored for their potential to modulate epigenetic markers in cancer cells (116). By decreasing lactylation levels, these inhibitors alter gene expression involved in tumor growth and immune evasion. For example, vorinostat and panobinostat, two prominent HDAC inhibitors, have efficacy in various types of cancers by disrupting epigenetic modifications and enhancing tumor suppressor gene expression (116,117). Vorinostat and panobinostat prevent removal of acetyl and, potentially, lactyl groups from histones, maintaining a more open chromatin structure conducive to gene expression that counteracts tumor growth (116,117).

Direct inhibitors of lactylation enzymes. Identifying and targeting specific enzymes responsible for lactylation, such as potential lactyltransferases, represents a promising research direction. Although these enzymes have not been definitively identified, studies have investigated small molecules that specifically inhibit lactylation, thereby disrupting its oncogenic effects (118,119). General control non-depressible 5 is a possible lactyltransferase for ERK in the MAPK signaling pathway (118,119). Inhibitors targeting such lactyltransferases could reduce tumor progression and metastasis by altering key signaling pathways involved in cancer cell survival and proliferation.

Combining lactylation inhibitors with other therapy. Combining lactylation inhibitors with other treatment modalities may enhance therapeutic efficacy (41). Integrating lactylation inhibition with immunotherapy or targeted therapy may provide a comprehensive approach to disrupting cancer progression and overcoming resistance to single-agent treatments. Studies have shown that combining lactylation inhibitors with immune checkpoint inhibitors or chemotherapeutic agents produces synergistic effects, enhancing overall anti-tumor response by reversing immunosuppression and decreasing tumor growth (41,120).

Targeting lactylation presents a potential therapeutic approach for GI cancer. HDAC and direct lactylation enzyme inhibitors and combination therapies offer multiple avenues to disrupt lactylation-driven oncogenic processes. Further research and clinical trials are key to translate these strategies into effective treatments for patients with cancer.

6. Future research directions

Identifying and characterizing enzymes directly responsible for protein lactylation is essential. Understanding specific mechanisms and regulatory pathways of lactylation will aid in developing targeted inhibitors. Therefore, research should prioritize discovering and validating lactyl transferases, which serve a key role in catalyzing lactylation. Identifying these enzymes may offer novel therapeutic targets to inhibit lactylation oncogenic effects and improve cancer treatment outcomes.

Developing reliable biomarkers for lactate metabolism and lactylation may enhance patient stratification and treatment monitoring. Biomarkers can identify patients likely to benefit from therapy targeting these pathways, thereby improving personalized treatment approaches. Efforts should prioritize

discovering biomarkers that reflect lactate metabolism and lactylation activity, such as specific lactylation markers on histones or lactate levels in the TME.

Expanding clinical trials to assess the safety and efficacy of lactate metabolism and lactylation inhibitors in GI cancer is crucial. These trials should explore various combinations of inhibitors with existing therapy to identify the most effective regimens. Clinical research should also investigate potential side effects and resistance mechanisms, ensuring safe and effective integration into cancer treatment protocols.

Elucidating the complex interactions between lactate, lactylation, and other metabolic and epigenetic processes in cancer cells requires in-depth mechanistic studies to reveal the broader implications of targeting these pathways and potential resistance mechanisms. Research should focus on understanding how lactate and lactylation affect gene expression, tumor metabolism and the immune microenvironment to identify new therapeutic targets and strategies, ultimately improving clinical outcomes for patients with GI cancer and potentially leading to more personalized and effective cancer treatment.

7. Conclusion

Lactate and lactylation serve a key role in the progression of GI cancers by modulating the TME, gene expression and immune response. Elevated lactate levels promote tumor growth, invasion and immune evasion through acidification and immune suppression. Lactylation regulates gene transcription and further supports tumor progression. Targeting lactate metabolism and lactylation presents potential therapeutic strategies, including glycolytic enzyme and MCT inhibitors and combination therapies. Future research should identify specific lactylation enzymes, develop reliable biomarkers, expand clinical trials and elucidate the underlying mechanisms to enhance personalized treatments and improve clinical outcomes for patients with GI cancer. Additionally, exploring the interplay between metabolic reprogramming and epigenetic modifications may reveal novel therapeutic targets and strategies, ultimately increasing the effectiveness of cancer therapy.

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Competing interests

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