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Research Article

Review: The Multifaceted Roles of Lactate in Gastric Cancer and Its Therapeutic Potential

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Abstract

Gastric cancer (GC) remains a leading cause of cancer-related mortality globally, with persistent challenges in overcoming treatment resistance and recurrence. Lactic acid was once considered a metabolic waste, but now it is considered a multifunctional coordinator of GC progression. This review synthesizes emerging evidence on lactate's multifaceted roles in GC progression, elucidating lactate's multifaceted roles in GC pathogenesis, including its regulation of tumor metabolic heterogeneity, epigenetic reprogramming, and immune microenvironment remodeling. Lactate fosters metabolic symbiosis between glycolytic and oxidative tumor cells, sustains chemoresistance via histone lactylation, RNA methylation, and chromatin phase separation, and promotes the immunosuppressive tumor microenvironment (TME) remodeling and immune evasion by suppressing CD8+ T-cell function and polarizing tumor-associated macrophages (TAMs) towards an M2 phenotype. and polarizing tumor-associated macrophages. Critically, lactate synergizes with Helicobacter pylori (Hp) to form a microbiome-metabolite axis that amplifies bacterial virulence, induces genomic instability, and accelerates malignant transformation. Therapeutic strategies targeting lactate production (LDH-A inhibitors), transport (MCT1/4 blockers), and signaling (epigenetic modulators/lactylation inhibitors) show promise in disrupting these oncogenic circuits. Nanotechnology-driven approaches and microbiome modulation (engineered probiotics) further enhance precision delivery and efficacy. Understanding the interplay between lactate, the tumor microenvironment (TME), and microbial communities offers novel avenues for overcoming therapeutic resistance and improving GC outcomes.

Keywords

Gastric Cancer, Lactate, Tumor Microenvironment, Metabolic Reprogramming, Epigenetics, Metabolic-epigenetic Crosstalk, Chemoresistance, Microbial Synergy

1. Introduction

Gastric cancer (GC) ranks as the fifth most common malignancy and the fourth leading cause of cancer-related deaths globally, with marked geographical disparities—highest incidence rates observed in Eastern Asia and Eastern Europe [1]. Despite advancements in surgical techniques, chemotherapy regimens (e.g., FLOT protocol), and targeted therapies (e.g., trastuzumab for HER2+ GC), treatment resistance and recurrence remain formidable challenges. Metabolic reprogramming, a hallmark of cancer, has gained prominence in understanding tumor progression. The Warburg ef-

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fect—aerobic glycolysis—drives lactate overproduction, which was historically dismissed as a metabolic waste product. However, emerging evidence positions lactate as a pleiotropic signaling molecule that orchestrates immune evasion, stromal remodeling, and therapeutic resistance within the TME [2]. This review comprehensively explores lactate's roles in GC pathogenesis, its interplay with the microbiome, and cutting-edge therapeutic strategies targeting lactate metabolism.

2. Lactate Production in Normal Physiology and Cancer

2.1. Physiological Lactate Generation

Lactate is one of the terminal products of glycolysis. In situations of limited oxygen availability, such as during vigorous physical activity, pyruvate is converted to lactate by lactate dehydrogenase, concurrently regenerating $NAD^+$to sustain the ongoing glycolytic process. Even in the presence of oxygen, certain cells, including erythrocytes and corneal cells, which are devoid of mitochondria, depend on glycolysis for lactate production as a source of energy [3]. Glycolysis is a mitochondrial-independent metabolic pathway capable of operating anaerobically, thus serving as an energy supply for these cells.

The released $H^+$from glycolysis combines with lactate anions to form non-dissociated lactate molecules, a process that can delay the rapid decline of intracellular pH [4]. The transcellular transport of lactate, commonly referred to as the lactate shuttle, is primarily facilitated by monocarboxylate transporters (MCTs).

MCT1 is a high-affinity transporter predominantly found in oxidative tissues such as the heart and slow-twitch muscle fibers, responsible for the uptake of lactate.

MCT4 is a low-affinity transporter mainly located in glycolytically active cells such as fast-twitch muscle fibers and tumor cells, responsible for the extrusion of lactate [5]. The co-transport of $H^+$and lactate to the extracellular space via MCTs helps to mitigate intracellular acidosis [6].

2.2. Lactate Overproduction in Tumors

Cancer cells are characterized by a high degree of metabolic plasticity, which allows them to prefer glycolysis as their primary metabolic pathway even in the presence of adequate oxygen, a phenomenon known as the Warburg effect. This form of "aerobic glycolysis" is driven by a combination of oncogenic signaling pathways, such as the activation of the PI3K/AKT/mTOR axis, the stabilization of hypoxia-inducible factor-1α(HIF-1α), and the overexpression of lactate dehydrogenase A (LDH-A). LDH-A catalyzes the conversion of pyruvate to lactate, contributing to the increased lactate production observed in cancer cells [7].

The TME is often acidic, with a pH ranging from approximately 6.5 to 6.9, which further promotes lactate accumulation. This acidic TME not only facilitates lactate buildup but also creates a pro-tumorigenic niche that supports cancer cell survival and progression. Positive feedback loop contributes to that: Lactic acid produced by glycolysis is excreted from cells through monocarboxylate transporter 4 (MCT4), leading to an increase in extracellular H^+ concentration (pH decrease). The acidic environment further activates HIF-1 α and glycolytic enzymes (such as LDHA), promoting more lactate production and forming a self reinforcing cycle. [8]

3. Molecular Mechanisms of Lactate in Gastric Cancer

3.1. Lactate and Tumor Metabolic Heterogeneity

The core of tumor metabolic heterogeneity lies in the lactate mediated "metabolic symbiosis" model. In this model, glycolytic cells (hypoxic zone) secrete lactate through the highly expressed MCT4 transporter protein. Oxidative phosphorylation cells (oxygen rich zone) take up lactate through MCT1 and use it as a raw material for mitochondrial energy (ATP) production. Therefore, if the treatment targets glycolysis (such as HK2 inhibitors), these cells can escape killing by enhancing oxidative phosphorylation. This metabolic division of labor not only maintains the energy balance of the tumor microenvironment, but is also closely related to treatment resistance and metastatic potential.

Metabolic heterogeneity is closely related to drug resistance mechanisms, such as through:

Metabolic reprogramming (MYC driven): MYC oncogenes reprogram metabolic pathways to confer chemotherapy resistance to tumor cells. MYC overexpression upregulates glucose transporters (such as GLUT1) and glutaminase (GLS1), promoting glycolysis and glutamine breakdown, providing a large amount of ATP and biosynthetic precursors. Meanwhile, MYC increases NADPH production by activating the pentose phosphate pathway (PPP), neutralizes reactive oxygen species (ROS) induced by chemotherapy drugs such as anthracyclines, and protects cells from oxidative damage [9]. It also influences microenvironmental effects (such as the role of adipocytes) [10], immune cell effects (macrophage polarization) [11], epigenetic regulation (metabolic epigenetic interactions) [12].

Next, we will gradually elaborate on the discussion of the content.

3.2. Epigenetic Regulation

Lactate plays a critical role in shaping the epigenetic landscape of gastric cancer (GC), contributing to tumor progression by modulating histone modifications, RNA methylation, chromatin phase separation and non-coding RNA

networks.

Lactate-Mediated HDAC Inhibition and Histone Acetylation

miR-21-5p/PTEN Axis

Lactate upregulates miR-21-5p, an oncogenic microRNA that directly targets and silences the tumor suppressor gene PTEN. Loss of PTEN results in constitutive activation of the PI3K/AKT/mTOR signaling pathway, promoting uncontrolled proliferation, survival, and metabolic reprogramming in GC cells. In patient-derived xenograft (PDX) models, lactate-enriched tumors exhibited a 3-fold increase in miR-21-5p levels and a corresponding 70% reduction in PTEN protein expression, correlating with accelerated tumor growth and chemotherapy resistance. Notably, pharmacological inhibition of HDACs (e.g., using trichostatin A) recapitulated these effects, confirming lactate's role as an HDAC antagonist [13].

Lactate-Driven Histone Methylation and Non-Coding RNA Networks

HIF-1α/lncRNA H19 Axis

Under normoxic conditions, lactate stabilizes hypoxia-inducible factor-1α (HIF-1α) by inhibiting prolyl hydroxylase (PHD)-mediated degradation. HIF-1α transcriptionally activates the long non-coding RNA H19, which recruits the polycomb repressive complex 2 (PRC2) via interaction with EZH2. This recruitment facilitates H3K27 trimethylation (H3K27me3) at the E-cadherin promoter, silencing its expression and driving epithelial-mesenchymal transition (EMT). Clinically, high H19 expression is associated with advanced TNM stage (HR = 2.3, $p< 0.001$) and reduced 5-year survival rates (28% vs. 65% in low H19 cohorts) [14].

Lactate and RNA methylation (m6A) Crosstalk in Gastric Cancer

Lactate dynamically interacts with N6-methyladenosine (m6A) modifications to orchestrate chemoresistance and immune evasion in gastric cancer (GC) through two distinct yet interconnected pathways:

Lactate Enhances m6A-Dependent tRNA-Derived Fragments (tRFs) to Stabilize HIF-1α and Promote Immune Evasion

Lactate upregulates the m6A methyltransferase METTL3 via activation of the lactate receptor GPR81. METTL3 catalyzes m6A modification of the tRNA-derived fragment 3'tRF-AlaAGC at position A36, enhancing its stability and abundance in GC cells. m6A-modified 3'tRF-AlaAGC binds directly to the 3' untranslated region (UTR) of HIF-1α mRNA, recruiting the m6A reader protein IGF2BP2. This interaction protects HIF-1α mRNA from degradation, increasing its half-life by 2.5-fold and elevating HIF-1α protein levels. HIF-1α transcriptionally activates glycolytic enzymes (e.g., LDHA, PDK1), further amplifying lactate production. Simultaneously, HIF-1α binds to the PD-L1 promoter, upregulating PD-L1 expression on tumor cells [15].

Lactate Induces METTL family Lactylation to Suppress Cuproptosis and Drive Chemoresistance

Lactate targets METTL family proteins through dual pathways: on one hand, it reduces FDX1 mRNA stability via METTL16, and on the other hand, it inhibits the copper ion-dependent functionality of FDX1 through METTL5. These synergistic effects lead to inactivation of the cuproptosis pathway, collectively promoting chemoresistance. The development of inhibitors targeting METTL16 or METTL5, or their combination with cuproptosis activators (e.g., copper ionophores such as elesclomol), may offer novel strategies to reverse GC chemoresistance. Additionally, targeting tumor microenvironment lactate metabolism (e.g., LDHA inhibitors) or lactylation-related enzymes (e.g., KAT2A) holds potential therapeutic value.

Lactic acid regulates METTL16 function through KAT2A mediated lactylation modification, thereby affecting chemotherapy resistance in gastric cancer (GC). Specifically, lactate induced lactylation modification of METTL16 at the K217 site significantly enhances its binding ability to FDX1 mRNA. METTL16, as an m6A methyltransferase, recruits YTHDF2 through m6A labeling of the FDX1 mRNA coding region (CDS), leading to degradation of FDX1 mRNA via the extracellular vesicle pathway. Downregulation of FDX1 protein levels can inhibit copper dependent mitochondrial cell death (copper ptosis), thereby endowing GC cells with resistance to copper ion carriers (such as elesclomol) and platinum based chemotherapy. It is worth noting that targeted knockout of METTL16 can restore FDX1 expression and significantly increase cisplatin sensitivity (4.2-fold), suggesting that the METTL16-FDX1 axis is a key regulatory node for reversing GC chemotherapy resistance [16].

Besides, lactate induces lactylation modification of METTL5 (methyltransferase like protein 5) at the K189 site, enhancing its interaction with copper chaperone protein CCS, blocking the transport of copper ions to FDX1 (iron sulfur cluster assembly protein), thereby inhibiting copper dependent mitochondrial cell death (copper death) and leading to cisplatin resistance [17].

Lactate-Induced Chromatin Phase Separation Drives Transcriptional Plasticity

Lactate induces chromatin structural remodeling and transcriptional activation through pH-dependent liquid-liquid phase separation (LLPS) in gastric cancer (GC). By lowering the nuclear pH, lactate creates an acidic microenvironment that alters the charge states of chromatin-associated proteins (e.g., histones and scaffold proteins), weakening their electrostatic interactions with DNA and resulting in chromatin decompaction. The loosened chromatin undergoes LLPS, forming dynamic condensates enriched with transcription factors (e.g., Mediator complex), RNA polymerase II, and super-enhancers. These condensates function as transcriptionally active hubs, significantly amplifying the expression of stemness-associated genes (e.g., ZEB1, SOX2), thereby promoting cancer stem cell-like properties and chemoresistance in GC cells [18].

NBS1 Lactylation Enhances Homologous Recombination (HR)

Lactic acid induces lysine lactylation (Kla) modification of DNA repair protein NBS1 (specific site K28), enhancing its binding ability to DNA double strand break (DSB) sites and accelerating the repair of DNA damage caused by chemotherapy drugs such as cisplatin. This modification directly enhances the tolerance of tumor cells to DNA damaging agents through epigenetic mechanisms. In GC organoids, lactate treatment reduces cisplatin sensitivity by 4.5-fold ($p < 0.001$), and NBS1 lactylation levels correlate with poor clinical response (HR = 2.3, $p = 0.002$) [19, 20].

Remodeling the Immune Microenvironment

The TME of gastric cancer represents a complex and dynamic ecosystem, encompassing a diverse array of tumor cells, various immune cell types, stromal elements, an extracellular matrix (ECM), and metabolic intermediates such as lactate. Within this intricate network, the GC immune microenvironment is meticulously sculpted by lactate-mediated metabolic reprogramming, alterations in ECM structure, and interactions with the microbiome. Recent scholarly advancements have shed light on novel mechanisms through which lactate and other components of the TME contribute to immunosuppression.

Lactate Suppresses CD8+ T-Cell Cytotoxicity

Epigenetic Silencing of IFN-γ

Mechanism: Lactate inhibits interferon-gamma (IFN-γ) production in CD8+ T cells by Inhibit mitochondrial oxidative phosphorylation (OXPHOS) of CD8+T cells and block their energy supply and inducing histone lactylation at the IFNG promoter. This epigenetic silencing correlates with increased expression of exhaustion markers (PD-1, TIM-3, LAG-3) [21].

In GC patients, high lactate levels correlate with elevated LAG-3+ CD8+ T cells ($r = 0.58$, $p< 0.001$) [22].

Blocking glycolysis and mitochondrial function of CD8+T cells

Glucose Deprivation: Lactic acid and glucose enter cells through the same transporter MCT1. High concentrations of lactic acid competitively inhibit the uptake of glucose by CD8+T cells, leading to a decrease in their glycolytic metabolic flux. This metabolic starvation reduces granzyme B levels by 50% and directly weakens its ability to kill tumor cells [23].

Lactate Polarizes TAMs to an Immunosuppressive M2 Phenotype

CSF1R/IL-10 Axis Activation

Lactate activates the colony-stimulating factor 1 receptor (CSF1R) on TAMs via GPR81 signaling, driving their differentiation into M2-like macrophages. These TAMs secrete IL-10 and TGF-β, which suppress CD8+ T-cell activity and promote angiogenesis [19]. That reflects the complex interaction of lactate in the tumor microenvironment.

In addition, Lactate induces upregulation of the transcription factor MAFB in TAMs, a master regulator of M2 polarization. MAFB knockout in TAMs restores CD8+ T-cell infiltration and suppresses tumor growth in GC mouse models ($p < 0.01$) [24].

Metabolic Reprogramming of TAMs

OXPHOS Activation: Lactate reshapes TAM metabolism via MCT1-dependent uptake, enhancing oxidative phosphorylation (OXPHOS). This metabolic shift stabilizes HIF-2α, which transcriptionally activates arginase-1 (ARG1), depleting arginine and impairing T-cell function. In GC patients, TAMs from high-lactate tumors exhibit 2.5-fold higher ARG1 activity ($p= 0.003$) and reduced overall survival (HR = 1.8, $p = 0.007$) [25].

Lactate regulates the expression of immune checkpoints

HIF-1α/PD-L1 Axis

Lactate stabilizes HIF-1α, which directly binds to the PD-L1 promoter, upregulating its expression on GC cells. Tumors with high lactate levels (≥10 mM) exhibit 3-fold higher PD-L1 positivity [26].

VISTA

Lactate activates NF-κB signaling in myeloid cells, inducing V-domain Ig suppressor of T-cell activation (VISTA). VISTA+ myeloid cells inhibit T-cell proliferation and IFN-γ production ($p< 0.01$) [27].

LAG-3

LAG-3 Induction: Lactate enhances LAG-3 expression on T cells via histone lactylation at the LAG3 promoter [28].

Driving Malignant Phenotypes

Different from the previously discussed Lactate Polarizes TAMs, which indirectly promote tumor immune escape by inhibiting anti-tumor immune responses (such as CD8+T cell function). In this section, we mainly focus on the direct regulation of molecular pathways (such as DNA repair, proliferation, autophagy) and interstitial interactions (such as ECM remodeling) in tumor cells by lactate Lactate fuels gastric cancer (GC) progression by promoting chemoresistance, enhancing proliferation, and driving metastasis through multiple molecular mechanisms.

Hippo-YAP/TAZ Pathway Drives Proliferation and MEK Resistance

LATS1/2 Inhibition and YAP/TAZ Activation

Lactate suppresses Hippo pathway kinases LATS1/2 via ROS-dependent degradation, enabling YAP/TAZ nuclear translocation. Activated YAP/TAZ upregulate pro-proliferative genes (e.g., CTGF, CYR61) and confer resistance to MEK inhibitors. YAP/TAZ enables tumor cells to survive under the pressure of MEK inhibitors through a triple mechanism of bypassing core pathway dependencies, reshaping metabolic/stress responses, and synergizing with other resistance pathways. Low YAP/TAZ activity in GC tumors correlates with higher 5-year survival rates than in low-YAP/TAZ cohorts ($p < 0.001$) [29].

Lactic Mediated Protective Autophagy and Mitophagy

In tumors, autophagy is often activated to help cells resist chemotherapy-induced damage. Mitophagy is a special form of autophagy that selectively clears dysfunctional mitochondria (such as those that produce excessive ROS), reducing oxidative stress damage to cells.

AMPK/mTOR pathway activation mediated autophagy

Lactic acid promotes the phosphorylation of AMPK by calmodulin dependent protein kinase 2 (CAMKK2) through a mechanism such as metabolic stress, leading to its activation. Activated AMPK inhibits mTORC1 activity, relieving its inhibition of ULK1/2. After ULK1/2 is released, autophagosome assembly is initiated to encapsulate damaged organelles (such as chemotherapy damaged mitochondria and endoplasmic reticulum) and degrade them, helping cells clear toxic substances and maintain survival [30].

BNIP3 mediated mitochondrial autophagy

Lactic acid inhibits the ubiquitination degradation of HIF-1 α by regulating the intracellular environment (such as acidosis or hypoxic microenvironment), leading to its accumulation in the nucleus. Stable HIF-1 α binds to the BNIP3 gene promoter, promoting its transcription and expression. BNIP3 is located on the damaged mitochondrial membrane and recruits mitochondria to autophagosomes by binding to autophagy related proteins such as LC3, which are then degraded by lysosomes. The mitochondrial damage caused by chemotherapy (such as excessive production of ROS) is selectively cleared, reducing the fatal impact of oxidative stress on cells and lowering ROS levels to prevent chemotherapy drugs from exerting their effects through oxidative damage, thereby enhancing drug resistance [31].

Low levels of ROS can act as signaling molecules to promote autophagy, but high levels of ROS can induce cell apoptosis. Lactic acid activates autophagy to clear some ROS, maintaining a low level of ROS in cells and avoiding apoptosis. Residual ROS may further stimulate lactate production (such as through metabolic reprogramming), forming a cycle of lactate accumulation → enhanced autophagy → partial clearance of ROS → continued lactate production, which continues to support tumor cell survival. This cycle maintains the redox balance of tumor cells under chemotherapy pressure, continuously activates autophagy, and forms drug resistance [45].

Lactate Modulates Non-Apoptotic Cell Death Mechanisms

Microbial Group-Lactate Axis in Gastric Cancer

The interplay between microbial communities and lactate metabolism plays a pivotal role in gastric carcinogenesis, immune modulation, and therapeutic resistance. Below, we dissect key mechanisms and clinical implications of the microbial-lactate axis in GC.

Helicobacter pylori (Hp) and Lactate Metabolic Adaptation

Lactic Acid Modulates Hp Virulence

Lactate produced by Hp and commensal bacteria (e.g., Lactobacillus) downregulates Hp motility genes (e.g., flgR) while enhancing acid resistance via the ArsRS two-component system. This metabolic adaptation allows Hp to thrive in the acidic gastric environment [32].

In addition, Hp infection upregulates LDH-A, amplifying lactate production. This creates a feedforward loop that sustains bacterial colonization and exacerbates gastritis, a precursor to GC [33].

Lactate Dynamics in the Gastric Microbiome

Hp Utilizes Lactate as a Nutrient Source: Hp metabolizes lactate via the lactate dehydrogenase complex, enhancing its survival and pathogenicity in acidic conditions. Lactate uptake also activates Hp's CagA virulence factor, promoting epithelial cell invasion [34].

Microbiome-Driven Pro-Inflammatory Microenvironment

Dysbiotic microbiota in GC patients overproduces lactate, which activates NLRP3 inflammasomes in macrophages, driving IL-1β secretion and chronic inflammation [35].

Microbial Lactate and Tumor Microenvironment

EMT and Immune Evasion

Hp-derived lactate induces epithelial-to-mesenchymal transition (EMT) in gastric cells via NF-κB/SNAIL activation. Concurrently, lactate polarizes macrophages to an M2 phenotype, secreting TGF-β to suppress CD8+ T-cell activity [36].

Synergistic Genomic Instability

Lactate synergizes with Hp's CagA toxin to induce reactive oxygen species (ROS), causing DNA double-strand breaks and genomic instability. This accelerates malignant transformation in TP53-mutant gastric epithelium [37].

Therapeutic Strategies Targeting Lactate

Inhibiting Lactate Production and Transport

LDH-A Inhibitors

Lactate dehydrogenase A (LDH-A) catalyzes the conversion of pyruvate to lactate. Selective inhibitors like block this reaction, reducing intratumoral lactate levels and disrupting the Warburg effect. In GC xenografts, GSK2837808A reduced tumor volume by 60% ($p < 0.001$) and suppressed metastasis by inhibiting HIF-1α stabilization [38].

MCT1 Inhibitors

Monocarboxylate transporter 1 (MCT1) mediates lactate uptake by oxidative cells. AZD3965, an oral MCT1 inhibitor, disrupts lactate shuttling, starving oxidative tumor cells and CAFs of metabolic fuel. In solid tumors, AZD3965 showed a manageable safety profile with dose-limiting cardiac toxicity in 15% of patients [39].

Nanotechnology-Driven Drug Delivery

pH-Responsive Nanoparticles

Poly(lactic-co-glycolic acid)-polyethylene glycol (PLGA-PEG) nanoparticles release oxaliplatin selectively in acidic TME (pH 6.5–6.9). In GC models, these nanoparticles increased tumor drug concentration by 3-fold and reduced systemic toxicity (e.g., neuropathy) compared to free oxaliplatin [40].

Lactate-Targeted Liposomes

Liposomes coated with lactate-binding peptides selectively accumulate in lactate-rich tumors. Lactate-modified liposomes improved doxorubicin delivery efficiency by 3-fold and extended median survival in GC-bearing mice from 45 to 68 days ($p < 0.01$) [40].

Microbiome Modulation

Probiotics Targeting Helicobacter pylori

Lactobacillus plantarum YT013 secretes bacteriocins (e.g.,

plantaricin) that inhibit Hp colonization by disrupting its membrane integrity.

In Hp-positive GC patients, YT013 supplementation reduced Hp load by 80% ($p < 0.001$) and enhanced chemotherapy response [41].

Engineered Probiotics for Immunomodulation

The CRISPR-Cas-based precision gene editing technology [42] has provided revolutionary tools for developing functional probiotics targeting gastric cancer. Recent studies have successfully engineered recombinant Lactobacillus reuteri with stable IL-10 secretion through CRISPR-mediated genomic integration strategies. Upon microenvironment-specific activation in gastric cancer, this engineered strain persistently releases IL-10 to suppress the NF-κB signaling pathway, achieving remarkable reductions in pro-inflammatory cytokines IL-6 and TNF-α levels (60–75% decrease), thereby effectively disrupting the tumor-associated inflammatory positive feedback loop [43]. In transgenic mouse models predisposed to gastric cancer, oral administration of this engineered probiotic demonstrated a 50% reduction in tumor incidence and a 32-day extension of median survival, showing synergistic effects with standard chemotherapy regimens. Notably, through metabolic reprogramming, this strain simultaneously targets key lactate metabolism pathways: its secreted IL-10 downregulates monocarboxylate transporter 4 (MCT4) expression, leading to intracellular lactate accumulation (2.1-fold concentration increase) in tumor cells. This metabolic shift subsequently induces cell cycle arrest at the G1 phase via activation of histone lactylation [44]. The distinctive "dual immune-metabolic targeting" capability exemplifies a paradigm shift in engineered probiotic design, transitioning from single-function modalities to system-level regulation approaches.

4. Conclusion and Future Directions

Lactate is now recognized as a key driver of gastric cancer (GC) progression, with far - reaching effects across multiple domains. Its roles in metabolic reprogramming, epigenetic changes, immune evasion, and microbial interactions are crucial. This review highlights lactate's dual role as a metabolic byproduct and a signaling molecule, driving tumor heterogeneity, chemoresistance, and immunosuppression through mechanisms such as histone lactylation, RNA methylation, and chromatin phase separation. Furthermore, the synergistic interplay between Helicobacter pylori (Hp) and lactate underscores the importance of the microbiome-metabolite axis in shaping gastric carcinogenesis and therapeutic resistance.

Nanotechnology further refines therapeutic approaches, with pH-responsive nanoparticles and exosome-mimetic vesicles normalizing tumor acidity and reactivating immunity, while CRISPR screens identify LDHA as a synthetic lethal target in TP53-mutant GC [46, 47].

Despite progress, challenges persist due to tumor metabolic plasticity and microenvironmental complexity. Future efforts must prioritize biomarker-driven stratification (e.g., MCT4-high tumors linked to poor immunotherapy response), microbiome modulation via probiotics to disrupt H. pylori-lactate symbiosis [48] and agents targeting lactate-induced T-cell exhaustion (e.g., LAG-3/PD-1 bispecific antibodies [49]. Innovations in nanomedicine, such as extracellular vesicles delivering LDHA siRNA and IL-15 [50], offer multifunctional solutions. By integrating metabolic, epigenetic, and immunotherapeutic strategies—guided by insights into lactate-driven stromal remodeling [51]—GC therapy may evolve from lethal to manageable, transforming patient outcomes through multidisciplinary precision.

Abbreviations

AKT	Protein Kinase B
AMPK	AMP-activated Protein Kinase
ARG1	Arginase-1
BNIP3	BCL2 interacting Protein 3
CAMKK2	Calcium/calmodulin-dependent Protein Kinase Kinase 2
CagA	Cytotoxin-associated Gene A
CAFs	Cancer-associated Fibroblasts
CDS	Coding Sequence
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CSF1R	Colony-stimulating Factor 1 Receptor
CTGF	Connective Tissue Growth Factor
CYR61	Cysteine-rich Angiogenic Inducer 61
ECM	Extracellular Matrix
EMT	Epithelial-mesenchymal Transition
EZH2	Enhancer of Zeste Homolog 2
FDX1	Ferredoxin 1
FLOT	Fluorouracil, Leucovorin, Oxaliplatin, Docetaxel
GC	Gastric Cancer
GPR81	G protein-coupled Receptor 81
HDAC	Histone Deacetylase
HER2	Human Epidermal Growth Factor Receptor 2
HIF-1 α	Hypoxia-inducible Factor-1 α
HL	Histone Lactylation
Hp	Helicobacter Pylori
IFN- γ	Interferon-gamma
IGF2BP2	Insulin-like Growth Factor 2 mRNA-binding Protein 2
IL-10	Interleukin-10
IL-1 β	Interleukin-1 Beta
Kla	Lysine Lactylation
LAG-3	Lymphocyte-activation Gene 3
LATS1/2	Large Tumor Suppressor Kinases 1/2
LC3	Microtubule-associated Protein 1A/1B-light Chain 3
LDH	Lactate Dehydrogenase

LDH-A	Lactate Dehydrogenase A
LLPS	Liquid-liquid Phase Separation
MAFB	MAF bZIP Transcription Factor B
m6A	N6-methyladenosine
MCT	Monocarboxylate Transporter
MCT4	Monocarboxylate Transporter 4
MEK	Mitogen-activated Protein Kinase Kinase
METTL3	Methyltransferase-like 3
mTOR	Mechanistic Target of Rapamycin
mTORC1	Mechanistic Target of Rapamycin Complex 1
NAD^+	Nicotinamide Adenine Dinucleotide
NF-κB	Nuclear Factor Kappa B
NLRP3	NLR Family Pyrin Domain Containing 3
NBS1	Nijmegen Breakage Syndrome 1
OXPHOS	Oxidative Phosphorylation
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-ligand 1
PDK1	Pyruvate Dehydrogenase Kinase 1
PDX	Patient-derived Xenograft
PI3K	Phosphoinositide 3-kinase
PPP	Pentose Phosphate Pathway
PRC2	Polycomb Repressive Complex 2
PTEN	Phosphatase and Tensin Homolog
ROS	Reactive Oxygen Species
siRNA	Small Interfering RNA
TAMs	Tumor-associated Macrophages
TAZ	Transcriptional Coactivator with PDZ-binding Motif
TGF-β	Transforming Growth Factor Beta
TIM-3	T-cell Immunoglobulin and Mucin-domain Containing-3
tRFs	tRNA-derived Fragments
ULK1/2	Unc-51-like Kinase 1/2
UTR	Untranslated Region
VISTA	V-domain Ig Suppressor of T-cell Activation
YAP	Yes-ASSOCIATED Protein
YTHDF2	YTH Domain Family Protein 2

Conflicts of Interest

The authors declare no conflicts of interest.

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