

Mechanisms of Lactate and Targeted Therapeutic Strategies in the Colorectal Cancer Microenvironment

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Abstract: Colorectal cancer (CRC) ranks among the most prevalent and lethal malignancies worldwide. Metabolic reprogramming is a hallmark of CRC, in which the Warburg effect drives massive lactate accumulation in the tumor microenvironment (TME) at concentrations far exceeding those in normal tissues. Traditionally recognized as a glycolytic waste product, lactate is now defined as a pleiotropic signaling molecule that profoundly remodels TME homeostasis and tumor progression. This review focuses on how lactate modulates CRC immunosuppressive networks via metabolic reprogramming, signal transduction and epigenetic regulation, and summarizes current advances in lactate-targeted therapeutic strategies for CRC.

Keywords: Colorectal cancer; Lactate; Tumor microenvironment; Metabolic reprogramming; Immunosuppression; Histone lactylation; Monocarboxylate transporter; Targeted therapy

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1. Introduction

CRC is the third most common human cancer and the second leading cause of cancer-related mortality globally ^[1]. Current therapeutic regimens, including surgery, chemotherapy, targeted therapy, and immunotherapy, have improved clinical outcomes for patients with partial CRC. However, the prognosis of advanced CRC remains poor, with low five-year survival rates. Accumulating evidence indicates that TME metabolic reprogramming is a central driver of CRC progression and immune evasion ^[2].

Aerobic glycolysis (the Warburg effect) constitutes a core metabolic signature of CRC. Regardless of oxygen availability, CRC cells preferentially utilize glycolysis rather than oxidative phosphorylation, leading to robust lactate production and secretion into the TME ^[3]. Lactate dehydrogenase A (LDHA), a rate-limiting enzyme converting pyruvate to lactate, is frequently upregulated in CRC and correlates with unfavorable clinical prognosis ^[4]. Physiologically, normal tissues contain 1.5–3 mM lactate, whereas the lactate

concentration in CRC TME reaches 10–40 mM. Such high lactate levels create an acidic TME that broadly regulates tumor malignant behaviors ^[5]. Lactate was previously considered a terminal glycolytic byproduct. Recent studies have revised this concept, identifying lactate as a vital signaling mediator in the TME ^[6]. Lactate shuttles between tumor and stromal cells via monocarboxylate transporters (MCTs) to sustain metabolic symbiosis within tumors ^[7]. Lactate metabolic signatures are tightly associated with immune infiltration and clinical prognosis in CRC ^[8,9]. In 2019, histone lactylation was identified as a novel epigenetic modification that links metabolic lactate to transcriptional regulation, establishing a new metabolism – epigenetics crosstalk paradigm ^[10]. Subsequent studies have validated the critical roles of lactylation in tumor immunosuppression, metabolic rewiring and therapeutic resistance ^[11]. This review systematically elucidates lactate-driven immunosuppressive mechanisms and discusses translational lactate-targeted strategies for CRC intervention.

2. Metabolic basis of lactate production and shuttling in CRC TME

2.1. Warburg effect and glycolytic reprogramming in CRC

The Warburg effect dominates metabolic reprogramming in CRC. Oncogenic alterations drive CRC cells to prioritize glycolysis over aerobic oxidation even under normoxic conditions ^[1]. KRAS mutations upregulate GLUT1 and glycolytic enzymes to enhance glucose uptake and glycolytic flux, while c-MYC activation transcriptionally induces LDHA expression. MicroRNAs negatively modulate LDHA overexpression in CRC and facilitate aerobic glycolysis and tumor proliferation ^[4]. Clinical cohort analyses have further verified the prognostic value of lactate metabolic signatures in CRC ^[12].

2.2. MCT1/MCT4-mediated lactate shuttling and metabolic symbiosis

MCT family members govern intercellular lactate transport in the TME. MCT4 (encoded by SLC16A3) possesses low lactate affinity and primarily exports lactate from glycolytic tumor cells. In contrast, high-affinity MCT1 (encoded by SLC16A1) mediates lactate uptake in oxidative tumor cells and stromal cells to support energy metabolism ^[7]. In CRC, NRF2 differentially regulates MCT1 and MCT4 expression to shape tumor–stroma metabolic coupling. CRC cells discharge lactate via MCT4, whereas cancer-associated fibroblasts (CAFs) uptake lactate through MCT1, forming a reverse Warburg effect that sustains tumor metabolic fitness ^[13,14].

2.3. Prognostic significance of lactate metabolic signatures

Lactate-related gene expression profiles reliably predict CRC prognosis and immune landscape. Lactate regulatory gene patterns correlate with immune cell infiltration, immune checkpoint expression and overall survival of CRC patients ^[8]. Integrated omics analyses further confirm lactate as a central hub bridging metabolic reprogramming and TME immunosuppression in CRC ^[9].

3. Lactate-mediated remodeling of CRC immune microenvironment

3.1. Lactate suppresses anti-tumor effector immune cells

CD8⁺ cytotoxic T lymphocytes (CTLs) are the primary anti-tumor immune effectors. TME lactate accumulation impairs CTL function by reducing intracellular pH and inhibiting NFAT transcriptional activity,

thereby suppressing IL-2 and IFN- γ production ^[15]. Lactate also blocks mTOR signaling, restraining CTL proliferation and effector differentiation. Moreover, lactate disrupts T cell metabolic flexibility and prohibits the glycolytic switch required for effector T cell activation ^[16].

Natural killer (NK) cell anti-tumor activity is also lactate-dependent. TME lactate downregulates NK cell activating receptors NKG2D and NKp46, reduces granzyme B and perforin release, and ultimately impairs NK-mediated tumor cytotoxicity, representing a major barrier for NK-based immunotherapy ^[17].

3.2. Lactate promotes immunosuppressive cell polarization and activation

Lactate actively recruits and activates immunosuppressive cell populations. It enhances latent TGF- β 1 activity to facilitate FoxP3+ regulatory T cell (Treg) differentiation, strengthening TME immune suppression ^[18]. For tumor-associated macrophages (TAMs), lactate activates HIF-1 α and STAT3 signaling to induce M2 polarization, upregulating M2 markers (ARG1, IL-10) and inhibiting pro-inflammatory cytokine secretion ^[19]. M2-TAMs further secrete IL-10 and TGF- β to amplify immunosuppression.

Myeloid-derived suppressor cells (MDSCs) are also lactate-responsive. LDHA-dependent lactate production promotes MDSC expansion and activation via STAT3 signaling in solid tumors, suggesting a conserved immunosuppressive axis applicable to CRC ^[20].

3.3. Lactate impairs antigen presentation

Lactate-induced histone lactylation in dendritic cells (DCs) disrupts antigen processing and presentation. This epigenetic impairment blocks adaptive immune priming and weakens systemic anti-tumor immune responses ^[21].

3.4. Positive feedback between immunosuppression and tumor glycolysis

Immunosuppressive TME sustains tumor glycolysis via a positive feedback loop. Tregs, M2-TAMs and MDSCs secrete IL-10 and TGF- β to upregulate HIF-1 α in CRC cells. HIF-1 α further transcriptionally activates glycolytic genes including GLUT1, HK2, LDHA and MCT4, which in turn increases lactate accumulation and exacerbates immunosuppression ^[22]. This self-reinforcing loop stabilizes the glycolytic and immunosuppressive TME phenotype.

3.5. Single-cell and spatial transcriptomic evidence for lactate-immune crosstalk

Single-cell RNA sequencing and spatial transcriptomics reveal distinct cell-cell interactions in CRC. Lactate-hyperactive CRC epithelial subpopulations are closely associated with T cell exhaustion and M2-TAM infiltration, confirming lactate as a core regulator of TME immune remodeling at high spatial and cellular resolution ^[23].

4. Lactate functions as a multifunctional signaling molecule

4.1. GPR81/HCAR1-dependent pro-tumor signaling

GPR81 (HCAR1) is a specific cell-surface lactate receptor. Lactate-GPR81 signaling drives tumor angiogenesis, immune escape and metabolic adaptation across multiple cancers ^[24]. In CRC, GPR81 activation enhances tumor cell proliferation and anti-apoptotic capacity ^[25]. GPR81 signaling also modulates antigen-presenting cell function and reshapes the immunosuppressive TME ^[26].

4.2. Lactate induces angiogenesis via NF-κB/IL-8 signaling

Endothelial MCT1-mediated lactate uptake activates NF-κB signaling, upregulates IL-8 expression and promotes tumor angiogenesis ^[27]. Targeting endothelial MCT1 abrogates lactate-induced HIF-1α activation and neovascularization, providing a novel anti-angiogenic strategy ^[28].

4.3. Lactate directly inhibits STING-mediated innate immunity

A recent 2026 study demonstrated that lactate directly binds and inhibits the STING sensor, thereby suppressing cGAS-STING-dependent type I interferon responses and facilitating tumor innate immune evasion. This receptor-independent mechanism defines lactate as a critical immune checkpoint modulator ^[29].

5. Histone lactylation: Metabolite-driven epigenetic reprogramming

5.1. Regulatory roles of histone lactylation in CRC

Histone lactylation bridges lactate metabolism and epigenetic regulation in CRC. Lactylation rewires tumor metabolic programs and sustains malignant progression ^[30]. Targeting lactylation improves immunotherapeutic efficacy in gastrointestinal cancers, indicating broad translational potential for CRC treatment ^[31]. Lactylation-associated positive feedback loops further stabilize tumor metabolic and epigenetic dysregulation ^[32].

5.2. Lactylation sustains immunosuppression and therapeutic resistance

Lactylation epigenetically locks immunosuppressive transcriptional programs, endowing the TME with epigenetic immune memory ^[33]. Additionally, lactylation contributes to CRC therapeutic resistance by modulating drug efflux, DNA damage repair and apoptotic escape, severely limiting clinical treatment efficacy ^[34].

6. Lactate-targeted therapeutic strategies for CRC

6.1. MCT1 inhibition

MCT1 is essential for stromal and oxidative tumor cell lactate utilization. High-resolution MCT1 structural analysis supports rational targeted drug design ^[35]. The clinical-stage MCT1 inhibitor AZD3965 exhibits favorable safety and anti-tumor activity in preclinical models ^[36]. In drug-resistant CRC, MCT1 dependency creates a metabolic vulnerability; MCT1 blockade suppresses resistant tumor growth and synergizes with chemotherapy and immunotherapy ^[37–39].

6.2. MCT4 inhibition and immunotherapy combination

MCT4 is overexpressed in metastatic CRC and drives tumor migration and invasion ^[40]. Pharmacological MCT4 inhibition reduces lactate efflux, reverses TME acidification, restores CD8+ T cell anti-tumor activity, and enhances immune checkpoint blockade efficacy ^[41]. Selective MCT4 chemical probes have been developed to support further drug development ^[42].

6.3. LDHA-targeted metabolic intervention

As a key lactate-producing enzyme, LDHA is an upstream therapeutic node. Although LDHA inhibitors

exert anti-tumor effects in preclinical models, clinical translation is hindered by poor selectivity and systemic toxicity^[43]. Alternatively, EGCG disrupts CAF glycolysis and tumor–stroma metabolic coupling, providing an indirect lactate-targeting strategy for CRC^[44].

6.4. Lactate-depleting nanotherapeutics

Nanoplateforms enable precise TME lactate depletion and acid neutralization, effectively reversing tumor immunosuppression^[45,46]. Although CRC-specific lactate-targeted nanomedicines remain under development, emerging nanotechnologies provide robust proof-of-concept for future clinical translation.

6.5. Targeting histone lactylation

Pharmacological inhibition of histone lactylation enhances gastrointestinal tumor immunotherapy responses, representing an innovative epigenetic strategy for CRC treatment^[47]. Nevertheless, the regulatory mechanisms and translational applications of lactylation require further investigation.

7. Discussion and conclusions

Lactate orchestrates a self-amplifying “metabolism–immunity–epigenetics” tripartite network in CRC TME. Warburg effect-derived lactate inhibits anti-tumor immune cells, recruits immunosuppressive populations and impairs antigen presentation. It also promotes immune evasion via GPR81 signaling and STING suppression. Furthermore, lactate-induced histone lactylation transforms transient metabolic stress into stable epigenetic memory, sustaining TME immunosuppression and tumor malignancy.

Future CRC therapeutic strategies will shift from single-target inhibition to multi-modal combinatorial interventions targeting lactate-centered networks, combined with molecular subtype-based precise stratification. Current limitations include insufficient clinical data on MCT inhibitors in CRC and incomplete understanding of lactylation regulatory mechanisms. Systematic preclinical evaluation of multi-node combination regimens is urgently needed to advance lactate-targeted therapy for clinical CRC.

Disclosure statement

The authors declare no conflict of interest.

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