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Molecular Orchestration of Lactylation in Colorectal Cancer: From Metabolic Reprogramming to Epigenetic Regulation

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Abstract: Lactylation, a recently discovered post-translational modification (PTM), involves lactyl group conjugation to lysine residues of histone and non-histone proteins. It regulates protein function and gene expression and is closely linked to tumorigenesis and therapeutic response. In colorectal cancer (CRC), Warburg effect-induced lactate accumulation activates lactylation, which drives CRC progression by promoting oncogene expression, tumor growth, metastasis and chemoresistance, and forms regulatory networks via crosstalk with other PTMs. This review summarizes the molecular mechanisms, functional roles and clinical relevance of lactylation in CRC, highlighting its potential as a promising target for novel CRC therapeutics.

Keywords: Lactylation; Post-translational modification; Colorectal cancer; Tumor metabolic environment; Warburg effe

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1. Introduction

Colorectal cancer (CRC) is a major global health concern, ranking third in incidence and second in cancer-related mortality worldwide[1]. Although traditionally an age-related malignancy, the rising incidence of early-onset CRC is associated with environmental and lifestyle factors such as obesity, physical inactivity, alcohol consumption, diabetes mellitus, and insulin resistance[2, 3].

The Warburg effect, a hallmark of malignant tumors including CRC, refers to the preferential reliance of tumor cells on glycolysis for energy production even under oxygen-rich conditions, instead of oxidative phosphorylation[4, 5]. At the final step of glycolysis, pyruvate is converted to lactate by lactate dehydrogenase (LDH) and transported across the cell membrane via monocarboxylate transporters (MCTs), mainly MCT1 and MCT4[6] **(Figure 1)**. Aberrant MCT activity disrupts lactate cycling, acidifies the tumor microenvironment (TME), and inhibits immune responses[7].

Recent studies have increasingly focused on the role of post-translational modifications (PTMs) in cancer progression[8]. In 2019, Zhang et al. first identified histone lactylation in humans, linking PTMs to elevated lactate levels[9]. Lactate is now recognized as a key precursor of lactylation rather than a metabolic waste. This review focuses on protein lactylation, exploring its molecular regulatory mechanisms, biological functions in CRC development, and potential clinical value.

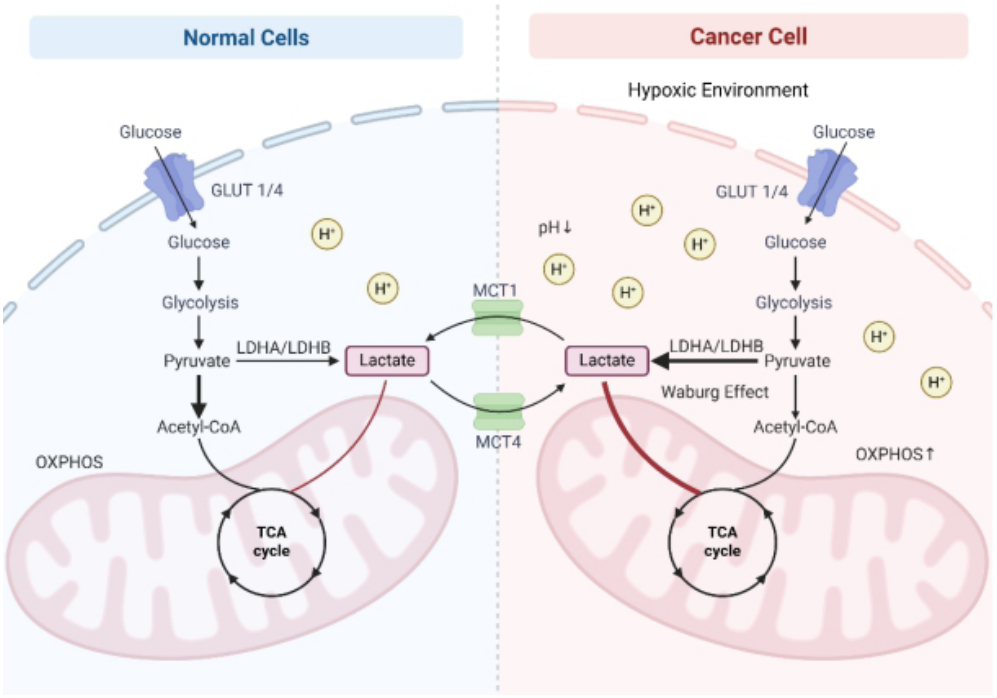

Figure 1. The overview of lactate metabolism in normal and tumor cells

2. Molecular regulatory mechanism of lactylation

Lactylation modulates the function or stability of the modified protein through the covalent attachment of a lactyl group to lysine residues in the target protein[10]. The biochemical basis of this mechanism relies on cellular lactate metabolism, which is catalyzed by lactate dehydrogenase A (LDHA) [11].

In the canonical lactylation enzymatic pathway, L-lactyl-CoA acts as the lactyl donor. Despite mechanistic parallels to acetylation, L-lactyl-CoA has an intracellular concentration approximately 1/1000 that of acetyl-CoA[10, 12], limiting lactyltransferase activity. When glycolytic flux exceeds glyoxalase cycle capacity, aminoacyl-tRNA synthetases 1/2 (AARS1/2) act as lactyltransferases, binding L-lactate to generate lactate-AMP and conjugate lactyl groups to protein lysine residues[10, 13, 14]. An alternative non-enzymatic pathway uses methylglyoxal (MGO)-derived lactylglutathione, converted to D-lactate as a lactyl donor[10, 15]. Lactylation is dynamically modulated by "writer" enzymes including p300, CBP and KAT8[16, 17] and "eraser" enzymes e.g., HDAC1/3, SIRT1/3 that mediate negative feedback via lactyl group removal[18, 19, 20], though their precise mechanisms and regulatory efficacy require further investigation.

3. Biological function of lacytlation in colorectal cancer

Histones are core nucleosome components[21]. Histone lactylation promotes CRC progression by driving chromatin remodeling and transcriptional activation, whereas non-histone lactylation regulates metabolic pathways through metabolic reprogramming and epigenetic modulation[22, 23]. These lactylation-dependent protein modifications drive malignant phenotypes including proliferation, metastasis and chemoresistance[23, 24], which is shown in **Figure 2**.

3.1. Histone lactylation and transcriptional reprogramming in CRC

In CRC, H3K18la and H4K12la levels are tightly correlated with tumor progression and poor clinical outcomes [25, 26]. Stress/ECM-induced CPR37/Hippo pathway dysregulation activates LATS1/YAP1 to upregulate LDHA, elevating lactate/

H3K18la and CXCL1/CXCL5 expression to promote CRC migration and liver metastasis[27, 28, 29]. H3K18la also mediates METTL3 upregulation to activate the JAK1/STAT3 pathway, inducing TIMs-related immunosuppression[28]. Meanwhile, H4K12la-driven GCLC overexpression in CCSCs enhances glutathione synthesis, inhibits chemotherapy-induced ferroptosis, and confers oxaliplatin resistance [25].

3.2. Non-histone lactylation regulating protein function in CRC

eEF1A2 is a conserved protein that facilitates ribosome binding to AARS1/2 during protein synthesis[30, 31]. The pan-lactyltransferase KAT8 mediates lactylation of this non-histone protein at the K408 site[19]. Lactylation also drives a negative feedback loop in cellular metabolism: in colon cancer cells, lactylation of glycolytic enzymes phosphofructokinase (PFKP) and aldolase A (ALDOA) impairs their enzymatic activity, whereby elevated lactate levels self-limit excessive glycolysis and reduce intracellular lactate accumulation[32]. In addition, the ALDOB–PDK1–LDHB–CEACAM6 metabolic axis mediates CRC chemoresistance via the Warburg effect[33].

3.3. Crosstalk of lactylation with other PTMs regulate tumor growth

Emerging evidence identifies extensive crosstalk between lactylation and other PTMs. Lactylation and m^{6}A modification form a positive feedback cascade: histone lactylation activates transcription of m^{6}A regulators including METTL3 and YTHDF2, and enhances their stability and catalytic activity[34, 35]. Activated m^{6}A in turn stabilizes key glycolytic enzymes e.g., LDHA, HK2, PKM2 to boost lactate production, further amplifying lactylation in a vicious cycle[36].

Histone lactylation is dynamically regulated by competitive enzyme binding to lactyl-CoA and acetyl-CoA[37]. In KRAS-mutant CRC, elevated lactate drives a H3K9 modification switch from acetylation to lactylation, which increases chromatin accessibility, upregulates cholesterol transporter GRAMD1A, and promotes CRC growth and metastasis[38, 39].

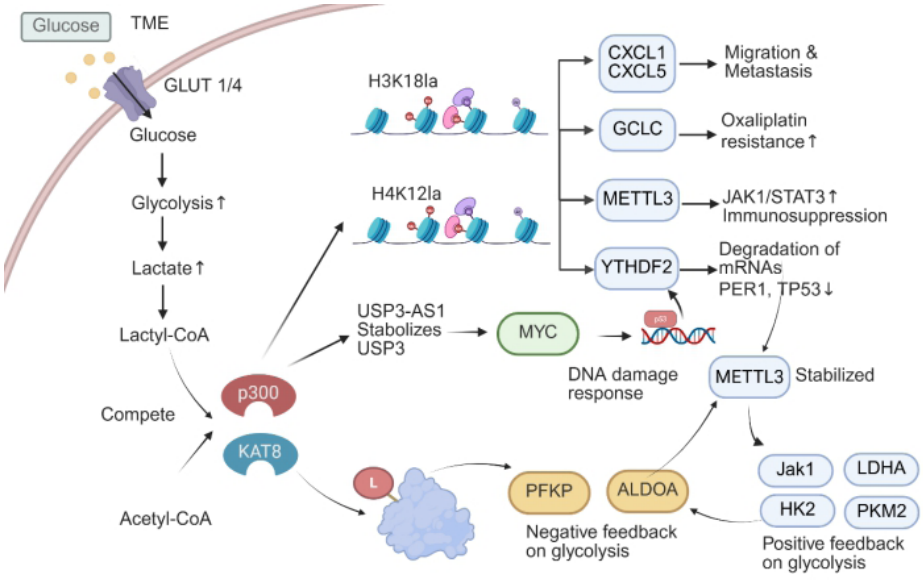

Figure 2. Mechanistic landscape of protein lactylation in CRC progression.

4. The role of lactylation in shaping TME in CRC

Lactylation critically regulates the immunosuppressive and angiogenic TME[26] and enhances CRC cell stemness and self-renewal under hypoxia[40, 41]. Targeting lactylation to remodel the TME and switch “cold tumors” to “hot tumors” thus provides a novel strategy to improve CRC therapeutic outcomes.

4.1. Lactate, lactylation, and the immune system

Lactate-enriched TME drives immunosuppression via modulating intracellular signaling and remodeling immune cell phenotypes[42,43]. High lactate/lactylation potently induces TAM polarization to the protumorigenic M2 phenotype[44]; lactylation downregulates RARγ to activate the TRAF6/IL-6/STAT3 axis, promoting a "cold tumor" immune-evasive phenotype[45,46], and upregulates CD39/CD73 on T cells and Tregs to trigger T cell dysfunction and immunosuppression[47,48]. Tumor-resident microbiota regulates gut disease progression. Intratumoral Escherichia coli enhances glycolysis and lactate production, inducing macrophage RIG-I lactylation to suppress NF-κB and NLRP3 inflammasome activation, thus weakening immune surveillance and promoting liver metastasis[44,49].

4.2. Lacate and lactylation influence angiogenesis

Angiogenesis, a hallmark of tumor progression, drives tumor growth and metastasis. Lactate stabilizes HIF1α in vascular endothelial cells via MCT1[18, 50, 51], induces TAM M2 polarization with Arg1/VEGF upregulation to enhance angiogenesis[52, 53], and upregulates pro-angiogenic interleukin-8 (IL-8) to promote neovascular maturation[54]. This angiogenic phenotype strongly correlates with immunotherapy resistance in metastatic CRC, especially MSS/MMR-proficient subtypes[55]. Furthermore, H3K18la confers bevacizumab and anti-angiogenic therapy resistance via RUBCNL-mediated autophagy[26].

5. Conclusion and perspective

Diverse oncogenic pathways converge on lactylation, making it a promising therapeutic target. Elevated specific lactylation marks can act as diagnostic biomarkers (verified by single-cell sequencing[13,26]), and lactylation-related gene signatures enable prognostic prediction of patient survival and immunotherapy response[56], despite diagnostic limitations of low sensitivity and high false-positive rates from non-specific binding [57].

Lactylation of DNA repair protein NBS1 enhances DNA repair, mediates chemo-radiotherapy resistance, and correlates with patient prognosis[58]. Lactylation can be targeted via inhibiting LDHA/MCT1 to limit lactyl supply[59], or blocking writer enzymes e.g.,, AARS2 to restore anti-tumor immunity[60], with safe dosage needing rigorous validation in clinical trials given lactylation's presence in normal cells.

This review systematically elaborates lactylation's molecular mechanisms and multifaceted roles in CRC, which bridges the Warburg effect and oncogenic programming. Lactylation drives CRC malignancy via regulating histone/non-histone proteins to mediate stemness, immune evasion and therapy resistance. Future research should focus on identifying lactylation-related enzymes and developing selective inhibitors, to provide novel strategies for overcoming CRC drug resistance and improving treatment outcomes.

Disclosure statement

The author declares no conflict of interest.

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