Perspective

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Histone lactylation as a driver of metabolic reprogramming and immune evasion

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Abstract: Lactate is the end product of glycolysis, and extensive research has shown that lactate participates in various pathophysiological processes. Along with associated hydrogen ions, lactate typically functions as an immunosuppressive negative factor and plays a crucial role in tumor metabolic reprogramming. The recently discovered lactylation is a novel epigenetic modification that, similar to other epigenetic modifications, modifies histones to alter chromatin spatial configuration, thereby affecting DNA accessibility and regulating gene expression. More importantly, the degree of lactylation is closely related to local lactate concentrations, establishing a link between epigenetics and metabolic reprogramming. During cellular metabolism, lactate accumulation promotes histone lysine lactylation in cancer cells and immune cells such as macrophages and T cells, playing an essential role in tumor immune evasion and resistance to immunotherapy. This paper details the role of lactylation modifications in cancer immune evasion and resistance to immunotherapy, providing novel therapeutic directions and targets for cancer treatment.

Keywords: cancer; immune escape; histone lactylation; immunotherapy resistance

Formation of histone lactylation

Histones are composed of repeating units called nucleosomes, each consisting of a core octamer, a monomeric histone, and approximately 200 base pairs of DNA. About 146 base pairs of DNA are wound around the core octamer, with approximately 55 base pairs linking the monomeric histone. Histone modifications, including methylation, acetylation, phosphorylation, and ubiquitination, involve attaching various acyl groups to histone amino acid residues, affecting the tightness of histone-DNA binding. According to the study by Zhang et al. the occurrence of histone lactylation is similar to histone acetylation [1]. When exogenous or endogenous lactate accumulates to a certain concentration, cellular lactylation-regulating molecules are activated. Relevant enzymes use lactyl-coenzyme A as a substrate to transfer lactate to histone residues. This process alters the tightness of histone-DNA binding, indirectly affecting mRNA transcription and protein translation. Lactate can move between cells through “lactate shuttles” involving MCT1 and MCT4, serving as a universal energy source. In tumor cells, even with sufficient oxygen, cells prioritize glycolysis over oxidative phosphorylation for rapid energy acquisition, leading to increased intracellular and extracellular lactate concentrations. High lactate concentrations can induce histone lactylation, regulating DNA damage repair and tumor chemotherapy resistance and impacting immune cell cytotoxicity [2]. This metabolic epigenetic modification links the high-lactate tumor microenvironment created by metabolic reprogramming to tumor immune evasion and resistance to immunotherapy (Figure 1).

Histone lactylation modifications and cancer immune evasion

Histone lactylation in tumor cells

Lactate-induced lactylation regulates and creates a tumor microenvironment favorable for immune evasion, facilitating tumor survival and development (Figure 2). In head

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and neck squamous cell carcinoma, lactate-induced expression of H3K9la accumulates in the *IL11* gene, increasing transcription of IL-11. This activates the JAK2/STAT3 pathway in CD8+ T cells, enhancing immune checkpoint genes such as *PD1*, *TIGIT*, and *CTLA4*, ultimately leading to CD8+ T cell exhaustion and impaired function [3]. In acute myeloid leukemia (AML), *STAT5* is highly expressed, activating glycolytic gene promoters and promoting glycolysis in AML cells. Accumulated lactate significantly induces lactylation modifications at H3K18, H4K5, H4K8, and H4K12. Specifically, H4K5 lactylation is enriched in the *PD-L1* promoter region of AML cells with *STAT5* overexpression. Additionally, E3BP interacts with H4K5 lactylation in AML cells, enhancing this modification. Lactate promotes nuclear import of E3BP, further elevating histone lactylation levels. The induced *PD-L1* expression significantly inhibits CD8+ T cell tumoricidal activity [4]. In non-small cell lung cancer (NSCLC), lactate-induced H3K18la directly binds to the *POM121* promoter, positively regulating *POM121* expression. This promotes MYC nuclear translocation, upregulating *PD-L1* expression and facilitating immune evasion. Blocking H3K18la in NSCLC cells restores CD8+ T cell function [5].

Histone lactylation in macrophages

The high-lactate environment of the tumor microenvironment induces histone lactylation in macrophages (Figure 2). Studies indicate that histone lactylation mediates the transformation of M1 macrophages, with immune-promoting and tumoricidal functions, into M2 macrophages, which are immunosuppressive and promote tissue repair and tumor progression. Under conditions such as hypoxia, interferon (IFN)-γ, lipopolysaccharide (LPS), or bacterial infection, macrophage lactate levels rise. Accumulated lactate increases histone lysine lactylation modifications at gene promoters, directly regulating gene expression. For instance, histone lactylation enrichment at the promoters of M2-like genes *ARG1* and *KLF4* increases their expression, shifting macrophages from M1 to M2 phenotype [1]. In colon cancer, lactate in tumor-infiltrating myeloid cells promotes *METTL3* expression through H3K18 lactylation and lactylates the zinc finger domain of METTL3. This enhances *Jak1* mRNA methylation, binding with *YTHDF1* to increase translation efficiency, activating the JAK1-STAT3 signaling pathway and initiating downstream immunosuppressive molecule expression [6]. In

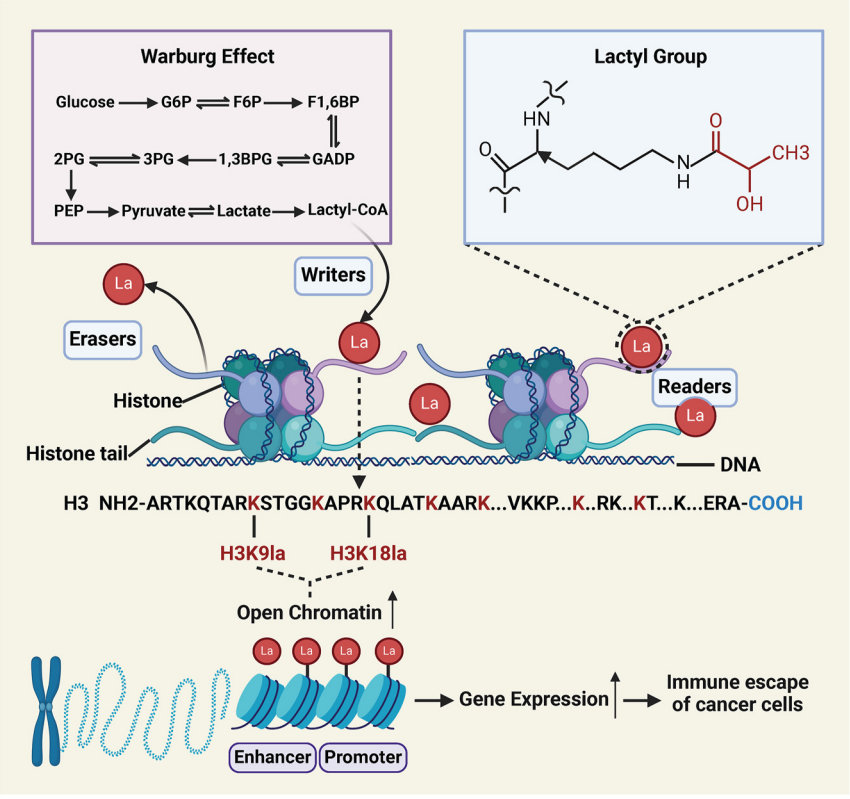

Figure 1: The molecular mechanism of histone lactylation modification formation. The warburg effect promotes glycolysis in tumor cells, leading to the production and accumulation of lactate. The accumulated lactate facilitates the generation of lactyl-CoA, which serves as a donor of lactyl groups for histone lactylation catalyzed by writers. Histone lactylation promotes chromatin opening, with modifications at H3K18 and H3K9 sites found to be closely associated with immune evasion.

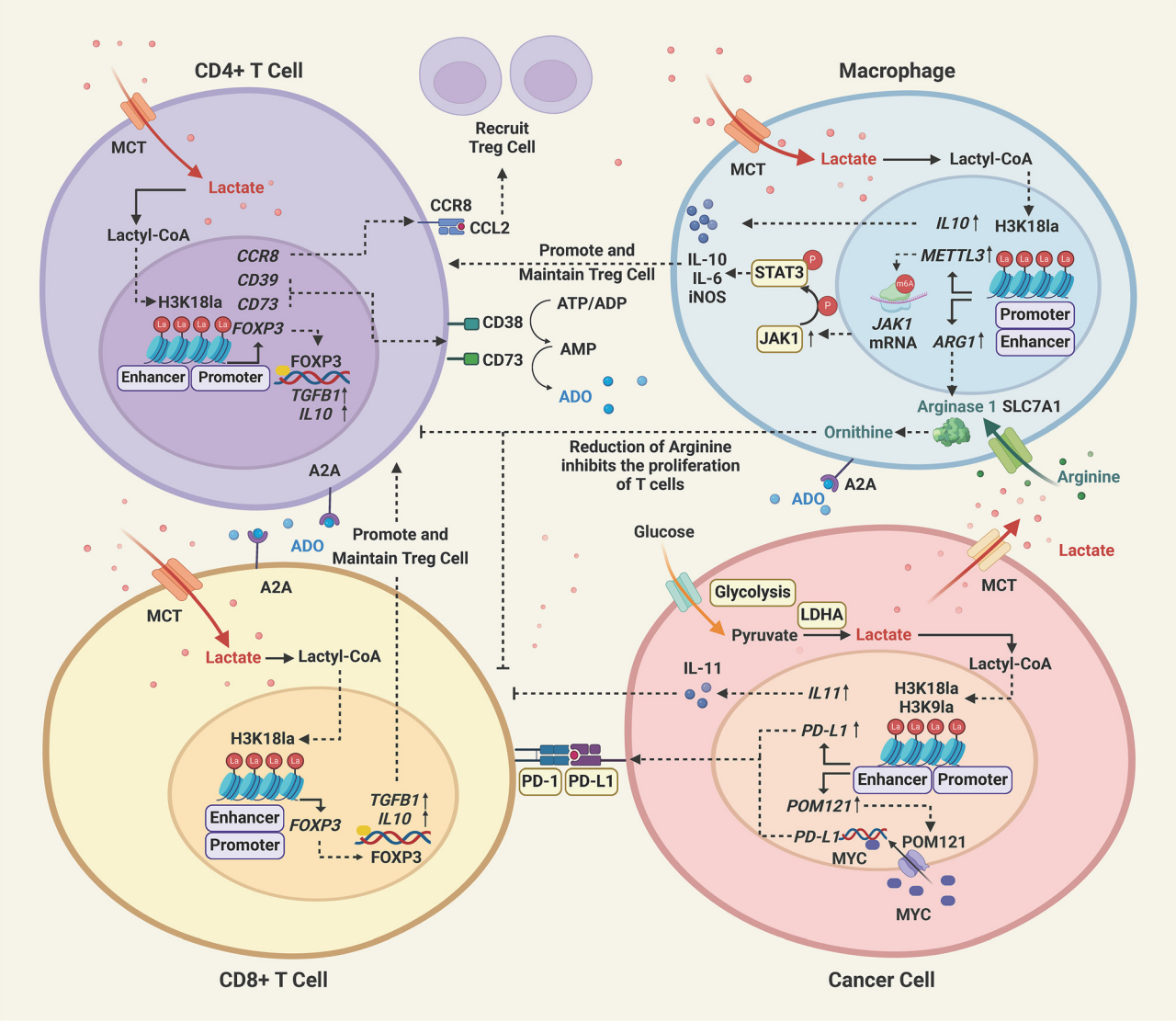

Figure 2: Histone lactylation modification promotes cancer immune evasion. The warburg effect promotes tumor production and secretion of lactate, which enhances histone lactylation in cells within the tumor microenvironment. This ultimately leads to the expression of PD-L1 in tumor cells, the production of TGFβ and IL-10 by CD8+ T cells, the expression of CCR8, CD39, CD73, and FOXP3 by CD4+ T cells, and the production of IL-10, IL-6, and iNOS by macrophages, along with the consumption of arginine. These changes collectively contribute to tumor immune evasion.

glioblastoma, endoplasmic reticulum stress-induced PERK drives glucose metabolism, promoting *IL10* expression in monocyte-derived macrophages (MDMs) through histone lactylation, exerting immunosuppressive effects [7]. In PTEN/p53-deficient prostate cancer, reduced lactate production after treatment with PI3K inhibitors reverses TAM histone lactylation-mediated inhibition, stimulating TAM phagocytosis and achieving long-term tumor control with manageable toxicity under intermittent dosing [8].

Histone lactylation in T cells

T cells in the tumor microenvironment are closely linked to immune evasion and resistance to immunotherapy (Figure 2). In malignant pleural effusion (MPE), a subset of FOXP3+ NKT-like cells with highly activated glycolysis and pyruvate metabolism expresses high levels of MCT1 and lactate dehydrogenase B, enabling lactate uptake and utilization to maintain immunosuppressive functions and high lactylation in MPE [9]. In Th17 cells, extracellular lactate dysregulates Th17-specific gene expression programs by altering their metabolic and epigenetic states. Lactate reduces IL-17 A production and induces *Foxp3* expression via ROS-driven IL-2 secretion, reprogramming pro-inflammatory T cells into regulatory T cells [10]. In the study by Sun et al. lactate induces Treg histone H3K18 lactylation, enhancing the activity of *CD39*, *CD73*, and *CCR8* gene promoters. Combined treatment with Oxamate and CAR-T therapy not only

reprograms glucose metabolism in cancer cells but also alters the immunosuppressive tumor microenvironment by reducing adenosine production and tumor-infiltrating Treg cells, potentially enhancing CAR-T efficacy in glioblastoma therapy [11].

Discussion

Lactate, as a core energy metabolism substrate, serves as a key intercellular metabolic molecule in the tumor microenvironment. Tumor cells undergoing metabolic reprogramming acquire large amounts of energy via aerobic glycolysis and transport lactate through "lactate shuttles" to other cells in the microenvironment. The significantly increased lactate concentration in tumor microenvironments not only creates a tumor-promoting acidic environment but also provides substrates for lactylation in tumor-associated cells. Research shows that lactate accumulation-induced lactylation directly affects immune checkpoint expression and activates immunosuppressive pathways in immune cells, reshaping the microenvironment. In conclusion, lactate and lactylation modifications play critical roles in tumor immune evasion and resistance to immunotherapy. Targeting lactate metabolism and lactylation modifications represents a promising therapeutic direction, warranting exploration to inhibit the tumor-promoting effects of lactate while preventing lactylation-induced suppression of immune cytotoxicity. In the future, vaccines targeting histone lactylation may be developed, especially circular RNA vaccines, which have the potential to treat histone lactylation related cancers [12]. Investigating these aspects is crucial for advancing cancer treatment strategies.

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References

1. Zhang D, Tang Z, Huang H, Zhou G, Cui C, Weng Y, et al. Metabolic regulation of gene expression by histone lactylation. Nature 2019;574:575–80.
2. Li J, Chen ZS, Pan Y, Zeng L. The important role of lactylation in regulating DNA damage repair and tumor chemotherapy resistance. Drug Resist Update 2024;78:101148.
3. Wang R, Li C, Cheng Z, Li M, Shi J, Zhang Z, et al. H3K9 lactylation in malignant cells facilitates CD8+ T cell dysfunction and poor immunotherapy response. Cell Rep 2024;43. https://doi.org/10.1016/j.celrep.2024.114957.
4. Huang ZW, Zhang XN, Zhang L, Liu LL, Zhang JW, Sun YX, et al. STAT5 promotes PD-L1 expression by facilitating histone lactylation to drive immunosuppression in acute myeloid leukemia. Signal Transduct Targeted Ther 2023;8:1–13.
5. Zhang C, Zhou L, Zhang M, Du Y, Li C, Ren H, et al. H3K18 lactylation potentiates immune escape of non-small cell lung cancer. Cancer Res 2024;84:3589–601.
6. Xiong J, He J, Zhu J, Pan J, Liao W, Ye H, et al. Lactylation-driven METTL3-mediated RNA m6A modification promotes immunosuppression of tumor-infiltrating myeloid cells. Mol Cell 2022;82:1660–77.e10.
7. De Leo A, Ugolini A, Yu X, Scirocchi F, Scocozza D, Peixoto B, et al. Glucose-driven histone lactylation promotes the immunosuppressive activity of monocyte-derived macrophages in glioblastoma. Immunity 2024;57:1105–23.e8.
8. Chaudagar K, Hieromnimon HM, Khurana R, Labadie B, Hirz T, Mei S, et al. Reversal of lactate and PD-1-mediated macrophage immunosuppression controls growth of PTEN/p53-deficient prostate cancer. Clin Cancer Res 2023;29:1952–68.
9. Wang ZH, Zhang P, Peng WB, Ye LL, Xiang X, Wei XS, et al. Altered phenotypic and metabolic characteristics of FOXP3+CD3+CD56+ natural killer T (NKT)-like cells in human malignant pleural effusion. OncoImmunology 2023;12. https://doi.org/10.1080/2162402x.2022.2160558.
10. Lopez KA, Nehring HP, Krause FF, Wempe A, Raifer H, Nist A, et al. Lactate induces metabolic and epigenetic reprogramming of pro-inflammatory Th17 cells. EMBO Rep 2022;23:e54685.
11. Sun T, Liu B, Li Y, Wu J, Cao Y, Yang S, et al. Oxamate enhances the efficacy of CAR-T therapy against glioblastoma via suppressing ectonucleotidases and CCR8 lactylation. Exp Clin Cancer Res 2023;42:1–14.
12. Xie J, Ye F, Deng X, Tang Y, Liang JY, Huang X, et al. Circular RNA: a promising new star of vaccine. J Transl Int Med 2023;11:372–81.