

Praca poglądowa/Review paper

Histone Lactylation in Cancer: Linking Hypoxia-Driven Metabolism to Epigenetic Regulation

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Abstract

Solid tumors are frequently characterized by hypoxia, which drives metabolic reprogramming toward glycolysis and increased lactate production. Beyond its role as a metabolic end product, lactate can influence gene regulation through histone lactylation, a recently identified post-translational modification linking cellular metabolism with epigenetic regulation. In cancer, hypoxia-associated lactate accumulation and histone lactylation have been implicated in tumor proliferation, invasion, epithelial–mesenchymal transition, immune modulation, and therapeutic resistance. This review summarizes current knowledge of the relationship between hypoxia, lactate metabolism, and histone lactylation, focusing on the molecular mechanisms regulating this modification and its potential role in cancer progression. We also discuss current methodological challenges and the potential of the lactate–histone lactylation axis as a target for future diagnostic and therapeutic strategies in oncology.

Keywords: Histone lactylation; lysine lactylation; epigenetics; cancer; hypoxia; lactate; tumor microenvironment

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1. Introduction

Epigenetic regulation plays a central role in cancer development by controlling gene expression without altering the underlying DNA sequence (1). Importantly, many epigenetic alterations are potentially reversible, making epigenetic regulatory mechanisms attractive targets for the development of novel diagnostic and therapeutic strategies (2). Cancer cells undergo metabolic reprogramming to support rapid proliferation and survival under unfavorable conditions. One of the best-characterized metabolic features of cancer is increased glycolytic activity and lactate production, commonly associated with the Warburg effect. Lactate was historically considered a metabolic end product of glycolysis; however, accumulating evidence demonstrates that it is an important signaling and regulatory molecule that can influence tumor metabolism, angiogenesis, immune responses, cellular plasticity, and therapeutic resistance (3). A major discovery was that lactate can also participate in epigenetic regulation through lysine lactylation (Kla).

Histone lactylation is a relatively recently identified post-translational modification in which a lactyl group is attached to lysine residues of histones. Zhang et al. first described it in 2019, showing that cellular lactate production is linked to histone lysine lactylation and transcriptional regulation (4). Histone lactylation therefore provides a potential molecular mechanism through which changes in cellular metabolism can be translated into changes in chromatin state and gene expression.

This mechanism may be particularly relevant in solid tumors, where rapid proliferation frequently results in an imbalance between oxygen supply and cellular oxygen consumption. Tumor hypoxia promotes metabolic adaptation, increases glycolysis, and contributes to lactate accumulation and extracellular acidification. Consequently, the hypoxic tumor microenvironment (TME) provides conditions in which lactylation may function as an adaptive metabolic–epigenetic response. Hypoxia is also strongly associated with aggressive tumor phenotypes and poor responses to chemotherapy, radiotherapy, and immunotherapy (5).

Histone lactylation has emerged as a potentially important mechanism linking tumor metabolism, hypoxia, chromatin regulation, and cancer progression. This article summarizes the current understanding of the relationship between hypoxia and histone lactylation.

2. Hypoxia in cancer

Hypoxia is a hallmark of the microenvironment in many solid tumors, resulting from rapidly proliferating cancer cells, abnormal tumor vasculature, and impaired blood flow, which together contribute to the formation of hypoxic regions. Hypoxia strongly affects cancer cell metabolism and promotes biological processes associated with tumor progression, including angiogenesis, invasion, metastasis, and treatment resistance (6, 7).

A central mediator of the cellular response to hypoxia is hypoxia-inducible factor 1 α (HIF-1 α) (8). In a low-oxygen microenvironment, HIF-1 α becomes stabilized and activates genes responsible for the metabolic shift toward glycolysis, including glucose transporter 1 (GLUT1/SLC2A1) and lactate dehydrogenase A (LDHA), as well as pyruvate dehydrogenase kinase 1 (PDK1), which inhibits the pyruvate dehydrogenase complex and thereby favors the conversion of pyruvate to lactate. HIF-1 α also induces monocarboxylate transporter 4 (MCT4/SLC16A3), facilitating lactate export from cells and thereby contributing to lactate accumulation in the tumor microenvironment (9, 10). The characteristic acidic environment of many hypoxic tumors is partly associated with increased glycolysis and accumulation of metabolic acids, including lactic acid (11). Tumor acidosis can promote an aggressive phenotype, affect cellular proliferation and migration, and influence interactions between cancer cells and stromal or immune populations (12).

3. Molecular machinery of histone lactylation

Lysine lactylation is a dynamic and potentially reversible post-translational modification regulated by proteins commonly described as “writers,” “erasers,” and “readers.” Lactate generated through glycolysis can be converted to lactyl-CoA, which serves as a source of lactyl groups for histone modification by lactyltransferase “writers.” The resulting lactylation marks can subsequently be removed by “erasers” or recognized by specific “reader” proteins, which translate these modifications into downstream functional effects, including changes in gene expression (13). Figure 1 summarizes the molecular machinery involved in histone lactylation.

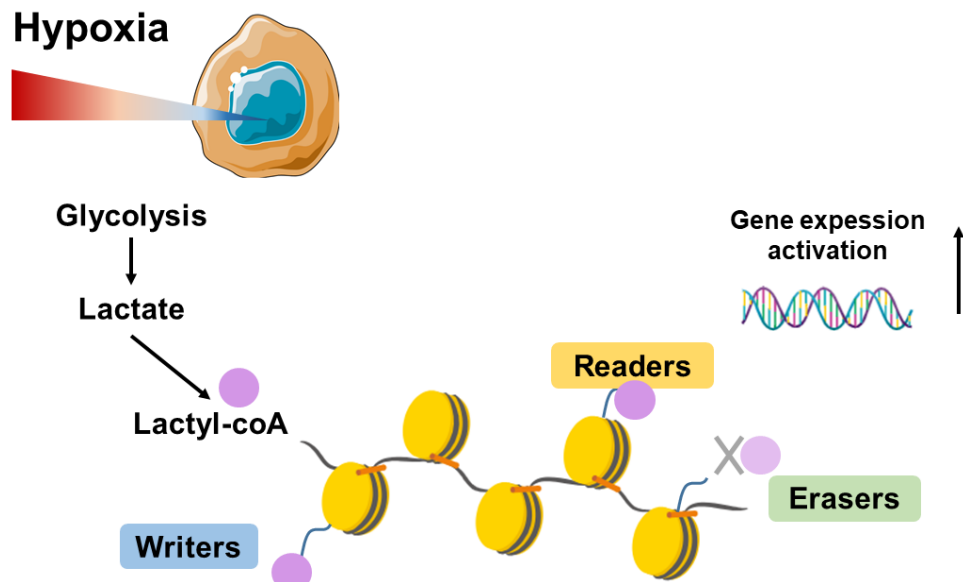


Figure 1. The process of histone lactylation. Under hypoxic conditions, cells shift toward glycolysis, resulting in increased lactate production. Lactate is converted into lactyl-CoA, which serves as a substrate for the addition of lactyl groups to histones by “writers.” Histone lactylation is recognized by “readers,” leading to the activation of gene expression, and is removed by “erasers.”

3.1 Writers

p300 (EP300), a histone acetyltransferase, was the first well-characterized enzyme shown to catalyze histone lactylation. Because lactylation and acetylation both involve lysine residues and share similarities in their enzymatic regulation, several histone acetyltransferases have subsequently been investigated as potential lactylation writers. The other known lactyltransferases include: KAT7/KAT8, AARS1/AARS2 (14).

Recent studies have identified KAT8 (lysine acetyltransferase 8) as a lactylation writer capable of modifying both histone and non-histone proteins. In colorectal cancer, KAT8-mediated lactylation of eEF1A2 has been associated with enhanced protein translation and tumor progression (15). KAT8 is also overexpressed in several cancer types and has been associated with poor clinical outcomes (16).

3.2 Erasers

The reversibility of lactylation is supported by evidence that several histone deacetylases and sirtuins can remove lactyl groups from proteins. HDAC1–3, HDAC8, and SIRT1–3 have been reported to exhibit delactylase activity (14). The involvement of these enzymes is particularly important because HDACs and sirtuins are already established regulators of chromatin structure, metabolism, DNA repair, and cancer progression. Therefore, their effects on tumor phenotype cannot necessarily be attributed exclusively to delactylation (17).

3.3 Readers

Several proteins have been proposed as readers of histone lactylation, including BRG1, DPF2, and TRIM33. BRG1 has been reported to interact with H3K18la and may facilitate chromatin accessibility and transcription. DPF2 can recognize H3K14la, whereas TRIM33 has been reported to recognize lactylated histone residues through its bromodomain (17). The reader field remains significantly less developed than the writer and eraser fields. Understanding whether specific readers recognize particular K1a sites and whether these interactions are dependent on cellular context will be essential for defining the functional consequences of histone lactylation.

4. Hypoxia-driven histone lactylation

Histone lactylation is increased under hypoxic conditions and is associated with activation of specific gene

expression (4). Subsequent studies have expanded these observations to cancer cells and the TME, suggesting that lactylation may contribute to tumor growth, immune regulation, cellular plasticity, and therapy resistance (14). Lactate production is associated with histone lactylation, and lactylation could directly affect transcription. Importantly, hypoxia increases glycolytic activity and histone K4a, supporting the concept that histone lactylation may function as a metabolic sensor (4). In macrophages, for example, H3K18la accumulated at promoters of genes involved in later stages of inflammatory responses and contributed to the expression of homeostatic genes. These observations suggested that lactylation may participate in cellular adaptation to metabolic stress rather than simply representing a passive consequence of elevated lactate (18). Hypoxia-induced lactylation has been reported to increase expression of LAMC2 in esophageal cancer, linking metabolic changes to transcriptional regulation and tumor-associated phenotypes (19).

5. Histone lactylation and cancer biology

Increasing evidence links histone and protein lactylation with multiple cancer-associated processes, including proliferation, survival, migration, invasion, metabolic adaptation, immune modulation, and therapy resistance (3). Histone lactylation may facilitate this adaptation by regulating genes involved in proliferation, survival, epithelial–mesenchymal transition (EMT), and cellular plasticity. Several studies have associated increased levels of specific K4a marks with aggressive tumor phenotypes. For example, H3K18la has been implicated in transcriptional regulation in multiple cancers, whereas other sites, including H3K9la and H3K14la, have been associated with cancer progression and oncogenic gene expression (17). In ocular melanoma, histone lactylation influences tumorigenesis by promoting YTHDF2 expression, which recognizes m6A-modified PER1 and TP53 mRNAs and facilitates their degradation (20). Moreover, in neuroendocrine prostate cancer, ZEB1 promotes lactate accumulation, which contributes to cancer progression (21). Lactate is also known to regulate cancer cell stemness and activate the MYC oncogene in colorectal cancer (22). Lactylation is also associated with macrophage polarization and immunosuppressive phenotypes (4). Lactate transport through MCT family proteins may therefore contribute to a broader metabolic–epigenetic pathway regulating immune-cell function (23).

6. Limitations and future perspectives

Despite the rapid expansion of research into histone lactylation, several important limitations remain. Although EP300 and several additional acetyltransferases have been implicated as lactylation writers, their substrate specificity may vary between cell types and lactylation sites. Similarly, HDACs can regulate lactylation but also have extensive functions in other epigenetic and metabolic processes.

A particularly important methodological challenge is the overlap between lactylation and other lysine acylations. Histone acetylation, for example, is regulated by some of the same enzymes implicated in lactylation. Therefore, inhibition or silencing of EP300 can simultaneously decrease acetylation and lactylation, making it difficult to determine which modification is responsible for an observed phenotype (24). Many studies measure global lactylation or rely on antibody-based detection of individual histone marks. Antibody specificity and differences in experimental protocols may complicate comparisons between studies. More quantitative approaches, including mass spectrometry-based proteomics and site-specific validation, will be essential to determine which lactylation sites are biologically relevant (25). Antibody specificity remains an important methodological consideration, as L-lactyl-lysine (K_L-la) and D-lactyl-lysine (K_D-la) are distinct lactylation isomers that may not be distinguished by conventional pan-lactylation antibodies unless specifically validated. Recent studies have demonstrated the development of isomer-specific antibodies capable of distinguishing K_L-la from K_D-la (26). This distinction is particularly relevant when interpreting enzymatic and non-enzymatic lactylation, as different lactylation isomers may arise through distinct biochemical mechanisms.

An additional challenge is translating lactylation measurements into clinically useful biomarkers. The potential association between lactylation patterns and tumor aggressiveness, treatment response, or immune status raises the possibility that specific K4a signatures could be used for patient stratification or treatment monitoring. However, standardized detection methods, validated clinical cohorts, and prospective studies are required before lactylation can be incorporated into routine clinical decision-making. The use of genetic or epigenetic biomarkers in personalized oncology has considerable potential, but reliable diagnostic testing and clinically validated assays remain necessary for their implementation (1).

7. Conclusions

Histone lactylation has emerged as an important link between cellular metabolism and epigenetic regulation. In cancer, hypoxia and metabolic reprogramming promote glycolytic activity and lactate production, creating conditions that can favor protein lactylation and potentially alter chromatin structure and gene expression. Through this mechanism, lactate may act not only as a metabolic intermediate but also as a regulator of transcriptional adaptation. The growing evidence indicates that lactylation can influence tumor proliferation, cellular plasticity, invasion, immune regulation, and therapeutic resistance. Nevertheless, the biological consequences of lactylation are highly context-dependent, and the relative contributions of lactate signaling, histone lactylation, and non-histone lactylation remain difficult to separate. The identification of writers, erasers, and readers has begun to define the molecular machinery controlling Kla, but this system remains incompletely characterized. Ultimately, understanding histone lactylation may provide an opportunity to target the metabolic–epigenetic interface of cancer rather than either metabolism or epigenetics in isolation.

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