

REVIEW ARTICLE

Lactylation: A novel metabolic–epigenetic link in pancreatic cancer

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Abstract

Lactylation, a recently discovered post-translational modification, represents a crucial nexus between cellular metabolism and epigenetic regulation. Driven by the accumulation of lactate, a byproduct of glycolysis, this modification involves the covalent attachment of a lactyl group to lysine residues on both histone and non-histone proteins. Emerging evidence highlights the profound impact of lactylation on various biological processes, including gene expression, cell proliferation, migration, invasion, autophagy, and immune responses, particularly in cancer. This comprehensive review examines the intricate mechanisms governing lactylation, its widespread presence across the proteome, and its specific roles in cancer pathogenesis, with a particular emphasis on pancreatic ductal adenocarcinoma (PDAC). We explore how lactylation at histone H3 lysine 18 (H3K18la), histone H4 lysine 12 (H4K12la), and histone H3 lysine (H3K9la) influences chromatin accessibility and gene transcription, thereby shaping tumor characteristics. Furthermore, we examine the diverse functions of non-histone protein lactylation in regulating metabolic pathways, immune evasion, epithelial–mesenchymal transition, and ferroptosis. The review also discusses the diagnostic and prognostic potential of lactylation markers in PDAC and evaluates the therapeutic implications of targeting lactylation pathways to overcome drug resistance and inhibit tumor progression. By consolidating current knowledge, this review underscores lactylation as a pivotal regulatory layer in cancer biology, offering novel avenues for therapeutic intervention.

Keywords: Lactylation; Pancreatic cancer; Post-translational modification; Cancer therapy; Immune evasion; Metabolic reprogramming

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1. Introduction

Cancer, a complex and heterogeneous disease, is characterized by uncontrolled cell growth, proliferation, and the ability to metastasize.¹ At its core, cancer development is driven by a series of genetic mutations and epigenetic alterations that collectively rewire cellular processes to favor malignant transformation. Among the hallmarks of cancer, metabolic reprogramming stands out as a fundamental adaptation, allowing tumor

cells to sustain rapid proliferation and survive in nutrient-deprived and hypoxic microenvironments.² The Warburg effect, a phenomenon in which cancer cells preferentially use glycolysis for energy production even in the presence of oxygen, leads to increased lactate production.^{3,4} Historically viewed as a mere waste product, lactate has recently been recognized as a critical signaling molecule and a substrate for a novel post-translational modification (PTM) known as lactylation.^{5,6}

Post-translational modifications are crucial regulatory mechanisms that expand the functional diversity of the proteome by altering protein activity, stability, localization, and interactions. These modifications, which include phosphorylation, acetylation, methylation, ubiquitination, and SUMOylation, play pivotal roles in nearly all cellular processes, from gene expression and signal transduction to metabolism and cell cycle control.⁷ The discovery of lactylation, specifically lysine lactylation, has added another layer of complexity to the intricate network of PTMs, establishing a direct link between cellular metabolic state and epigenetic regulation.^{6,8,9}

Lactylation involves the enzymatic or non-enzymatic attachment of a lactyl group to the ϵ -amino group of lysine residues on proteins.¹⁰ This modification is particularly significant because its abundance is directly coupled to intracellular lactate levels, thereby acting as a metabolic sensor that translates metabolic flux into functional changes in protein activity and gene expression.¹¹ The initial discovery of histone lactylation, particularly histone H3 lysine 18 lactylation (H3K18la), revealed its role in regulating gene transcription by modulating chromatin structure.⁵ Since then, lactylation has been found to occur on a wide array of non-histone proteins, influencing diverse cellular functions.¹²

Pancreatic ductal adenocarcinoma (PDAC), one of the most aggressive and lethal malignancies, is characterized by an extremely poor clinical prognosis, primarily due to the lack of reliable early diagnostic markers and the fact that most patients are diagnosed at an advanced, unresectable stage.¹³ Despite advances in imaging and systemic therapies, the five-year survival rate for PDAC has shown only marginal improvement over recent decades. Recent large-scale clinical and translational studies emphasize that significant survival benefits can only be achieved through early detection and intervention, underscoring the urgent need to identify novel molecular signatures associated with early tumorigenesis and metabolic reprogramming.^{14,15} In this context, lactylation, a metabolism-responsive PTM, has garnered increasing attention as a potential indicator of early oncogenic metabolic shifts rather than a late-stage epiphenomenon. Characterized by a highly desmoplastic

stroma, poor vascularization, and a hypoxic, nutrient-deprived microenvironment, PDAC cells rely heavily on altered metabolic pathways, including enhanced glycolysis, to fuel their rapid growth and survival.² This metabolic shift invariably leads to elevated lactate production, making PDAC an ideal context to investigate the functional implications of lactylation.¹⁶ Indeed, recent studies have begun to unravel the profound involvement of lactylation in various aspects of PDAC biology, from diagnosis and prognosis to proliferation, invasion, immune evasion, and therapeutic resistance.^{17–20}

This review aims to provide a comprehensive overview of the current understanding of lactylation, focusing on its mechanisms, regulatory enzymes, and diverse biological functions. We examine the specific roles of both histone and non-histone protein lactylation in cancer development, with a particular emphasis on PDAC. Furthermore, we explore the diagnostic and prognostic potential of lactylation markers and discuss emerging therapeutic strategies that target lactylation pathways to combat cancer. By synthesizing the latest research, this review highlights lactylation as a critical and actionable target in the ongoing fight against cancer.

2. The landscape of lactylation: From discovery to diverse biological roles

The discovery of lactylation as a novel PTM has significantly expanded our understanding of how cellular metabolism directly influences protein function and gene expression. Initially identified in macrophages, where it plays a critical role in regulating gene expression during bacterial infection, lactylation has since been recognized as a widespread and functionally diverse PTM across various cell types and organisms.⁵ This section discusses the fundamental aspects of lactylation, including its chemical nature, widespread occurrence, and the enzymatic machinery that governs its addition and removal.

2.1. Discovery and nature of lactylation

Lactylation, specifically lysine lactylation, involves the covalent attachment of a lactyl group ($\text{CH}_3\text{--CH}(\text{OH})\text{--CO--}$) to the ϵ -amino group of lysine residues on proteins.¹⁰ This modification differs from other acylations, such as acetylation, propionylation, or butyrylation, due to the presence of a hydroxyl group on the α -carbon of the lactyl moiety. The lactate molecule, a metabolic byproduct of glycolysis, serves as the direct precursor for this modification.⁵ The intracellular concentration of lactate is highly dynamic, fluctuating significantly in response to metabolic demands, oxygen availability, and nutrient status. This direct coupling between lactate levels and lactylation

status positions lactylation as a unique metabolic sensor, allowing cells to rapidly translate changes in metabolic flux into alterations in protein function and gene expression.¹¹

The initial groundbreaking work identified histone lactylation, particularly H3K18la, as a key epigenetic mark that directly links glycolysis to gene expression.⁵ This discovery provided a mechanistic explanation for how metabolic reprogramming, a hallmark of cancer, could exert profound effects on the epigenome and cellular phenotype. Beyond histones, subsequent proteomic studies have revealed that lactylation is widely distributed across the human proteome, affecting numerous non-histone proteins involved in diverse cellular processes.¹² This widespread occurrence underscores its fundamental importance in cellular regulation.

2.2. Widespread presence and regulation of glycolysis

The extensive lactylation of various proteins suggests its broad involvement in regulating cellular physiology. Proteomic analyses have identified hundreds of lactylated proteins, many of which are key players in metabolic pathways, signal transduction, gene regulation, and structural integrity.¹² The fact that numerous lactylated proteins are directly involved in glycolysis itself suggests a sophisticated feedback loop where lactate, the end-product of glycolysis, can regulate the enzymes that produce it, thereby fine-tuning metabolic flux.¹² This intricate regulatory mechanism allows cells to adapt their metabolism efficiently to changing environmental conditions, a capability that is often hijacked and amplified in cancer cells.

The regulation of glycolysis is central to cancer cell survival and proliferation.³ Cancer cells often exhibit an exaggerated Warburg effect, leading to significantly elevated lactate production.⁴ This high lactate microenvironment not only fuels lactylation but also creates an acidic extracellular milieu that promotes tumor invasion, angiogenesis, and immune evasion.^{16,20} Therefore, understanding how lactylation regulates glycolysis and other metabolic pathways is crucial for unraveling its role in cancer progression.

2.3. Methods for detection

The accurate detection and quantification of protein lactylation are essential for deciphering its biological roles. Early studies relied on pan-anti-lactyllysine antibodies and mass spectrometry-based proteomics to identify lactylated proteins and specific lactylation sites.⁵ Mass spectrometry remains a powerful tool for unbiased identification of lactylation sites and for quantitative analysis of lactylation

changes under different physiological or pathological conditions.¹²

Recently, innovative chemical biology tools have been developed to facilitate the study of lactylation. For instance, the YnLac chemical reporter has emerged as a valuable tool for detecting protein lactylation.²¹ This reporter molecule can be metabolically incorporated into cells and subsequently detected using click chemistry, allowing for sensitive and specific visualization and quantification of lactylated proteins. Such advancements in detection methodologies are critical for advancing our understanding of lactylation dynamics and its functional consequences in various biological contexts, including cancer. Furthermore, computational tools such as DeepKla have been developed to predict protein lactylation sites, thereby aiding the identification of potential targets for further investigation.²²

2.4. Enzymes involved: Lactyltransferases and delactylases

Like other PTMs, lactylation is a dynamic and reversible process, tightly regulated by specific “writer” (lactyltransferase) and “eraser” (delactylase) enzymes. The identification of these enzymes is crucial for understanding the precise control of lactylation levels and their downstream effects:

- (i) Lactyltransferases (writers): Initial studies suggested that lactylation might occur non-enzymatically due to the reactivity of lactoyl-coenzyme A (CoA) or lactoyl-adenosine monophosphate intermediates. However, recent research has identified specific enzymes capable of catalyzing lactylation, indicating a more regulated process: (i) Acetyl-CoA synthetase 2 (ACSS2)–lysine acetyltransferase 2A (KAT2A) complex: The ACSS2 and KAT2A (also known as general control non-depressible 5, GCN5) complex has been identified as a lactyltransferase.²³ ACSS2 is known for its role in converting acetate to acetyl-CoA, a precursor for acetylation. Its involvement in lactylation suggests a broader role for acyl-CoA synthetases in generating acyl-CoA derivatives that can then be utilized by lysine acetyltransferase (KAT) family members for various acylation events. The ACSS2–KAT2A complex has been shown to promote tumor immune escape through lactylation, highlighting its oncogenic potential.²³ (ii) KAT8, also known as MOF, is another enzyme implicated in catalyzing lactylation. KAT8 has been shown to catalyze the lactylation of eukaryotic elongation factor 1 alpha 2 (eEF1A2), thereby promoting protein synthesis.²⁴ This finding suggests that KAT8, traditionally known for its role in histone

acetylation and gene regulation, also participates in non-histone protein lactylation, linking metabolic status to translational control.

- (ii) Delactylases (erasers): The reversibility of lactylation is mediated by delactylases, which remove the lactyl group from lysine residues. Several sirtuins (SIRT) and histone deacetylases (HDACs) have been identified as delactylases, indicating an overlap in the regulatory machinery for different acylation events: (i) SIRT1, a well-known nicotinamide adenine dinucleotide (NAD⁺)-dependent deacetylase, has been shown to possess delactylase activity. Specifically, SIRT1 can delactylate histone H3 at lysine 18 (H3K18), thereby regulating gene expression.²⁵ This delactylation activity of SIRT1 has been implicated in modulating the H19–glycolysis positive feedback loop, which is critical in cancer progression.²⁵ (ii) SIRT6, another member of the sirtuin family, also exhibits delactylase activity. SIRT6 has been shown to delactylate histone H3 at lysine 9 (H3K9), leading to the inhibition of O6-methylguanine-DNA methyltransferase (MGMT) transcription.²⁶ This finding suggests a role for SIRT6 in DNA repair pathways and resistance to certain chemotherapies. (iii) HDAC1–3, traditionally known for removing acetyl groups from histones, have also been identified as histone lysine delactylases.²⁷ This promiscuity of HDACs in removing various acyl groups highlights the complexity of PTM regulation and suggests potential crosstalk between different acylation events. The involvement of HDACs in delactylation opens new avenues for therapeutic intervention, as HDAC inhibitors are already used in cancer treatment.

The dynamic interplay between lactyltransferases and delactylases precisely controls the levels of protein lactylation, ensuring appropriate cellular responses to metabolic cues. Dysregulation of these enzymes in cancer can lead to aberrant lactylation patterns, contributing to tumor initiation, progression, and therapeutic resistance. Understanding the specific substrates and regulatory mechanisms of these enzymes is crucial for developing targeted therapies.

2.5. Non-enzymatic lactylation mediated by the glyoxalase system

In addition to enzymatically regulated lysine lactylation, emerging evidence supports a non-enzymatic lactylation pathway driven by reactive metabolic intermediates. Under conditions of high glycolytic flux, methylglyoxal is detoxified through the glyoxalase system, consisting of glyoxalase (GLO) 1 and 2, leading to the generation of S-D-lactylglutathione.^{28,29} This thioester intermediate has

been shown to non-enzymatically modify lysine residues, resulting in lactyl-lysine adducts that are chemically distinct from enzyme-installed lactylation marks.

Importantly, dysregulation of the glyoxalase pathway is a common feature of metabolic reprogramming in cancer. Elevated GLO1 expression and activity have been reported in multiple malignancies, including PDAC, and are associated with enhanced glycolysis, redox homeostasis, and resistance to metabolic stress.^{30,31} In this context, non-enzymatic lactylation may represent an underappreciated mechanism linking altered glucose metabolism to widespread protein modification, potentially affecting protein stability, enzymatic activity, and signaling pathways independently of canonical “writer” enzymes.

Compared to enzymatic lactylation, non-enzymatic lactylation is likely to be less site-specific and more directly driven by intracellular metabolite abundance. This raises important conceptual questions regarding the coexistence, competition, and functional interplay between enzymatic and non-enzymatic lactylation in cancer cells. Future studies distinguishing these two modes of modification at the proteomic and functional levels will be essential for a complete understanding of lactylation biology in pancreatic cancer and other metabolically rewired tumors.

In summary, lactylation is a dynamic PTM regulated by specific enzymes (e.g., writer enzymes such as ACSS2–KAT2A and KAT8, and eraser enzymes such as SIRT1/6 and HDACs), with its abundance directly coupled to intracellular lactate flux. This mechanism establishes a direct bridge between cellular metabolic status and functional regulation, particularly epigenetics. To provide an integrative overview of this complex metabolic–epigenetic crosstalk network and its core regulatory cycle, the key components are summarized in [Figure 1](#).

3. Histone lactylation: A direct link between metabolism and epigenetics

Epigenetic modifications, such as DNA methylation and histone modifications, play a critical role in regulating gene expression without altering the underlying DNA sequence. Histone modifications, including acetylation, methylation, phosphorylation, and ubiquitination, alter chromatin structure and accessibility, thereby influencing transcriptional activity.⁷ The discovery of histone lactylation has added a novel dimension to this intricate epigenetic landscape, providing a direct molecular link between cellular metabolic state, particularly lactate production, and gene expression.^{6,8,9} This section explores the general concept of histone modifications, the unique characteristics of histone lactylation, and the specific histone sites implicated in cancer, particularly pancreatic cancer.

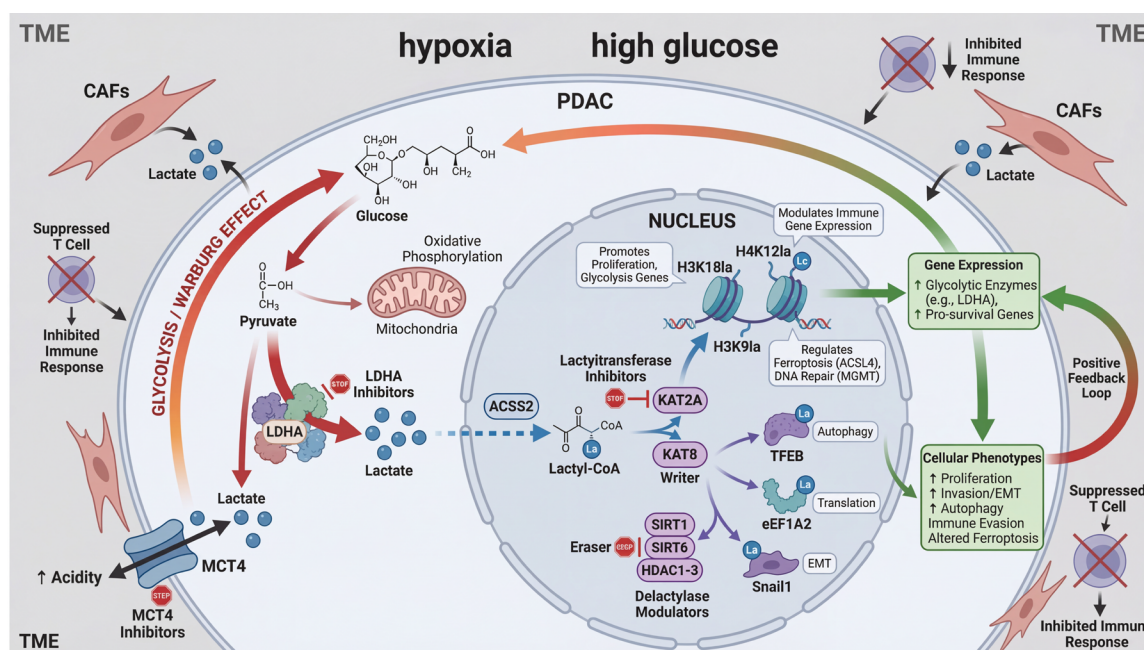


Figure 1. The lactylation cycle in PDAC. The hypoxic, nutrient-depleted tumor microenvironment promotes glycolytic flux (Warburg effect) in PDAC cells, leading to lactate accumulation. Lactate serves as a precursor for lactyl-CoA, used by lactyltransferases (e.g., ACSS2–KAT2A, KAT8) to install La marks on histone (e.g., H3K18, H4K12, H3K9) and non-histone (e.g., TFEB, eEF1A2, Snail1) proteins. These modifications alter gene expression and protein function, driving hallmark cancer phenotypes, including proliferation, invasion, immune evasion, and metabolic adaptation. Delactylases (e.g., SIRT1, SIRT6, HDAC1–3) remove La marks, providing dynamic regulation. A key positive feedback loop exists where lactylation-induced expression of glycolytic enzymes further fuels lactate production. Key therapeutic strategies under investigation include inhibiting LDHA, lactate transporters (MCTs), lactyltransferases, or modulating delactylases. Image created with the Adobe Illustrator.

Abbreviations: ACSS2: Acetyl coenzyme A synthase 2; CAF: Cancer-associated fibroblast; CoA: Coenzyme A; eEF1A2: Eukaryotic elongation factor 1 alpha 2; EMT: Epithelial–mesenchymal transition; H3K18: Histone H3 lysine 18; H3K9: Histone H3 lysine 9; H4K12: Histone H4 lysine 12; HDAC: Histone deacetylase; KAT: Lysine acetyltransferase; La: Lactyl; LDHA: Lactate dehydrogenase A; MCTs: Monocarboxylate transporters; PDAC: Pancreatic ductal adenocarcinoma; SIRT: Sirtuin; TFEB: Transcription factor EB; TME: Tumor microenvironment.

3.1. General concept of histone modifications and gene expression

Chromatin, the complex of DNA and proteins that forms chromosomes, is dynamically organized to regulate gene expression. The fundamental repeating unit of chromatin is the nucleosome, which consists of approximately 147 base pairs of DNA wrapped around an octamer of histone proteins (two copies each of H2A, H2B, H3, and H4). The N-terminal tails of histones are highly accessible and are subject to a myriad of PTMs. These modifications can influence chromatin structure in several ways: by altering histone charge, thereby affecting their interaction with DNA; by creating binding sites for “reader” proteins that recruit transcriptional machinery; or by directly influencing nucleosome stability and positioning. The collective pattern of these modifications, often referred to as the “histone code,” dictates whether a gene is actively transcribed or silenced.

3.2. Histone lactylation as a unique post-translational modification

Histone lactylation is unique among histone acylations because its precursor, lactate, is a direct end-product of glycolysis, making it a direct readout of cellular metabolic activity.⁵ Unlike acetyl-CoA, which is a common precursor for both acetylation and fatty acid synthesis, lactate’s primary metabolic fate is either oxidation or conversion back to pyruvate. Its role as a signaling molecule and a substrate for lactylation highlights its multifaceted importance. When lactate levels rise, particularly under conditions of enhanced glycolysis (e.g., in cancer cells or during inflammation), the availability of lactyl groups for histone modification increases, leading to elevated histone lactylation.¹¹ This direct metabolic link allows for rapid and dynamic changes in gene expression in response to metabolic shifts, thereby connecting metabolic reprogramming to epigenetic regulation.^{6,8}

Histone lactylation, similar to histone acetylation, is generally associated with active gene transcription. The addition of a bulky lactyl group to lysine residues can reduce the positive charge of histones, potentially weakening the interaction between histones and negatively charged DNA, leading to a more open chromatin structure that is permissive for transcription. This mechanism allows for the activation of genes that support metabolic adaptation, cell proliferation, and other cancer-associated processes.

3.3. Specific histone sites and their implications

Several specific lysine residues on histones have been identified as targets for lactylation, each potentially regulating distinct sets of genes and cellular pathways. The most extensively studied sites include H3K18la, histone H4 lysine 12 lactylation (H4K12la), and histone H3 lysine 9 lactylation (H3K9la).

3.3.1. Histone H3 lysine 18 lactylation: A key player in pancreatic cancer and metabolic regulation

Histone H3 lysine 18 lactylation was among the first histone lactylation sites identified and has garnered significant attention due to its prominent role in various biological contexts, especially cancer. H3K18la has been shown to be associated with pancreatic cancer diagnosis and prognosis.¹⁷ Its elevated levels in PDAC tissues or patient samples could serve as a potential biomarker for early detection or for predicting disease aggressiveness. Further validation of H3K18la in pancreatic cancer is still ongoing, but initial findings suggest its critical involvement.³² Demethylzeylasteral, a natural compound isolated from *Tripterygium wilfordii*, has been shown to downregulate H3K18la levels in pancreatic cancer cells by reducing lactate production.³³ Unlike an enzymatic eraser, demethylzeylasteral does not directly remove lactylation marks; rather, it lowers the substrate (lactate) for histone lactylation, and because it is an exogenous phytochemical, it is not subject to dysregulation in cancer.

High glucose levels, a common feature of the tumor microenvironment and a risk factor for PDAC in diabetic patients, have been shown to drive PDAC progression through the H3K18la/TTK/budding uninhibited by benzimidazoles 1 mitotic checkpoint serine kinase B (BUB1B) pathway.³⁴ This pathway highlights how metabolic stress (hyperglycemia) can directly impact epigenetic marks (H3K18la), promoting cancer cell proliferation and survival. TTK and BUB1B are kinases involved in the mitotic spindle checkpoint, and their activation can lead to chromosomal instability, a hallmark of cancer. A positive feedback loop between glycolysis and H3K18la has been identified in PDAC.³⁵ Elevated glycolysis leads to increased lactate production, which in turn enhances H3K18la.

This increased H3K18la then promotes the expression of glycolytic enzymes, further fueling glycolysis. This vicious cycle amplifies metabolic reprogramming and contributes to the aggressive nature of PDAC.

Proteasome 26S subunit, non-ATPase 14 has been found to stabilize lactate dehydrogenase A (LDHA), an enzyme critical for converting pyruvate to lactate.³⁶ This stabilization of LDHA increases lactate production and subsequently promotes H3K18la.³⁶ This pathway provides a mechanistic link between proteasomal regulation, lactate metabolism, and histone lactylation in cancer. As mentioned earlier, SIRT1 acts as a delactylase for H3K18, modulating its levels and thereby regulating gene expression.²⁵ This delactylation activity of SIRT1 is crucial for controlling the H19–glycolysis positive feedback loop, which is involved in various cancer processes.²⁵

3.3.2. Histone H4 lysine 12 lactylation: Impact on anaplastic thyroid carcinoma and pancreatic ductal adenocarcinoma immunity

Histone H4 lysine 12 lactylation is another significant histone lactylation site with distinct functional roles. In anaplastic thyroid carcinoma (ATC), a highly aggressive form of thyroid cancer, the BRAFV600E mutation has been shown to promote ATC proliferation through H4K12 lactylation.³⁷ This finding suggests that oncogenic mutations can directly influence histone lactylation patterns to drive tumor growth. The LDHA–H4K12la axis plays a critical role in regulating pancreatic cancer immunity.¹⁹ LDHA-mediated lactate production leads to increased H4K12la, which can modulate the expression of genes involved in immune responses, potentially contributing to immune evasion in PDAC. This highlights the intricate interplay between tumor metabolism, epigenetics, and the immune microenvironment.

3.3.3. Histone H3 lysine 9 lactylation: Modulating ferroptosis and DNA repair

Histone H3 lysine 9 lactylation regulates critical cellular processes, including ferroptosis and DNA repair. Inhibition of CD147, a transmembrane glycoprotein involved in cancer progression, has been shown to upregulate acyl-CoA synthetase long-chain family member 4 through H3K9 lactylation, thereby inducing ferroptosis.³⁸ Ferroptosis is a form of regulated cell death characterized by iron-dependent lipid peroxidation, and its induction is a promising strategy for cancer therapy. This finding suggests that H3K9la can modulate the susceptibility of cancer cells to ferroptosis. Additionally, SIRT6 acts as a delactylase for H3K9, and its activity inhibits MGMT transcription.²⁶ MGMT is a DNA repair enzyme that removes alkyl groups from the O6 position

of guanine, thereby conferring resistance to alkylating chemotherapeutic agents. By delactylating H3K9 and inhibiting MGMT, SIRT6 could potentially sensitize cancer cells to certain chemotherapies, highlighting its role in DNA damage response and therapeutic resistance.

3.3.4. Overall impact on gene expression and cellular fate

The collective impact of histone lactylation on gene expression is profound. By modulating chromatin structure, histone lactylation can activate specific gene programs that support cancer cell proliferation, survival, metastasis, and immune evasion.¹¹ This direct link between metabolic state and epigenetic regulation allows cancer cells to rapidly adapt to their challenging microenvironment, making histone lactylation a critical determinant of cellular fate.

3.3.5. Connection to Warburg effect and DNA repair

The Warburg effect, characterized by increased glycolysis and lactate production, is a hallmark of cancer metabolism.⁴ Histone lactylation serves as a direct molecular bridge connecting this metabolic phenomenon to epigenetic regulation. The elevated lactate levels in cancer cells drive increased histone lactylation, which in turn promotes the expression of genes that further enhance glycolysis, creating a positive feedback loop.³⁵ This metabolic–epigenetic axis is crucial for sustaining the high energy demands and biosynthetic needs of rapidly proliferating cancer cells.

Furthermore, lactylation has been implicated in DNA repair pathways.⁴ The ability of SIRT6 to delactylate H3K9 and inhibit MGMT transcription suggests a role for histone lactylation in modulating DNA damage response and sensitivity to genotoxic agents.²⁶ This connection highlights the broad regulatory scope of lactylation, extending beyond metabolism and gene expression to critical genome maintenance processes.

In summary, histone lactylation is a dynamic, reversible epigenetic mark that directly links cellular metabolism to gene expression. Its specific sites, such as H3K18la, H4K12la, and H3K9la, play distinct roles in regulating various cancer-associated processes, including proliferation, immune evasion, ferroptosis, and DNA repair. The intricate interplay between lactyltransferases, delactylases, and metabolic pathways underscores the complexity and significance of histone lactylation as a pivotal regulator in cancer biology.

4. Non-histone protein lactylation: Expanding the regulatory network

While histone lactylation has garnered significant attention for its role in epigenetic regulation, the discovery

of lactylation on a wide array of non-histone proteins has revealed an even broader and more intricate regulatory network. This expansion signifies that lactate, through lactylation, can directly modulate the function of enzymes, transcription factors, structural proteins, and other key cellular components, thereby influencing diverse biological processes beyond chromatin dynamics.^{10,12} This section delves into the diverse functional consequences of non-histone protein lactylation, highlighting its impact on metabolic regulation, autophagy, cell proliferation, epithelial–mesenchymal transition (EMT), metastasis, and immune modulation.

4.1. Beyond histones: Diverse functional consequences

The widespread presence of lactylation across the human proteome suggests its fundamental role in cellular regulation.¹² Non-histone protein lactylation can alter protein activity, stability, localization, and interactions, similar to other PTMs. The specific functional outcome depends on the protein, the site of lactylation, and the cellular context. This novel lysine lactylation has been found to regulate various aspects of tumor biology.¹⁰

4.2. Metabolic regulation

Lactylation plays a crucial role in fine-tuning metabolic pathways, often in response to altered lactate levels. Nicotinamide mononucleotide adenylyltransferase 1 (NMNAT1) is a key enzyme in NAD⁺ biosynthesis. Lactate has been shown to enhance NMNAT1 lactylation, which in turn helps maintain cellular NAD⁺ levels.³⁹ NAD⁺ is a critical coenzyme involved in numerous metabolic reactions, including glycolysis, oxidative phosphorylation, and DNA repair. By regulating NAD⁺ homeostasis, NMNAT1 lactylation can profoundly impact cellular energy metabolism and redox balance, which are often dysregulated in cancer. In addition, Glutamate-cysteine ligase modifier subunit (GCLM) is a component of the rate-limiting enzyme in glutathione synthesis, a crucial antioxidant system. Acetyl-CoA acetyltransferase 2 (ACAT2) has been shown to mediate GCLM lactylation, conferring resistance to ferroptosis.⁴⁰ Ferroptosis, an iron-dependent form of regulated cell death, is a promising therapeutic target in cancer. By promoting GCLM lactylation, ACAT2 can enhance the antioxidant capacity of cancer cells, protecting them from ferroptotic stress and contributing to therapeutic resistance. Conversely, alanyl-tRNA synthetase 2 (AARS2) lactylation has been shown to promote ferroptosis.⁴¹ This highlights the context-dependent and protein-specific nature of lactylation's effects. While GCLM lactylation protects against ferroptosis, AARS2 lactylation promotes it, suggesting a

complex regulatory network where lactylation can either enhance or suppress cell death pathways.

4.3. Autophagy and lysosomal activity

Autophagy, a cellular recycling process, and lysosomal activity are critical for maintaining cellular homeostasis and adapting to stress. Lactylation has emerged as a regulator of these processes. Transcription factor EB (TFEB) is a master regulator of lysosomal biogenesis and autophagy. TFEB lactylation has been shown to enhance both autophagy and lysosomal activity.⁴² By promoting TFEB lactylation, lactate can stimulate the cellular machinery responsible for degrading and recycling cellular components, thereby benefiting cancer cell survival under nutrient-deprived conditions.

Forkhead box protein O3 (FOXO3) is a transcription factor involved in various cellular processes, including stress resistance and autophagy. Matrix stiffness, a characteristic feature of the tumor microenvironment, has been shown to induce FOXO3 lactylation via LDHA, which in turn drives autophagy.⁴³ This mechanism highlights how mechanical cues from the microenvironment can be translated into metabolic and epigenetic signals (lactate/lactylation) that regulate cellular processes such as autophagy, contributing to cancer cell adaptation. More broadly, lactate has been shown to connect glycolysis with autophagy.⁴⁴ This connection underscores the central role of lactate in coordinating metabolic flux with cellular recycling pathways, which is particularly relevant to cancer cell survival and stress adaptation.

4.4. Cell proliferation and migration

Uncontrolled cell proliferation and enhanced migration are hallmarks of cancer. Non-histone protein lactylation can directly influence these processes. Chromobox homolog 3, a component of heterochromatin, has been found to undergo lactylation, which promotes gastrointestinal cancer progression.⁴⁵ This suggests that lactylation of chromatin-associated proteins can influence gene expression and cellular behavior in ways that favor tumor growth. As mentioned earlier, KAT8 catalyzes the lactylation of eEF1A2, which promotes protein synthesis.²⁴ Enhanced protein synthesis is crucial for the rapid proliferation of cancer cells, and this lactylation-mediated mechanism provides a direct link between metabolic state and translational control, supporting tumor growth.

4.5. Epithelial–mesenchymal transition and metastasis

Epithelial–mesenchymal transition is a crucial process in cancer metastasis, where epithelial cells acquire mesenchymal characteristics, enabling them to invade

and migrate. Lactylation has been implicated in regulating EMT. Snail1 is a master transcription factor that drives EMT. Rho family GTPase 4 (RHOF), through pyruvate kinase M2 (PKM), has been shown to promote Snail1 lactylation, which in turn induces EMT.⁴⁶ This pathway reveals a novel mechanism by which metabolic enzymes (PKM2) and signaling molecules (RHOF) can converge to regulate EMT through lactylation, thereby facilitating cancer cell invasion and metastasis.

Hypoxia, a common feature of the tumor microenvironment, induces protein arginine methyltransferase 1 (PRMT1) lactylation, which promotes vimentin methylation, driving metastasis.⁴⁷ Vimentin is an intermediate filament protein often associated with mesenchymal cells and increased invasiveness. This finding highlights how environmental cues like hypoxia can trigger lactylation events that ultimately lead to enhanced metastatic potential.

4.6. Immune modulation

The tumor microenvironment is a complex ecosystem where cancer cells interact with immune cells, often leading to immune evasion. Lactylation has emerged as a key regulator of immune responses in cancer. Endosulfine alpha (ENSA) lactylation at lysine 63 (K63) has been shown to activate the signal transducer and activator of transcription 3 (STAT3)/C-C motif chemokine ligand 2 (CCL2) axis, which promotes immune suppression and resistance.^{48,49} STAT3 is a transcription factor involved in immune regulation and cancer cell survival, while CCL2 is a chemokine that recruits immunosuppressive cells to the tumor microenvironment. By promoting ENSA lactylation, cancer cells can create an immunosuppressive environment that favors their growth and survival. Lactylation has also been shown to regulate cholesterol metabolism, which in turn influences immune suppression.⁵⁰ This suggests a feedback loop in which metabolic changes (lactate, cholesterol) are integrated through lactylation to modulate immune responses, contributing to tumor immune evasion. As previously mentioned, the ACS2–KAT2A complex, acting as a lactyltransferase, promotes tumor immune escape through lactylation.²³ This further underscores the critical role of lactylation in shaping the immune microenvironment and facilitating cancer progression.

In conclusion, lactylation of non-histone proteins represents a vast and rapidly expanding field of research. Its ability to regulate diverse cellular processes, including metabolism, autophagy, proliferation, EMT, and immune responses, positions it as a central player in cancer biology. Understanding the specific targets and functional consequences of non-histone lactylation will be crucial

for developing novel therapeutic strategies that target this intricate regulatory network.

5. Lactylation in pancreatic cancer: A detailed perspective

Pancreatic ductal adenocarcinoma is one of the most aggressive and lethal cancers, characterized by late diagnosis, rapid progression, and resistance to conventional therapies. Its unique tumor microenvironment, marked by dense desmoplasia, hypoxia, and metabolic reprogramming, creates a challenging landscape for treatment.² In this context, lactylation has emerged as a critical regulatory mechanism, profoundly influencing various aspects of PDAC biology. This section provides a detailed perspective on the role of lactylation in PDAC, covering its diagnostic and prognostic significance, involvement in metabolic reprogramming, effects on proliferation, migration, invasion, and its contribution to immune evasion and cancer stemness.

5.1. Diagnostic and prognostic significance

The identification of reliable biomarkers for early diagnosis and accurate prognosis remains a significant challenge in PDAC. Lactylation, particularly histone lactylation, shows promise in this regard. H3K18la has been found to be associated with pancreatic cancer diagnosis and prognosis.¹⁷ Elevated levels of H3K18la in patient samples could potentially serve as a diagnostic indicator for PDAC or as a prognostic marker to predict disease aggressiveness and patient outcomes. While promising, further studies are needed to validate its clinical utility.³²

Beyond individual lactylation marks, gene expression signatures related to lactylation have been developed to predict the prognosis of pancreatic cancer patients.⁵¹ These gene sets often include enzymes involved in lactate metabolism, lactyltransferases, delactylases, and genes whose expression is regulated by lactylation. Such signatures can provide a more comprehensive assessment of the lactylation landscape within a tumor and its correlation with patient survival. The hypoxic tumor microenvironment is a prominent feature of PDAC and is known to influence both metabolism and epigenetic modifications. Gene features related to both hypoxia and lactylation have been identified as predictive markers for PDAC prognosis.⁵² This highlights the interplay between environmental stress (hypoxia), metabolic adaptation (lactate production), and epigenetic regulation (lactylation) in shaping PDAC progression and patient outcomes. The pathological significance of protein lactylation has been recognized in pancreatic epithelial tumors.⁵³ This suggests that aberrant lactylation patterns are not merely bystanders

but actively contribute to the malignant phenotype of these tumors, making them potential targets for diagnostic and therapeutic interventions.

5.2. Metabolic reprogramming and lactate microenvironment

Pancreatic ductal adenocarcinoma cells exhibit profound metabolic reprogramming, relying heavily on glycolysis even in the presence of oxygen (Warburg effect), leading to a high lactate microenvironment. This metabolic shift is crucial for tumor growth and creates the substrate for lactylation. Lactate metabolism plays a critical role in the development and progression of pancreatic cancer.² The high glycolytic flux in PDAC cells generates substantial amounts of lactate, which is then secreted into the tumor microenvironment, creating an acidic milieu that promotes tumor invasion, angiogenesis, and immune suppression. A feedforward loop involving nucleolar- and spindle-associated protein 1 (NUSAP1), LDHA, glycolysis, and lactate production has been identified in PDAC.³ NUSAP1 promotes LDHA expression, which enhances glycolysis and lactate production. This increased lactate then further fuels tumor progression, creating a self-sustaining cycle that drives the Warburg effect in PDAC.

Cancer-associated fibroblasts (CAFs), a major component of the PDAC stroma, contribute significantly to the high lactate microenvironment.¹⁶ CAFs can undergo metabolic reprogramming themselves, often exhibiting enhanced glycolysis, and secrete lactate, which is then utilized by cancer cells or contributes to the acidic milieu. This high-lactate microenvironment, driven by CAFs, has been shown to drive nerve invasion in PDAC, a major contributor to pain and poor prognosis.¹⁶ Lactate can also reshape Schwann cells, a type of glial cell that forms myelin sheaths around nerves, to promote PDAC development.⁵⁴ This interaction between lactate, Schwann cells, and cancer cells highlights the complex role of the tumor microenvironment in supporting PDAC progression.

5.3. Proliferation, migration, and invasion

Lactylation directly impacts the aggressive behavior of PDAC cells, including their ability to proliferate, migrate, and invade surrounding tissues. Mitochondrial calcium uniporter (MCU) has been shown to promote pancreatic cancer cell proliferation, migration, and invasion.¹⁸ While the direct lactylation of MCU or its regulators is not explicitly stated in this reference, its role in promoting these aggressive phenotypes suggests that it could be indirectly influenced by or interact with lactylation pathways, given the strong link between metabolism, calcium signaling, and cancer progression. Further research is needed to explore potential lactylation-mediated regulation of

MCU. As discussed earlier, high glucose levels drive PDAC progression through the H3K18la/TTK/BUB1B pathway.³⁴ This pathway directly links metabolic stress (hyperglycemia) to an epigenetic modification (H3K18la) that promotes cell cycle progression and proliferation, thereby contributing to the rapid growth of PDAC.

5.4. Immune evasion

Pancreatic ductal adenocarcinoma is notoriously resistant to immunotherapy, largely due to its highly immunosuppressive tumor microenvironment. Lactylation plays a significant role in fostering this immune evasion. The LDHA–H4K12la axis regulates pancreatic cancer immunity.¹⁹ Elevated LDHA activity leads to increased lactate production and subsequent H4K12la, which can modulate the expression of genes involved in immune cell recruitment, activation, and function. This epigenetic modification can promote the expression of immunosuppressive factors or inhibit the expression of immunostimulatory ones, thereby contributing to the “cold” immune phenotype of PDAC. The overall lactate metabolic reprogramming in PDAC promotes immune escape.²⁰ High lactate levels in the tumor microenvironment can directly inhibit the function of various immune cells, including T cells and natural killer cells, by altering their metabolism, pH, and signaling pathways. Lactate can also promote the differentiation of myeloid-derived suppressor cells and regulatory T cells, both of which contribute to immune suppression. The lactylation of immune-related proteins or proteins in immune cells could be a key mechanism by which lactate exerts these immunosuppressive effects. Collectively, this evidence indicates that lactylation plays a central role in PDAC immune evasion and therapy resistance by reshaping the tumor immune microenvironment and conferring resistance to cell death. Specifically, the immunosuppressive signaling axis mediated by H4K12la and the cell death resistance mechanisms mediated by lactylation of specific non-histone proteins (e.g., GCLM) and histone marks (e.g., H3K9) represent major barriers to PDAC treatment. These pivotal mechanisms are illustrated in [Figure 2](#).

5.5. Cancer stemness

Cancer stem cells (CSCs) are a subpopulation of tumor cells with self-renewal capacity and the ability to initiate and sustain tumor growth, metastasis, and therapeutic resistance. Lactylation has been implicated in promoting PDAC stemness. SIRT4 has been shown to promote pancreatic cancer stemness through histone lactylation.⁵⁵ While the specific histone sites are not detailed in the study, the finding suggests that SIRT4, a mitochondrial sirtuin

known for its role in metabolic regulation, can influence the epigenetic landscape via lactylation to maintain the stem-like properties of PDAC cells. Targeting SIRT4 or the associated lactylation pathways could offer a strategy to eliminate CSCs and improve therapeutic outcomes.

5.6. Other relevant factors

While not directly lactylation-related, other regulatory axes are crucial for PDAC progression and often interact with metabolic and epigenetic pathways. CTCF (CCCTC-binding factor) has been shown to regulate the filaggrin antisense RNA 1 (FLG-AS1)/insulin-like growth factor 2 mRNA binding protein (IGF2BP2)/colony-stimulating factor 1 (CSF1) axis, promoting pancreatic cancer progression.⁵⁶ CTCF is an architectural protein involved in chromatin organization and gene regulation, and its interactions with long non-coding RNAs like FLG-AS1 can influence gene expression. While this pathway is distinct from lactylation, it highlights the complex regulatory networks that drive PDAC, where epigenetic factors (CTCF) can interact with RNA biology (FLG-AS1, IGF2BP2) and growth factor signaling (CSF1) to promote tumor growth. Future research may reveal potential crosstalk between this axis and lactylation pathways.

In conclusion, lactylation plays a profound and multifaceted role in pancreatic cancer, influencing its diagnosis, prognosis, metabolic adaptation, aggressive behavior, immune evasion, and stemness. The intricate interplay between lactate metabolism, histone lactylation, and non-histone protein lactylation creates a complex regulatory network that drives PDAC progression. A deeper understanding of these mechanisms is essential for developing effective diagnostic tools and targeted therapies for this devastating disease.

6. Therapeutic implications and challenges

The burgeoning understanding of lactylation's critical roles in cancer pathogenesis, particularly in aggressive malignancies like pancreatic cancer, positions it as a promising novel target for therapeutic intervention. By linking metabolism and epigenetics, lactylation offers unique opportunities to disrupt cancer cell survival, proliferation, and resistance mechanisms. This section explores the emerging therapeutic implications of targeting lactylation pathways, discusses potential strategies, and addresses the inherent challenges in translating these findings into clinical practice.

6.1. Targeting lactylation to overcome drug resistance

One of the most significant challenges in cancer treatment is the development of drug resistance. Lactylation has been

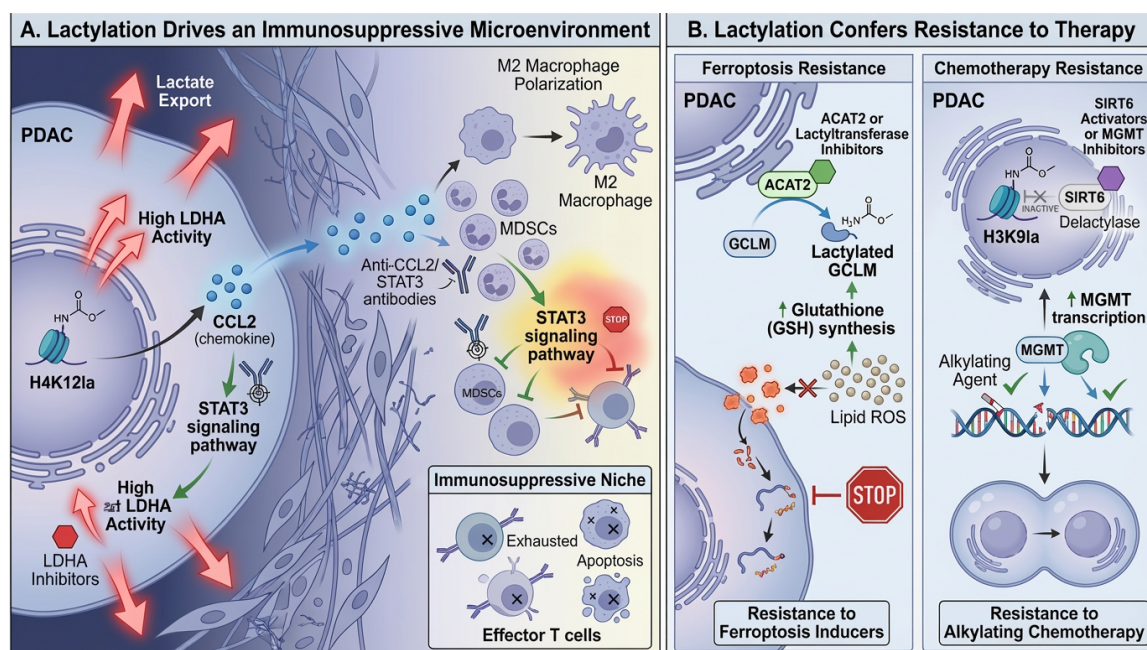


Figure 2. Mechanisms of lactylation in fostering immune evasion and therapeutic resistance in PDAC. (A) Lactylation promotes an immunosuppressive tumor microenvironment. In PDAC cells, the LDHA–H4K12la axis drives the expression and secretion of CCL2 and activates STAT3 signaling. CCL2 recruits immunosuppressive cells, such as MDSCs, and polarizes macrophages towards an M2 phenotype, while STAT3 signaling further dampens anti-tumor immunity. Together, this creates a niche that inhibits the function and survival of effector T cells. (B) Lactylation confers resistance to different therapeutic modalities. Left: Ferroptosis resistance: ACAT2-mediated lactylation of GCLM enhances glutathione synthesis, which scavenges lipid ROS, thereby protecting PDAC cells from ferroptosis. Right: Chemotherapy resistance: Persistent histone H3K9 lactylation, due to low SIRT6 delactylase activity, promotes the transcription of the DNA repair enzyme MGMT. Elevated MGMT levels repair DNA damage induced by alkylating chemotherapeutic agents, leading to treatment failure. These mechanisms highlight lactylation as a critical node in the development of combination therapies to reverse immunosuppression and overcome drug resistance. Image created with Adobe Illustrator.

Abbreviations: ACAT2: Acetyl-CoA acetyltransferase 2; CCL2: C-C motif chemokine ligand 2; GCLM: Glutamate-cysteine ligase modifier subunit; GSH: Glutathione; H3K9: Histone H3 lysine 9; H4K12la: Histone H4 lysine 12 lactylation; LDHA: Lactate dehydrogenase A; MDSC: Myeloid-derived suppressor cell; MGMT: O6-methylguanine-DNA methyltransferase; PDAC: Pancreatic ductal adenocarcinoma; ROS: Reactive oxygen species; SIRT: Sirtuin; STAT3: Signal transducer and activator of transcription 3.

implicated in mediating cancer cell resistance to various therapies, suggesting that targeting this modification could be a viable strategy to overcome such resistance.^{57,58} Lactylation can contribute to drug resistance through several mechanisms. For instance, by promoting the expression of genes involved in drug efflux, DNA repair, or anti-apoptotic pathways, lactylation can render cancer cells less susceptible to chemotherapy or targeted agents. The lactylation of proteins involved in ferroptosis resistance (e.g., GCLM lactylation)⁴⁰ or the modulation of DNA repair enzymes (e.g., H3K9la/SIRT6/MGMT axis)²⁶ are examples of how lactylation can influence therapeutic efficacy. Inhibiting lactyltransferases, activating delactylases, or directly interfering with lactate metabolism could potentially resensitize resistant cancer cells to existing therapies. For example, if a specific lactylation event promotes resistance, inhibiting the enzyme responsible

for that lactylation or enhancing its removal could restore drug sensitivity.

6.2. Lactate dehydrogenase A inhibitors

Lactate dehydrogenase A is a key enzyme in glycolysis, catalyzing the conversion of pyruvate to lactate. Given that lactate is the direct precursor of lactylation, inhibiting LDHA is a logical strategy to reduce lactate levels and subsequently decrease lactylation.^{19,36} LDHA is often overexpressed in cancer cells due to the Warburg effect, making it an attractive therapeutic target. By inhibiting LDHA, not only would lactate production be reduced, but also the entire glycolytic flux could be disrupted, starving cancer cells of energy and biosynthetic precursors.

The development of small-molecule inhibitors specifically targeting LDHA is an active area of research.

Hydroxy-pyrimidinone derivatives, for example, have been developed as potent LDHA inhibitors.⁵⁹ These inhibitors aim to reduce lactate levels, thereby decreasing global lactylation and impacting various lactylation-dependent processes in cancer. Reducing lactate levels through LDHA inhibition would directly decrease the availability of the lactyl group for protein modification, thereby reducing lactylation, including histone lactylation (e.g., H3K18la, H4K12la) and non-histone protein lactylation. This broad effect could simultaneously target multiple cancer-promoting pathways regulated by lactylation, such as immune evasion^{19,20} and proliferation.¹⁸

6.3. Modulating lactate metabolism for cancer therapy

Beyond direct LDHA inhibition, broader strategies to modulate lactate metabolism hold therapeutic potential.⁶⁰ Monocarboxylate transporters (MCTs), particularly MCT1 and MCT4, are responsible for lactate transport across cell membranes. Inhibiting these transporters could prevent lactate efflux from cancer cells, leading to intracellular acidification and toxicity, or prevent lactate uptake by cancer cells that rely on exogenous lactate. Additionally, several existing drugs might indirectly affect lactate metabolism or lactylation. Identifying and repurposing such compounds could accelerate the development of lactylation-targeting therapies. Lactate has been shown to regulate the cell cycle, and modulating its levels can be exploited for cancer therapy.⁶⁰ By disrupting lactate-mediated cell cycle progression, tumor growth can be inhibited.

6.4. Histone modification mechanisms as therapeutic targets

The broader field of histone modification mechanisms has long been recognized as a rich source of therapeutic targets.⁷ Inhibitors of HDAC and histone methyltransferases are already in clinical use or trials. Given that sirtuins (SIRT1, SIRT6) and HDACs (HDAC1–3) act as delactylases^{25–27}, modulating their activity could influence lactylation levels. For instance, specific activators of delactylases could reduce oncogenic lactylation marks, while inhibitors might be used to enhance beneficial lactylation (if such cases are identified). The identification of specific lactyltransferases like ACS2–KAT2A and KAT8^{23,24} opens avenues for developing small-molecule inhibitors that specifically block lactylation. Such inhibitors could offer more targeted approaches compared to broad metabolic interventions.

6.5. Challenges in targeting lactylation

Despite the promising therapeutic potential, several challenges need to be addressed:

- (i) Specificity and off-target effects: Lactylation is a widespread modification affecting numerous proteins. Developing highly specific inhibitors for lactyltransferases or activators for delactylases without causing significant off-target effects on essential cellular processes is crucial.
- (ii) Context-dependent effects: The functional consequences of lactylation can be highly context-dependent, with the same modification potentially having different effects in different cell types or at different stages of cancer. A comprehensive understanding of these context-specific roles is necessary to avoid unintended consequences.
- (iii) Delivery and pharmacokinetics: Ensuring efficient delivery of lactylation-targeting agents to tumor cells and achieving optimal pharmacokinetic profiles are critical for clinical success.
- (iv) Combination therapies: Given the complexity of cancer, it is likely that lactylation-targeting therapies are most effective when used in combination with existing treatments, such as chemotherapy, radiation, or immunotherapy. Identifying optimal combination strategies requires extensive preclinical and clinical investigation.
- (v) Biomarker development: Robust biomarkers are needed to identify patients who are most likely to respond to lactylation-targeting therapies and to monitor treatment efficacy. This includes developing reliable assays for measuring lactylation levels in patient samples.

Targeting lactylation pathways represents a novel and exciting frontier in cancer therapeutics. By leveraging the direct link between metabolism and epigenetics, these strategies hold the potential to overcome drug resistance, inhibit tumor progression, and improve patient outcomes, particularly in challenging cancers such as PDAC. However, careful and rigorous research is required to translate these promising preclinical findings into effective clinical treatments.

7. Discussion

Lactylation, a recently discovered PTM, has emerged as a pivotal regulatory mechanism that intricately links cellular metabolism, particularly lactate production, with epigenetic control and diverse protein functions.^{61,62} This comprehensive review has highlighted the profound and multifaceted roles of lactylation in cancer biology, with a specific focus on PDAC, one of the most aggressive and therapeutically challenging malignancies.

We have explored how histone lactylation at sites such as H3K18, H4K12, and H3K9 directly modulates chromatin

structure and gene expression, thereby influencing critical cancer hallmarks including proliferation, immune evasion, and DNA repair. The dynamic interplay between lacyltransferases (e.g., ACSS2–KAT2A, KAT8) and delactylases (e.g., SIRT1, SIRT6, HDAC1–3) ensures the precise regulation of these epigenetic marks, which are often dysregulated in cancer to promote tumor progression.

Beyond histones, the widespread lactylation of non-histone proteins has unveiled an expansive regulatory network that impacts numerous cellular processes. From fine-tuning metabolic pathways (e.g., NMNAT1, GCLM, AARS2) and orchestrating autophagy (e.g., TFEB, FOXO3) to driving EMT (e.g., Snail1, PRMT1) and modulating immune responses (e.g., ENSA-K63), non-histone protein lactylation acts as a metabolic sensor that translates the high-lactate tumor microenvironment into functional alterations that favor cancer cell survival, invasion, and metastasis.^{63,64}

In PDAC, lactylation plays a particularly critical role. Elevated H3K18la is associated with diagnosis and prognosis, while lactylation-related gene signatures offer prognostic insights. The intense metabolic reprogramming characteristic of PDAC, driven by a NUSAP1–LDHA–glycolysis–lactate feedforward loop and exacerbated by cancer-associated fibroblasts, creates a high-lactate milieu that fuels lactylation.³ This, in turn, promotes PDAC cell proliferation, migration, and invasion, contributes to immune evasion via the LDHA–H4K12la axis, and fosters cancer stemness through mechanisms involving SIRT4.⁵⁵

The recognition of lactylation as a central player in cancer biology opens exciting avenues for therapeutic intervention. Strategies aimed at targeting lactylation pathways, such as inhibiting LDHA to reduce lactate production, modulating the activity of lacyltransferases or delactylases, or directly interfering with lactate metabolism, hold immense promise for overcoming drug resistance and inhibiting tumor growth. However, the development of highly specific and effective lactylation-targeting agents, coupled with a comprehensive understanding of their context-dependent effects and potential off-target activities, remains a significant challenge.

Although accumulating studies suggest that lactylation plays important roles in cancer biology, several limitations should be carefully considered. First, many mechanistic conclusions are derived from preclinical models or correlative analyses in limited patient cohorts. Causal evidence directly linking specific lactylation events to clinical outcomes in pancreatic cancer remains scarce, and robust validation in large, well-annotated patient populations remains lacking. Second, the functional

consequences of lactylation appear to be highly context-dependent. While multiple reports describe lactylation as promoting immune evasion, EMT, or stemness, other studies indicate that lactylation may facilitate ferroptosis or stress adaptation in a manner that is not uniformly oncogenic.^{65–67} The relative balance between histone and non-histone lactylation, cell-type specificity, and temporal dynamics is likely the key determinant of these divergent outcomes. Third, lactylation should be interpreted within a broader hierarchy of acylation modifications, including acetylation, crotonylation, and succinylation, which share common metabolic precursors and partially overlapping enzymatic machinery.^{68–70} How lactylation competes with or complements these modifications under fluctuating metabolic conditions remains an open question. Finally, significant technical challenges complicate the study of lactylation. Issues related to antibody specificity, quantitative reproducibility, and mass spectrometry sensitivity limit confident site identification and cross-study comparisons. These methodological constraints should be acknowledged when interpreting existing data and designing future translational studies.

8. Conclusion

In conclusion, lactylation stands as a crucial nexus between cellular metabolism and epigenetic regulation, profoundly influencing the initiation, progression, and therapeutic response of cancer. Its intricate mechanisms and widespread impact underscore its potential as a novel diagnostic, prognostic, and therapeutic target. Rather than positioning lactylation as an immediately actionable therapeutic target, future research should prioritize defining context-specific functions, establishing causal relationships in clinically relevant models, and resolving technical limitations in detection and quantification. Addressing these gaps will be essential before lactylation-based strategies can be meaningfully translated into pancreatic cancer diagnosis or therapy. Continued research into the precise molecular mechanisms and physiological consequences of lactylation will undoubtedly pave the way for innovative strategies to combat cancer, particularly in aggressive and metabolically reprogrammed malignancies such as pancreatic cancer.

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