

# Effects of lactylation on the hallmarks of cancer (Review)

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**Abstract.** Lactylation, an emerging metabolism-dependent post-translational modification, serves as a core mechanism linking metabolic reprogramming with epigenetic regulation in establishing the multifaceted hallmarks of cancer. The present review systematically elucidates how lactylation dynamically regulates the functions of both histone and non-histone proteins, driving the acquisition of classical cancer hallmarks including sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, induction of angiogenesis, activation of invasion and metastasis and replicative immortality. Furthermore, lactylation is intricately involved in enabling the emerging hallmarks of cancer, such as the maintenance of genome instability, shaping of a pro-inflammatory tumor microenvironment (TME), immune escape, metabolic reprogramming, unlocking phenotypic plasticity and non-mutational epigenetic reprogramming. By reshaping the interaction networks among cancer, stromal and immune cells within the TME, lactylation promotes the formation of an immunosuppressive microenvironment and enhances resistance to therapy. Targeting lactylation regulatory pathways (such as lactate dehydrogenase A inhibitors, monocarboxylate transporter inhibitors and delactylase activators) can reverse key hallmark phenotypes, highlighting novel therapeutic avenues for the development of precision anticancer strategies based on interrupting metabolic-epigenetic crosstalk.

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## 1. Introduction

Lactylation, a novel post-translational modification (PTM) characterized by the covalent attachment of lactate to lysine residues, has emerged as a critical regulatory mechanism in cancer biology (1). Initially identified as a metabolic byproduct of anaerobic glycolysis, lactate is now recognized as a dynamic signaling molecule that orchestrates cellular adaptation through lactylation. This modification, first reported on histones in 2019, bridges metabolic reprogramming and epigenetic regulation, influencing key oncogenic processes such as proliferation, metastasis, immune evasion and resistance to therapy (2). Within the tumor microenvironment (TME), lactate accumulation drives lactylation of histones and non-histone proteins, modulating interactions among cancer cells, cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs) and immune cells (3). Notably, lactylation reshapes chromatin structure, alters enzymatic activities in glycolysis and the tricarboxylic acid cycle, and sustains immunosuppressive niches by polarizing TAMs towards an M2 phenotype and impairing cytotoxic T-cell function (4). Furthermore, lactylation contributes to genomic instability, angiogenesis and phenotypic plasticity through mechanisms involving DNA repair modulation and metabolic-epigenetic crosstalk. Emerging therapeutic strategies targeting lactylation-associated enzymes [such as lactate dehydrogenase A (LDHA) and monocarboxylate transporter (MCT1/4)] or disrupting lactate-driven feedback loops hold promise for overcoming chemoresistance and enhancing the efficacy of immunotherapy (5). The present review summarizes the current insights into the role of lactylation across the hallmarks of cancer, highlighting its potential as a diagnostic biomarker and therapeutic target in precision oncology.

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## 2. Lactate and lactylation

Initially regarded as a metabolic byproduct of anaerobic glycolysis, lactate is now recognized as more than its historical perception as mere waste. Emerging evidence highlights its critical roles in energy metabolism (6), signaling regulation (7,8) and cellular homeostasis (9). Lactylation, a PTM involving covalent attachment of lactate to lysine residues, mirrors acetylation in mechanism and importance. First identified on histones by Zhang *et al* (2) in 2019, lactylation has since been detected on non-histone proteins, establishing a metabolic-epigenetic link. This modification, driven by glycolytic end-product lactate, is mechanistically associated with cancer progression, inflammatory responses and stem cell regulation (1). Previous studies underscore the profound impact of lactylation on the hallmarks of cancer, including proliferation, metastasis and drug resistance, through modulation of metabolic enzyme activity (10).

## 3. Lactylation-related proteins

*Histone lactylation and non-histone lactylation.* PTMs involve the covalent addition of chemical groups to amino acid residues, altering protein function. Common PTMs, including phosphorylation, acetylation and ubiquitination regulate chromatin dynamics and gene expression (11). Histones, comprising core (H2A, H2B, H3 and H4) and linker (H1 and H5) subtypes, undergo PTM, and these PTMs are involved in epigenetic regulation (12). Lactylation modification modulates chromatin structure, DNA-histone interactions and transcriptional activity. Hypoxia-induced pyruvate accumulation drives lactylation, particularly at histone 3 lysine 18 (H3K18), H4K5 and H4K18 residues, while H4K5 lactylation (H4K5la) is associated with a poor prognosis in neuroblastoma (13,14). In neuroblastoma studies, elevated lactylation levels of the 5th lysine residue of histone H4 (H4K5la) were found to be notably associated with a poor clinical prognosis in patients (15).

Non-histone lactylation occurs across organelles (nucleus, mitochondria and lysosomes) and regulates several processes, including glycolysis, inflammation and oxidative stress (16-18). By altering protein conformation, charge and stability, lactylation impacts enzyme activity and molecular interactions. For example, in hepatocellular carcinoma (HCC), adenylate kinase 2 lactylation at K28 suppresses mitochondrial function, driving metastasis (19). In lung squamous cell carcinoma, glucose transporter 1-driven lactate accumulation induces lactylation of non-histone proteins [such as N6-adenosine-methyltransferase 70 kDa subunit (METTL3)], thereby enhancing the immunosuppressive tumor microenvironment, reducing the response to immunotherapy and promoting tumor progression (20). Similarly, in pancreatic ductal adenocarcinoma (PDAC), lactylation of the ENSA protein inhibits the phosphatase PP2A, activating the STAT3/CCL2 axis. This axis recruits tumor-associated TAMs and impairs cytotoxic T cell activity (21).

Non-histone protein lysine lactylation (Kla), an emerging PTM, has gained notable attention in oncology research. However, elucidating its mechanisms and achieving clinical translation present substantial challenges. Although enzymes

such as p300, alanyl-tRNA synthetase (AARS1) and lysine acetyltransferase 8 (KAT8) have been reported as potential lactyltransferases, most possess acyltransferase activity for acetylation and crotonylation (Kcr). For example, KAT8 catalyzes eukaryotic translation elongation factor 1a2 K408 lactylation to promote protein synthesis in colorectal cancer (CRC). However, its affinity for lactoyl-CoA ( $K_m \approx 28 \mu\text{M}$ ) is markedly lower compared with for acetyl-CoA ( $K_m \approx 12 \mu\text{M}$ ), raising questions about its preferential catalysis of lactylation under high-lactate conditions (22). Non-enzymatic lactylation mediated by lactoylglutathione has been reported in liver and breast cancer; this type of modification is not enzyme-regulated, making it difficult to target via catalytic enzyme inhibition, and its physiological importance remains unclear. Functional outcomes of lactylation also exhibit tissue-specific discrepancies. For example, p53 K120 lactylation suppresses its tumor-suppressive function in gastric cancer (23) yet stabilizes the protein and enhances DNA repair in glioma (24). Such context-dependent effects underscore that lactylation functions are highly dependent on the microenvironment, suggesting that single mechanistic models can oversimplify the actual complexity.

*Regulatory machinery of protein lactylation.* Lactylation, a dynamic PTM, is regulated by three classes of proteins: Writers (lactyltransferases), erasers (delactylases) and readers (lactylation-recognition factors). Collectively, these components orchestrate lactate modification on histones and non-histone proteins by mediating its addition, removal and functional interpretation, thereby modulating gene expression and cellular physiology (Fig. 1). Writers catalyze the addition of a lactate group to lysine residues: p300, a histone acetyltransferase (HAT) with dual roles in acetylation and lactylation, was first identified as a lactyltransferase by Zhang *et al* (2), linking it to pathologies including pulmonary fibrosis (25), several types of cancer (26) and Parkinson's disease (27). Lysine acetyltransferase 7 (HBO1), a MYST-family acyltransferase, mediates several histone modifications such as acetylation, Kcr and lactylation (28). HBO1 preferentially targets H3K9la, and elevated H3K9la levels in cervical cancer are strongly associated with HBO1 overexpression (5), driven by its high affinity for lactyl-CoA to regulate oncogenic genes. Erasers remove lactate modifications to reset histone states: Histone deacetylase (HDAC) 1-3 and sirtuin (SIRT) 1-3 function as zinc- and  $\text{NAD}^+$ -dependent deacetylases with broad delactylase activity, cleaving both  $\epsilon$ -N-L-lactylated and D-lactylated residues (29). SIRT2 specifically removes H3K18la/H4K8la to suppress neuroblastoma proliferation and migration (30), while SIRT3 inhibits HCC by regulating cyclin E2 lactylation levels (31). Readers transduce lactylation signals: SWI/SNF related BAF chromatin remodeling complex subunit ATPase 4 (Brg1), a chromatin remodeler, recognizes H3K18la at promoters of pluripotency genes to facilitate transcriptional reprogramming (32).

*Interaction of lactylation with other PTMs.* Lysine lactylation, as a novel metabolism-dependent PTM, engages in a complex and dynamic interplay with other PTMs. This network orchestrates tumor progression through mechanisms including competitive occupancy of modification sites, shared catalytic

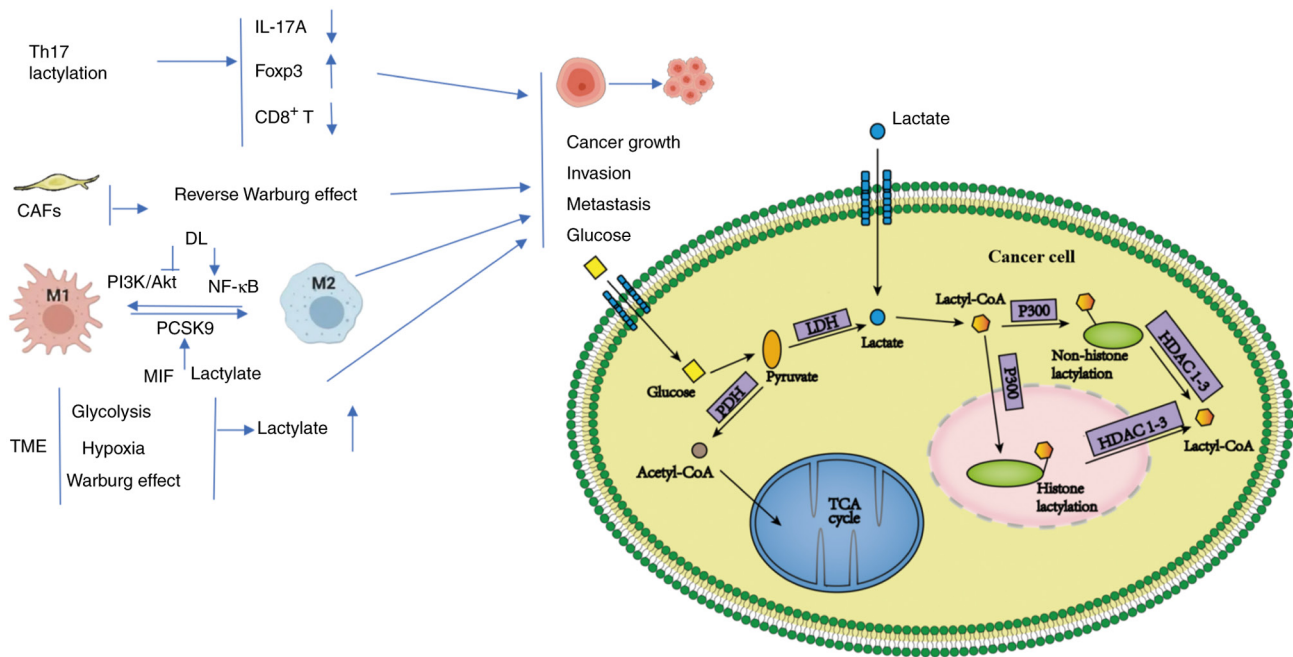


Figure 1. In the TME, lactate polarizes TAMs to the M2 phenotype through histone lactylation. Lactate-treated Th17 cells markedly reduce IL-17A and upregulate Fcγ3. The high-energy metabolites (such as lactate and pyruvate) produced by CAFs via aerobic glycolysis are translocated into adjacent epithelial cancer cells. DL can promote the transformation of M2 to M1 macrophages by regulating the lactylation of macrophages, specifically through the inhibition of the PI3K/Akt pathway and the activation of the NF-κB pathway. PCSK9 affect the polarization of TAMs in colon cancer by regulating MIF and lactate levels. Higher glycolysis, hypoxia and the Warburg effect elevate lactate levels and promote tumor growth, evasion and metastasis. In cancer cells, lactate produced from glucose and exogenous lactate is further metabolized to produce lactyl-CoA, which can enter and exit the nucleus. p300, as a writer of lactylations, can add lactyl groups to lysine residues of histones or non-histone proteins to form lactylations, while erasers HDAC1-3 remove lactate modification motifs from histones or non-histone proteins and restore them to their original state. MIF, macrophage migration inhibitory factor; DL, D-lactic acid; TCA cycle, tricarboxylic acid cycle; TME, tumor microenvironment; PDH, pyruvate dehydrogenase; LDH, lactate dehydrogenase; PCSK9, proprotein convertase subtilisin/kexin type 9; CAFs, cancer-associated fibroblasts; TAMs, tumor-associated macrophages; HDAC, histone deacetylase.

enzymes, cascading signaling and epigenetic reprogramming. Klc exhibits substrate competition with lysine acetylation (Kac) and Kcr, a relationship governed by fluctuating metabolite concentrations and shared enzymatic machinery. HATs p300/CREB-binding protein (CBP) and HBO1 possess dual lactyltransferase/acetyltransferase activity and can catalyze multiple acylation types. For example, HBO1 preferentially catalyzes either lactylation (H3K9la) or acetylation (H3K9ac) at histone H3K9, with the type of modification dictated by the intracellular lactate-to-acetyl-CoA ratio (33,34). Similarly, de-modifying enzymes HDAC1-3 and SIRT1-3 exhibit both deacetylase and delactylase activities; SIRT2, for example, removes H3K18la and H4K8la modifications (33). Lactate and acetyl-CoA compete for the same lysine residues. In the acidic TME, lactate accumulation drives H3K18la to replace H3K18ac, activating immunosuppressive genes such as programmed death-ligand 1 (PD-L1). Conversely, under glucose-replete conditions, acetylation predominates, promoting oncogene transcription (35,36).

Kcr, another prominent Kac, serves key roles in diseases such as liver cancer (37) and glioblastoma (GBM) stem cells (38) by modulating histone structure and function. A previous study suggested potential synergistic roles for Klc and Kcr in processes such as neural differentiation and cell proliferation (39). However, due to its greater hydrophobicity, Kcr can antagonize Klc modifications in open chromatin regions; for example, H3K56la suppresses Kcr-mediated activation of inflammatory genes (40). Klc and phosphorylation

mutually amplify oncogenic signals through positive feedback loops. Histone lactylation (such as H3K18la) activates genes encoding cell cycle kinases (for example TTK protein kinase and BUB1 mitotic checkpoint serine/threonine kinase B). Their protein products phosphorylate LDHA at Tyr239, enhancing LDHA activity and lactate production, promoting further lactylation (14). Similarly, AMPK phosphorylation of p300 at Ser89 enhances its lactyltransferase activity, establishing a metabolic stress-p300 lactylation amplification loop (34). Furthermore, transcription factor EB (TFEB) lactylation at K91 impedes binding via the action of the E3 ubiquitin ligase WW domain containing E3 ubiquitin protein ligase 2, reducing TFEB ubiquitination and degradation. This stabilization enhances autophagy and lysosomal biogenesis, supporting tumor survival (41).

Klc is intricately integrated within the intricate dynamic PTM network and is particularly interconnected with other types of lysine acylation (such as Kac and Kcr) via shared core enzymatic machinery (such as p300/CBP and HBO1 with dual lactyl/acetyl transferase activity; HDACs/SIRTs with dual deacetylase/delactylase activity). This interdependence underpins the 'metabolite-concentration-dependent substrate competition' hypothesis: Fluctuations in metabolite abundance (such as lactate and acetyl-CoA) competitively regulate the balance between different types of acylation, with cascading effects, and pyruvate dehydrogenase complex component X acetylation inhibits lactate production, subsequently downregulating H3K56 lactylation (29,39). However, the

downstream mechanistic effects of these interactions remain largely unknown. Critical unresolved questions include: Do K1a and K1c directly compete for occupancy at identical lysine residues? How do the distinct chemical properties of the modifying groups (lactyl, acetyl and the more hydrophobic crotonyl) lead to the recruitment of specific reader proteins and functional divergence (such as the Brg1-specific recognition of H3K181a)? How are these interactions tissue- or tumor-type dependent?

For the emerging K1c, evidence for functional synergy or antagonism with K1a in cancer is limited, and the differential impact of their chemical properties on chromatin remodeling and signal transduction is poorly understood. The hijacking of shared regulatory factors by drug-induced modifications (such as lysine isonicotinylations) highlights the sensitivity and complexity of the PTM network, yet the pathological importance of endogenous analogues remains unknown.

Current research often remains descriptive or focused on isolated pathways. Notable limitations include insufficient investigation of spatiotemporal dynamics, lack of rigorous causal validation and inadequate critical assessment of model systems and technological constraints. These gaps hinder a comprehensive understanding of the precise role of this sophisticated metabolic-epigenetic coupling network in tumorigenesis. Future research should employ tools such as site-specific mutagenesis, time-resolved omics and metabolic gradient models to evaluate the kinetics of inter-modification competition, identify specific effector molecules and assess the consequences of network perturbation. Overcoming the current fragmented understanding is essential to providing a solid theoretical foundation for the development of precision anticancer strategies targeting key nodes within the PTM network.

#### 4. Lactylation and the TME

Under aerobic conditions, cancer cells often metabolize glucose to lactate rather than producing carbon dioxide and water via mitochondrial oxidative phosphorylation (OXPHOS). This phenomenon, known as the Warburg effect (42,43), leads to increased intracellular and extracellular lactate concentrations. As a hallmark of cancer metabolism, the Warburg effect enables cancer cells to meet their high ATP demands by upregulating glycolysis even when oxygen is sufficient. In the TME, lactate regulates interactions between cells, CAFs, TAMs and tumor-infiltrating lymphocytes (TILs), thereby establishing a microenvironment favorable for tumor cell growth and immune evasion (3).

TAMs, a key immune cell component in the TME, serve a crucial role in carcinogenesis and progression. Based on their functions, TAMs are classified into the pro-inflammatory, anticancer M1 type and the anti-inflammatory, pro-cancer M2 type. Lactate can promote the polarization of TAMs towards an immunosuppressive M2 phenotype through histone lactylation when lactate levels are increased (2). T cells serve a central role in antitumor immunity while also being key components of the TME. Lactylation of moesin at K72 enhances the suppressive function of regulatory T cells (Tregs). Concurrently, extracellular lactate upregulates programmed cell death protein 1 (PD-1) expression via G protein-coupled receptor 81 (GPR81) signaling, inducing exhaustion in CD8<sup>+</sup>

T cells (44). Furthermore, lactate promotes the expansion of PD-L1<sup>+</sup> neutrophils through the MCT1/NF- $\kappa$ B axis, ultimately compromising antitumor immunity (45).

The formation of the TME is primarily based on glycolysis, hypoxia and the Warburg effect, which collectively influence tumor cell growth, invasion and metastasis. In the TME, CAFs, rather than cancer cells themselves, utilize aerobic glycolysis, a phenomenon known as the reverse Warburg effect (46). The high-energy metabolites (such as lactate and pyruvate) produced by CAFs through aerobic glycolysis are transported into adjacent epithelial cancer cells, where they undergo aerobic mitochondrial metabolism. This metabolic pattern increases ATP production in cancer cells, thereby promoting cancer growth and metastasis (47).

In summary, the metabolic characteristics of TME, notably the Warburg effect and reverse Warburg effect, drive substantial lactate accumulation. Lactylation serves as a pivotal metabolic-epigenetic coupling mechanism that extensively regulates the functional states and interactions of a range of cell types in the TME, including cancer cells, CAFs, immune cells and other stromal components. Collectively, these lactate-driven modifications foster an immunosuppressive and pro-tumorigenic microenvironment that supports tumor growth, invasion, metastasis and immune evasion. This understanding provides a crucial foundation for deciphering tumor progression and developing novel therapeutic strategies targeting the TME.

#### 5. Lactylation and the hallmarks of cancer

The hallmarks of cancer are pivotal characteristics employed in cancer research to distinguish tumor cells from normal cells. Since their conception, the hallmarks have expanded from the initial six to 14 (48,49), including sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, genome instability and mutation, promoting inflammation, reprogramming energy metabolism, evading immune destruction, unlocking phenotypic plasticity, non-mutational epigenetic reprogramming, polymorphic microbiomes and senescent cells. Enabling replicative immortality and activating invasion and metastasis are closely associated with cancer growth and metastasis. These 14 hallmarks are collectively summarized in Fig. 2. The hallmarks of cancer provide a systematic framework for understanding tumor biology. Lactylation serves as a central node (Fig. 3), exerting a pivotal role across the 10 established cancer hallmarks via a metabolic-epigenetic bidirectional regulatory axis.

*Metabolic reprogramming-driven malignant proliferation and metastasis.* Lactylation serves as both a core effector and driver of metabolic reprogramming. By establishing self-reinforcing positive feedback loops, it not only directly couples glycolysis with epigenetic reprogramming but also maintains cancer stem cell properties and promotes angiogenesis. This multifaceted mechanism drives tumor growth, invasion and metastasis across multiple dimensions.

*Lactylation and metabolic reprogramming.* Lactylation directly couples glycolysis with epigenetic reprogramming,

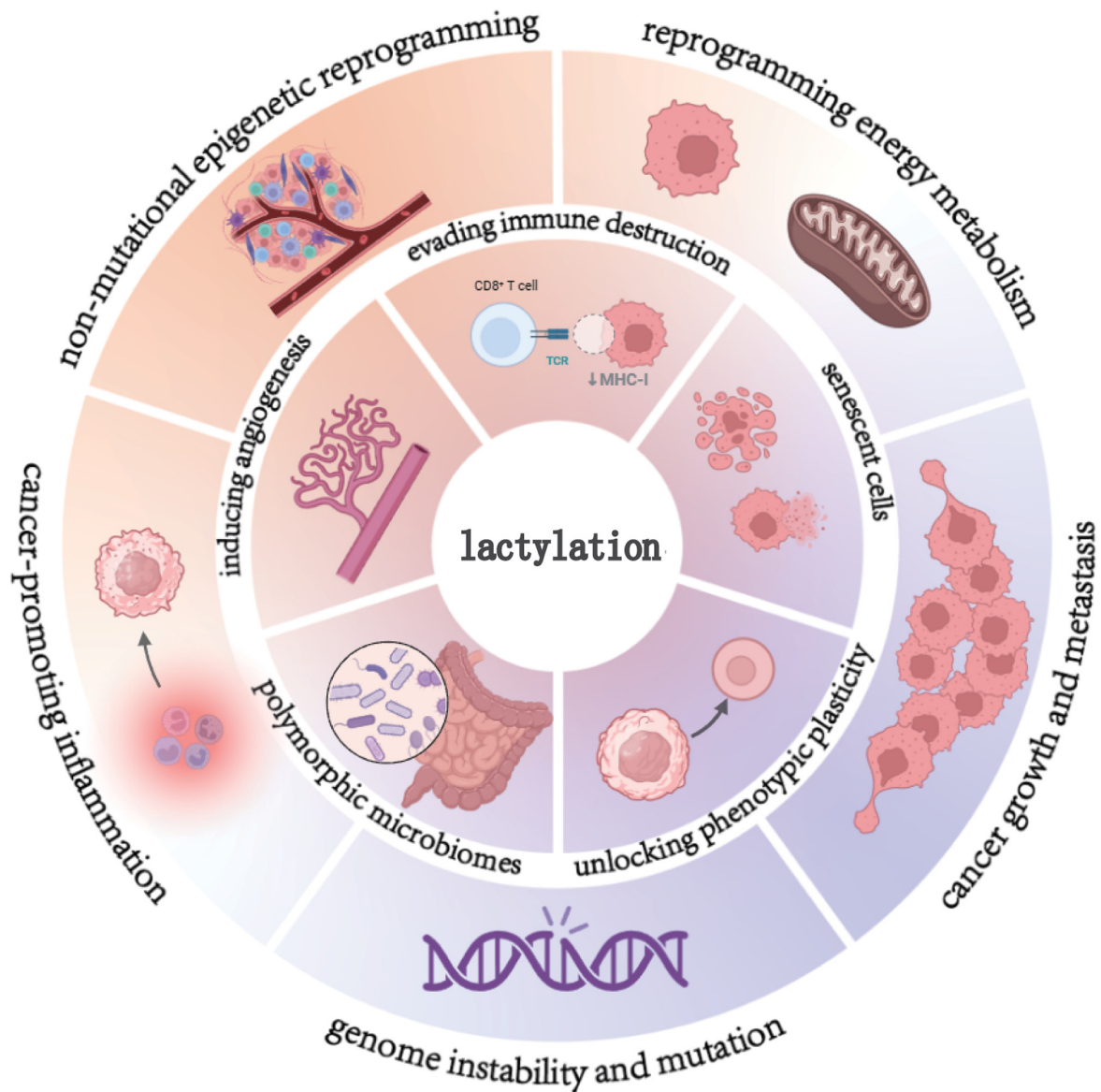


Figure 2. Relationship between lactylation and cancer hallmarks. The hallmarks of cancer are pivotal characteristics employed in cancer research to distinguish tumor cells from normal cells. MHC, major histocompatibility complex; TCR, T-cell receptor.

forming self-reinforcing pro-tumorigenic circuits. Histone lactylation serves as a critical link between metabolic reprogramming and transcriptomic dysregulation in cancer cells (4). In malignant cells, metabolic alterations induce fluctuations in lactate levels, which manifest as changes in histone lactylation. Conversely, shifts in the histone lactylation landscape reshape the transcriptomic profile to accommodate the metabolic reprogramming demands within the TME. This establishes a metabolic reprogramming-lactylation positive feedback loop that accelerates tumor progression. For example, in clear cell renal cell carcinoma (ccRCC), lactylation levels are markedly elevated compared with normal kidney tissue (50). This increase is particularly pronounced upon loss of the key tumor suppressor von Hippel-Lindau (VHL) protein. VHL deficiency leads to hypoxia-inducible factor (HIF) accumulation, which directly promotes lactate production via glycolysis. Furthermore, lactylation enhances the transcriptional activity of platelet-derived growth factor receptor  $\beta$  (PDGFR $\beta$ ).

Activation of the PDGFR $\beta$  signaling pathway subsequently elevates lactylation levels, establishing a self-reinforcing circuit that drives ccRCC progression (50). Similarly, in pancreatic cancer, lactate from TAMs induces lactylation of nucleolar and spindle-associated protein 1 (NUSAP1), upregulating its expression. NUSAP1 forms a transcriptional complex with c-Myc and HIF-1 $\alpha$ . These transcription factors bind to the LDHA promoter, enhancing LDHA expression, thereby promoting glycolysis and increasing lactate production. This creates another positive feedback loop (51). Collectively, these metabolic reprogramming-lactylation positive feedback circuits serve a pivotal role in driving tumor growth and metastasis.

**Lactylation in tumor growth and metastasis.** Tumor growth and metastasis are governed by multiple factors, including cancer stemness and tumor angiogenesis. Cancer stemness refers to the capacity of tumor cells for self-renewal and differentiation into a range of cell types, which is

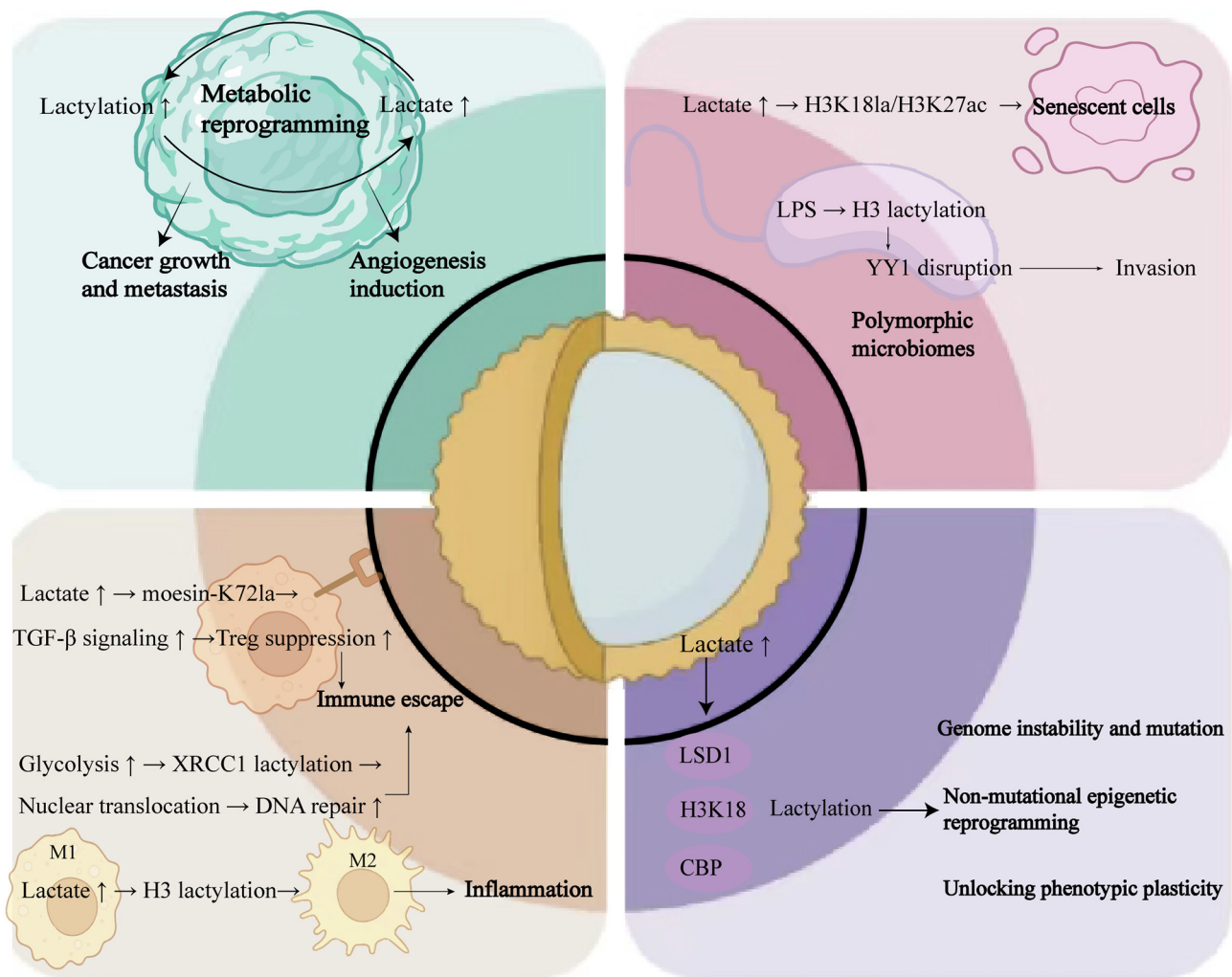


Figure 3. Schematic overview depicting lactylation as a metabolic-epigenetic hub that integrates tumor metabolism, immune evasion and cancer hallmark acquisition within the tumor microenvironment. LPS, lipopolysaccharide; Treg, regulatory T cells; TGF- $\beta$ , transforming growth factor  $\beta$ ; M1, classically activated (pro-inflammatory) macrophages; M2, alternatively activated (anti-inflammatory) macrophages; LSD1, lysine-specific histone demethylase 1; YY1, yin yang 1 (transcription factor); XRCC1, X-ray repair cross-complementing protein 1.

essential for tumor progression and dissemination. Activation of the NF- $\kappa$ B signaling pathway induces histone H3 lactylation, increasing expression of the long non-coding RNA LINC01127. LINC01127 sustains GBM stemness through the MAP4K4/JNK/NF- $\kappa$ B axis (52). Furthermore, Feng *et al* (53) demonstrated that liver cancer stem cells (LCSCs) exhibit elevated glycolytic flux, lactate accumulation and lactylation levels compared with HCC cells. Notably, histone H3K56la is closely associated with the tumorigenicity and stemness maintenance of LCSCs. High glycolytic flux provides the lactate substrate driving H3K9la/H3K56la modifications, while lactylation, in-turn, upregulates glycolytic enzyme expression. This establishes an LCSC-specific metabolic-epigenetic memory that perpetuates a self-sustaining loop.

**Lactylation and inducing angiogenesis.** As the circulatory system is a major route of metastasis, tumor angiogenesis is critically important for both tumor metastasis and growth. Lactate, functions as a potent pro-angiogenic factor and promotes angiogenesis through multiple mechanisms (54-56). Lactate activates the GPR81 receptor on endothelial cells, stimulating angiogenesis and subsequently promoting tumor

cell proliferation and survival (55). Through HIF-dependent pathways, lactate, transported via MCT1, inhibits prolyl hydroxylases, thereby stabilizing HIF-1 $\alpha$ . This stabilization enhances VEGF expression and angiogenesis. In HIF-independent pathways, lactate promotes angiogenesis via ROS generation and NF- $\kappa$ B/IL-8 signaling (54,55). Mounting evidence has established lactylation as a critical regulator of tumor angiogenesis. For example, Luo *et al* (57) demonstrated that lactylation of HIF1 $\alpha$  at K672 promotes angiogenesis in prostate cancer by enhancing transcription of the cell migration-inducing and hyaluronan-binding protein gene. Furthermore, as previously discussed, NUSAP1 forms a transcriptional complex with c-Myc and HIF-1 $\alpha$  that binds to the LDHA promoter, augmenting LDHA expression to drive angiogenesis and metastasis in pancreatic ductal adenocarcinoma (51).

**Microbiota, senescence and the lactylation epigenetic regulatory axis**

**Lactylation and polymorphic microbiomes.** Emerging evidence has demonstrated that gut microbiota exerts autonomous regulatory effects on oncogenesis and tumor

evolution (49). Notably, intestinal microbial diversity and compositional dynamics markedly modulate cancer initiation, malignant transformation and therapeutic responsiveness (58,59). Mechanistically, microbial-epigenetic crosstalk may involve lactylation-mediated pathways.

In pathogen-induced epigenetic remodeling, enteropathogens (such as *Salmonella*) induce marked alterations in long non-coding RNA networks within colonic epithelia. Wang *et al* (60) revealed that lipopolysaccharide (LPS)-mediated histone lactylation at the LINC00152 promoter disrupts YY1 transcription factor binding, facilitating CRC invasion and metastatic dissemination. In bacterial metabolic adaptation, quantitative lactylome profiling of *Escherichia coli* identified 1,047 modification sites, with NAD-dependent lysine deacetylase-mediated delactylation of pyruvate kinase I K382 serving as a critical regulator of bacterial glycolysis. This post-translational control enhances pyruvate kinase activity, potentiating bacterial glycolytic flux and proliferation (61).

**Lactylation and senescent cells.** Cellular senescence is characterized by irreversible cell cycle exit accompanied by distinct morphological and metabolic alterations, including activation of the senescence-associated secretory phenotype (SASP). The SASP entails secretion of bioactive mediators (chemokines, cytokines and proteases) that exert paracrine oncogenic effects within TME, driving neoplastic proliferation, apoptotic resistance, angiogenesis, metastatic dissemination and immune suppression (49). Pioneering work by Maekawa and Yamanaka (62) identified GLIS1 family zinc finger 1 (GLIS1) as a pluripotency-associated transcription factor capable of reprogramming both normal and senescent cells. During early reprogramming, GLIS1 directly binds glycolytic gene loci to activate their transcription while repressing somatic gene chromatin, inducing metabolic rewiring from OXPHOS to dominance of glycolysis with concomitant lipogenesis. This glycolytic surge increases intracellular acetyl-CoA and lactate pools, fueling secondary epigenetic modifications including H3K27 acetylation (H3K27ac) and H3K18 lactylation (H3K18la) at loci associated with pluripotency. These chromatin accessibility changes facilitate transcriptional reprogramming through structural relaxation (63). Notably, Rong *et al* (64) revealed that GLIS1 overexpression in exhausted HCC-infiltrating CD8<sup>+</sup> T cells promotes T cell dysfunction via a serum/glucocorticoid regulated kinase 1-STAT3-PD-1 axis activation, mechanistically linking metabolic control to immune evasion.

**Immune microenvironment remodeling and immune evasion.** Within the TME, lactate modulates interactions among a range of cell types, including tumor cells, CAFs, TAMs and TILs, to shape an immunosuppressive milieu conducive to tumor growth and immune evasion. This process is fundamentally associated with key hallmarks of cancer: Tumor-promoting inflammation, inducing angiogenesis and evading immune destruction.

**Lactylation and tumor-promoting inflammation.** Lactate-mediated polarization of TAMs toward the M2 phenotype constitutes a central mechanism in its promotion of tumor-associated inflammation. Beyond histone lactylation, multiple specific pathways have been elucidated. Wang *et al* (65) demonstrated that PCSK9 inhibition reduced M2 polarization

by modulating MIF and lactate levels. Han *et al* (66) reported that D-lactate promotes M2-to-M1 transition through PI3K/AKT pathway suppression and NF- $\kappa$ B pathway activation. Liu *et al* (67) established that lactate stabilizes HIF-2 $\alpha$  via mTORC1-dependent inhibition of the TFEB/ATP6V0d2 axis, enhancing expression of M2-associated genes (such as VEGF). Zhang *et al* (8) identified lactate binding to mitochondrial antiviral-signaling protein as an inhibitor of retinoic acid-inducible gene I signaling, indirectly facilitating M2 polarization. Lactate-induced histone lactylation functions as a 'lactate clock', enabling macrophages to acquire LPS tolerance and sustain M2-related gene expression (2,68). Collectively, these mechanisms program TAMs to exert immunosuppressive, pro-angiogenic and tumor-promoting functions.

**Lactylation and evading immune destruction.** Evading immune destruction, a defining hallmark of cancer (10), is garnering increasing attention. Lactate within the TME serves a pivotal role in tumor immune evasion. It not only drives the polarization of T cells and macrophages toward immunosuppressive phenotypes, such as promoting Treg differentiation and M2-type TAM formation, but also enhances the functionality of these immunosuppressive cells through multiple mechanisms, thereby facilitating tumor cell escape from immune surveillance (69).

Lactate amplifies immunosuppression by expanding the population and augmenting the activity of myeloid-derived suppressor cells (MDSCs), resulting in impaired cytotoxic T cell and natural killer cell function (70). Furthermore, lactylation modulates DNA repair capacity, indirectly promoting immune evasion. Li *et al* (71) demonstrated that glycolytic reprogramming enhanced X-ray repair cross-complementing protein 1 (XRCC1) lactylation at K247, promoting its nuclear translocation and DNA repair function, ultimately conferring resistance to radiotherapy. Similarly, Chen *et al* (72) found that nibrin (NBS1) lactylation markedly enhanced DNA repair efficiency. This enhanced genomic maintenance capability indirectly supports immune escape.

In summary, lactylation orchestrates immune evasion by constructing a multi-tiered immunosuppressive network through reprogramming TAM functionality, suppressing effector T cell activity, activating inhibitory immune cells (Tregs, MDSCs and PD-L1<sup>+</sup> neutrophils), and bolstering tumor cell intrinsic resistance (via enhanced DNA repair). This highlights lactylation as a central metabolic-epigenetic mechanism underpinning tumor immune evasion, providing a compelling rationale for therapeutic strategies targeting lactylation to enhance immunotherapy efficacy.

**Tumor phenotypic plasticity.** Lactylation serves as a central metabolic-epigenetic coupling hub that simultaneously drives genomic instability, non-mutational epigenetic reprogramming and phenotypic plasticity. This dynamic adaptive capacity enables tumor cells to overcome differentiation barriers and acquire hallmark malignant progression capabilities under microenvironmental stress.

**Lactylation in genome instability and mutation.** Genomic mutations fundamentally involve alterations in DNA sequences, including nucleotide additions/substitutions/deletions, single/double-strand breaks and structural rearrangements such as translocations, duplications or deletions.

Chen *et al* (73) demonstrated that MRE11 homolog, double strand break repair nuclease (MRE11), a core nuclease in DNA repair, undergoes robust lactylation catalyzed by the acetyltransferase CBP. Lactylation at MRE11-K673 enhances MRE11-DNA binding, thereby promoting DNA end resection and homologous recombination repair. Epigenetic alterations notably impact genomic stability through two primary mechanisms. DNA methylation dysregulation is where aberrant hyper/hypomethylation at regulatory regions can mimic mutational effects to drive carcinogenesis. Additionally, histone modification-mediated chromatin remodeling is where an altered chromatin architecture may induce chromosomal rearrangements and instability, disrupting cell cycle progression and checkpoint control. For example, p53 (the guardian of the genome) maintains genomic integrity. Zong *et al* (74) identified AARS1 as a lactate sensor and lactyltransferase that mediates global lysine lactylation in tumor cells, targeting key proteins including p53. Beyond proteins, lactylation may potentially occur on DNA/RNA sequences, analogous to documented mRNA acetylation (75).

**Lactylation and non-mutational epigenetic reprogramming.** Epigenetic reprogramming, alterations in gene expression without changes in DNA sequence, serves fundamental roles in development, differentiation and tissue homeostasis (49). Within the TME, aberrant conditions such as hypoxia and nutrient deprivation drive extensive epigenetic modifications that enable cancer cells to acquire hallmark malignant capabilities. Hypoxia-induced lactate accumulation suppresses ten-eleven translocation demethylase activity by reducing  $\alpha$ -ketoglutarate levels (76). This leads to CpG island hypermethylation and subsequent silencing of tumor suppressor gene promoters (such as CDK inhibitor 2A), a mutation-independent mechanism enriched in gliomas and CRC (63,77). In IDH-mutant gliomas, lactylation-mediated metabolic dysregulation further induces aberrant methylation of CCCTC-binding factor insulators, reducing oncogene expression (such as PDGFRA) to drive tumorigenesis. Stromal cells within the TME, including CAFs, innate immune cells and endothelial cells, undergo non-genetic epigenetic reprogramming upon recruitment to solid tumors, enhancing their pro-tumorigenic functions. Lactate additionally facilitates cancer cell migration by modulating integrin binding to extracellular matrix components (78). Furthermore, CAFs alter cancer cell NAD<sup>+</sup>/NADH ratios via lactate shuttling, activating SIRT1-dependent PPARG coactivator 1 $\alpha$  to increase mitochondrial biogenesis and activity, thereby remodeling cancer cell metabolism (79).

**Lactylation and unlocking phenotypic plasticity.** The relationship between lactylation and tumor phenotypic plasticity, an emerging cancer hallmark enabling malignant progression through evasion of terminal differentiation, remains incompletely elucidated (49). Phenotypic plasticity subverts normal developmental processes wherein terminally differentiated cells exit the cell cycle irreversibly, instead promoting dedifferentiation (progenitor-like reversion), differentiation blockade (progenitor-stage arrest) or trans-differentiation (heterologous trait acquisition). Mechanistic evidence reveals context-dependent functions. In BRAF inhibitor-resistant melanoma, lactate accumulation induces lysine-specific histone demethylase 1A (LSD1)-K503 lactylation, impeding

tripartite motif-containing protein 21-mediated degradation to stabilize LSD1-FosL1 complexes, which suppress transferrin receptor transcription and confer ferroptosis resistance, and this is reversed by LSD1 inhibitors (80). GBM utilizes GTP cyclohydrolase I-synthesized lactoyl-CoA to cooperate with p300, driving H3K18la-mediated growth/differentiation factor 15 upregulation, and this sustains cancer stemness and radioresistance (81).

Age-related macular degeneration models further demonstrate that histone lactylation and alkB homolog 3, a-ketoglutarate dependent dioxygenase-driven glycolysis form a feedforward loop accelerating mesenchymal transition and fibrosis (82). Beyond oncology, lactylation remodels chromatin accessibility during embryonic stem cell differentiation toward extraembryonic endoderm and coordinates mesenchymal-epithelial transition in somatic reprogramming. Notably, tissue-specific functional paradoxes exist; loss of  $\alpha$ -major histocompatibility complex-K1897 lactylation exacerbates heart failure in cardiomyocytes (83), while neuronal arrestin b1-K195 lactylation induces S100A9-mediated mitochondrial apoptosis (84).

These opposing outcomes underscore the microenvironmental context, including lactate gradients and substrate specificity, as determinants of the functional directionality of lactylation. The spatiotemporal dynamics of lactylation constitute a master regulator of phenotypic plasticity. Future research should integrate high-resolution spatiotemporal mapping (single-cell lactylome profiling across TME niches), multi-omics dynamic modeling (lactylation-metabolism-oscillation coupling) and context-specific delivery tools (precision interventions) to elucidate the global roles of lactylation in TME heterogeneity, cell fate decisions and therapeutic resistance, providing novel paradigms to overcome plasticity-driven treatment failure and metastasis.

Table I systematically summarizes the lactylation sites, regulatory mechanisms and clinical implications across key cancer hallmarks, providing a comprehensive overview of its multifaceted roles.

## 6. Lactylation and cancer development

As research into lactylation progresses, evidence is mounting that this modification, affecting both histones and non-histone proteins, serves an oncogenic role across various malignancies (85,86). Pan *et al* (87) demonstrated that LCSCs exhibited higher lactylation levels compared with HCC cells. Lactate, as a metabolic substrate, promotes histone lactylation, particularly at H3K9la and H3K56la sites, driving LCSC proliferation and tumorigenicity. Demethylzeylasteral, a triterpenoid from *Tripterygium wilfordii* Hook F, curbs histone H3 lactylation by inhibiting lactate production, thus restraining LCSC proliferation, migration and inducing apoptosis.

In CRC, Li *et al* (88) revealed lactylation, especially H3K18la, enhanced Rubicon like autophagy enhancer (RUBCNL) gene transcription, associated with a worse CRC prognosis. Such modifications boost RUBCNL/Pacer protein expression, crucial for autophagosome maturation. This process aids cancer cell survival in harsh conditions such as hypoxia. In renal cancer, Yang *et al* (50) found a positive association

Table I. Lactylation hallmarks in cancer.

| Cancer hallmark                            | Lactylation site                                | Tumor type                     | Key enzymes/regulators                       | Pathway/mechanism                                                                                                                                            | Clinical function/impact                                                                | (Refs.)         |
|--------------------------------------------|-------------------------------------------------|--------------------------------|----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------------|
| 1. Metabolic reprogramming                 | H3K18la<br>NUSAP1 K34                           | ccRCC<br>PDAC                  | HIF, PDGFRβ<br>c-Myc, HIF-1α, LDHA           | VHL loss → HIF accumulation → lactate production → PDGFRβ activation → lactylation ↑<br>TAM lactate → NUSAP1 lactylation → LDHA transcription → glycolysis ↑ | Drives tumor progression; poor prognosis<br>Promotes metastasis; therapy resistance     | (50)<br>(51)    |
| 2. Tumor growth and metastasis             | H3K56la<br>H3 lactylation                       | Liver cancer stem cells<br>GBM | LDHA, p300<br>NF-κB                          | Glycolysis ↑ → lactate ↑ → H3K56la → stemness maintenance<br>NF-κB → H3 lactylation → LINC01127 lncRNA → MAP4K4/JNK axis                                     | Enhances tumorigenicity; stemness<br>Sustains cancer stemness                           | (53)<br>(52)    |
| 3. Angiogenesis induction                  | HIF1α-K672la<br>NUSAP1 K34 (indirect)<br>H4K8la | Prostate cancer<br>PDAC        | MCT1, HIF1α, KIAA1199<br>c-Myc, HIF-1α, LDHA | HIF1α lactylation → KIAA1199 transcription → angiogenesis<br>NUSAP1 complex → LDHA activation → lactate ↑ → angiogenesis                                     | Promotes vascular mimicry; metastasis<br>Drives metastasis                              | (57)<br>(51)    |
| 4. Polymorphic microbiomes                 | H3K18la, H3K27ac                                | CRC<br>HCC                     | YY1<br>GLIS1                                 | LPS → H3 lactylation at LINC00152 promoter → YY1 disruption → invasion<br>Glycolysis ↑ → lactate ↑ → H3K18la/H3K27ac → chromatin relaxation                  | Promotes metastatic dissemination<br>Facilitates cellular reprogramming; immune evasion | (60)<br>(63,64) |
| 5. Senescent cells                         | H3 lactylation                                  | Macrophages/TAMs               | p300, SIRT6                                  | Lactate → H3 lactylation → M2 polarization → VEGF/IL-10 secretion                                                                                            | Immunosuppression; angiogenesis                                                         | (2,67)          |
| 6. Tumor-Promoting Inflammation            | H3 lactylation                                  | Tregs                          | MCT1, LDHA, LDHB                             | Lactylation → moesin activation → TGF-β signaling ↑ → Treg suppression ↑                                                                                     | Immune escape; immunotherapy resistance                                                 | (44,100)        |
| 7. Evading immune destruction              | Moesin-K72la<br>XRCC1-K247la                    | GBM                            | ALDH1A3, LDHA                                | Glycolysis ↑ → XRCC1 lactylation → nuclear translocation → DNA repair ↑<br>Lactylation → enhanced DNA repair efficiency                                      | Radio/chemoresistance                                                                   | (71)            |
| 8. Genomic instability                     | NBS1 lactylation<br>MRE11-K673la                | Pan-cancer<br>Breast cancer    | AARS1, LDHA CBP                              | CBP-mediated lactylation → MRE11-DNA binding ↑ → homologous recombination repair ↑                                                                           | Chemotherapy resistance<br>Chemoresistance; genomic instability                         | (72)<br>(73)    |
| 9. Non-mutational epigenetic reprogramming | Histone methylation                             | Glioma, CRC                    | TET inhibition                               | Lactate ↑ → α-KG ↓ → TET suppression → CpG hypermethylation (such as CDKN2A)                                                                                 | Silencing of tumor-suppressors; therapy resistance                                      | (76,77)         |
| 10. Phenotypic plasticity                  | LSD1-K503la<br>H3K18la                          | Melanoma<br>GBM                | p300, GTPCS<br>p300                          | Lactate → LSD1 lactylation → stabilization → TFRC suppression → ferroptosis resistance<br>GTPCS → lactoyl-CoA → H3K18la → GDF15 ↑ → stemness/radioresistance | Targeted therapy resistance<br>Radiation resistance; recurrence                         | (80)<br>(81)    |

ccRCC, clear cell renal cell carcinoma; HIF, hypoxia inducible factor; PDGFRβ, platelet-derived growth factor receptor β; VHL, von Hippel-Lindau protein; NUSAP1, nucleolar and spindle-associated protein 1; PDAC, pancreatic ductal adenocarcinoma; LDHA, lactate dehydrogenase A; lncRNA, long non-coding RNA; MCT1, monocarboxylate transporter 1; KIAA1199, cell migration-inducing and hyaluronan-binding protein; CRC, colorectal carcinoma; YY1, yin yang 1; LPS, lipopolysaccharide; HCC, hepatocellular carcinoma; GLIS1, GLIS family zinc finger 1; TAMs, tumor-associated macrophages; Tregs, regulatory T cells; SIRT, sirtuin; XRCC1, X-ray repair cross-complementing protein 1; ALDH1A3, aldehyde dehydrogenase 1 family, member A3; NBS1, nibrin; AARS1, alanyl-tRNA synthetase; MRE11, MRE11 homolog, double strand break repair nuclease; α-KG, α-ketoglutarate; TET, ten-eleven translocation demethylase; CDKN2A, CDK inhibitor 2A; LSD1, lysine-specific histone demethylase 1A; GTPCS, GTP cyclohydrolase 1; TFRC, transferrin receptor; GDF15, growth/differentiation factor 15.

between lactylation and disease progression, particularly in ccRCC. Inactive VHL triggers PDGFR $\beta$  transcription via histone lactylation, driving ccRCC progression. PDGFR $\beta$  signaling activation further stimulated histone lactylation, creating a vicious cycle promoting ccRCC progression.

In bladder cancer, Xie *et al* (89) reported that the circular RNA, circXRN2, suppressed cancer progression by activating the Hippo signaling pathway, countering histone lactylation-driven cancer. circXRN2 is downregulated in bladder cancer tissues and cell lines. Its overexpression inhibited cancer cell proliferation and migration, acting as a negative regulator of glycolysis and lactate production. In thyroid cancer, Wang *et al* (90) noted enhanced glycolysis in BRAFV600E mutation-positive thyroid cancers raised intracellular lactate levels, promoting histone lactylation, especially at H4K12la. This lactylation activated cell cycle regulation-related genes, fostering thyroid cancer proliferation. In ocular melanoma, Yu *et al* (91) found higher lactylation levels in ocular melanoma tissues compared with in normal melanocyte tissues, associated with early recurrence and increased cancer invasiveness. Lactylation promoted cancer formation by increasing N6-methyladenosine RNA binding protein 2 (YTHDF2) protein expression. YTHDF2 was shown to recognize m6A-modified RNAs and accelerate the degradation of PER1 and TP53 mRNA, two cancer suppressor genes, expediting ocular melanoma formation. In non-small cell lung cancer (NSCLC), Jiang *et al* (92) demonstrated that lactate not only accumulates in lung cancer but was also associated with cancer progression. Lactate adjusts the expression of specific metabolic enzyme genes [such as hexokinase 1 and isocitrate dehydrogenase [NAD(+)] (IDH) 3 non-catalytic subunit  $\gamma$ ] by increasing histone lactylation in their promoter regions, thereby influencing NSCLC cell proliferation and migration.

Lactylation can both drive and suppress cancer. For example, METTL16 lactylation in gastric cancer cells promoted m6A modification on ferritin oxidoreductase protein 1 mRNA, inducing copper death and curbing gastric cancer progression (93). In cervical cancer cells, glucose-6-phosphate dehydrogenase (G6PD) lactylation at K45 may lower its binding affinity with NADP<sup>+</sup>, dampening G6PD enzyme activity and inhibiting cancer cell proliferation (94). Lactate, as a metabolic byproduct, can markedly suppress uveal melanoma (UM) cell proliferation and migration, and alter cellular metabolism by increasing oxidative phosphorylation. Lactate-treated UM cells exhibited higher heterochromatin content and a quiescent state compared to untreated controls, which correlated with reduced proliferation and metastatic capacity (95).

As lactylation research deepens, its clinical importance becomes more evident. Lactylation levels can predict patient survival, prognosis and aid in disease diagnosis. In pancreatic cancer, Peng *et al* (96) identified a set of lactylation-related genes associated with pancreatic cancer prognosis by combining RNA-sequencing data and clinical information. A prognostic model based on lactylation was developed using intersection analysis of differentially expressed genes and lactate-associated genes, along with univariate and multivariate Cox regression models. In breast cancer, lactate levels were notably associated with the Nottingham Prognostic

Index (NPI). Grade III breast cancer tissues showed markedly higher lactate levels compared with grade II tissues, and were positively associated with the NPI but negatively with LDHA levels (97). In liver cancer, specific lactylation sites on ubiquitin specific peptidase 14 (USP14) and ATP binding cassette subfamily F member 1 proteins can serve as diagnostic markers for liver cancer and its metastasis (98).

The current understanding of lactylation-driven tumorigenesis remains fragmented, primarily due to unresolved tissue-specific differences and insufficient clinical research. While lactylation promotes tumorigenesis in most malignancies (such as H3K9la/H3K56la-mediated stemness maintenance in LCSCs), it suppresses metastasis in UM by inducing metabolic quiescence and heterochromatinization.

This bidirectional regulation implies the existence of a 'lactylation threshold', which is likely determined by the microenvironmental lactate concentration, substrate specificity (such as differential effects of H3K56la vs. mitochondrial targets) and spatiotemporal dynamics, factors inadequately integrated into current mechanistic models. Reported causal relationships lack molecular verification: The antitumor effect of circXRN2 in bladder cancer is attributed to activation of the Hippo pathway, yet its association with the lactylation machinery (for example, YAP/TAZ-mediated suppression of p300 lactyltransferase activity) remains undetermined. RUBCNL-driven autophagy in CRC is described as lactylation-dependent, but quantitative evidence linking lactate flux to H3K18la levels at the RUBCNL promoter is lacking. Furthermore, findings, such as USP14 lactylation as a liver cancer biomarker, lack actionable diagnostic frameworks. The present review proposes mapping lactylation modification thresholds by integrating lactate biosensors (such as Laconic) with single-cell lactylomics. To functionally assess specific lactylation sites identified through this approach, CRISPR-dCas9-mediated site-specific delactylation will be implemented, exemplified by targeting H4K12la in thyroid cancer models. The diagnostic potential of key lactylation marks will subsequently be evaluated using tissue microarrays and receiver operating characteristic curve analysis; for instance, comparing the diagnostic efficacy of USP14-K1a vs.  $\alpha$ -fetoprotein for detecting liver cancer metastasis.

## 7. Lactylation and cancer therapy

Due to the growing evidence that lactylation is positively associated with carcinogenesis, lactate producers or lactate transporters, such as LDHA and MCT1/4, have been proposed as novel targets for tumor therapy, either alone or in combination with other anticancer strategies. In the present review, the role of lactate in targeted therapy, traditional therapy and immunotherapy is discussed.

**Lactylation and targeted therapies.** Targeting lactylation has emerged as a promising anticancer strategy, offering novel therapeutic avenues for drug development. Current approaches focus on key nodes in lactate metabolism, transport and modification. Peng *et al* (96) demonstrated that inhibiting solute carrier family 16 member 1, a lactate transporter that is upregulated in pancreatic cancer and associated with lactylation levels, reduced intracellular lactate levels, suppressed

lactylation and inhibited tumor proliferation and migration. Similarly, BRAFV600E inhibitors decreased glycolysis and lactylation, inducing cell cycle arrest in thyroid cancer, suggesting potential synergy with existing targeted therapies through modulation of a glycolysis-lactylation axis (94).

LDHA, the key enzyme converting pyruvate to lactate, represents another critical target. Its upregulation is associated with a poor prognosis across several types of cancer. The competitive inhibitor oxamate reduced cancer proliferation by blocking glycolysis (99), while gossypin directly inhibited LDHA activity, decreasing lactate accumulation and promoting apoptosis (100). However, LDHA inhibitors face notable limitations: Off-target effects and unpredictable side effects from non-selective inhibition necessitate strategies to improve drug specificity and a deeper mechanistic understanding. Emerging agents aim to address these challenges through more precise modulation. Simeprevir and oxamate inhibit LDHA to reduce NBS1-K388 lactylation, whereas L-alanine competes with lactate for AARS1 binding. These targeted approaches show notable potential for advancing lactylation-based cancer therapies.

*Lactylation and conventional therapy.* Tumor resistance remains a major barrier to effective cancer therapy, with emerging evidence implicating lactylation as a key mediator. Chen *et al* (73) demonstrated that MRE11 lactylation enhances DNA-binding capacity, promoting homologous recombination repair and chemoresistance in a lactate-abundant TME. Similarly, NBS1 lactylation markedly increases DNA repair efficiency, while XRCC1-K247 lactylation facilitated nuclear translocation to confer chemo/radioreistance in GBM (71,72). These findings establish lactylation as a promising therapeutic target to overcome treatment resistance.

Proof-of-concept studies validate this approach; a cell-penetrating peptide blocking MRE11-K673 lactylation sensitized tumors to cisplatin and PARP inhibitors by inhibiting DNA repair (73). Additionally, the small molecule D34-919 disrupted an aldehyde dehydrogenase 1 family, member A3-pyruvate kinase M1/2 interaction, reducing lactate production and XRCC1 lactylation, thus restoring radiosensitivity in GBM (71). These targeted strategies demonstrate that inhibiting specific lactylation events can reverse treatment resistance mechanisms, providing a rational foundation for combining lactylation-directed therapies with conventional cancer treatments. Further investigations should focus on optimizing lactylation-targeted agents for clinical translation.

*Lactylation and immunotherapy.* Emerging evidence has established lactylation as a pivotal epigenetic regulator of resistance to cancer immunotherapy. Tumor-derived lactate drives immunosuppression within the TME through lactylation-dependent mechanisms, including moesin-K72 lactylation, which enhances Treg immunosuppressive activity (101). Critically, reducing TME lactate levels improves anti-PD-1 efficacy, positioning lactate modulation as a promising immunotherapeutic adjuvant (101). In HCC, lactate activates the MCT1/NF- $\kappa$ B/cyclooxygenase 2 (COX-2) axis to generate PD-L1<sup>+</sup> neutrophils that mediate immune evasion, a phenotype reversed by COX-2 inhibition with celecoxib,

synergizing with Lenvatinib (45). Similarly, STAT5-driven glycolytic flux in acute myeloid leukemia (AML) elevates histone lactylation, upregulating PD-L1 and impairing CD8<sup>+</sup> T cell function. PD-1/PD-L1 blockade restores T cell activity in STAT5-high AML models, supporting biomarker-guided immunotherapy for glycolytic subtypes (102).

Pharmacological inhibition of lactate transport via AZD3965 (an MCT1 inhibitor) disrupts immunosuppression and attenuates tumor growth (103), while genetic lactylation inhibition overcomes VEGF resistance in CRC (88). These findings highlight the therapeutic promise of dual-targeting lactylation pathways and immune checkpoints. Current strategies targeting lactate synthesis (LDHA inhibitors), transport (MCT blockers) and lactylation modifiers require improved precision. Future efforts should prioritize developing site-specific lactylation inhibitors and combinatorial regimens leveraging metabolic-immune crosstalk. Despite promising preclinical validation of the chemosensitizing role of lactylation, translational challenges, including tissue-specific dynamics and off-target effects, necessitate deeper mechanistic exploration to improve clinical translation.

Current therapeutic strategies targeting lactylation focused on three pillars: Disrupting lactate metabolism (LDHA/MCT inhibition), reversing treatment resistance (blocking lactylation of DNA repair proteins) and overcoming immunosuppression (reprogramming Tregs/myeloid cells). However, notable challenges remain in utilizing these approaches clinically. Firstly, the mechanistic understanding *in vitro* and in animal models often fails to translate effectively, as exemplified by LDHA inhibitors paradoxically inducing protective autophagy, which enhances drug resistance. Secondly, targeting specificity conflicts with physiological complexity, as demonstrated by MCT1 inhibitor AZD3965 simultaneously impairing T cell antitumor functions. Thirdly, static interventions ignore the spatiotemporal heterogeneity of lactylation dynamics, particularly regarding optimal dosing windows. Notably, lactate metabolism targeting (such as oxamate inhibiting LDHA) frequently overlooks compensatory metabolic pathways. Resistance-reversal strategies (such as targeting MRE11-K673la) lack tissue selectivity, risking collateral damage to normal DNA repair mechanisms. Immunotherapy combinations often disregard the dual regulatory roles of lactylation in the TME, where suppressing Treg lactylation may destabilize immune homeostasis.

Future research must advance toward dynamic precision modulation: Developing spatiotemporally responsive delivery systems (such as pH-sensitive nanocarriers with SIRT2 activators) to inhibit oncogenic lactylation (for example MRE11-K673la) while sparing normal tissues; integrating multi-omic biomarkers (such as plasma exosomal H3K18la or PET-based p300 activity tracing) for patient stratification and triple-targeting (production-transportation-'reader') combination therapies; and pioneering innovative tools such as CRISPR-dCas9-mediated site-specific delactylation and microbiome-engineered bacteria modulating gut lactylation. Collectively, these advances will transition lactylation-targeted therapy from single-node inhibition toward artificial intelligence-guided reprogramming of epigenetic-metabolic networks, ultimately establishing curative paradigms for cancer treatment.

## 8. Conclusions

Despite revealing the critical roles of lactylation in tumor metabolic reprogramming, immune microenvironment remodeling and resistance to therapy, three fundamental challenges persist: i) An incomplete mechanistic understanding, exemplified by tissue-specific functional contradictions (pro-tumorigenic vs. suppressive effects); ii) technical limitations in capturing dynamic modifications and discriminating D/L-lactylation isomers; and iii) inadequate spatiotemporally precise intervention strategies. Future breakthroughs require reconstructing research paradigms through the following integrated approaches: i) Deepening mechanistic insights by decoding lactylation context-dependent regulatory logic (such as concentration-dependent modification thresholds and substrate specificity) and quantifying microenvironment-modification dynamics using metabolic gradient organoid models; ii) advancing technical innovation through single-cell spatiotemporal lactylomics and development of isomer-specific probes for D/L-lactylation; and iii) developing precision targeting via microenvironment-responsive delivery systems (such as pH-responsive nanocarriers loaded with SIRT2 activators) to modulate specific effectors such as DNA repair proteins (MRE11-K673la) or epigenetic regulators (H4K12la), combined with metabolic-immune dual-targeting strategies (such as MCT4 inhibitors + anti-PD-1) to overcome resistance. Only by contextualizing lactylation within dynamic modification networks can this biological concept transform clinical oncology practice.

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## Authors' contributions

YF drafted the manuscript and ZC revised the manuscript. LD collected the literature and revised the manuscript. JL designed the whole review and provided funding support. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

## Ethics approval and consent to participate

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## Competing interests

The authors declare that they have no competing interests.

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