Metabolic-epigenetic coupling via lysine lactylation drives cancer stemness and multidrug resistance (Review)

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Abstract. Lysine lactylation couples glycolytic flux with epigenetic regulation, driving cancer stemness and therapeutic resistance. The Warburg effect generates L-lactate, which through enzymatic (*AARS1/2*, *HBO1*, *KAT8*) and non-enzymatic mechanisms deposits lactyl groups on histones and non-histone proteins. This modification sustains cancer stem cell self-renewal via histone mark deposition at stemness gene promoters and non-histone modification of key regulators (*SOX9* and β-catenin). Concurrently, lactylation enhances DNA repair, suppresses ferroptosis and stabilizes stemness-associated transcription factors, conferring resistance to chemotherapy, targeted agents and immunotherapy. Crosstalk with acetylation, ubiquitination and phosphorylation adds regulatory complexity. Preclinical targeting of lactate metabolism, lactyltransferases, or delactylases shows therapeutic promise, while lactylation-based signatures may stratify patient responses. The present review synthesized current evidence establishing lactylation as a metabolic-epigenetic node and summarized convergent resistance mechanisms that may inform future therapeutic strategies.

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Abbreviations: AARS1/2, alanyl-tRNA synthetase 1/2; *ANTXR1*, anthrax toxin receptor 1; *BRAF*, B-Raf proto-oncogene; CAF, cancer-associated fibroblast; CAR-T, chimeric antigen receptor T-cell; CCR8, C-C chemokine receptor type 8; cGAS, cyclic GMP-AMP synthase; CSC, cancer stem cell; DHCR7, 7-dehydrocholesterol reductase; DPF2, double PHD fingers 2; eEF1A2, eukaryotic translation elongation factor 1 alpha 2; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; *ENO1*, enolase 1; ERK, extracellular signal-regulated kinase; FX11, a small-molecule inhibitor of lactate dehydrogenase A; GCLC, glutamate-cysteine ligase catalytic subunit; GCN5, general control non-derepressible 5; GSC, glioblastoma stem cell; GTPSCS, GTP-specific succinyl-CoA synthetase; H3K9la, histone H3 lysine 9 lactylation; H3K14la, histone H3 lysine 14 lactylation; H3K18la, histone H3 lysine 18 lactylation; H4K12la, histone H4 lysine 12 lactylation; HBO1, histone acetyltransferase binding to ORC1; HCC, hepatocellular carcinoma; HDAC, histone deacetylase; HIF1α, hypoxia-inducible factor 1-alpha; IGF2, insulin-like growth factor 2; JNK, c-Jun N-terminal kinase; KAT2A, lysine acetyltransferase 2A; KAT8, lysine acetyltransferase 8; Kla, lysine lactylation; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; LDH, lactate dehydrogenase; LINC01127, long intergenic non-protein coding RNA 1127; LSD1, lysine-specific demethylase 1; MAP4K4, mitogen-activated protein kinase kinase kinase kinase 4; MCM7, minichromosome maintenance complex component 7; MCT, monocarboxylate transporter; *METTL3*, methyltransferase-like 3; *MGMT*, O6-methylguanine-DNA methyltransferase; MOESIN, membrane-organizing extension spike protein; m6A, N6-methyladenosine; MRE11, meiotic recombination 11 homolog; MVP, major vault protein; NNMT, nicotinamide N-methyltransferase; NSCLC, non-small cell lung cancer; PCBP2, poly(rC)-binding protein 2; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; *PFKFB2*, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2; POLR2A, RNA polymerase II subunit A; PRMT1, protein arginine methyltransferase 1; *PSMD14*, proteasome 26S subunit, non-ATPase 14; PTBP1, polypyrimidine tract-binding protein 1; *PTEN*, phosphatase and tensin homolog; PTM, post-translational modification; SHMT2, serine hydroxymethyltransferase 2; SIRT3, sirtuin 3; *SIRT4*, sirtuin 4; SIRT6, sirtuin 6; *SOX9*, SRY-box transcription factor 9; TME, tumor microenvironment; TMZ, temozolomide; TKI, tyrosine kinase inhibitor; TRIM33, tripartite motif-containing protein 33; Wnt, wingless-related integration site; YBX1, Y-box binding protein 1; YTHDF2, YTH N6-methyladenosine RNA binding protein 2; *ZMIZ1*, zinc finger MIZ-type containing 1

Key words: lactylation, cancer stem cells, drug resistance, metabolic reprogramming, epigenetic regulation, tumor microenvironment, post translational modification, targeted therapy

5. Lactylation orchestrates cancer drug resistance via metabolic-epigenetic remodeling
6. Crosstalk between lactylation and other post-translational modifications
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1. Introduction

Cancer stemness and drug resistance represent interconnected drivers of tumor progression, recurrence, and therapeutic failure. The persistence of cancer stem cells (CSCs) has been increasingly recognized as a fundamental barrier to durable treatment response across multiple malignancies. Duval *et al* (1) recently demonstrated that SRY-box transcription factor 9 (*SOX9*) drives a stem-like transcriptional state and platinum resistance in high-grade serous ovarian cancer, establishing that stemness regulators directly mediate chemoresistance. Hubert *et al* (2) further identified an epigenetic axis of stem cell maintenance and chemoresistance in colon cancer, highlighting how epigenetic programs sustain CSC populations despite chemotherapy exposure. These findings establish that stemness and drug resistance are intimately linked through epigenetic mechanisms, although the upstream metabolic signals that coordinate this relationship remain incompletely understood.

Metabolic reprogramming and epigenetic dysregulation constitute hallmarks of CSC maintenance and multidrug resistance. The Warburg effect generates substantial lactate accumulation that extends beyond its traditional role as a metabolic waste product. Li *et al* (3) revealed a positive feedback regulation between glycolysis and histone lactylation that drives oncogenesis in pancreatic ductal adenocarcinoma, providing direct evidence linking glycolytic flux to malignant progression. Yang *et al* (4) further demonstrated that histone lactylation-driven feedback loops modulate cholesterol-linked immunosuppression in pancreatic cancer, illustrating how metabolic-epigenetic circuits sustain tumor growth. Notably, lactate functions not merely as a metabolic intermediate but also a signaling molecule that coordinates the metabolic-epigenetic interface, although the precise molecular mechanisms bridging glycolysis to epigenetic regulation in CSCs require further elucidation.

Protein lysine lactylation (Kla) has emerged as a post-translational modification that directly couples the cellular metabolic state to epigenetic regulation. Yang *et al* (5) conducted a comprehensive lactylome analysis in hepatocellular carcinoma, revealing lactylation-dependent mechanisms of metabolic adaptation that enable cancer cells to thrive under nutrient stress. Liu *et al* (6) recently reported that nuclear GTP-specific succinyl-CoA synthetase (GTPSCS) functions as a lactyl-CoA synthetase to promote histone lactylation and gliomagenesis, establishing compartment-specific regulatory mechanisms. Sun *et al* (7) provided a conceptual framework linking the Warburg effect to DNA damage repair through lactylation, synthesizing how metabolic reprogramming directly affects genome stability and therapeutic response. A critical comparison across these studies reveals that lactylation exerts context-dependent effects on both chromatin dynamics and DNA repair pathways, suggesting that the functional consequences vary substantially across cancer types.

The convergence of lactylation with cancer stemness and drug resistance has recently emerged as a frontier in cancer biology. Feng *et al* (8) performed comprehensive lactylome analysis in liver CSCs, unveiling lactylation-dependent mechanisms of stemness remodeling and identifying pathways specifically activated in the CSC compartment compared with differentiated tumor cells. Lv *et al* (9) demonstrated that sirtuin 4 (*SIRT4*) promotes pancreatic cancer stemness by enhancing histone lactylation and epigenetic reprogramming stimulated by calcium signaling, highlighting the interplay between metabolic signals and stemness maintenance. Regarding drug resistance, Gan *et al* (10) established that a tumor-derived lactate/enolase 1 (*ENO1*) lactylation feedback loop facilitates osimertinib resistance in lung adenocarcinoma, demonstrating how lactylation creates self-reinforcing circuits that sustain therapeutic escape. Zhao *et al* (11) further reported a deubiquitination-lactylation circuit in gastric adenocarcinoma stemness, as detailed in the CSC stemness as a hub for lactylation-driven multidrug resistance section. Importantly, lactylation-driven stemness and drug resistance operate through convergent mechanisms including enhanced DNA repair capacity, suppression of cell death pathways, and activation of pluripotency-associated programs, although the relative contribution of each mechanism varies across cancer types and therapeutic contexts. The present review systematically synthesized current evidence establishing lactylation as a critical node linking metabolic reprogramming to cancer stemness and drug resistance, evaluated therapeutic opportunities and identified key unresolved questions in this rapidly evolving field.

2. Biochemical basis and regulatory machinery of protein lactylation

The biochemical foundation of lactylation rests on the stereospecific recognition of L-lactate as the primary substrate, with enzymatic systems including both alanyl-tRNA synthetase 1/2 (*AARS1/2*) and classical acetyltransferases [histone acetyltransferase binding to ORC1 (HBO1), lysine acetyltransferase 8 (KAT8), lysine acetyltransferase 2A (KAT2A)] catalyzing lactyl group deposition. Reversibility is conferred by delactylases such as histone deacetylases 1-3 (HDAC1-3), sirtuin 3 (SIRT3), and sirtuin 6 (SIRT6), while reader proteins including tripartite motif-containing protein 33 (TRIM33) and double PHD fingers 2 (DPF2) interpret lactylation marks to drive transcriptional programs. Subcellular compartmentalization, including nuclear, mitochondrial, and cytoplasmic distribution, adds regulatory specificity. Fig. 1 provides a comprehensive overview of the lactylation regulatory machinery, depicting writers, erasers, readers, and their subcellular distribution.

Chemical and enzymatic basis of lactylation. Lysine lactylation represents a covalent modification wherein a lactyl group is attached to the ε-amino group of lysine residues. The discovery by Zhang *et al* (12) first demonstrated that histone lactylation occurs in response to elevated lactate

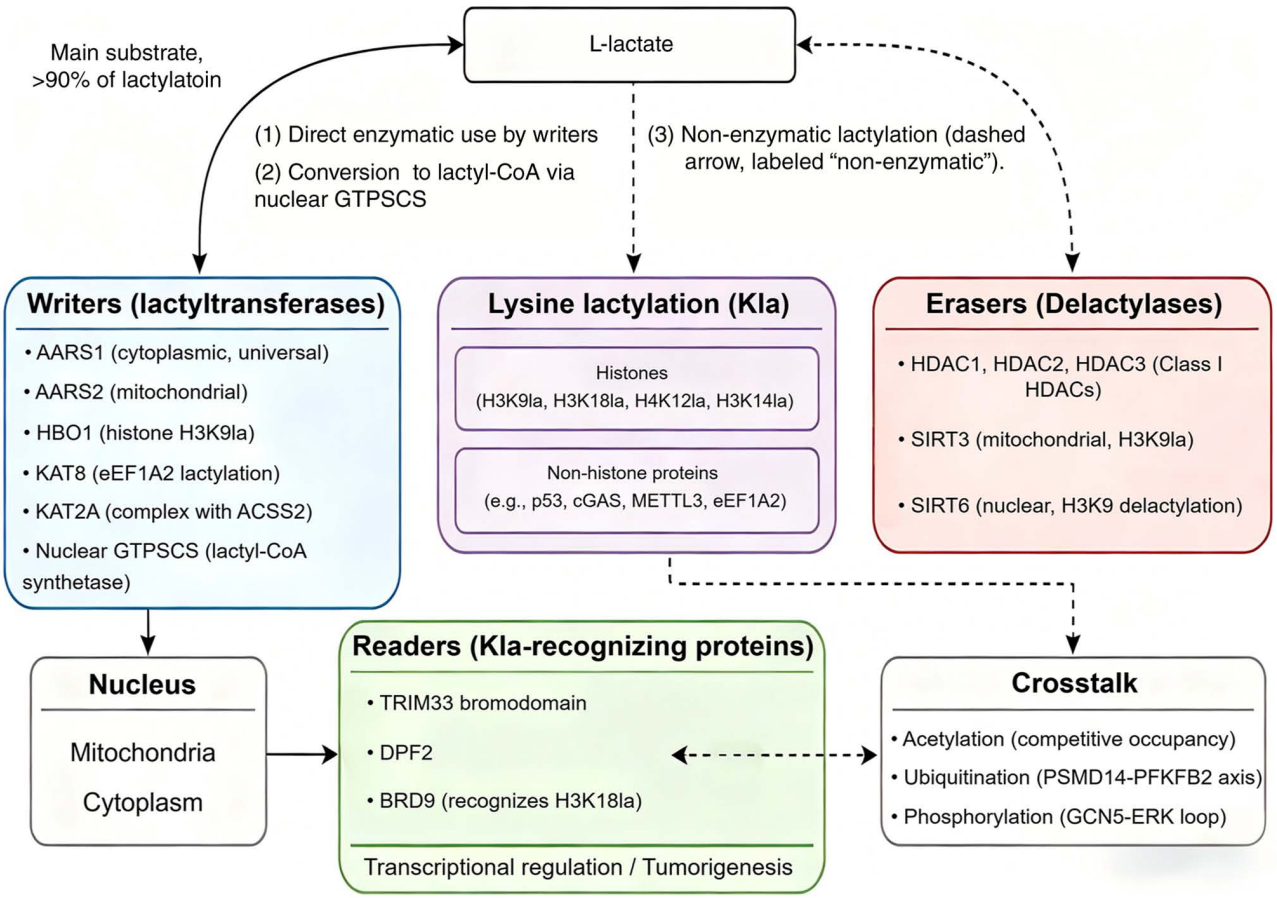


Figure 1. Regulatory machinery of protein lactylation. L-lactate is converted to lactyl-CoA or directly used by writers (AARS1/2, HBO1, KAT8, KAT2A, GTPSCS) to deposit lactyl groups on histones and non-histone proteins. Erasers (HDAC1-3, SIRT3, SIRT6) remove lactylation. Readers (TRIM33, DPF2, BRD9) interpret Kla marks. The process occurs in nucleus, cytoplasm and mitochondria, with crosstalk to other PTMs. AARS1/2, alanyl-tRNA synthetase 1/2; HBO1, histone acetyltransferase binding to ORC1; KAT8, lysine acetyltransferase 8; KAT2A, lysine acetyltransferase 2A; GTPSCS, GTP-specific succinyl-CoA synthetase; HDAC1-3, histone deacetylases 1-3; SIRT3, sirtuin 3; SIRT6, sirtuin 6; TRIM33, tripartite motif-containing protein 33; DPF2, double PHD fingers 2; BRD9, bromodomain-containing protein 9; Kla, lysine lactylation; PTM, post-translational modification.

levels, establishing a direct connection between glycolytic metabolism and epigenetic control. Liberti and Locasale (13) subsequently highlighted that this modification serves as a metabolic sensor, enabling cells to translate glucose-derived lactate into chromatin-based transcriptional programs. From a stereochemical perspective, lactate exists as L-lactate and D-lactate enantiomers in biological systems. Recent work by Zhang *et al* (14) demonstrates that L-lactate is the predominant isoform driving lysine lactylation under glycolytic conditions, with quantitative proteomics revealing that over 90% of lactylation sites are modified by L-lactate. Moreno-Yruela *et al* (15) provided critical insights into the chiral specificity of this modification, emphasizing that stereoselective recognition by reader proteins determines downstream functional outcomes.

The enzymatic basis of lactylation has been substantially advanced through identification of writer and eraser machineries. Zong *et al* (16) and Ju *et al* (17) independently identified alanyl-tRNA synthetase *AARS1* as a primary lactyltransferase that directly transfers lactate to lysine residues, demonstrating that *AARS1* senses intracellular lactate and catalyzes global protein lactylation. Mechanistically, *AARS1* binds lactate with high affinity and utilizes ATP to generate lactyl-AMP as an activated intermediate. Complementing these findings, Li *et al* (18) showed that both *AARS1* and *AARS2* function as universal lactyltransferases, with *AARS2* localizing to mitochondria to regulate mitochondrial protein lactylation. In parallel, Liu *et al* (6) identified nuclear GTPSCS as a lactyl-CoA synthetase that generates lactyl-CoA specifically in the nucleus to promote histone lactylation, revealing compartment-specific lactylation regulatory mechanisms. Niu *et al* (19) demonstrated that HBO1 serves as a histone lactyltransferase catalyzing histone H3 lysine 9 lactylation (H3K9la), while Xie *et al* (20) showed KAT8 mediates eukaryotic translation elongation factor 1 alpha 2 (eEF1A2) lactylation in colorectal cancer. Zhu *et al* (21) further revealed that acyl-CoA synthetase short-chain family member 2 acts as a lactyl-CoA synthetase coupling with KAT2A to form a functional lactyltransferase complex. Collectively, these studies establish that multiple enzymatic systems, including both aminoacyl-tRNA synthetase-family enzymes and classical histone acetyltransferases, contribute to the mammalian lactylome. Notably, Zhang *et al* (22) provided evidence for non-enzymatic lysine lactylation under high-lactate conditions, suggesting both enzymatic and non-enzymatic mechanisms operate in cancer cells.

Delactylation machinery and reader proteins. The reversibility of lactylation is mediated by specific eraser enzymes.

Moreno-Yruela *et al* (23) demonstrated that class I HDAC1-3 possess intrinsic delactylase activity, catalyzing removal of lactyl groups from histones. These findings were further supported by independent studies (24,25). Nickel *et al* (26) identified SIRT6 as a histone delactylase, expanding the repertoire of eraser enzymes to the sirtuin family. Chen *et al* (27) showed SIRT3 specifically removes H3K9la to suppress esophageal cancer progression, while Zou *et al* (28) demonstrated SIRT6-mediated H3K9 delactylation inhibits O6-methylguanine-DNA methyltransferase (*MGMT*) transcription to reverse temozolomide resistance. Jin *et al* (29) revealed SIRT3-dependent delactylation of cyclin E2 prevents hepatocellular carcinoma growth. He *et al* (30) reported that HDAC2-mediated methyltransferase-like 3 (*METTL3*) delactylation promotes DNA repair and chemotherapy resistance. These discoveries establish that multiple deacetylases exhibit delactylase activity, though substrate specificity and context-dependent regulation remain active areas of investigation.

Functional interpretation of lactylation marks requires reader proteins that recognize specific Kla sites. Nuñez *et al* (31) demonstrated that the TRIM33 bromodomain recognizes histone lactylation with selectivity distinct from acetylation recognition. Zhai *et al* (32) identified DPF2 as a histone lactylation reader that drives transcription and tumorigenesis. Wei *et al* (33) showed that BRD9 recognizes histone H3 lysine 18 lactylation (H3K18la) to drive oncogenic chromatin remodeling. The identification of specific readers remains incomplete, representing a critical gap in understanding lactylation-mediated signaling.

Subcellular compartmentalization and regulatory integration. Lactylation exhibits distinct subcellular distribution patterns in cancer cells. Bao *et al* (34) performed systematic subcellular proteomic mapping, revealing that lactylated proteins are predominantly enriched in the nucleus, mitochondria, and cytoplasm. He *et al* (35) demonstrated that Numb/Parkin-directed mitochondrial fitness governs histone lactylation via metabolic regulation, linking organellar homeostasis to nuclear epigenetic modifications. Mao *et al* (36) showed hypoxia induces mitochondrial protein lactylation to limit oxidative phosphorylation, establishing that mitochondrial lactylation directly impacts metabolic adaptation. The interplay between lactylation and other post-translational modification (PTM) adds regulatory complexity. Huang *et al* (37) revealed a general control non-derepressible 5 (GCN5)-extracellular signal-regulated kinase (ERK) lactylation-phosphorylation amplification loop that accelerates cancer progression. Sun *et al* (38) demonstrated crosstalk between HDAC6-catalyzed α-tubulin lactylation and acetylation in cytoskeleton regulation. Zhou *et al* (39) reported hypoxia-induced protein arginine methyltransferase 1 (PRMT1) lactylation drives vimentin arginine asymmetric dimethylation. These findings indicate that lactylation integrates with established PTM networks to fine-tune oncogenic signaling.

Lactylation is detected mainly by antibody-based methods, mass spectrometry-based proteomics, and genetic code expansion, each with distinct limitations. Pan-Kla antibodies are widely used but may cross-react with acetylation and other short-chain acylations because of structural similarity; site-specific antibodies require validation against competing acyl modifications and modification-deficient controls (14,15). Mass spectrometry enables unbiased site mapping but is limited by low lactylation stoichiometry, enrichment bias, isobaric interference, and the general inability to distinguish enzymatic from non-enzymatic deposition or L- from D-lactate without chiral resolution (22,34). Genetic code expansion allows site-specific incorporation of lactyl-lysine in living cells and can provide causal evidence, but remains technically demanding and limited in scale. Accordingly, the strongest mechanistic claims are those supported by orthogonal validation, ideally combining MS-based site identification with validated site-specific antibodies and functional rescue (22).

In summary, the biochemical machinery of lactylation encompasses diverse writers (*AARS1, AARS2, HBO1, KAT8, KAT2A*) and erasers (*HDAC1-3, SIRT3, SIRT6*) operating across subcellular compartments. Compared with acetylation, lactylation exhibits distinct stereospecificity, substrate preferences, and metabolic sensitivity. Notably, the relative contributions of enzymatic vs. non-enzymatic lactylation in cancer cells remain debated and systematic identification of lactylation readers represents an urgent priority for the field. However, writer and reader assignments often rely on overexpression, pan-Kla antibodies, or a limited set of bromodomain proteins, and chiral specificity is rarely resolved in cancer models (14,15,22,31,32,34). These limitations should be considered when interpreting the lactylation machinery.

3. Metabolic reprogramming drives the lactylation landscape in cancer

The Warburg effect establishes a metabolic foundation wherein aerobic glycolysis generates substantial lactate accumulation, creating a substrate reservoir for protein lactylation in malignant cells. Metabolic reprogramming shapes the cancer lactylation landscape through four interconnected mechanisms: lactate production as the biochemical cornerstone, oncogenic pathway regulation of lactylation dynamics, tumor microenvironment (TME) metabolic crosstalk, and spatial heterogeneity of lactylation patterns within tumor tissues (Fig. 2). Recent advances have substantially expanded understanding of how glycolytic flux translates into epigenetic marks, with emerging evidence implicating lactylation in cancer stemness and therapy resistance.

The Warburg effect and lactate accumulation. The pioneering discovery by Zhang *et al* (12) demonstrated that histone lactylation directly responds to elevated lactate levels, establishing a mechanistic link between glycolytic metabolism and epigenetic control. Subsequent work confirmed that lactate modulates cellular metabolism through histone lactylation-mediated gene expression in non-small cell lung cancer, showing that exogenous lactate supplementation induces H3K18la and histone H4 lysine 12 lactylation (H4K12la) at concentrations corresponding to tumor microenvironmental levels (40). Lactate functions as an active signaling metabolite that orchestrates pro-tumor microenvironment during carcinogenesis (41). Gu *et al* (42) demonstrated that tumor metabolite lactate promotes tumorigenesis by modulating membrane-organizing extension spike

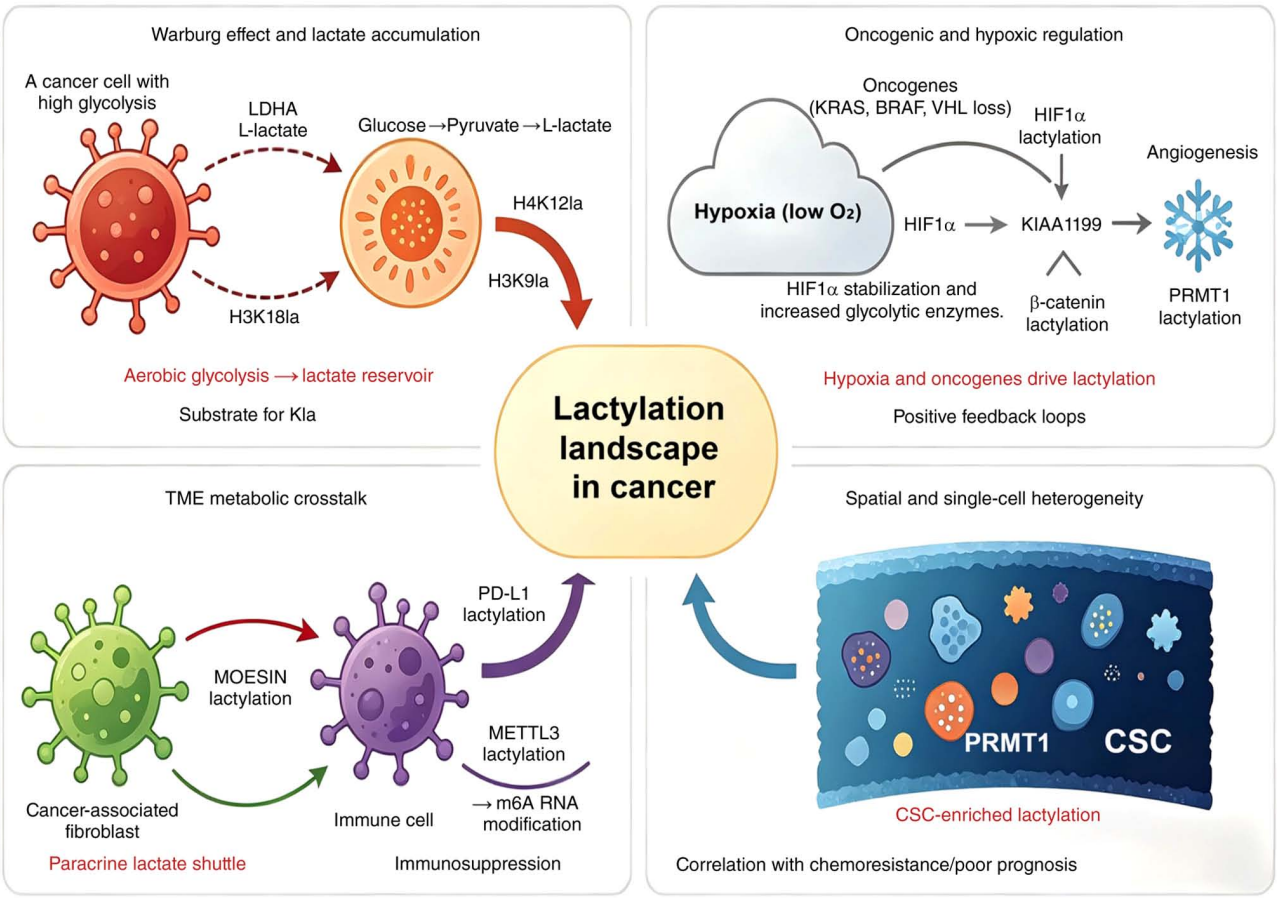


Figure 2. Metabolic reprogramming drives the cancer lactylation landscape. There are four interconnected mechanisms: Warburg effect and lactate accumulation; aerobic glycolysis produces L-lactate, the substrate for lactylation, oncogenic and hypoxic regulation; HIF1α, KRAS, BRAF and hypoxia enhance glycolysis/lactate production, promoting histone/non-histone lactylation; TME metabolic crosstalk; CAFs provide lactate; lactate induces MOESIN, METTL3 and PD-L1 lactylation in immune cells, fostering immunosuppression; spatial and single-cell heterogeneity; lactylation is enriched in CSCs and varies across tumor regions, correlating with therapy resistance. HIF1α, hypoxia-inducible factor 1α; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *BRAF*, B-Raf proto-oncogene; TME, tumor microenvironment; CAF, cancer-associated fibroblast; MOESIN, membrane-organizing extension spike protein; *METTL3*, methyltransferase-like 3; PD-L1, programmed death-ligand 1; CSC, cancer stem cell; LDHA, lactate dehydrogenase A.

protein (MOESIN) lactylation and enhancing transforming growth factor beta signaling in regulatory T cells, revealing that lactate functions beyond histone modifications to influence non-histone protein function.

Quantitative proteomic analyses have established the breadth of the lactylation landscape. Yang *et al* (43) identified hundreds of lysine-lactylated substrates in gastric cancer cells across diverse functional categories, establishing that lactylation is a widespread modification rather than restricted to histones. Global profiling in hepatocellular carcinoma by Hong *et al* (44) identified over 2,000 lactylation sites, with enrichment in proteins involved in metabolic processes and RNA splicing. Yang *et al* (5) performed comprehensive lactylome analysis in hepatocellular carcinoma, demonstrating lactylation-dependent mechanisms of metabolic adaptation. More recently, lactylation has been shown to stabilize transcription factor EB to elevate autophagy and lysosomal activity, linking lactate accumulation to organellar homeostasis (45). The quantitative relationship between glycolytic flux and lactylation intensity has been systematically examined through integrated multi-omics approaches (46,47). Collectively, these studies establish that the magnitude of the Warburg effect directly correlates with global lactylation levels, though non-enzymatic mechanisms may predominate under extreme metabolic stress conditions. However, most evidence is correlative because lactate supplementation, LDHA inhibition, or glycolytic blockade alters multiple metabolites and PTMs simultaneously; few studies rescue lactylation at defined sites.

Oncogenic and hypoxic regulation. Oncogenic signaling pathways profoundly shape the cancer lactylation signature through transcriptional and post-transcriptional control of glycolytic enzymes. Luo *et al* (48) demonstrated that hypoxia-inducible factor 1-alpha (HIF1α) lactylation enhances KIAA1199 transcription to promote angiogenesis and vasculogenic mimicry in prostate cancer, revealing a feed-forward loop wherein HIF1α both responds to and drives lactylation. A positive feedback loop between inactive Von Hippel-Lindau tumor suppressor-triggered histone lactylation and platelet-derived growth factor receptor beta signaling drives clear cell renal cell carcinoma progression, establishing that tumor suppressor loss can initiate lactylation-dependent oncogenic cascades (49). The functional consequences of oncogene-driven lactylation were further elaborated by studies showing that *BRAF* V600E restructures cellular lactylation

to promote anaplastic thyroid cancer proliferation (50), while Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutation increases histone H3K9 lactylation to promote colorectal cancer progression (51).

Hypoxia represents a dominant physiological driver of lactylation. Recent work by Gao *et al* (52) performed dynamic investigation of hypoxia-induced L-lactylation, revealing time-dependent accumulation of lactylation marks under oxygen deprivation. Hypoxia induces mitochondrial protein lactylation to limit oxidative phosphorylation, establishing that mitochondrial lactylation directly impacts metabolic adaptation (36). Hypoxia also promotes H3K9 lactylation to enhance LAMC2 transcription in esophageal squamous cell carcinoma (53) and induces β-catenin lactylation to promote colorectal cancer cell proliferation and stemness via the wingless-related integration site (Wnt) signaling pathway (54). Zhou *et al* (39) reported that hypoxia-induced PRMT1 lactylation drives vimentin arginine asymmetric dimethylation in tumor metastasis, demonstrating crosstalk between lactylation and other post-translational modifications. A comparative analysis across studies reveals that hypoxia-induced lactylation preferentially targets chromatin-associated proteins, whereas normoxia-driven lactylation exhibits broader subcellular distribution. He *et al* (35) provided mechanistic integration by demonstrating that Numb/Parkin-directed mitochondrial fitness governs cancer cell fate via metabolic regulation of histone lactylation, showing that mitochondrial homeostasis determines the availability of lactate for nuclear epigenetic modifications.

Tumor microenvironment and metabolic crosstalk. The TME creates a complex metabolic ecosystem wherein lactate produced by one cell type drives lactylation in neighboring cells. Tumor-derived lactate promotes MOESIN lactylation in regulatory T cells, establishing paracrine lactylation as a mechanism for immune modulation (42). Lactylation-driven *METTL3*-mediated RNA N6-methyladenosine (m6A) modification promotes immunosuppression of tumor-infiltrating myeloid cells, revealing a cascade from metabolic signal through epigenetic modification to RNA-level regulation (55). Previous studies have extended this concept to multiple immune cell types. Cai *et al* (56) demonstrated that lactylation-driven nuclear protein 1 promotes immunosuppression of tumor-infiltrating macrophages in hepatocellular carcinoma, while Huang *et al* (57) showed that signal transducer and activator of transcription 5 promotes programmed death-ligand 1 (PD-L1) expression by facilitating histone lactylation to drive immunosuppression in acute myeloid leukemia. De Leo *et al* (58) demonstrated that glucose-driven histone lactylation promotes the immunosuppressive activity of monocyte-derived macrophages in glioblastoma, with mechanistic evidence linking glycolytic flux to PD-L1 expression.

Cancer-associated fibroblasts (CAFs) represent a major source of lactate in many tumors. Li *et al* (59) demonstrated that CAF-secreted lysyl oxidase promotes PD-L1 expression via histone lactylation and regulates tumor epithelial-mesenchymal transition (EMT) through TGFβ/insulin-like growth factor 1 signaling in gastric cancer. Kong *et al* (60) showed that histone lactylation-related genes correlate with the molecular patterns and functions of CAFs in clear cell renal cell carcinoma. The metabolic coupling between CAFs and cancer cells creates a 'lactate shuttle' wherein CAF-derived lactate fuels oxidative metabolism in adjacent cancer cells while simultaneously engaging epigenetic regulation. Recent evidence indicates that CAF-derived lactate induces oxaliplatin treatment resistance by promoting cancer stemness via anthrax toxin receptor 1 (*ANTXR1*) lactylation in colorectal cancer (61), and CAFs promote epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) resistance via the collagen triple helix repeat containing 1/glycolysis/H3K18la positive feedback loop (62). Importantly, the relative contribution of tumor cell-autonomous vs. stroma-derived lactate to the overall lactylation landscape remains debated, with evidence supporting context-dependent predominance of each source. This debate is also influenced by model systems: CAF-derived lactate effects are largely shown in co-culture or xenografts (61,62), whereas immune-cell lactylation is mostly studied in isolated populations (42,55-58). Direct isotope tracing of tumor- vs. stroma-derived lactate into defined lactylation sites in patient tumors is still lacking. CAF-derived lactate also contributes to oxaliplatin resistance via stemness regulation (61).

Spatial and single-cell heterogeneity. Emerging evidence indicates that lactylation exhibits marked spatial heterogeneity within tumor tissues and CSC niches. Histone lactylation-derived long intergenic non-protein coding RNA 1127 (LINC01127) promotes the self-renewal of glioblastoma stem cells via cis-regulation of mitogen-activated protein kinase kinase kinase kinase 4 (MAP4K4) to activate the c-Jun N-terminal kinase (JNK) pathway, establishing that lactylation signatures are enriched within CSC populations compared with differentiated tumor cells (63). Feng *et al* (8) performed comprehensive lactylome analysis in liver cancer stem cells, unveiling lactylation-dependent mechanisms of stemness remodeling and identifying pathways specifically activated in the CSC compartment. Pan *et al* (64) showed that demethylzeylasteral targets lactate by inhibiting histone lactylation to suppress the tumorigenicity of liver cancer stem cells, providing pharmacological evidence that CSC-specific lactylation is therapeutically accessible.

Single-cell transcriptomic analyses have begun to resolve lactylation heterogeneity. Zhang *et al* (65) developed a comprehensive gene signature linking hypoxia, glycolysis and lactylation in gastric cancer through integration of bulk and single-cell RNA-seq data, identifying cell subpopulations with distinct lactylation-associated transcriptional programs. Lu *et al* (66) integrated single-cell and bulk RNA-sequencing data to reveal molecular subtypes based on lactylation-related genes in glioma, demonstrating prognostic and therapeutic response associations. Yu *et al* (67) performed single-cell RNA sequencing and spatial transcriptomics analyses to reveal how hepatic stellate cells promote hepatocellular carcinoma development by regulating histone lactylation. Recent studies have integrated single-cell and spatial transcriptomics to identify lactylation-associated tumor cell clusters and define prognostic risk models in glioblastoma (68) and to reveal the association between histone lactylation and cisplatin resistance in bladder cancer (69). A critical insight from these studies is that lactylation heterogeneity correlates with therapeutic response: Tumor regions with high lactylation

signatures exhibit increased resistance to chemotherapy and immunotherapy. However, current single-cell approaches infer lactylation activity from gene expression rather than directly measuring the modification, representing a technical limitation that will require advances in single-cell proteomics to overcome. Therefore, current claims of spatial lactylation heterogeneity should be regarded as hypothesis-generating. Lactylation-associated signatures may reflect general hypoxia, glycolysis, or CSC programs rather than lactylation itself (65,66,68,69). Future integration of spatial transcriptomics with lactylation-specific imaging approaches will be essential to fully resolve the spatial architecture of the lactylation landscape in the tumor microenvironment.

4. Lactylation-mediated epigenetic regulation of cancer stemness

Lactylation acts as a metabolic-epigenetic coupling effector governing cancer stem cell (CSC) maintenance, self-renewal and plasticity. The regulatory landscape encompasses histone mark deposition at pluripotency gene loci, non-histone protein modification in core signaling cascades, and lactylation-driven EMT and CSC plasticity. Cancer type-specific lactylation patterns further reveal the contextual dependency of this modification. Table I summarizes key lactylation targets, their downstream effectors, and functional consequences in CSC regulation.

Histone lactylation in CSC pluripotency and self-renewal. Histone lactylation directly couples glycolytic flux to the transcriptional programs that sustain CSC identity. In glioblastoma stem cells (GSCs), Li *et al* (63) demonstrated that histone lactylation-derived LINC01127 promotes self-renewal via cis-regulation of MAP4K4 to activate the JNK pathway, establishing a mechanistic link between lactate metabolism and GSC maintenance. Complementing this finding, Li *et al* (70) recently showed that histone lactylation-driven upregulation of vaccinia-related kinase 1 promotes stemness and proliferation of GSCs through the Y-box binding protein 1 (YBX1)/SRY-box transcription factor 2 (SOX2) axis, further expanding the epigenetic network controlling glioma stemness.

Beyond glioblastoma, histone lactylation-mediated stemness regulation operates across diverse tumor types. In hepatocellular carcinoma (HCC), Liu *et al* (71) demonstrated that histone lactylation facilitates minichromosome maintenance complex component 7 (MCM7) expression to sustain stemness and radio-resistance, while *SIRT4* was identified by Lv *et al* (9) as a promoter of pancreatic cancer stemness through enhancing histone lactylation and epigenetic reprogramming stimulated by calcium signaling. In colorectal cancer, Zhang *et al* (72) showed that hypoxia facilitates colon cancer cell stemness via histone lactylation. Notably, a study by Nguyen *et al* (73) provided functional evidence that lactate controls cancer stemness and plasticity through epigenetic regulation in intestinal organoid models, demonstrating that lactate directly influences the balance between self-renewal and differentiation. Collectively, these findings establish histone lactylation as a conserved epigenetic node for CSC maintenance, though the specific histone marks [(H3K9la, H3K18la, H4K12la, histone H3 lysine 14 lactylation (H3K14la)] and downstream target genes vary substantially across cancer types.

Non-histone protein lactylation in stemness maintenance. While histone lactylation provides a global epigenetic framework, non-histone protein lactylation directly modulates the activity of key stemness-regulating factors. In esophageal cancer cells, Qiao *et al* (74) demonstrated that hypoxia-induced serine hydroxymethyltransferase 2 (SHMT2) protein lactylation facilitates glycolysis and stemness, revealing a feed-forward loop wherein metabolic enzyme lactylation reinforces the glycolytic phenotype. Similarly, Li *et al* (75) showed that hypoxia exposure induces Axin1 lactylation to promote glycolysis in esophageal carcinoma cells, establishing that lactylation of signaling proteins can rewire metabolic and stemness pathways simultaneously.

Critical insights into non-histone lactylation mechanisms have emerged from studies of transcription factor regulation. Yan *et al* (76) demonstrated that hypoxia promotes non-small cell lung cancer (NSCLC) cell stemness, migration, and invasion via lactylation of *SOX9*, a master transcription factor for stem cell identity. In gastric cancer, Zhao *et al* (77) revealed that histone lactylation-driven YTH N6-methyladenosine RNA binding protein 2 (YTHDF2) promotes NSCLC cell glycolysis and stemness by recognizing m6A modification of secreted frizzled-related protein 2, demonstrating crosstalk between lactylation and RNA epigenetic modifications in stemness control. More recently, Yuan *et al* (78) showed that biphenyl hydrolase-like promotes triple-negative breast cancer stemness by resolving R-loops via RNA polymerase II subunit A (POLR2A) lactylation inhibition and BARD1-mediated ubiquitination, revealing a sophisticated interplay between lactylation, transcriptional regulation and genome stability in CSC maintenance. A comparative analysis across these studies reveals that non-histone lactylation predominantly targets either metabolic enzymes (SHMT2, Axin1) or stemness-associated transcription factors (*SOX9*, YTHDF2), suggesting context-dependent selection of lactylation substrates.

Lactylation in EMT and metastatic stemness. The acquisition of CSC traits during EMT is intimately linked to lactylation-dependent gene regulation. In prostate carcinoma, Fiaschi *et al* (79) provided early evidence that carbonic anhydrase IX from CAFs drives EMT, establishing that stromal-derived metabolic signals influence cancer cell plasticity. More recent work has directly implicated lactylation in this process. In colorectal cancer, CAF-derived lactate promotes cancer stemness through ANTXR1 lactylation (61), establishing a paracrine mechanism whereby stromal metabolic signals drive CSC plasticity.

Tumor-associated stromal cells beyond CAFs also contribute to lactylation-mediated stemness reprogramming. Chen *et al* (80) found that tumor-associated Schwann cells promote salivary adenoid cystic carcinoma stem-like reprogramming via insulin-like growth factor 2 (IGF2)/insulin-like growth factor 1 receptor-induced histone H3K18 lactylation, expanding the repertoire of stromal cell types that orchestrate CSC plasticity through lactylation. In lung cancer, Shi *et al* (81) demonstrated that exosomal lncRNA Mir100hg from lung CSCs activates H3K14 lactylation to enhance metastatic

Table I. Key studies on lactylation-mediated epigenetic regulation of cancer stemness.

First author/s, year	Mechanism category	Cancer type	Lactylation target (site/mark)	Mechanism/pathway	Functional consequence on stemness	Validation model/key note	(Refs.)
Lv *et al*, 2025	Histone lactylation-mediated	Pancreatic cancer	H3K9la, H3K18la	α2δ1-mediated Ca^{2+} signaling → SIRT4 upregulation → ENO1 deacetylation (K358) → glycolysis → histone lactylation	Promotes TIC stemness via epigenetic reprogramming	PDAC organoids, *in vivo* limiting dilution	(9)
Zhao *et al*, 2026		Gastric adenocarcinoma	H3K27la	PSMD14-mediated PFKFB2 deubiquitination → enhanced glycolysis/ lactate → H3K27la at stemness promoters	Drives cancer stemness	Gastric cancer cells, *in vivo* limiting dilution	(11)
Li *et al*, 2023		Glioblastoma	Histone lactylation-derived LINC01127	NF-κB-induced lactate → H3la → LINC01127 → cis-activation of MAP4K4 → JNK/NF-κB	Promotes GSC self-renewal and orthotopic tumor growth	Patient-derived GSCs, intracranial xenograft	(63)
Li *et al*, 2025		Glioma	H3K18la at VRK1 promoter	Lactate → H3K18la → VRK1 upregulation → YBX1 stabilization → YBX1/SOX2 axis	Enhances GSC stemness and proliferation	GSC lines, limiting dilution assay	(70)
Liu *et al*, 2025		HCC	Histone lactylation at MCM7 promoter	Histone lactylation → MCM7 transcription → DNA replication licensing	Maintains LCSC stemness and radio-resistance	LCSCs, irradiation models	(71)
Zhang *et al*, 2025		Colon cancer	Histone lactylation	Hypoxia → elevated lactate → histone lactylation at stemness gene promoters	Enhances colon CSC stemness under hypoxia	Colon cancer cells, hypoxia exposure	(72)
Nguyen *et al*, 2025		Intestinal organoids	Histone lactylation	Lactate → histone lactylation → epigenetic reprogramming of differentiation genes	Controls CSC plasticity and self-renewal/ differentiation balance	Mouse intestinal organoids, primary human tumor organoids	(73)
Zhao *et al*, 2025		NSCLC	Histone lactylation-driven YTHDF2 upregulation	Histone lactylation → YTHDF2 → recognition of m^6A-SFRP2 → SFRP2 silencing → glycolysis/stemness	Promotes NSCLC glycolysis and stemness	NSCLC cells, m^6A-seq	(77)
Chen *et al*, 2025		Salivary adenoid cystic carcinoma	H3K18la	Tumor-associated Schwann cells → IGF2/IGF1R → glycolysis → H3K18la at stemness promoters	Induces stem-like reprogramming	SACC cells, xenograft	(80)

Table I. Continued.

First author/s, year	Mechanism Category	Cancer type	Lactylation target (site/mark)	Mechanism/pathway	Functional consequence on stemness	Validation model/key note	(Refs.)
Shi *et al*, 2025		Lung cancer	H3K14la	CSC-derived exosomal Mir100hg → ALDOA upregulation → lactate → H3K14la → 169 metastasis-related genes	Enhances metastatic activity in non-CSCs	Lung cancer cells, exosome transfer model	(81)
Yao and Yang, 2024		HCC	Histone lactylation	Hypoxia → lactate → histone lactylation → stemness/glycolysis gene activation; reversed by Glypican-3 knockdown	Drives hypoxia-induced stemness	HCC cells under hypoxia	(85)
Miao *et al*, 2023	Non-histone lactylation-mediated	Colorectal cancer	β-catenin lactylation	Hypoxia → β-catenin lactylation → Wnt pathway activation	Promotes cell proliferation and stemness	Colon cancer cells, TOPFlash reporter	(54)
He *et al*, 2025		Colorectal cancer	ANTXR1 K453 lactylation	CAF-derived lactate → ANTXR1 K453la → ANTXR1 stabilization → RhoC/ROCK1/ SMAD5 pathway	Promotes CSC stemness and oxaliplatin resistance	CRC organoids, CAF co-culture	(61)
Qiao *et al*, 2024		Esophageal cancer	SHMT2 lactylation	Hypoxia → SHMT2 lactylation → SHMT2 enzymatic activity → glycolysis feed-forward	Facilitates glycolysis and stemness	ESCC cells, sphere formation	(74)
Li *et al*, 2024		Esophageal carcinoma	Axin1 lactylation	Hypoxia → Axin1 lactylation → glycolysis enhancement	Promotes glycolysis and stemness	ESCC cells, xenograft	(75)
Yan *et al*, 2024		NSCLC	SOX9 lactylation	Hypoxia → glycolysis → SOX9 lactylation → SOX9 transcriptional activity	Promotes NSCLC cell stemness, migration, invasion	NSCLC cells, tumorsphere assay	(76)
Yuan *et al*, 2026		TNBC	POLR2A lactylation (inhibition)	BPHL → POLR2A lactylation inhibition → BARD1-mediated ubiquitination/R-loop resolution → β-catenin nuclear translocation	Sustains CSC stemness; expands CSC compartment	TNBC cell lines, patient-derived xenograft	(78)
Zhou *et al*, 2025		Glioma	PTBP1 lactylation	PTBP1 lactylation → PFKFB4-driven glycolysis → lactate feed-forward → histone lactylation	Promotes GSC maintenance; forms vicious metabolic-epigenetic cycle	GSCs, glycolysis flux assay	(83)

Table I. Continued.

First author/s, year	Mechanism Category	Cancer type	Lactylation target (site/mark)	Mechanism/pathway	Functional consequence on stemness	Validation model/key note	(Refs.)
Liu *et al*, 2025		Breast cancer	ZMIZ1 K843 lactylation	Lactate → ZMIZ1 lactylation (suppresses SUMOylation/ ubiquitination) → ZMIZ1 binding to Nanog → Nanog transcription (OCT4, NPC2)	Induces tamoxifen resistance via stemness and cholesterol uptake	ER+ breast cancer cells, xenograft	(86)
Feng *et al*, 2024	Histone and non-histone lactylation-mediated (dual)	HCC (LCSCs)	Global lactylome (H3K56la; ALDOA K230/322la)	H3K56la elevates gene transcription; ALDOA lactylation weakens ALDOA-DDX17 binding → liberates DDX17	Maintains LCSC stemness; defines LCSC-specific lactylation signature	Primary LCSCs vs. differentiated HCC cells	(8)

ALDOA, aldolase A; ANTXR1, anthrax toxin receptor 1; BARD1, BRCA1-associated RING domain 1; BPHL, biphenyl hydrolase-like protein; CAF, cancer-associated fibroblast; CRC, colorectal cancer; CSC, cancer stem cell; DDX17, DEAD-box helicase 17; ENO1, enolase 1; ER+, estrogen receptor-positive; ESCC, esophageal squamous cell carcinoma; GSC, glioma stem cell; H3K9la, H3K18la, H3K27la, H3K56la, H4K12la, histone H3/H4 lysine lactylation; HCC, hepatocellular carcinoma; IGF1R, insulin-like growth factor 1 receptor; IGF2, insulin-like growth factor 2; JNK, c-Jun N-terminal kinase; LCSC, liver cancer stem cell; LINC01127, long intergenic non-protein coding RNA 1127; MAP4K4, mitogen-activated protein kinase kinase kinase kinase 4; MCM7, minichromosome maintenance complex component 7; m^6A, N^6-methyladenosine; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NPC2, Niemann-Pick disease type C2; NSCLC, non-small cell lung cancer; OCT4, octamer-binding transcription factor 4; PDAC, pancreatic ductal adenocarcinoma; PFKFB4, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 4; POLR2A, RNA polymerase II subunit A; PSMD14, proteasome 26S subunit non-ATPase 14; PTBP1, polypyrimidine tract-binding protein 1; ROCK1, Rho-associated coiled-coil containing protein kinase 1; SACC, salivary adenoid cystic carcinoma; SFRP2, secreted frizzled related protein 2; SHMT2, serine hydroxymethyltransferase 2; SIRT4, sirtuin 4; SOX2, SOX9, SRY-box transcription factors; TIC, tumor-initiating cell; TNBC, triple-negative breast cancer; VRK1, vaccinia-related kinase 1; Wnt, wingless-related integration site; YBX1, Y-box binding protein 1; YTHDF2, YTH N^6-methyladenosine RNA binding protein F2; ZMIZ1, zinc finger MIZ-type containing 1.

activity in non-stem lung cancer cells, revealing that CSCs themselves can propagate stemness-associated epigenetic marks to neighboring cells. These findings collectively indicate that lactylation-mediated EMT and metastatic stemness operate through both autocrine and paracrine mechanisms, with the relative contribution of each mode likely determined by tumor type and microenvironmental context.

Lactylation-mediated control of CSC plasticity and dormancy. The remarkable plasticity of CSCs, their ability to transition between quiescent and proliferative states and to dedifferentiate from non-stem populations, is increasingly recognized as being regulated by lactylation. Nguyen *et al* (73) provided foundational evidence that lactate controls cancer stemness and plasticity through epigenetic regulation, showing in organoid systems that lactate exposure promotes a dedifferentiated, stem-like state. This plasticity is not unidirectional; rather, lactylation levels appear to define a rheostat that determines the position of cancer cells along the differentiation continuum.

Hypoxia serves as a dominant driver of lactylation-mediated plasticity. In colon cancer, Zhang *et al* (72) demonstrated that hypoxia facilitates stemness via histone lactylation. Hypoxia-induced β-catenin lactylation promotes colorectal cancer cell proliferation and stemness via Wnt signaling (54), as introduced in the oncogenic and hypoxic regulation section, reinforcing the convergence of hypoxia, lactylation and Wnt signaling in CSC plasticity. Wang *et al* (82) further expanded this concept by showing that Zeb1-controlled metabolic plasticity enables remodeling of chromatin accessibility in neuroendocrine prostate cancer, although direct lactylation involvement in this context requires additional investigation. A critical unresolved question is whether lactylation actively maintains the dormant CSC population or primarily drives the transition from dormancy to proliferation, a distinction with significant therapeutic implications given that dormant CSCs are thought to mediate minimal residual disease and late recurrence.

Cancer type-specific lactylation programs in CSCs. The lactylation landscape exhibits marked heterogeneity across types of cancer and CSC subpopulations. Feng *et al* (8) performed comprehensive lactylome analysis in liver CSCs,

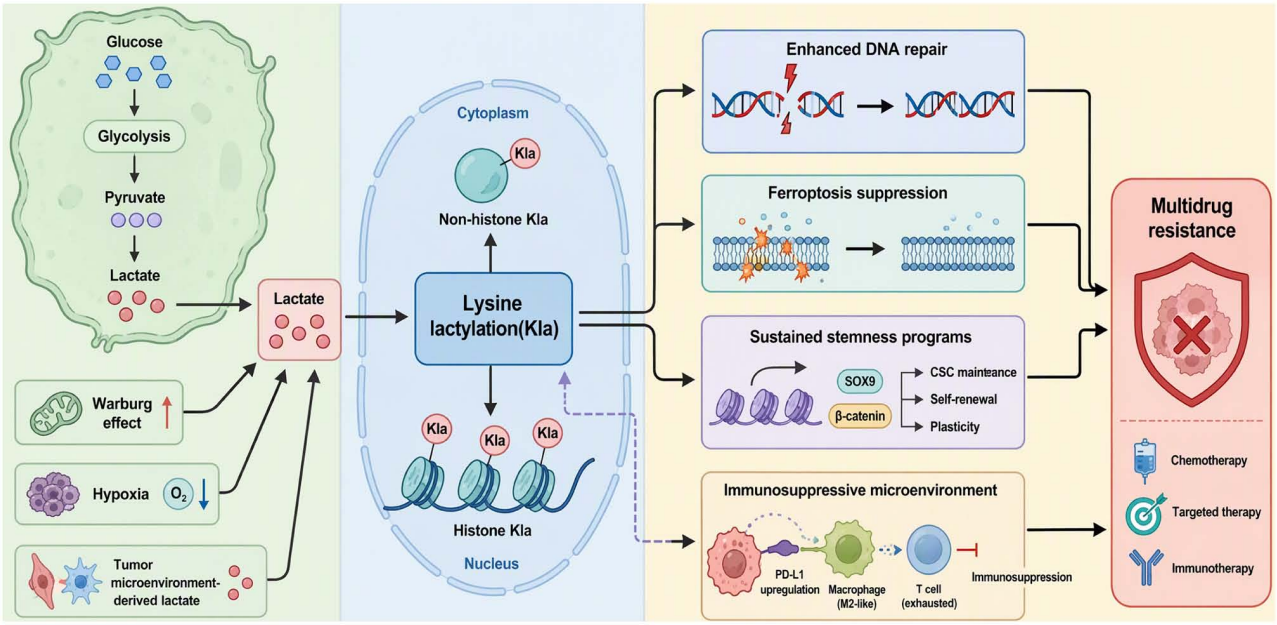


Figure 3. Metabolic-epigenetic remodeling by lactylation drives therapy resistance through four core mechanistic taxonomies. Lactate derived from glycolysis or the tumor microenvironment fuels Kla on histones and non-histone proteins. The four color-coded mechanistic branches represent the core taxonomies of lactylation-mediated resistance: Enhanced DNA-damage repair, including homologous recombination enhancement and DNA repair pathway activation; Ferroptosis evasion, including glutathione biosynthesis upregulation and lipid peroxidation neutralization; Oncogenic stem-cell transcriptional programming, including stemness transcription factor lactylation and pluripotency gene activation; and immunosuppressive microenvironment remodeling, including PD-L1 stabilization, immunosuppressive myeloid cell polarization and CD8+ T cell dysfunction. These mechanistic branches converge to confer resistance across chemotherapy, targeted therapy and immunotherapy, ultimately driving CSC-originated multidrug resistance and tumor relapse Kla, lysine lactylation; CSC, cancer stem cell.

unveiling lactylation-dependent mechanisms of stemness remodeling and identifying pathways specifically activated in the CSC compartment compared with differentiated HCC cells. This study revealed that liver CSCs exhibit distinct lactylation signatures enriched for proteins involved in RNA splicing and metabolic adaptation. In glioma, Zhou *et al* (83) demonstrated that polypyrimidine tract-binding protein 1 (PTBP1) lactylation promotes GSC maintenance through PFKFB4-driven glycolysis, while Tang *et al* (84) deciphered the lactylation landscape in glioma to establish a novel gene signature predicting patient survival.

Emerging evidence has identified cancer type-specific lactylation regulators. In pancreatic cancer, Lv *et al* (9) identified *SIRT4* as a key promoter of stemness through enhancing histone lactylation. In HCC, Liu *et al* (71) showed that histone lactylation facilitates MCM7 expression, while Yao and Yang (85) demonstrated that Glypican-3 knockdown inhibits HCC cell stemness under hypoxic conditions through lactylation. In gastric cancer, PSMD14-mediated 6-phospho-fructo-2-kinase/fructose-2 and 6-biphosphatase 2 (PFKFB2) deubiquitination activates H3K27 lactylation to drive cancer stemness (11), as discussed in detail in the CSC stemness as a hub for lactylation-driven multidrug resistance section. Notably, recent studies have linked lactylation to therapy resistance in a cancer type-specific manner: Liu *et al* (86) reported that zinc finger MIZ-type containing 1 (*ZMIZ1*) lactylation induces tamoxifen resistance in breast cancer through Nanog-dependent stemness regulation, whereas the *ANTXR1* lactylation axis in colorectal cancer is discussed in the 'CSC stemness as a hub for lactylation-driven multidrug resistance' section in the context of CSC-mediated multidrug resistance. The *PSMD14-PFKFB2*-H3K27la regulatory axis driving gastric adenocarcinoma stemness is discussed in detail in the 'CSC stemness as a hub for lactylation-driven multidrug resistance' section (11). These observations support the concept that lactylation-driven stemness programs are context-dependent, suggesting that therapeutic targeting of lactylation may require cancer type-specific strategies informed by the underlying epigenetic architecture. However, many cancer type-specific programs are derived from bulk lactylome or transcriptomic signatures without direct CSC vs. non-CSC comparison using site-specific assays. The apparent heterogeneity may therefore partly reflect differences in models, lactate exposure, and detection methods rather than true cancer type-specific biology (8,63,69,73,84). Notably, several lactylation substrates described above also participate in therapeutic-resistance phenotypes in Section 5. Crosstalk with other post-translational modifications shared by stemness and drug-resistance programs is discussed comprehensively in Section 6 to avoid redundant mechanistic restatement.

5. Lactylation orchestrates cancer drug resistance via metabolic-epigenetic remodeling

Therapeutic failure induced by chemotherapy, targeted agents and immunotherapy is frequently fueled by CSC-associated metabolic-epigenetic plasticity. Building upon the metabolic-epigenetic cascades outlined in Sections 2-4, lactylation translates glycolytic and microenvironmental lactate signals into stable pro-survival transcriptional programs to establish multidrug resistance. Fig. 3 illustrates core regulatory networks

linking lactylation to therapy resistance, including enhanced DNA repair, ferroptosis suppression, sustained stemness transcriptional programs, and reshaping of the immunosuppressive tumor microenvironment.

Conventional chemotherapy resistance. Histone and non-histone lactylation mediates chemotherapeutic resistance via three predominant effector axes: Enhancing DNA-damage repair, repressing ferroptotic cell death and activating stemness-related survival signaling. In colorectal cancer, Deng *et al* (87) demonstrated that histone lactylation enhances glutamate-cysteine ligase catalytic subunit (GCLC) expression, thereby inhibiting ferroptosis and promoting chemoresistance of cancer stem cells. Mechanistically, elevated lactylation at H3K18 loci drives GCLC transcription, increasing glutathione biosynthesis and neutralizing chemotherapy-induced lipid peroxidation. Complementing this finding, Zhao *et al* (88) showed that lncRNA BASP1-AS1 drives poly(rC)-binding protein 2 (PCBP2) K115 lactylation to suppress ferroptosis and confer oxaliplatin resistance in gastric cancer. The lactylation-stabilized PCBP2 enhances antioxidant capacity, demonstrating convergent evolution of lactylation-mediated ferroptosis evasion across gastrointestinal malignancies.

In ovarian cancer, histone lactylation has been implicated in cisplatin resistance through multiple pathways. Gao *et al* (89) reported that H3K18la facilitates transformer 2 alpha homolog-mediated alternative splicing of SCL/TAL1 interrupting locus, suppressing ferroptosis and reducing cisplatin sensitivity. Sun *et al* (90) further established that targeting platinum-resistant ovarian cancer can be achieved by disrupting histone and RAD51 lactylation, with combined approaches showing therapeutic promise. Mechanistically, RAD51 lactylation enhances homologous recombination repair efficiency, directly counteracting cisplatin-induced DNA crosslinks. A critical comparison across these studies reveals that lactylation promotes chemoresistance primarily by either i) enhancing DNA repair capacity, ii) suppressing ferroptosis, or iii) activating stemness programs, with cancer type-specific predominance of each mechanism. A further limitation is that many chemoresistance studies use single agents, short-term viability assays, or established cell lines; fewer test whether lactylation inhibition reverses resistance in patient-derived organoids or established tumors (28,87,89,91). Studies using genetic or site-specific perturbation provide stronger causal evidence than those relying only on lactate-lowering agents.

In glioblastoma, lactylation confers temozolomide (TMZ) resistance through distinct epigenetic mechanisms. Yue *et al* (91) demonstrated that histone H3K9 lactylation confers TMZ resistance via LUC7-like 2 pre-mRNA splicing factor-mediated MutL homolog 1 intron retention, leading to mismatch repair deficiency. Importantly, Zou *et al* (28) showed that SIRT6-mediated delactylation of H3K9 inhibits *MGMT* transcription and reverses TMZ resistance, establishing that targeting the lactylation-delactylation balance represents a therapeutically accessible strategy. In bladder cancer, Li *et al* (69) performed single-cell transcriptome analysis revealing the association between histone lactylation and cisplatin resistance, identifying cell subpopulations with elevated lactylation signatures that exhibit increased chemoresistance. These findings collectively establish lactylation as a conserved driver of chemoresistance, though the specific histone marks and downstream effectors vary substantially across tumor types and chemotherapeutic agents.

Targeted therapy resistance. Lactylation-mediated resistance extends to molecularly targeted agents, including EGFR inhibitors, B-Raf proto-oncogene (*BRAF*) inhibitors, lenvatinib and enzalutamide. In NSCLC, Dai *et al* (92) demonstrated that nicotinamide N-methyltransferase (NNMT) promotes acquired EGFR-TKI resistance by forming early growth response protein 1 and lactate-mediated double positive feedback loops. Mechanistically, lactate accumulation drives H3K18 lactylation at NNMT promoter regions, creating a self-reinforcing cycle that sustains resistance. Complementing this finding, Gan *et al* (10) identified a tumor-derived lactate/*ENO1* lactylation feedback loop that facilitates osimertinib resistance in lung adenocarcinoma. *ENO1* lactylation enhances its enzymatic activity, further increasing lactate production and establishing a feed-forward loop that maintains resistance even in the presence of EGFR inhibition.

In melanoma, Li *et al* (93) demonstrated that lactylation of lysine-specific demethylase 1 (LSD1) represents an acquired epigenetic vulnerability of *BRAF* inhibitor/MEK inhibitor-resistant melanoma. LSD1 lactylation alters its substrate specificity and chromatin occupancy, driving a transcriptional program that bypasses MAPK pathway inhibition. This finding is particularly significant as it reveals that resistance-conferring lactylation events can occur on non-histone epigenetic regulators, expanding the mechanistic repertoire of lactylation-mediated resistance. In HCC, Lu *et al* (94) showed that lactylation-driven insulin-like growth factor 2 mRNA-binding protein 3-mediated serine metabolism reprogramming and RNA m6A modification promote lenvatinib resistance. The integration of lactylation with RNA epigenetic modifications represents a sophisticated multi-layered resistance mechanism. Dong *et al* (95) further demonstrated that lactylation-driven HECT domain E3 ubiquitin protein ligase 2 limits the response of HCC to lenvatinib, while Zeng *et al* (96) established that histone lactylation promotes multidrug resistance in HCC by forming a positive feedback loop with phosphatase and tensin homolog (*PTEN*). A notable insight across these studies is that lactylation-mediated targeted therapy resistance frequently involves positive feedback loops that amplify the initial resistance signal, making therapeutic intervention more challenging once established.

In prostate cancer, lactylation contributes to enzalutamide resistance through multiple mechanisms. Chen *et al* (97) identified solute carrier family 4 member 4 as a novel driver of enzalutamide resistance, with mechanistic links to lactate metabolism and histone lactylation. Sun *et al* (98) further demonstrated that lysine demethylase 5B-driven glucose metabolic reprogramming promotes enzalutamide resistance via the lactate/heterogeneous nuclear ribonucleoprotein A1 lactylation/androgen receptor splice variant 7 axis. The conversion of metabolic reprogramming to alternative splicing regulation through lactylation illustrates the remarkable adaptability of resistance mechanisms.

Immunotherapy resistance. Lactylation plays an increasingly recognized role in driving resistance to immune checkpoint

inhibitors (ICIs) by remodeling the tumor immune microenvironment toward immunosuppression. Tong *et al* (99) reported dual effects of serine/glycine-free diet in enhancing antitumor immunity while promoting evasion via PD-L1 lactylation, revealing that metabolic interventions can paradoxically induce resistance through lactylation-dependent mechanisms. In HCC, Liu *et al* (100) showed that lactylation-driven major vault protein (MVP) upregulation boosts immunotherapy resistance by inhibiting PD-L1 degradation. MVP lactylation stabilizes PD-L1 protein, reducing its turnover and maintaining high surface expression even in the presence of programmed cell death protein 1 (PD-1) blockade.

In pancreatic cancer, Yang *et al* (4) demonstrated that histone lactylation-driven feedback loop modulates cholesterol-linked immunosuppression, creating a metabolic-epigenetic barrier to effective immunotherapy. Mechanistically, elevated H3K18 lactylation drives expression of cholesterol biosynthesis genes, altering membrane lipid composition of immune cells and impairing T cell function. Chen *et al* (101) further showed that targeting lactylation and the signal transducer and activator of transcription 3/CCL2 axis overcomes immunotherapy resistance in pancreatic ductal adenocarcinoma, providing a rational combination strategy. Sun *et al* (102) extended these findings by demonstrating that elevated protein lactylation promotes immunosuppressive microenvironment and therapeutic resistance in pancreatic cancer, with high lactylation signatures correlating with poor response to anti-PD-1 therapy.

In lung cancer, Wang *et al* (103) established that H3K9 lactylation in malignant cells facilitates CD8+ T cell dysfunction and poor immunotherapy response. Zhang *et al* (104) similarly showed that H3K18 lactylation potentiates immune escape of NSCLC. A critical insight emerging from these studies is that lactylation promotes immune checkpoint inhibitor resistance primarily through three convergent mechanisms: i) Direct upregulation of PD-L1 expression, ii) induction of immunosuppressive macrophage and myeloid-derived suppressor cell polarization and iii) impairment of CD8+ T cell metabolic fitness and cytotoxic function.

CSC stemness as a hub for lactylation-driven multidrug resistance. CSCs represent a central reservoir for multidrug resistance, and lactylation serves as a key epigenetic driver of CSC maintenance across therapy contexts. Li *et al* (86) demonstrated that *ZMIZ1* lactylation induces tamoxifen resistance in breast cancer through increasing transcriptional activity of Nanog to impact cell stemness. This finding mechanistically links lactylation to pluripotency factor regulation, showing that lactylation directly enhances Nanog-driven transcriptional programs that sustain CSC identity. In colorectal cancer, the ANTXR1 lactylation axis illustrates how microenvironment-derived signals converge on CSC maintenance to confer resistance (61); the upstream CAF-lactate mechanism is described in the lactylation in EMT and metastatic stemness section. This finding is conceptually important because it shows that lactylation-driven multidrug resistance need not arise from cell-autonomous metabolic rewiring; instead, the tumor microenvironment can impose a lactylation-dependent CSC state that subsequently confers resistance to mechanistically distinct agents. This paracrine mode of resistance is consistent with the integrated circuit model proposed below, in which therapy-induced stromal and tumor-derived lactate feed into a self-reinforcing CSC-resistance loop (61).

In gastric cancer, Zhao *et al* (11) revealed that *PSMD14*-mediated *PFKFB2* deubiquitination activates H3K27 lactylation to drive cancer stemness. This study elegantly demonstrates crosstalk between ubiquitination and lactylation pathways, showing that *PSMD14* stabilizes *PFKFB2* to increase glycolytic flux, which in turn elevates lactate production and H3K27 lactylation at stemness gene promoters. In hepatocellular carcinoma, Zeng *et al* (96) showed that histone lactylation promotes multidrug resistance by forming a positive feedback loop with *PTEN*. *PTEN* loss further activates protein kinase B signaling, which upregulates glycolysis and lactate production, creating a self-reinforcing cycle. Notably, the convergence of multiple resistance mechanisms on CSC maintenance suggests that targeting lactylation within the CSC compartment might produce more durable therapeutic responses than targeting individual resistance pathways, although this hypothesis remains to be tested prospectively.

Comparative analysis across these studies reveals that lactylation-driven multidrug resistance operates through an integrated circuit wherein: i) Chemotherapy induces metabolic stress and lactate accumulation, ii) elevated lactylation activates stemness-associated transcriptional programs, iii) CSC expansion drives resistance to diverse therapeutic agents and iv) therapy-induced cell death releases additional lactate, perpetuating the cycle. This model explains why lactylation signatures correlate with resistance to mechanistically distinct drugs and suggests that interrupting this cycle at the level of lactate production, lactylation deposition, or stemness gene activation may overcome multidrug resistance.

Clinical correlations and therapeutic implications. The translational relevance of lactylation in drug resistance is supported by retrospective clinical correlation studies across multiple types of cancer. High H3K18 lactylation levels have been associated with poor prognosis in epithelial ovarian cancer and with reduced response to platinum-based chemotherapy in retrospective cohorts (105). In pancreatic cancer, elevated protein lactylation has been associated with therapeutic resistance and poor survival, and lactylation signatures have been reported to predict response to gemcitabine-based regimens in retrospective analyses (102). In glioblastoma, lactylation-associated gene signatures have been associated with stratification by TMZ response in retrospective cohorts, with high lactylation scores associated with reduced survival and increased recurrence risk (84).

Several studies have established prognostic signatures based on lactylation-related genes that predict treatment responsiveness. In bladder cancer, Zhao *et al* (106) developed a lactylation prognostic signature identifying 7-dehydrocholesterol reductase (DHCR7) as a modulator of chemoresistance and immunotherapy efficacy. In lung adenocarcinoma, lactylation-related gene signatures predict prognosis and treatment response in radiation-resistant NSCLC (107). In colorectal cancer, lactylation-based prognostic models predict chemotherapeutic efficacy and guide treatment selection (108). Several retrospective studies have

reported prognostic signatures based on lactylation-related genes that are associated with treatment responsiveness. In bladder cancer, Zhao *et al* (106) developed a lactylation prognostic signature identifying 7-dehydrocholesterol reductase (DHCR7) as a modulator of chemoresistance and immunotherapy efficacy. In lung adenocarcinoma, lactylation-related gene signatures have been associated with prognosis and treatment response in radiation-resistant NSCLC (107). In colorectal cancer, lactylation-based prognostic models have been reported to predict chemotherapeutic efficacy and guide treatment selection in retrospective cohorts (108). These clinical correlation studies provide a foundation for developing lactylation-based biomarkers for patient stratification, though prospective validation in clinical trial cohorts remains necessary before clinical implementation. Nonetheless, most signatures are retrospective, platform-dependent, and not externally validated. Lactylation marks are often measured by bulk immunohistochemistry or inferred from RNA, which may not capture CSC-specific or spatial heterogeneity. Prospective trials with pre-specified assays are required (84,105,106,108).

6. Crosstalk between lactylation and other post-translational modifications

The functional output of protein lactylation in cancer stemness and drug resistance is not executed in isolation but rather integrated into a complex PTM network. Crosstalk between lactylation and other PTMs, including acetylation, ubiquitination, phosphorylation and short-chain acylations, adds regulatory sophistication to metabolic-epigenetic programming. Table II summarizes key examples of PTM crosstalk and their functional consequences in therapy resistance.

Reciprocal regulation with acetylation. Acetylation represents the most extensively studied PTM that functionally intersects with lactylation. Both modifications target lysine residues and are regulated by overlapping enzymatic machineries, yet they convey distinct metabolic signals. Zhang *et al* (12) demonstrated that histone lactylation occurs in response to elevated lactate levels, whereas acetylation responds primarily to acetyl-CoA availability, establishing that different metabolic inputs drive these modifications. Competitive occupancy of the same lysine residues by lactylation vs. acetylation has been documented on histones, suggesting that the relative abundance of each modification determines transcriptional outcomes.

The functional interplay extends beyond competitive exclusion. Huang *et al* revealed a GCN5-ERK lactylation-phosphorylation amplification loop wherein GCN5-mediated lactylation enhances ERK activity, which in turn promotes GCN5 acetylation and nuclear translocation (37). This positive feedback loop accelerates lactate-driven cancer progression, demonstrating that lactylation and acetylation can synergistically amplify oncogenic signaling. Chen *et al* (109) showed that meiotic recombination 11 homolog (MRE11) lactylation at lysine 673 promotes homologous recombination repair, while acetylation at the same residue exerts distinct regulatory effects on DNA end resection. The functional divergence between lactylation and acetylation at identical sites suggests that cells employ modification-specific readers to decode distinct metabolic states. Notably, Yang *et al* (110) demonstrated that HDAC1 lactylation at lysine 432 confers resistance to ferroptosis in colorectal cancer by inhibiting HDAC1 deacetylase activity, thereby altering the acetylation status of downstream targets. This represents a hierarchical crosstalk mechanism wherein lactylation of an eraser enzyme globally reprograms the acetylation landscape.

Interplay with other short-chain acyl modifications. Beyond acetylation, lactylation coexists with other short-chain acyl modifications including succinylation, crotonylation and butyrylation. These modifications utilize distinct acyl-CoA precursors and respond to different metabolic fluxes. Fu *et al* (111) highlighted that histone acylation biomarkers such as lactylation, crotonylation and succinylation provide complementary readouts of cellular metabolic states. The functional specificity of lactylation compared with other acylations likely derives from its unique metabolic sensor role for glycolytic flux and lactate concentration.

Emerging evidence suggests that lactylation can influence the deposition of other acyl modifications through metabolic regulation. Sun *et al* (112) demonstrated that methyltransferase-like 16 lactylation promotes cuproptosis via m6A modification on FDX1 mRNA, revealing crosstalk between lactylation and RNA methylation pathways. Xiong *et al* (55) established that lactylation-driven *METTL3*-mediated RNA m6A modification promotes immunosuppression of tumor-infiltrating myeloid cells, indicating that lactylation can indirectly regulate RNA-level modifications. This multi-layered regulatory cascade, from metabolic signal to protein lactylation to RNA epigenetic modification, exemplifies the integrative capacity of lactylation within cellular regulatory networks. However, direct competition between lactylation and other short-chain acylations for the same lysine residues remains incompletely characterized, representing an important direction for future investigation.

Integration with ubiquitination and phosphorylation. Ubiquitination governs protein stability and degradation, and recent evidence indicates that lactylation can either promote or antagonize ubiquitin-dependent proteolysis. Rao *et al* (113) demonstrated that cyclic GMP-AMP synthase (cGAS) lactylation orchestrates ubiquitin-independent degradation, revealing that lactylation can bypass canonical ubiquitination pathways to regulate protein turnover. Deubiquitinase-controlled lactylation in gastric adenocarcinoma is described in the 'CSC stemness as a hub for lactylation-driven multidrug resistance' section (11). The reciprocal regulation is equally important: ubiquitination can limit lactylation by reducing substrate availability, while lactylation can protect proteins from ubiquitin-mediated degradation.

Phosphorylation represents another major PTM that functionally crosstalks with lactylation. Huang *et al* (37) demonstrated that the GCN5-ERK lactylation-phosphorylation loop amplifies lactate-driven cancer progression, wherein ERK phosphorylation promotes GCN5-mediated lactylation and lactylation reciprocally enhances ERK phosphorylation. Chen *et al* (109) showed that MRE11 lactylation is potentiated by ATM-mediated phosphorylation, coupling

Table II. Crosstalk between lactylation and other post-translational modifications in cancer regulation.

First author/s, year	Crosstalk type	PTM Type	Target protein/ residue(s)	Regulation direction	Modification site(s)	Functional consequence	(Refs.)
Zhang *et al*, 2019	Competitive	Acetylation	Histones (general)	Competitive occupancy	Unspecified lysine residues	Lactylation responds to while acetylation responds to acetyl-CoA; both modifications compete for the same histone lysine residues	(12)
Huang *et al*, 2026	Cooperative/ Positive feedback	Acetylation/ Phosphorylation	GCN5/ ERK	Positive feedback loop	GCN5: lactylation; ERK: phosphorylation	GCN5 lactylation enhances ERK activity; ERK phosphorylation promotes GCN5 acetylation and nuclear translocation, accelerating lactate-driven cancer progression	(37)
Yang *et al*, 2025	Hierarchical	Acetylation	HDAC1 (K432)	Hierarchical regulation	K432	HDAC1 lactylation inhibits its deacetylase activity, conferring ferroptosis resistance and globally reprogramming the acetylation landscape	(110)
Xiong *et al*, 2022	Indirect/ sequential	Lactylation + RNA m^6A modification	METTL3	Indirect regulation	Unspecified	Lactylation-driven METTL3-mediated RNA m^6A modification promotes immunosuppression of tumor-infiltrating myeloid cells	(55)
Sun *et al*, 2023	Indirect/ sequential	Lactylation + RNA m^6A modification	METTL16 (K229)	Sequential crosstalk with SIRT2	K229	METTL16 lactylation promotes cuproptosis via m^6A modification on FDX1 mRNA; SIRT2 antagonizes this lactylation	(112)

Table II. Continued.

First author/s, year	Crosstalk type	PTM Type	Target protein/ residue(s)	Regulation direction	Modification site(s)	Functional consequence	(Refs.)
Rao *et al*, 2025	Indirect/ sequential	Lactylation + Ubiquitination (independent)	cGAS, (K21 K415)	Ubiquitin-independent degradation	K21, K415	Lactylation promotes proteasomal degradation of cGAS bypassing ubiquitin, repressing interferon production and promoting tumor growth	(113)
Fu *et al*, 2023	Integrative/multi-PTM framework	Crotonylation/ Succinylation (comparison)	Histones	Complementary readouts	Unspecified	Histone acylation biomarkers (lactylation, crotonylation, succinylation) provide complementary information on cellular metabolic states	(111)
Lao *et al*, 2024	Integrative/multi-PTM framework	Multiple PTMs (integrative framework)	Various targets	Combinatorial PTM code	Multiple residues	Deciphering multi-PTM-associated regulatory patterns and therapeutic opportunities in hepatocellular carcinoma	(114)
Chen *et al*, 2025	Integrative/multi-PTM framework	Multiple PTMs (integrative analysis)	Various targets	Network-based	Multiple residues	Integrative analysis of bulk RNA-seq, scRNA-seq and spatial transcriptomics to identify PTM-related molecular subtypes and therapeutic responses in HCC	(115)

PTM, post-translational modification; Ac, acetylation; cGAS, cyclic GMP-AMP synthase; ERK, extracellular signal-regulated kinase; FDX1, ferredoxin 1; GCN5, general control nonderepressible 5 (KAT2A); HCC, hepatocellular carcinoma; HDAC1, histone deacetylase 1; Kla, lysine lactylation; m^6A, N6-methyladenosine; METTL3/16, methyltransferase-like 3/16; scRNA-seq, single-cell RNA sequencing; SIRT2, sirtuin 2; Ub, ubiquitination.

DNA damage signaling to metabolic status. This integration ensures that DNA repair responses are modulated according to cellular metabolic context, with potential implications for chemotherapy resistance. A critical insight emerging from these studies is that lactylation often operates within positive feedback loops with phosphorylation, creating self-reinforcing circuits that sustain oncogenic signaling and therapy resistance once established.

Combinatorial PTM code and therapeutic implications. The convergence of multiple PTMs on common target proteins generates a combinatorial PTM code that fine-tunes protein function in a context-dependent manner (114). Lactylation does not function as an isolated switch but rather as one node within an integrated PTM network that decodes metabolic, signaling and stress inputs. The crosstalk mechanisms aforementioned, including competitive occupancy, hierarchical

regulation, and reciprocal feedback (11,37), collectively enable cancer cells to coordinate stemness maintenance and drug resistance across multiple regulatory layers. Therapeutically, targeting the writers, erasers, or readers of lactylation may have unintended consequences on acetylation and other PTMs given the shared enzymatic machinery. Conversely, the interconnected nature of PTM networks suggests that combination therapies simultaneously targeting multiple modification pathways may be required to overcome resistance (115). Understanding the context-specific rules governing PTM crosstalk will be essential for developing precision strategies that disrupt lactylation-driven stemness and drug resistance without perturbing essential homeostatic functions. The current PTM crosstalk literature is also uneven. Most claims derive from single-PTM perturbation experiments and few studies map lactylation and acetylation, ubiquitination, or phosphorylation on the same residue in the same model (109,110,114,115). Thus, the combinatorial PTM code remains a conceptual framework rather than a fully resolved mechanism.

7. Therapeutic targeting of lactylation for overcoming cancer stemness and drug resistance

Targeting the lactylation pathway has emerged as a promising therapeutic strategy to counteract cancer stemness and drug resistance. Preclinical advances demonstrate that interventions targeting lactate metabolism, lactylation writers and erasers and natural products can reverse lactylation-driven malignancy. Table III summarizes key preclinical agents and their mechanisms of action in overcoming therapy resistance.

Targeting lactate metabolism and transport. Disrupting lactate production and transport represents the most direct approach to modulate the lactylation landscape. The lactate dehydrogenase (LDH) family, particularly LDHA, catalyzes the final step of glycolysis converting pyruvate to lactate. Pharmacological inhibition of LDHA using small molecules such as FX11 (a small-molecule inhibitor of lactate dehydrogenase A) and oxamate has demonstrated efficacy in reducing histone lactylation and suppressing tumor progression (116,117). Mechanistically, oxamate enhances chimeric antigen receptor T-cell (CAR-T) therapy efficacy against glioblastoma by suppressing ectonucleotidases and C-C chemokine receptor type 8 (CCR8) lactylation, establishing that metabolic modulation can synergize with immunotherapy (117). Similarly, inhibition of LDHB suppresses the metastatic potential of lung cancer by reducing mitochondrial GSH catabolism, indicating isoform-specific therapeutic opportunities (118).

Monocarboxylate transporters (MCTs), particularly MCT1 and MCT4, mediate lactate export and import across cellular membranes. Pharmacological blockade of MCT1 using AZD3965 has shown promise in preclinical models. Importantly, MCT-1 blockade improves chimeric antigen receptor T-cell therapy against B-cell malignancies, demonstrating that lactate transport inhibition can enhance immunotherapeutic efficacy (119). In acute myeloid leukemia, targeting lactate metabolism by inhibiting MCT1 or MCT4 impairs leukemic cell proliferation and increases chemotherapeutic sensitivity (120). Combined targeting of LDH and MCTs is being explored, with synthetic catalysts working synergistically with MCT inhibitors to disrupt lactate metabolism (121). However, redundancy between MCT isoforms and potential metabolic adaptation mechanisms may limit monotherapy efficacy, suggesting that dual targeting strategies may be required for durable responses.

Pharmacological modulation of lactylation writers and erasers. Direct targeting of the enzymatic machinery that deposits or removes lactyl groups offers an alternative strategy. The identification of *AARS1* and *AARS2* as primary lactyltransferases has opened new therapeutic avenues (122,123). Small molecules that interfere with *AARS1*'s lactate-sensing function or its lactyltransferase activity could potentially reduce global lactylation levels. Complementing this approach, inhibition of nuclear GTPSCS, which functions as a lactyl-CoA synthetase promoting histone lactylation and gliomagenesis, represents a compartment-specific targeting strategy (124). HBO1, identified as a histone lactyltransferase catalyzing H3K9la, may be targeted using existing acetyltransferase inhibitors, though selectivity remains a concern (116).

Targeting delactylases represents an equally valid approach, though context-dependent effects must be considered. Class I HDAC inhibitors (HDAC1-3) block both deacetylase and delactylase activities (125). SIRT6 inhibitors have been shown to reverse temozolomide resistance in glioblastoma by preventing H3K9 delactylation-mediated *MGMT* repression (126). The dual roles of these enzymes in regulating both acetylation and lactylation complicate therapeutic targeting, as global inhibition may produce unintended consequences on other PTM networks. Notably, the development of isoform-specific delactylase inhibitors that preferentially target lactylated substrates over acetylated ones represents an important future direction.

Natural products targeting the lactylation pathway. Natural products have emerged as a rich source of lactylation-modulating agents with favorable safety profiles. Demethylzeylasteral, a compound isolated from *Tripterygium wilfordii*, targets lactate by inhibiting histone lactylation to suppress the tumorigenicity of liver cancer stem cells (64,127). Mechanistically, this natural product reduces H3K18la levels at stemness gene promoters, decreasing CSC self-renewal capacity.

Other natural compounds have shown similar promise. Emodin regulates lactate metabolism by inhibiting MCT1 to delay non-small cell lung cancer progression (128). Royal jelly acid suppresses hepatocellular carcinoma tumorigenicity by inhibiting H3 histone lactylation at H3K9la and H3K14la sites (129). Evodiamine impairs HIF1A histone lactylation to inhibit semaphorin 3A-mediated angiogenesis and PD-L1 by inducing ferroptosis in prostate cancer (130). Ginsenoside Rk1 suppresses epithelial-mesenchymal transition of hepatic stellate cells via *PFKFB2*-mediated aerobic glycolysis (131). A critical comparative analysis reveals that most natural products indirectly modulate lactylation by reducing glycolytic flux or lactate production rather than directly targeting the lactylation machinery. Whether this indirect mechanism provides superior therapeutic windows compared with direct enzymatic inhibition remains to be determined.

Table III. Preclinical and clinical strategies targeting lactylation to overcome cancer stemness and drug resistance.

First author/s, year	Strategy category	Agent/intervention	Target/mechanism	Cancer type/model	Effect on lactylation	Therapeutic outcome	Evidence level	(Refs.)
Krishnamoorthy *et al*, 2020	Therapeutic strategies: targeting lactate metabolism/ transport	FX11	LDHA inhibitor	Mycobacterium tuberculosis model (extrapolated to cancer)	Reduces histone lactylation	Suppresses tumor progression	*In vitro*	(116)
Sun *et al*, 2023		Oxamate	LDHA inhibitor	Glioblastoma	Suppresses CCR8 lactylation	Enhances CAR-T therapy efficacy	*In vitro*/animal	(117)
Ge *et al*, 2024		LDHB inhibitor	LDHB	Lung cancer	Reduces mitochondrial GSH catabolism (indirect)	Suppresses metastatic potential	*In vitro*	(118)
Lopez *et al*, 2023		AZD3965	MCT1 inhibitor	B-cell malignancies	Blocks lactate transport, lowering substrate for lactylation	Improves CAR-T therapy	*In vitro*	(119)
Saulle *et al*, 2020		MCT1/MCT4 inhibitors	MCT1 or MCT4	Acute myeloid leukemia	Reduces lactate availability	Impairs leukemic proliferation, increases chemosensitivity	*In vitro*	(120)
Bridgewater *et al*, 2023		Synthetic catalysts + MCT inhibitors	Lactate metabolism	Cancer cells (*in vitro*)	Disrupts lactate pools	Synergistic anti-metabolic effect	*In vitro*	(121)
Chen *et al*, 2020		MSN-based nanoplatform	Lactate metabolism (AARS1-related pathway)	Tumor models	Interferes with lactate utilization	Induces tumor acidosis, suppresses metastasis	*In vitro*/animal	(122)
Hu *et al*, 2020		DRP1 targeting	Lactate utilization (KRAS-mutant NSCLC)	Non-small cell lung cancer	Modulates lactate flux	Reduces lactate-driven proliferation	*In vitro*	(123)
Zhang *et al*, 2022		ROS-activatable nanoassembly	Lactate metabolism modulation; ferroptosis sensitization	Tumor models	Reduces H3 lactylation	Enhances ferroptosis therapy	*In vitro*/animal	(127)

Table III. Continued.

First author/s, year	Strategy category	Agent/intervention	Target/mechanism	Cancer type/model	Effect on lactylation	Therapeutic outcome	Evidence level	(Refs.)
Khamoui *et al*, 2020	Therapeutic strategies: targeting lactylation writers/erasers	Nuclear GTPSCS inhibition	Lactyl-CoA synthetase	Colon-26 cachexia model	Blocks nuclear lactyl-CoA production	Suppresses histone lactylation and tumor growth	Animal model	(124)
Zeng *et al*, 2020		Class I HDAC inhibitors	HDAC1-3 (delactylase)	Hepatocellular carcinoma	Blocks delactylation, increases global lactylation	Synergistic anti-cancer effect (with ODC1/PKM2 inhibition)	*In vitro*	(125)
Qin *et al*, 2021		SIRT6 inhibitor	SIRT6 (delactylase)	Glioblastoma	Prevents H3K9 delactylation	Reverses temozolomide resistance	*In vitro*	(126)
Pan *et al*, 2022	Therapeutic strategies: natural products	Demethylzeylasteral	Histone lactylation	Liver cancer stem cells	Inhibits H3K18la at stemness gene promoters	Suppresses tumorigenicity	*In vitro*/animal	(64)
Zhang *et al*, 2024		Emodin	MCT1	Non-small cell lung cancer	Lowers lactate import, reduces lactylation substrate	Delays tumor progression	*In vitro*	(128)
Xu *et al*, 2023		Royal jelly acid	H3K9la/H3K14 la	Hepatocellular carcinoma	Directly inhibits H3 histone lactylation	Suppresses tumorigenicity	*In vitro*/animal	(129)
Yu *et al*, 2023		Evodiamine	HIF1A histone lactylation	Prostate cancer	Impairs HIF1A lactylation	Inhibits angiogenesis and PD-L1, induces ferroptosis	*In vitro*	(130)
Li *et al*, 2025		Ginsenoside Rk1	PFKFB2-mediated glycolysis	Hepatic stellate cells	Reduces aerobic glycolysis and lactate production	Suppresses EMT	*In vitro*	(131)
Kumstel *et al*, 2022	Therapeutic strategies: combination approaches	CPI-613+lactate metabolism inhibitors	Mitochondrial complex I + lactate metabolism	Pancreatic cancer	Lowers lactate pools	Enhanced anti-tumor activity	Animal model	(132)

Table III. Continued.

First author/s, year	Strategy category	Agent/intervention	Target/mechanism	Cancer type/ model	Effect on lactylation	Therapeutic outcome	Evidence level	(Refs.)
Zhang *et al*, 2025		Biomimetic heavy-atom-free photosensitizer	T cell and cancer cell metabolism	Tumor models	Reverses lactate-driven immunosuppression	Boosts photoimmunotherapy	Animal model	(133)
Deng *et al*, 2024		Bimetallic nanomodulator	Sonodynamic-ferroptosis + lactate metabolism	Tumor models	Modulates lactate to reduce immunosuppression	Reverses immunosuppression	Animal model	(134)
Li *et al*, 2026		Dual-transformable MgGa-MOF	Lactate metabolism blockade + immune reactivation	Hepatocellular carcinoma	Blocks lactate production and histone lactylation	Immune reactivation and tumor suppression	Animal model	(135)
Chao *et al*, 2024	Biomarker strategies: prognostic signatures	High H3K18 lactylation level	Prognostic indicator	Epithelial ovarian cancer	Elevated H3K18la	Correlates with poor prognosis and reduced platinum response	Clinical (retrospective; prognostic + predictive of platinum response)	(105)
Zhao *et al*, 2025		Lactylation prognostic signature (DHCR7)	Chemoresistance/ immunotherapy modulator	Bladder cancer	Identifies DHCR7 as lactylation-related modulator	Predicts chemoresistance and immunotherapy efficacy	Clinical (retrospective; prognostic + predictive of chemoresistance and immunotherapy efficacy)	(106)
Yang *et al*, 2025		Lactylation-related gene signature	Prognostic biomarker	Radiation-resistant NSCLC	-	Predicts prognosis and treatment response	Clinical (retrospective; prognostic + predictive of treatment response)	(107)

Table III. Continued.

First author/s, year	Strategy category	Agent/intervention	Target/mechanism	Cancer type/model	Effect on lactylation	Therapeutic outcome	Evidence level	(Refs.)
Hu *et al*, 2025		Lactylation-related gene signature	Chemotherapeutic efficacy prediction	Colorectal carcinoma	-	Prognostic for chemotherapeutic efficacy	Clinical (retrospective; predictive of chemotherapeutic efficacy)	(108)
Cheng *et al*, 2023		Lactylation-related gene signature	Prognostic biomarker	Hepatocellular carcinoma	-	Predicts prognosis and treatment responsiveness	Clinical (retrospective; prognostic + predictive of treatment responsiveness)	(136)
Xie *et al*, 2023		CircXRN2 (Hippo pathway)	Histone lactylation regulation	Bladder cancer	Suppresses histone lactylation-driven progression	Predicts better outcome	Clinical (retrospective; prognostic)	(137)
Wu *et al*, 2023		Histone lactylation-specific genes (NR6A1, OSBP2, UNC119B)	Therapeutic targets	Hepatocellular carcinoma	Identifies Kla-specific gene signatures	Novel therapeutic targets	Clinical (retrospective; target discovery)	(138)
Wu, 2023		Protein lactylation profiling	Diagnostic/ prognostic marker	Hepatocellular carcinoma	In-depth lactylome analysis	Provides prognostic information	Clinical (retrospective; prognostic)	(139)

Prognostic=association with clinical outcome. Predictive=association with response to a specific treatment. Both=both types of evidence reported. This distinction applies only to clinical biomarker studies; preclinical cell and animal studies are not classified as prognostic or predictive. AARS1, alanyl-tRNA synthetase 1; AMPK, AMP-activated protein kinase; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CAR-T, chimeric antigen receptor T-cell; CCR8, C-C motif chemokine receptor 8; CPI-613, a mitochondrial complex I inhibitor; DHCR7, 7-dehydrocholesterol reductase; DRP1, dynamin-related protein 1; EMT, epithelial-mesenchymal transition; GSH, glutathione; H3K9la, H3K14la, H3K18la, histone H3 lysine lactylation; HCC, hepatocellular carcinoma; HDAC, histone deacetylase; HIF1A, hypoxia-inducible factor 1-alpha; Kla, lysine lactylation; LDHA, lactate dehydrogenase A; LDHB, lactate dehydrogenase B; MCT1/4, monocarboxylate transporter 1/4; MgGa-MOF, magnesium-gallium metal-organic framework; MnSOD, manganese superoxide dismutase; MSN, mesoporous silica nanoparticle; NSCLC, non-small cell lung cancer; ODC1, ornithine decarboxylase 1; PD-L1, programmed death-ligand 1; PFKFB2, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2; PKM2, pyruvate kinase M2; ROS, reactive oxygen species; SIRT6, sirtuin 6.

Rational combination therapeutic strategies. Given that lactylation-driven resistance involves multiple interconnected pathways, combination strategies may offer the greatest therapeutic promise. Co-targeting lactate metabolism with conventional chemotherapy has shown synergistic effects. Simultaneous inhibition of ornithine decarboxylase 1 and pyruvate kinase M2 exerts synergistic effects against hepatocellular carcinoma cells, suggesting that multi-node metabolic targeting may be more effective than single-agent approaches (125). In pancreatic cancer, combinatorial treatment with CPI-613 (a mitochondrial complex I inhibitor) and inhibitors of lactate metabolism shows enhanced anti-tumor activity (132).

The combination of lactylation-targeting agents with immunotherapy represents a particularly attractive strategy. As discussed in the 'Immunotherapy resistance' section, lactylation promotes PD-L1 expression and immunosuppressive microenvironment formation. Therefore, combining lactate metabolism inhibitors with immune checkpoint blockade may overcome immunotherapy resistance. A biomimetic heavy-atom-free photosensitizer-based combination therapy simultaneously reverses T lymphocyte and cancer cell metabolism to boost photoimmunotherapy (133). Similarly, a bimetallic nanomodulator reverses immunosuppression via sonodynamic-ferroptosis and lactate metabolism modulation (134). A dual-transformable MgGa- males absent on the first nanoplatform for HCC therapy operates via lactate metabolism blockade and immune reactivation (135). Notably, the success of these combination approaches may depend on careful sequencing, as metabolic perturbations may temporarily impair T cell function before enhancing anti-tumor immunity. Most combination data remain preclinical and use heterogeneous schedules. Evidence that lactylation targeting improves survival in patient-derived or immunocompetent models without impairing normal lactate-dependent tissues is still limited (132-135).

Lactylation-based biomarkers for patient stratification. The clinical translation of lactylation-targeted therapies requires robust biomarkers to identify patients most likely to benefit. Multiple studies have developed lactylation-related gene signatures that have been associated with prognosis and treatment response across cancer types in retrospective cohorts. In hepatocellular carcinoma, lactylation-related gene signatures have been associated with prognosis and treatment responsiveness (136). In lung adenocarcinoma, lactylation-related gene signatures have been associated with prognosis and treatment response in radiation-resistant NSCLC (107,137). In colorectal cancer, integrative machine learning identifies lactylation-related gene signatures reported to be prognostic for chemotherapeutic efficacy (108,129).

Specific lactylation marks have been reported as prognostic indicators, although independent validation remains limited. High histone H3K18 lactylation levels have been associated with poor prognosis in epithelial ovarian cancer and with reduced response to platinum-based chemotherapy in retrospective cohorts (105,138). Lactylation prognostic signatures have been proposed for bladder cancer, identifying DHCR7 as a modulator of chemoresistance and immunotherapy efficacy (106,139). For glioblastoma, lactylation-associated gene signatures have been associated with stratification by temozolomide response and with survival outcomes in retrospective analyses (84). A critical limitation of current signature-based approaches is the lack of standardization across platforms and cancer types. Most signatures are constructed from bulk RNA-seq data and infer lactylation from gene expression rather than measuring the modification itself (84,105,106,108). They are largely retrospective, lack independent external validation and have not been compared with established clinical markers; their predictive value therefore remains uncertain. Prospective validation in clinical trial cohorts and development of clinically deployable assays (such as immunohistochemistry for specific lactylation marks) will be essential before these biomarkers can guide treatment decisions. Until then, lactylation-based signatures should be regarded as hypothesis-generating rather than clinically actionable. The integration of lactylation markers with existing clinical and molecular parameters may ultimately enable precision targeting of this metabolic-epigenetic axis.

8. Challenges, unresolved questions and future perspectives

Despite substantial progress in understanding lactylation-driven cancer stemness and drug resistance, several critical challenges and unresolved questions remain that warrant careful consideration. A fundamental technical limitation concerns the distinction between enzymatic and non-enzymatic lactylation in cancer cells. Although Zhang *et al* (22) provided evidence for non-enzymatic lysine lactylation under high-lactate conditions, the relative contribution of *AARS1/2*-mediated vs. non-enzymatic lactylation to the global lactylome in the context of cancer stem cell maintenance has not been systematically quantified. Bao *et al* (34) performed subcellular proteomic mapping of lysine lactylation, revealing distinct compartmentalization patterns, yet whether enzymatic and non-enzymatic mechanisms exhibit different subcellular preferences remains unexplored. This distinction carries therapeutic implications, as targeting *AARS1* may not fully abrogate lactylation driven by extreme metabolic stress (16). A major limitation is that many studies infer lactylation from pan-Kla immunoblotting or global lactylome data without site-specific validation, chiral resolution, or rescue experiments (14,15,22,34,140). Consequently, some reported associations may reflect general metabolic stress rather than a defined lactylation-dependent mechanism.

Another pressing unresolved question concerns the identity and specificity of lactylation reader proteins. Zhai *et al* (32) identified DPF2 as a histone lactylation reader that drives transcription and tumorigenesis, while Nuñez *et al* (31) characterized TRIM33 bromodomain recognition of histone lactylation with selectivity distinct from acetylation recognition. However, systematic identification of readers remains incomplete compared with the well-established acetylation reader repertoire and whether distinct readers recognize different lactylation marks (such as H3K9la vs. H3K18la) or whether lactylation-specific readers exist beyond bromodomain-containing proteins remains unknown. The development of lactylation-specific antibodies and affinity purification strategies may be essential to address this gap.

The functional interplay between lactylation and other post-translational modifications represents an area requiring deeper mechanistic investigation. Chen *et al* (109,141) revealed that MRE11 lactylation at lysine 673 promotes homologous recombination repair, while acetylation at the same residue exerts distinct regulatory effects on DNA end resection, demonstrating functional divergence between these modifications at identical sites. However, compared with the well-characterized crosstalk between acetylation and other acyl modifications, systematic investigation of lactylation-acetylation interplay at the same lysine residue remains limited. Lao *et al* (114) deciphered multiple PTM-associated regulatory patterns in hepatocellular carcinoma, but integrative frameworks that predict context-dependent PTM crosstalk are lacking.

Translational barriers for lactylation-targeted therapies are substantial. Although natural products such as demethylzeylasteral (64,127,142) has shown preclinical efficacy in suppressing cancer stemness by inhibiting histone lactylation, the selectivity of these agents for malignant vs. normal tissues remains concerning given the essential role of lactate metabolism in physiological processes. Li *et al* (69) performed single-cell transcriptome analysis revealing the association between histone lactylation and cisplatin resistance in bladder cancer, yet whether lactylation signatures can reliably stratify patients for therapy remains to be validated in prospective clinical cohorts. Furthermore, the development of isoform-specific delactylase inhibitors that preferentially target lactylated substrates over acetylated ones represents an urgent priority, as current HDAC inhibitors broadly block both deacetylase and delactylase activities (24,143).

Emerging research directions offer promising opportunities to overcome these challenges. The integration of single-cell and spatial transcriptomics, as exemplified by Yu *et al* (67) in hepatocellular carcinoma, enables elucidation of how stromal cells regulate histone lactylation to promote tumor progression. Such approaches will facilitate precise mapping of lactylation heterogeneity within the tumor microenvironment and cancer stem cell niches. Advances in genetic code expansion technology reported by Shao *et al* (140) enable site-specific lactylation in living cells, providing powerful tools to dissect causal roles of individual lactylation sites in stemness regulation. Lastly, machine learning approaches for predicting lactylation sites and readers may accelerate discovery of context-specific regulatory mechanisms (144). Addressing these challenges through coordinated efforts in chemical biology, structural biology, and clinical translation may ultimately determine whether targeting the lactylation landscape can be successfully translated into therapeutic strategies for overcoming cancer stemness and drug resistance.

9. Conclusions

Lysine lactylation serves as a central metabolic-epigenetic hub that integrates Warburg-effect-derived lactate signals to sustain cancer stem cell self-renewal, foster multidrug resistance and remodel an immunosuppressive tumor microenvironment. The writer and eraser machinery (AARS1/2, HBO1, KAT8, KAT2A, HDAC1-3, SIRT3, SIRT6) and several lactylation marks (H3K9la, H3K18la, H3K14la) are well supported, whereas enzymatic vs. non-enzymatic deposition, reader identity and spatial heterogeneity remain preliminary. The principal gap is the absence of site-selective modulators discriminating lactylation from other acylations. Future work must validate causal mechanisms at defined sites, develop selective inhibitors, and prospectively validate lactylation-based biomarkers with standardized assays before clinical translation.

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YY and NZ contributed equally to conceptualization, literature review and drafting the original manuscript. DW and DY performed literature searching and figure preparation. YZ and XL critically revised the manuscript for important intellectual content and gave final approval. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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