

Lactylation enzymes in cancer: Mechanisms and novel therapeutic approaches (Review)

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Abstract. Metabolic reprogramming, particularly the Warburg effect, drives tumor progression not only by supplying energy

but also by reshaping the epigenetic landscape through lysine lactylation. The present review summarizes the molecular organization of the lactylation regulatory network, highlighting two distinct writer mechanisms: i) A classical acyl-coenzyme A (acyl-CoA)-dependent pathway mediated by the MYST (MOZ, Ybf2/Sas3, Sas2 and Tip60) family; and ii) a recently described acyl-CoA-independent pathway driven by the metabolic sensors, alanyl-tRNA synthetases 1 and 2. The present review further explains how these ‘writers’, together with specific ‘erasers’ and ‘readers’, convert intracellular lactate accumulation into stable transcriptional programs that support immunosuppression, metabolic plasticity and therapeutic resistance. In addition, the current review discusses emerging therapeutic strategies targeting this axis, shifting from broad lactate metabolism inhibition towards more precise approaches that reduce the off-target toxicity of conventional epigenetic drugs. Finally, the present review outlines lactylation-associated gene signatures as potential biomarkers, providing a framework for the development of metabolic-epigenetic therapies.

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Abbreviations: AARS1/2, alanyl-tRNA synthetase 1/2; ACSS2, acyl-CoA synthetase short-chain family member 2; BRD, bromodomain; Brg1, brahma-related gene 1; CC, cervical cancer; CBP, CREB-binding protein; CRC, colorectal cancer; DPF2, double PHD Finger Protein 2; EMT, epithelial-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; FDX1, ferredoxin 1; GC, gastric cancer; GLO1/2, glyoxalase 1/2; GTPSCS, GTP-specific succinyl-CoA synthetase; HATs, histone acetyltransferases; HCC, hepatocellular carcinoma; HDACs, histone deacetylases; Hla, histone lactylation modifications; Kac, acetylation modification; KAT, lysine acetyltransferase; Kce, *N*-ε-(carboxyethyl) lysine; Kd-la, D-lactyl-lysine; Kla, lysine lactylation; Kl-la, L-lactylation; LDHA/B, lactate dehydrogenase A/B; LGSH, S-D-lactoylglutathione; MCT, monocarboxylate transporter; MGO, methylglyoxal; NAM, nicotinamide; n-Hla, Non-Hla; NLS, nuclear localization signal; NSCLC, non-small cell lung cancer; OXPHOS, oxidative phosphorylation; PD-L1, programmed death-Ligand 1; PHD, plant homeodomain; PKM2, pyruvate kinase M2; PROTACs, proteolysis-targeting chimeras; PTM, post-translational modification; SIRT6, Sirtuin6; TAMs, tumor-associated macrophages; TME, tumor microenvironment; TRIM33, tripartite motif containing 33; YAP, yes-associated protein; YTHDC1, YTH domain containing 1

Key words: lactylation, metabolism, post-translational modification, cancer

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1. Introduction

Metabolic reprogramming has become the main topic of a growing number of investigations examining the fundamental origins of cancer. A artefact of this reprogramming

is the Warburg effect (1), a metabolic shift defined by elevated glycolysis that leads to the excessive accumulation of lactate (2). Long dismissed as a simple metabolic ‘waste product’, lactate is now understood to be a pivotal effector molecule; it functions as a key energy substrate, a potent regulator of the tumor microenvironment (TME) and an essential signaling molecule (3-5). The recent identification of lysine lactylation (Kla) (6), a novel post-translational modification (PTM) directly originating from lactate, has enhanced the new understanding of the role of lactate. This finding has established a direct and critical link between the metabolic state of a cell and its epigenetic regulation. Lactylation represents a core metabolic-epigenetic axis, translating the accumulation of lactate into durable transcriptional programs. This axis is considered a key driver of tumor cell proliferation, invasion, migration and, most critically, therapeutic resistance (3,7,8). Given its central role, understanding the enzymatic machinery that governs this axis is paramount. The present review focuses on the regulatory enzymes (‘writers’, ‘erasers’ and ‘readers’) that control protein lactylation, discusses their mechanisms in cancer and explores their therapeutic potential.

2. Lactate in tumor biology: Energy source and signaling molecule

Recent tumor biology has shown that lactate is a key source of energy for tumor cells. The ‘lactate shuttle’ enables aerobic and hypoxic tumor cells to sustain a metabolic symbiosis, in which glycolysis-derived lactate is continuously produced, exchanged and reutilized. This coordinated circulation of lactate fuels tumor proliferation, invasion and adaptation to an oxygen-limited microenvironment (9,10). Neurons can also uptake lactate through monocarboxylate transporter (MCT)2 to use it as a fuel source (11). Research has revealed that lactate can buffer dietary glucose and be utilized for energy almost as efficiently as glucose (12). This dual function of lactate connects tumor metabolism with systemic energy balance.

Lactate is known to be a key regulator of cellular metabolism and phenotype; it modulates metabolic reprogramming, inflammatory responses and immune regulation. Lactate signaling through G protein-coupled receptor (GPR)81 directly promotes energy metabolism (13) or lactate itself enters mitochondria to be incorporated into the TCA cycle, activates the respiratory chain and increases ATP synthesis (14). Most critically, lactate serves as a central driver of immunosuppression within the TME. Lactate activates GPR81, inhibiting MHCII presentation on the cell surface, while reducing IL-12 secretion. This further weakens antigen presentation capacity, preventing effective T cell activation (15). In melanoma, lactate is taken up by tumor-associated macrophages (TAMs), reprogramming them toward a pro-tumor phenotype (16). While promoting tissue homeostasis, lactate functions as both an immunosuppressant and a pro-carcinogen (16). Concurrently, lactate induces polarization of helper T (Th) and CD4⁺ T cells, fostering an immunosuppressive environment that suppresses Th1 subsets critical for antitumor activity (17). Lactate inhibits the upregulation of nuclear factor of activated T cells in T cells and natural killer (NK) cells, leading to reduced interferon γ production. This suppresses the tumor immune surveillance

and antitumor functions of T cells and NK cells, ultimately resulting in tumor immune escape (18).

In conclusion, the function of lactate in tumor biology has been entirely redefined. Large production of lactate implies that metabolic reprogramming can be linked to epigenetic regulation through lactylation (19). Fig. 1 demonstrates the direct conversion of the lactate metabolic into durable transcriptional programs that drive tumor malignancy.

3. Emerging landscape of lactylation modification

Kla provided the first evidence that lactate directly modifies histones, leading to transcriptional changes in macrophages and regulating the cellular transcriptome. This finding has expanded the current understanding of the functions of lactate (6). Subsequent studies (20-24) revealed Kla as a versatile regulatory mechanism influencing gene expression, metabolism and tumor progression. Tables I (writers) and II (erasers) (3,7,20-62) collectively provide an enzymatic perspective on the functional consequences of Kla, offering a comprehensive summary of specific lactylation sites and their associated biological functions.

Histone lactylation (Hla) modification: Rewiring the transcriptional landscape. Lactate accumulation produced by glycolysis in tumor cells is converted into lactyl-CoA, which serves as the donor of the lactyl group. This lactyl group is subsequently transferred to lysine residues on histone tails. This binding weakens the attraction between histones and DNA, leading to a relaxed chromatin structure and a more open state that is conducive to transcription, thereby creating favorable conditions for gene transcription initiation (63,64). Hla modifications, including at sites such as H3K18 and H4K12, have been shown to play a key role in the initiation, development, immune evasion and therapeutic resistance of various cancer types. For example, H3K18la promotes cell cycle and proliferation by specifically enriching at and directly activating the promoters of key oncogenes, such as TTK protein kinase, BUB1 mitotic checkpoint serine/threonine kinase B in pancreatic ductal adenocarcinoma (PDAC) and c-Myc in colorectal cancer (CRC) (20,65); it also drives cell invasion and migration by activating the AKT-mTOR signaling pathway in gastric cancer (GC) or enhancing epithelial-mesenchymal transition (EMT) (66,67). Furthermore, H3K18la facilitates immune evasion by promoting programmed death-ligand 1 (PD-L1) expression and inhibiting CD8⁺ T cell function in GC and lung adenocarcinoma (LUAD) (68,69), and contributes to chemotherapy and radiotherapy resistance by activating protective autophagy or ferroptosis resistance in CRC and prostate cancer (70,71). Similar findings have been reported for H4K12la (52,72). Recently, newly identified sites such as H4K79la and H4K91la have also been shown to be involved in breast cancer (BC) progression (73), indicating that, despite substantial existing research, Hla continues to offer valuable potential for the identification of new targets.

Throughout these tumor progression processes, the persistently high lactate levels resulting from the Warburg effect disrupt normal lactate metabolism. Since H3K18la affects DNA transcriptional activity by enriching at the promoters of target genes, such as the oncogene c-Myc (20),

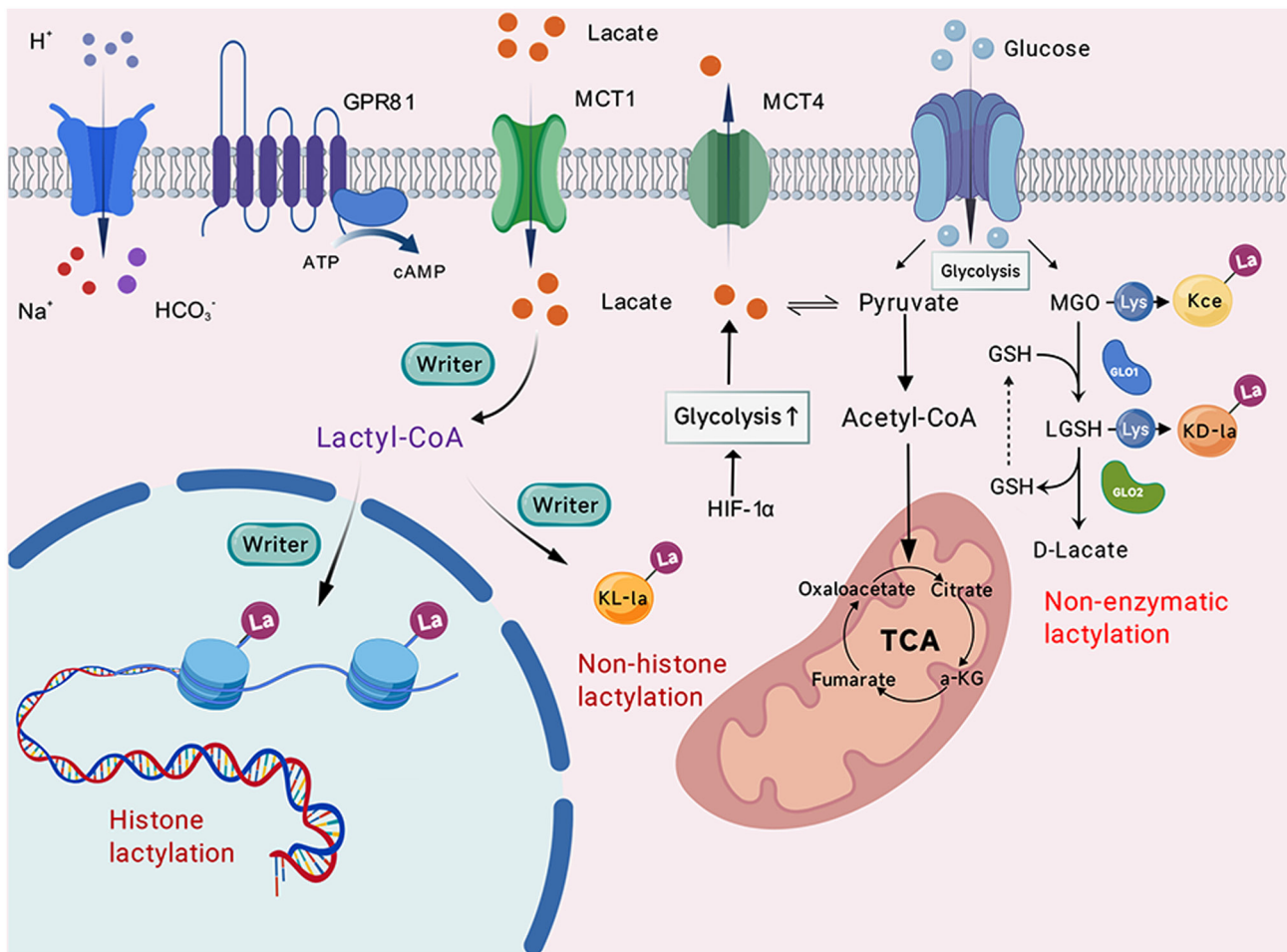


Figure 1. Mechanism of lactate-mediated epigenetic regulation. Lactate metabolism facilitates protein lactylation through two separate pathways. Lactate is converted to lactyl-CoA in the enzymatic pathway, serving as a substrate for 'writer' enzymes that modify histone and non-histone proteins. A non-enzymatic pathway concurrently employs the glycolysis byproduct MGO to produce LGSH, enabling direct lactylation of proteins without enzymatic involvement. Both mechanisms directly convert the metabolic state of the cell into epigenetic modifications that regulate gene expression and promote malignant progression. MGO, methylglyoxal; LGSH, S-D-lactoylglutathione; GRP, glucose-regulated protein; MCT, monocarboxylate transporter; La, lactate; KL-La, L-lactylation; HIF-1α, hypoxia-inducible factor 1-alpha; GSH, glutathione; GLO, glyoxalase; Kce, N-ε-(carboxyethyl)lysine; KD-La, D-lactylation; TCA, tricarboxylic acid cycle.

this lactylation modification consequently confers therapy resistance by activating survival-related genes, including glutamate-cysteine ligase catalytic subunit (52). Concurrently, some of those modifications (such as H3K18la and H4K12la) further promote the expression of lactate metabolism enzymes, leading to even higher intracellular lactate levels. This creates a vicious positive feedback loop where lactate produced by glycolysis reinforces glycolysis and lactate production through Hla (74,75). In this manner, lactate is transformed into a pivotal signaling molecule that governs epigenetics and affects various processes, emerging as a critical factor for the persistent malignant progression and therapeutic suppression of cancer cells.

Non-Hla (n-Hla) modification: Expanding the regulatory network. Unlike Hla, n-Hla occurs widely in the cell due to the abundance of its substrate; it occurs in several cellular compartments, including the nucleus, cytoplasm and mitochondria (22,29,55), and has broader biological consequences than Hla. First, n-Hla can enhance protein stability, thereby amplifying oncogenic signaling or promoting metabolic

reprogramming. By competitively occupying these sites, n-Hla inhibits proteasomal degradation and stabilizes critical onco-proteins such as β-catenin (76), transcription factor EB (48), polypyrimidine tract binding protein 1 (38) and YTH domain containing 1 (YTHDC1) (3), thereby sustaining oncogenic signaling and immune evasion. Second, n-Hla dynamically reshapes the assembly, localization and function of signaling complexes by regulating the conformation of proteins, thereby enhancing or weakening their interactions with other proteins (77). In addition, n-Hla can enhance protein-nucleic acid interactions, which is evident in its crosstalk with other modifications (such as m6A methylation and m5C RNA modification), facilitating downstream signal transduction and RNA processing (78-80). n-Hla can regulate energy metabolism to facilitate signal transduction and the activation of oncogenic pathways, including the AMP-activated protein kinase (21) and pentose phosphate (81) pathways. These effects not only alter cellular energy metabolism but also expedite the malignant development of tumor cells by supplying substrates for processes such as nucleic acid synthesis. More notably, n-Hla is a mechanism by which tumors utilize metabolic products

Table I. Regulatory roles of lactylation writers in cancer.

A, p300/CBP						
First author, year	Substrate	Cancer type	Mechanisms	Outcome	Inhibitor ^a	(Refs.)
Li <i>et al.</i> , 2024	H3K18la	PDAC	TTK, BUB1B ↑, glycolysis ↑	Proliferation, migration ↑	C646	(20)
Yang <i>et al.</i> , 2023	AK2 K28	HCC	AK2 activity ↓, disrupt ATP/AMP balance	Proliferation and migration ↑	-	(21)
Hong <i>et al.</i> , 2025	ABCF1 K430	HCC	KDM3A-H3K9me2-HIF1A ↑	Malignant progression ↑	-	(22)
Dai <i>et al.</i> , 2025	H3K18la	NSCLC	EGR1/NNMT/EGR1, NNMT/ALDH3A1/lactate/NNMT ↑	EGFR-TKI resistance	-	(24)
Liu <i>et al.</i> , 2024	H3K18la	GBM	GTPSCS-p300-H3K18la, GPF15 ↑	Proliferation and radioresistance ↑	A-485	(47)
Chen <i>et al.</i> , 2024	APOC2 K70	NSCLC	FFAs ↑, Tregs accumulation, immunosuppressive TME ↑	Immunotherapy resistance	-	(32)
Huang <i>et al.</i> , 2024	TFEB K91	PCa	TFEB ubiquitination, proteasome degradation ↓	Autophagy, lysosomal activity ↑	-	(48)
Liu <i>et al.</i> , 2025	TPX2 K249	HCC	Disrupts PP1-AURKA, AURKA phosphorylation ↑	Cell cycle progression ↑	-	(26)
Sun <i>et al.</i> , 2025	ENSA K63	PDAC	Inhibits PP2A, STAT3/CCL2 ↑, TAMs ↑, immunosuppressive TME ↑	Immunotherapy resistance	A-485, K63-pe-3	(49)
Dai <i>et al.</i> , 2025	YTHDC1 K82	RCC	Phase separation ↑, stabilizes oncogenic mRNAs (BCL2 and E2F2)	Progression	-	(3)
Yang <i>et al.</i> , 2024	NCL K477	iCCA	Stabilize MADD, ERK activation	iCCA proliferation, invasion ↑	-	(50)
Wang <i>et al.</i> , 2025	PD-L1 K189	HCC	Cholesterol synthesis ↑	Liver cancer growth ↑	-	(29)
Jiang <i>et al.</i> , 2025	Rab7A	HCC	Exosome biogenesis and secretion ↑	Metastasis ↑	C646	(51)
Deng <i>et al.</i> , 2025	H4K12la	CRC	GCLC ↑, ferroptosis ↓	Chemoresistance	p300i	(52)
Lv <i>et al.</i> , 2025	H3K18la	CRC	Brg ↑, activates MMP9	Liver metastasis in CRC	-	(33)
Ji <i>et al.</i> , 2025	H3K18la	HCC	YBX1-glycolysis-H3K18la ↑	Accelerates HCC progression	-	(53)
Yang <i>et al.</i> , 2025	H3K18la	PDAC	H3K18la/ACAT2/MTCH2	Cholesterol-linked immunosuppression	C646	(54)

B, AARS1/2

First author, year	Substrate	Cancer type	Mechanisms	Outcome	Inhibitor ^a	(Refs.)
Zong <i>et al.</i> , 2024	p53 K120/K139	BC	Liquid-liquid phase separation, DNA binding, transcriptional ↓	Tumor-suppressive function ↓	β-alanine	(23)
Xing <i>et al.</i> , 2025	YTHDC1	BLCA	RNF183-YTHDC1-JUND-NECTIN4 axis ↓	EV sensitivity ↓	β-alanine	(55)
Sun <i>et al.</i> , 2023	METTL16 K229	GC	FDX1 mRNA m6A modification ↑	Cuproptosis ↑	-	(40)
Ju <i>et al.</i> , 2024	YAP K90, TEAD K108	GC	AARS1-YAP-TEAD, Hippo pathway ↑	Proliferation ↑	-	(36)

Table I. Continued.

B, AARS1/2						
First author, year	Substrate	Cancer type	Mechanisms	Outcome	Inhibitor ^a	(Refs.)
Li <i>et al</i> , 2025	BLM K24	BLCA	BLM ubiquitination ↓, DNA end resection, HR-mediated DNA repair ↑	Anthracycline resistance	Irinotecan ^b	(56)
Lin <i>et al</i> , 2025	NUDT21 K23	ESCC	Interaction with CPSF6 ↑, FDX1 3'UTR lengthening ↑, expression ↓	Cuproptosis resistance	-	(30)
Han <i>et al</i> , 2025	ASH2L K312	HCC	VEGFA ↑, tumor angiogenesis ↑	Malignant progression	-	(28)
Shan <i>et al</i> , 2025	SUMO2 K11	LUAD	SUMO2-ACSL4 interaction ↓, disrupts lipid metabolism	Ferroptosis resistance	-	(27)
C, KAT2A						
First author, year	Substrate	Cancer type	Mechanisms	Outcome	Inhibitor ^a	(Refs.)
Sun <i>et al</i> , 2025	H3K9la, RAD51 K73la	OC	RAD51, BRCA2 ↑, HR-mediated DNA repair ↑	Cisplatin resistance	MB-3	(57)
Zheng <i>et al</i> , 2025	RCC2 K124	BC	Recruits SERBP1, MAD2L1 ↑	Proliferation ↑	SBDA	(58)
Jin <i>et al</i> , 2025	XLF K288	CRC	XLF-Ku80 interaction ↑, NHEJ DNA repair ↑	Chemotherapy resistance	MB-3	(37)
Tong <i>et al</i> , 2024	PD-L1	CRC	PD-L1 lysosomal degradation ↓	Antitumor immunity ↑, evasion ↑	-	(59)
D, KAT5						
First author, year	Substrate	Cancer type	Mechanisms	Outcome	Inhibitor ^a	(Refs.)
Chen <i>et al</i> , 2024	NBS1 K388	GC	Form MRE11-RAD50-NBS1 complex, HR DNA repair ↑	Chemotherapy resistance	KU-55933 ^c	(34)
Jia <i>et al</i> , 2023	Vps34, K356 K781	Lung cancer	Interaction with Beclin1, Atg14L, UVRAG ↑, lipid kinase activity ↑	Autophagy ↑	MG149	(60)
E, KAT7						
First author, year	Substrate	Cancer type	Mechanisms	Outcome	Inhibitor ^a	(Refs.)
Chen <i>et al</i> , 2025	H3K9la	ESCC	Tumorigenesis gene transcription ↑	Proliferation, migration ↑	-	(41)
Niu <i>et al</i> , 2024	H3K9la	CC	Tumorigenesis gene transcription ↑	Proliferation, migration, invasion ↑	WM-3835	(61)
F, KAT8						
First author, year	Substrate	Cancer type	Mechanisms	Outcome	Inhibitor ^a	(Refs.)
Xie <i>et al</i> , 2024	eEF1A2 K408	CRC	Translational elongation ↑, protein synthesis ↑	Proliferation ↑	-	(62)
Tang <i>et al</i> , 2025	MDH2 K239	RCC	MDH2 enzymatic activity, interaction with SLC25A1 ↑	Mitochondrial function, stress resistance ↑	EVT-12529733 ^d	(42)

Table I. Continued.

First author, year	Substrate	Cancer type	Mechanisms	Outcome	Inhibitor ^a	(Refs.)
G, NAA10						
Niu <i>et al.</i> , 2025	NSUN2 K508	GC	GCLC m5C and expression ↑, GSH ↑, lipid peroxidation ↓	Ferroptosis resistance	-	(7)

^aUnless otherwise specified, 'Inhibitor' refers to those reported to target the corresponding lactylation regulatory enzymes. ^bInhibits DNA duplication. ^cATM inhibitor. ^dAlso referred to as MC4171-compound. BC, breast cancer; BLCA, bladder cancer; CC, cervical cancer; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; GBM, glioblastoma; GSCs, glioma stem cells; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; iCCA, intrahepatic cholangiocarcinoma; LUAD, lung adenocarcinoma; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PCa, prostate cancer; PDAC, pancreatic ductal adenocarcinoma; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer.

to enhance the function of immunosuppressive cells (32,82) and inhibit tumor-killing cells (83), thereby shaping an inhibitory immune microenvironment. By suppressing various immune cells, favorable conditions are created for diminished tumor-inhibitory functions and the onset of immune evasion, ultimately leading to a series of immunotherapy resistance or suboptimal efficacy outcomes.

In summary, both Hla and n-Hla form a lactate-derived network that reshapes gene expression and signaling to drive tumor progression. Governed by specific writers, erasers and readers, these regulatory nodes are fundamental for understanding the lactylation landscape. Consequently, elucidating their functions is crucial for translating this metabolic modification into precise therapeutic targets and clinical applications.

4. Lactylation regulatory enzymes in cancer

Writers: Lactylation-catalyzing enzymes

p300/cAMP-responsive element-binding protein (CBP). p300 [also known as EP300/lysine acetyltransferase (KAT)3B] and its homologue CBP are well-studied histone acetyltransferases (HATs) in acetylation modification (Kac) (84,85). p300 is a prominent member of the MYST family of acetyltransferases. Recent research indicates that they also have lactyltransferase activity, as the HAT domain of p300 contains a hydrophobic pocket that can accommodate a variety of short-chain acyl-CoA molecules; it can recognize both acetyl-CoA and structurally similar lactyl-CoA (26,48,49).

As the initially identified and most thoroughly examined lactyl transferase, p300 significantly alters numerous essential substrates. Thus, p300 is widely recognized as the principal catalytic enzyme of K1a (20,24,29,33,53). Lactylation of transcription factors regulated by p300/CBP activates downstream signaling pathways, participating in tumor growth and other biological processes including angiogenesis, cell invasion and migration. For instance, under hypoxic conditions, lactylation of the transcription factor Yin Yang 1 at its K183 site by p300 directly activates the fibroblast growth factor 2 signaling pathway, leading to tumor angiogenesis (86). Moreover, in several malignancies, p300-mediated lactylation of ATP-binding cassette subfamily F member 1 at K430 (22) and Snail1 (87) facilitates tumor cell invasion and migration by advancing downstream processes such as EMT.

The targeting specificity of p300 determines its precise modifying activity. Recent findings have indicated that p300, in combination with the histone chaperone anti-silencing function protein 1 homolog A (ASF1A), directly regulates H3K18la accumulation in the Snail1 promoter region, hence specifically activating transcription and inducing atherosclerosis via endothelial-to-mesenchymal transition (EndMT) (88). This shows that p300 may be led to specific gene loci by different types of cofactors, triggering changes at distinct places. Thus, examining these histone chaperones could aid in understanding the mechanisms by which writers precisely detect and bind targets, deciphering the targeting specificity of lactylation changes and enabling the development of novel intervention strategies.

Other MYST family members. Similar to p300/CBP, HATs of the MYST family have also been found to function as lactyltransferases, likewise depending on lactyl-CoA. Members of this family include KAT2A (also known as GCN5), KAT8 (MOF), KAT5 (Tip60) and KAT7 (also known as HBO1). For instance, KAT8-mediated lactylation of elongation factor 1 α 2 at its K408 site enhances its GTPase activity, thereby promoting protein synthesis as well as the proliferation and migration of tumor cells (62). Notably, the lactylation catalytic activity of KAT8 is dependent on intracellular lactate levels, specifically requiring the recognition of lactyl-CoA as a donor. However, knocking down KAT8 significantly reduces the modification level at lactylation sites, without affecting lactate concentration, indicating its direct involvement in the modification process rather than in regulating lactate metabolism. That is, its mechanism of action is to transfer the lactyl group from lactyl-CoA without affecting the metabolism of lactate itself (62). In addition, KAT8-mediated lactylation is also closely associated with collagen synthesis (89) and ferroptosis resistance (90). Meanwhile, KAT2A and KAT5, which are involved in lactylation at various sites, are closely related to processes such as promoting DNA double-strand breaks and chemotherapy resistance (34,37,57).

Although MYST family enzymes, including p300, are widely regarded as major contributors to K1a, their involvement largely reflects a functional extension of classical acetyltransferases rather than a dedicated lactylation system. This repurposed activity exposes several limitations of the CoA-dependent model. First, the intracellular source and abundance of lactyl-CoA remain insufficiently defined, and,

Table II. Regulatory roles of lactylation erasers in cancer.

A, HDAC1						
First author, year	Substrate	Writer	Cancer type	Delactylation function	Inhibitor	(Refs.)
Dai <i>et al</i> , 2025	H3K18	p300	NSCLC	Gene activation ↓	TSA	(24)
Liu <i>et al</i> , 2025	TPX2 K249	CBP	HCC	TPX2 K249la ↓	-	(26)
Shan <i>et al</i> , 2025	SUMO2 K11	AARS1	LUAD	SUMO2 K11la ↓	-	(27)
Han <i>et al</i> , 2025	ASH2L K312	AARS1	HCC	Maintains ASH2L-lac dynamic equilibrium	-	(28)
B, HDAC2						
First author, year	Substrate	Writer	Cancer type	Delactylation function	Inhibitor	(Refs.)
Li <i>et al</i> , 2024	H3K18	p300	PDAC	Reverses chromatin opening	-	(20)
Wang <i>et al</i> , 2025	PD-L1 K189	p300	HCC	Control PD-L1 lactylation level	TSA, CAY-10683	(29)
Lin <i>et al</i> , 2025	NUDT21 K23	AARS1	ESCC	Reduces NUDT21-CPSF6 interaction	-	(30)
He <i>et al</i> , 2025	METTL3 K27	p300	TNBC	DNA damage repair, chemotherapy resistance↑	Tucidinostat	(31)
C, HDAC3						
First author, year	Substrate	Writer	Cancer type	Delactylation function	Inhibitor	(Refs.)
Chen <i>et al</i> , 2024	APOC2 K70	p300	NSCLC	Destabilizes APOC2, FFAs ↓	-	(32)
Dai <i>et al</i> , 2025	YTHDC1 K82	p300	RCC	Disrupt phase separation	TSA	(3)
Lv <i>et al</i> , 2025	H3K18	p300	CRC	Gene activation ↓	-	(33)
Chen <i>et al</i> , 2024	NBS1 K388	KAT5	GC	NBS1 K388la ↓	-	(34)
D, HDAC5						
First author, year	Substrate	Writer	Cancer Type	Delactylation function	Inhibitor	(Refs.)
Li <i>et al</i> , 2025	MRE11 K673	-	TNBC	Radiotherapy efficacy ↑	-	(35)
E, SIRT1						
First author, year	Substrate	Writer	Cancer Type	Delactylation function	Inhibitor	(Refs.)
Ju <i>et al</i> , 2024	YAP K90, TEAD K108	AARS1	GC	YAP transcriptional ↓	NAM	(36)
Jin <i>et al</i> , 2025	XLF K288	GCN5	CRC	NHEJ-mediated DNA repair ↓	NAM	(37)
Zhou <i>et al</i> , 2025	PTBP1 K436	-	GSCs	Progression, maintenance ↓	EX527	(38)
Du <i>et al</i> , 2024	PKM2 K207		HEK293T and HepG2 cell lines	Regulates glycolysis	-	(39)
F, SIRT2						
First author, year	Substrate	Writer	Cancer Type	Delactylation function	Inhibitor	(Refs.)
Sun <i>et al</i> , 2023	METTL16 K229	AARS1	GC	METTL16 activity ↓, cuproptosis ↓	AGK2	(40)
G, SIRT3						
First author, year	Substrate	Writer	Cancer Type	Delactylation function	Inhibitor	(Refs.)
Chen <i>et al</i> , 2025	H3K9	HBO1	ESCC	Tumor suppressor genes transcriptional ↓	3-TYP	(41)

Table II. Continued.

G, SIRT3						
First author, year	Substrate	Writer	Cancer Type	Delactylation function	Inhibitor	(Refs.)
Tang <i>et al.</i> , 2025	MDH2 K239	KAT8	RCC	Mitochondrial function ↓	3-TYP	(42)
Jin <i>et al.</i> , 2023	CCNE2 K348	-	HCC	Growth ↓	-	(43)
Li <i>et al.</i> , 2025	ME2 K352	-	CRC	Disrupts redox balance, growth ↓	NAM	(44)
Fan <i>et al.</i> , 2023	H4K16	-	-	Bind with lactyl-motif	NAM	(45)
Shi <i>et al.</i> , 2025	H3K18	-	Pulmonary fibrosis	NOS2 ↑, M1 polarization	-	(46)
H, SIRT1/SIRT3						
First author, year	Substrate	Writer	Cancer Type	Delactylation function	Inhibitor	(Refs.)
Du <i>et al.</i> , 2024	ENO1 K228	-	HEK293T and HepG2 cell lines	-	-	(39)
I, SIRT6						
First author, year	Substrate	Writer	Cancer Type	Delactylation function	Inhibitor	(Refs.)
Zou <i>et al.</i> , 2025	H3K9	-	GBM	Reverses temozolomide resistance	-	(25)

CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; GSCs, glioma stem cells; HCC, hepatocellular carcinoma; LUAD, lung adenocarcinoma; NAM, nicotinamide; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer; 3-TYP, 3-(1H-1,2,3-triazol-4-yl)pyridine; AGK2, 2-cyano-3-[5-(2,5-dichloro phenyl)-2-furanyl]-N-5-quinolinyl-2-propenamide; EX527, selisistat; NAM, nicotinamide; TSA, trichostatin A.

even under optimized conditions, its level is markedly lower than that of acetyl-CoA (~1/1,000) (91), suggesting that CoA-dependent lactylation may occur only within restricted metabolic niches. Second, since these enzymes use both acetyl-CoA and lactyl-CoA, K1a inevitably competes (92) or synergizes (75) with Kac at shared lysine residues, raising unresolved questions regarding how these PTMs are selectively regulated. These constraints indicate that CoA-dependent acyltransferases may not fully account for the efficiency or specificity of K1a, suggesting the potential existence of non-enzymatic pathways that influence the progression of this modification.

Alanyl-tRNA synthetases 1 and 2 (AARS1/2): CoA-independent lactylation enzymes. In contrast to lactyl-CoA-dependent HATs, AARS1/2 represent a mechanistically distinct class of lactylation writers and their identification has resolved the dilemma of lactyl-CoA scarcity. AARS1 functions as a direct lactate sensor; it binds to L-lactate and utilizes ATP to catalyze the formation of a lactyl-AMP intermediate, subsequently transferring the lactyl group covalently to the lysine residues of target proteins and releasing AMP (93). Previous molecular docking research has shown that conserved residues within AARS1 (M46, R77, N216 and D239) directly bind lactate in a reaction that requires only L-lactate and ATP (23). This mechanism is considerably more direct than that proposed for p300 and explains the presence of active

lactylation in tumor tissues where a lactyl-CoA-producing enzyme had not been previously identified.

AARS1 and AARS2 have different intracellular localizations and thus regulate distinct biological processes. AARS1 is primarily distributed in the cytoplasm and nucleus. In the nucleus, it can lactylate key oncoproteins, such as yes-associated protein (YAP) and TEA domain transcription factor 1, thereby activating the Hippo signaling pathway and promoting GC cell proliferation (36). Concurrently, AARS1 can also lactylate the tumor suppressor p53, which inhibits its DNA-binding ability and transcriptional activity, thereby impairing its tumor-suppressive function (23). By contrast, AARS2 is localized to the mitochondria and it regulates key enzymes involved in mitochondrial aerobic metabolism, such as pyruvate dehydrogenase E1 α subunit 1 and carnitine palmitoyltransferase 2, through lactylation, thereby reducing their activity and suppressing oxidative phosphorylation (OXPHOS). In a high-lactate environment, this inhibition of OXPHOS decreases cellular oxygen consumption and enhances resistance to mitochondrial oxidative stress, ultimately facilitating tumor cell adaptation to metabolic stress conditions (94).

AARS1-mediated lactylation is also closely linked to therapeutic resistance. In bladder cancer cells under high-glucose conditions, lactylation of YTHDC1 downregulates JunD proto-oncogene, AP-1 transcription factor subunit and reduces Nectin4 expression, thereby diminishing the sensitivity of

the cells to the Nectin4-targeted antibody-drug conjugate, enfortumab vedotin (55). Lactylation of the key homologous recombination (HR) helicase BLM RecQ like helicase (BLM) at K24 prevents its ubiquitin-dependent degradation, thereby stabilizing the protein and promoting DNA end resection and HR repair, ultimately leading to chemoresistance to anthracyclines (56). Furthermore, lactylation of nudix hydrolase 21 at K23 induces 3'-untranslated region lengthening of ferredoxin 1 (FDX1) mRNA, resulting in reduced protein expression. The decreased FDX1 levels weaken the capacity of FDX1 to reduce Cu^{2+} to the more cytotoxic Cu^+ , thereby conferring resistance to cuproptosis in esophageal squamous cell carcinoma (ESCC) (30).

These findings indicate that AARS1 functions far beyond a simple writer enzyme; it serves as a central hub integrating metabolic signaling, protein synthesis and oncogenic pathways. Canonically, AARS1 catalyzes the attachment of alanine to its cognate tRNA, initiating protein synthesis. However, under high-lactate conditions, lactate competes with the traditional substrate L-alanine for binding to the active site of AARS1, allowing it to operate as a lactyltransferase (23,95). This functional shift effectively translates metabolic signals into long-term activation of oncogenic pathways and malignant phenotypes. Mechanistically, the lactyltransferase activity of AARS1 depends on its nuclear translocation, which requires a C-terminal, evolutionarily conserved nuclear localization signal (NLS) motif. The importin protein karyopherin subunit alpha 4 binds to this NLS, allowing AARS1 to enter the nucleus (36). Therefore, blocking AARS1 nuclear translocation can selectively disrupt tumor cell signaling without affecting normal cellular lactate metabolism, thus representing a promising therapeutic strategy.

However, AARS1 appears to lack a highly specific recognition mechanism for lactate and may not distinguish it from homologous amino acids such as serine and glycine, potentially leading to confounding effects from other amino acid modifications (93). Furthermore, the lactylation of targets by AARS1 may not be precise, as its substrate scope appears to be broad, possibly leading to the simultaneous lactylation of numerous other proteins that could also promote tumor progression (23).

Acyl-CoA synthetase short-chain family member (ACSS2) and GTP-specific succinyl-CoA synthetase (GTPSCS): Providers of lactyl-CoA. Recent research has identified several enzymes responsible for synthesizing lactyl-CoA, thereby confirming the physiological relevance and research potential of the CoA-dependent pathway.

ACSS2. ACSS2 is the first identified mammalian lactyl-CoA synthetase (93); it can convert lactate produced by lactate dehydrogenase (LDH)A into lactyl-CoA and works in concert with the histone lactyltransferase KAT2A to catalyze the lactylation of histone H3 at the K14 and K18 sites. The complex formed by the binding of LDHA-ACSS2-KAT2A can act on the promoter regions of key genes in pathways such as the Wnt signaling, NF- κ B signaling and PD-L1 pathways, thus promoting the proliferation and growth of glioma (96). Notably, KAT2A can directly bind to lactyl-CoA, with the R533 residue forming a hydrogen bond with the -OH group of the lactyl moiety, which shows greater selectivity compared

with its binding to acetyl-CoA (96). This selectivity implies that for acyltransferases like the MYST family, the equilibrium between K1a and Kac is largely determined by the local concentration of respective acyl-CoA substrates competing for conserved catalytic sites.

GTPSCS. GTPSCS has also been identified as a lactyl-CoA synthetase in glioma. After entering the nucleus, it binds with p300 to form a lactyltransferase complex. A hydrogen bond at the N308 site binds to lactate to generate lactyl-CoA, specifically enhancing H1a (such as H3K181a), thereby upregulating the expression of growth differentiation factor 15 and driving glioma proliferation and radiotherapy resistance (47).

The identification of these enzymes provides a solid biochemical foundation for the lactyl-CoA-dependent lactylation pathway, resolving the issue of lactyl-CoA production; it indicates that cells have evolved specialized mechanisms to ensure that, when needed, these regulatory enzymes can undergo nuclear translocation, provide an adequate supply of lactyl-CoA substrate and act in concert with downstream lactyl-CoA transferases (such as p300) to achieve precise epigenetic regulation of specific genes.

Erasers: Lactylation-removing enzymes. Histone deacetylases (HDACs) comprise a family of 18 enzymes. Notably, specific members, particularly the class I HDACs (HDAC1-3) and the class III sirtuins (SIRT1-3), have been confirmed to possess robust delactylase activity.

Class I HDACs: HDAC1-3. Members of the HDAC family are the primary erasers of lactylation. Specifically, class I HDACs (HDAC1, HDAC2 and HDAC3) have been confirmed to possess strong delactylase activity. The catalytic activity of classical HDACs (classes I, II, and IV) is dependent on a Zn^{2+} located at the bottom of the active site pocket. This ion activates the carbonyl bond of the lactyl group, making it easier for water molecules to hydrolyze it through nucleophilic attack. This mechanism is structurally comparable to their conventional deacetylation action; both processes restore chromatin to its compact shape and repress gene transcription (97,98). Among these enzymes, HDAC3 exhibits the strongest activity and can remove both L- and D-isomers of lactylation (98). HDAC1-3 can reduce the K1a levels of H1a (20,24,33) and n-H1a (26,30,34), acting as negative regulators in this process. For instance, HDAC3 associates with p300 and Brahma-related gene 1 (Brg1), which is a key chromatin remodeling factor, to control the expression of H3K181a. This activates ETS-related gene and MMP9, which leads to liver metastasis in CRC (33).

In addition, deacetylation modifications can also promote malignant cancer progression. HDAC2 is deeply involved in regulating multiple K1a-mediated mechanisms of therapeutic resistance. Specifically, HDAC2-driven delactylation of methyltransferase-like 3 (METTL3), a key m⁶A RNA methyltransferase, enhances m⁶A methylation associated with DNA damage repair, contributing to cisplatin resistance in triple-negative breast cancer (31). Furthermore, HDAC2 decreases p300-mediated PD-L1 K1891a, thereby promoting PD-L1 nuclear translocation and cholesterol biosynthesis, which in turn drives hepatocellular carcinoma (HCC) growth (29). Moreover, HDACs display broad substrate adaptability, showing robust activity not only against L-lactylation

but also against D-lactylation and various other short-chain acyl modifications (97).

Class III SIRT5: SIRT1-3. Beyond the zinc-dependent HDACs, the SIRT family of class III NAD⁺-dependent deacetylases also participate in the delactylation process; they achieve the removal of lactyl groups by consuming NAD⁺ and generating nicotinamide (NAM) along with 2'-O-lactyl-ADP-ribose (99). This mechanism suggests that NAM could serve as a non-selective deacetylase inhibitor to reverse the delactylation process, thereby controlling SIRT family activity (100). SIRT activity is linked to intracellular NAD⁺ concentrations, affecting lactylation stability and energy levels (43,101). SIRT2 has been previously identified as a key delactylase that removes the lactyl group from pyruvate kinase M2 (PKM2)-derived synthetic peptides (99). In the neuroblastoma cell model (SH-SY5Y neuroblastoma cells), the catalytic activity of SIRT2 is significantly higher than that of SIRT1 and SIRT3, and its activity can be inhibited by Tenovin-6 (102). In GC, SIRT2 reverses METTL16 K229la, thereby preventing cuproptosis (40). A previous study on HCC cell lines has expanded the current understanding of SIRT5, showing that SIRT1 specifically regulates PKM2 K207la, while SIRT1 and SIRT3 cooperatively regulate Enolase 1 K228la, thus controlling glycolytic flux (99). In addition, the demodifying activity of SIRT3 has been observed in HCC, CRC and renal cancer (42-44).

SIRT6 has been reported to be involved in the delactylation of H3K9 and H3K18, demonstrating a complementary role with class I HDACs in deacylation. While single knockout of SIRT6 does not significantly elevate global histone acetylation levels, H3K9 acetylation markedly increases when SIRT6 is knocked out concurrently with HDAC inhibition. This indicates a functional compensation or overlap between SIRT6 and HDACs in deacetylation (103). Furthermore, previous research indicates that NAM has no significant effect on either the delactylation activity in cell lysates or on intracellular K1a levels, which suggests that HDAC1-3 may function as the primary intracellular erasers for lactylation, rather than SIRT5 (98).

Readers: Recognizing and binding proteins. Reader proteins of protein lactylation specifically recognize and bind to lactyl groups, thereby influencing gene expression and cellular activities by modulating chromatin structure or protein function. Research on K1a reader proteins remains limited. Drawing parallels from Kac studies, readers primarily include proteins containing bromodomains [BRDs; such as BRD4 and tripartite motif containing 33 (TRIM33)], plant homeodomain (PHD) zinc finger domains (such as bromodomain PHD finger transcription factor) and YEATS domains.

Brg1. Brg1 is a core subunit of the BAF (Brg1/Brm-associated factor) chromatin remodeling complex and specifically recognizes and marks H3K18la during the reprogramming of induced pluripotent stem cells (33,104). Brg1 collaborates with Dux proteins to promote metabolic reprogramming and mesenchymal-to-epithelial transition; it also recruits writer enzymes such as p300/CBP, forming a positive feedback loop that further upregulates H3K18la levels, thus enhancing chromatin accessibility and transcriptional activity (104). A previous study has shown that the long non-coding RNA (lncRNA) STEAP3-AS1 may

regulate Brg1 in H3K18la, leading to liver metastasis in CRC (33). This suggests that readers do not control the K1a process independently; instead, the lactylation signal needs to be recognized and marked by a reader, which then recruits powerful chromatin remodeling machinery to execute subsequent functions.

Double PHD finger protein 2 (DPF2). DPF2 was one of the first highly specific lactylation reader proteins to be identified (105). DPF2 is a member of the BAF chromatin regulatory complex and has been identified as a specific reader that regulates H3K14 lactylation in cervical cancer (CC); its double PHD finger domain directly binds to H3K14la through hydrogen bonds and hydrophobic interactions, showing no affinity for the structurally similar H3K14 acetylation, thus exhibiting high specificity. Functionally, DPF2 is recruited by H3K14la to the promoter regions of genes, where it recruits the BAF chromatin remodeling complex to activate the transcription of the downstream target oncogenes MYC and cyclin cyclin D1, thereby driving cell proliferation and progression in cancer types such as CC (105). However, a limitation of the aforementioned study is that it did not clarify whether DPF2 recognizes and binds H3K14la independently or relies on the BAF complex, with DPF2 merely serving as a key binding site. An important future direction of research will be to determine whether DPF2 recognizes H3K14la independently or as part of the BAF complex, and to what extent this specific recognition mechanism is conserved across different cancer types

TRIM33. BRDs are a classic reader module for acetylated lysine, present in >40 human proteins, which plays a core role in transcriptional regulation (106,107). The BRD of TRIM33 achieves high-affinity binding with K1a by forming a hydrogen bond between a unique glutamate residue (E1041) in its binding pocket and the hydroxyl group of K1a. The PHD domain of TRIM33 recognizes H3K9me3, while its BRD binds H3K18ac or K1a. This 'multi-recognition' further enhances its ability to recognize and bind chromatin, enabling it to translate metabolic signals from lactate into epigenetic regulation at the chromatin level, making it a potential therapeutic target for diseases associated with metabolic-epigenetic dysregulation (108). Since BRDs can recognize both acetylation and lactylation sites (for example, BRD4 is involved in the malignant progression caused by both K1a and Kac) (109,110), BRD4 inhibitors such as JQ1 (111) are likely to inhibit both signals simultaneously, achieving a multi-inhibitory effect. This could play a broad role in various cancer types caused by metabolic reprogramming.

Although research on the readers of K1a is still in its early stages, these proteins are becoming recognized as the main reason for the specific recognition and downstream signaling of this modification. Reader proteins have the unique ability to bind to the lactyl group and send its signal to downstream gene targets. This is different from the less specific writer and eraser enzymes, which often control multiple types of acyl modifications. This intrinsic specificity indicates that targeting the distinct binding sites of reader proteins constitutes a highly attractive therapeutic approach, potentially providing a more accurate intervention than the inhibition of the generally active writers and erasers. Fig. 2 depicts the structural interplay of the 'writer-eraser-reader' system, demonstrating how these

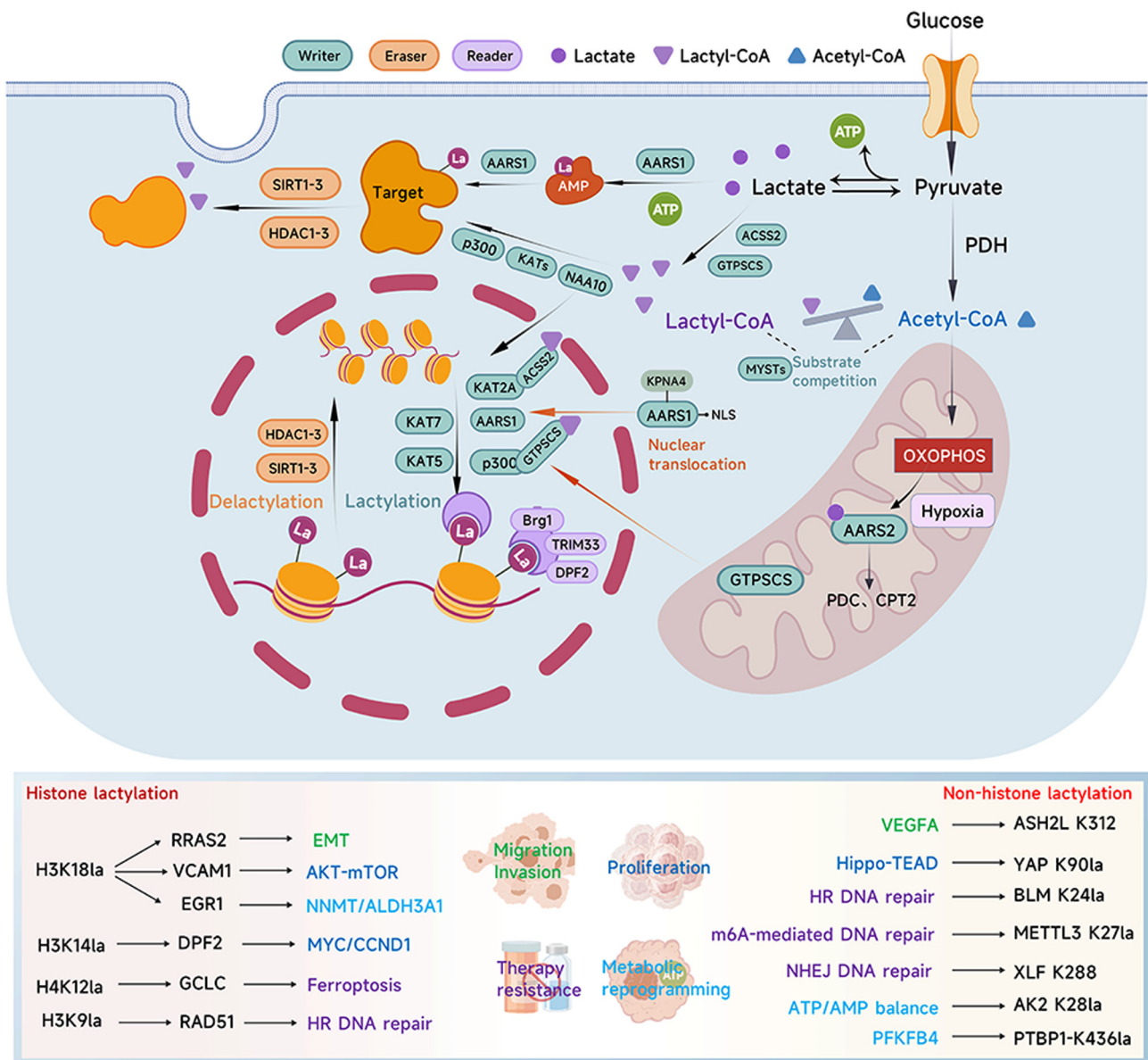


Figure 2. Enzymatic machinery of protein lactylation. Lactylation is dynamically regulated by three classes of enzymes: writers (green boxes), which install lactyl groups; erasers (orange boxes), which remove lactylation; and readers (purple boxes), which recognize lactylated substrates to trigger downstream effects. Lactylation regulatory enzymes in cancer (including p300, AARS1/2 and HDACs) achieve precise and context-dependent control through multiple mechanisms, such as substrate competition between lactyl-CoA and acetyl-CoA, differential subcellular localization and crosstalk with metabolic and oncogenic signaling pathways. These coordinated layers of regulation govern both histone and non-histone lactylation, ultimately shaping tumor-associated outcomes illustrated in the lower panel, including proliferation, migration and invasion, metabolic reprogramming and therapy resistance. AARS1/2, alanyl-tRNA synthetase 1/2; HDACs, histone deacetylases; SIRT, sirtuins; La, lactate; KATs, lysine acetyltransferases; PDH, pyruvate dehydrogenase; NAA10, N-alpha-acetyltransferase 10; GTPSCS, succinyl-CoA synthetase (GTP-forming); MYSTs, MYST family of histone acetyltransferases; OXOPHOS, oxidative phosphorylation; PDC, pyruvate dehydrogenase complex; CPT2, carnitine palmitoyltransferase 2; KAT2A, lysine acetyltransferase 2A; KAT7, lysine acetyltransferase 7; Brg1, Brahma-related gene-1; TRIM33, tripartite motif-containing 33; DPF2, double PHD fingers 2; RRAS2, related RAS viral oncogene homolog 2; EMT, epithelial-mesenchymal transition; VCAM1, vascular cell adhesion molecule 1; EGR1, early growth response 1; NNMT, nicotinamide N-methyltransferase; ALDH3A1, aldehyde dehydrogenase 3 family member A1; CCND1, cyclin D1; GCLC, glutamate-cysteine ligase catalytic subunit; HR, homologous recombination; ASH2L, absent small and homeotic 2-like; YAP, Yes-associated protein; BLM, Bloom syndrome helicase; METTL3, methyltransferase-like 3; NHEJ, non-homologous end joining; XLF, XRCC4-like factor; AK2, adenylate kinase 2; PFKFB4, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 4; PTBP1, polypyrimidine tract binding protein 1.

enzymes coordinate to translate intracellular lactate levels into precise gene expression outcomes.

Non-enzymatic reactions. Three isomers of K1a have been reported: L-lactyl-lysine (K1-la), D-lactyl-lysine (Kd-la) and N-ε-(carboxyethyl)lysine (Kce). While K1-la is enzymatically regulated and serves as the dominant form due to the abundance

of L-lactate in mammalian cells (112,113), Kd-la and Kce are generated through non-enzymatic mechanisms central to the metabolism of the glycolysis byproduct methylglyoxal (MGO). Kce is formed through the direct binding of MGO to lysine residues. Concurrently, MGO is catalyzed by glyoxalase 1 (GLO1) to conjugate with glutathione, forming S-D-lactoylglutathione (LGSH), which is subsequently hydrolyzed by GLO2 to

produce D-lactate. The generation of the reactive intermediate LGSH can lead to the non-enzymatic lactylation of lysine residues, forming Kd-la (114,115). This process is driven directly by LGSH and does not depend on traditional lactyl-transferases. Since mammalian LDH and glycolysis almost exclusively produce L-lactate (113), the physiological pool of D-lactate is generally limited. Apart from the MGO pathway, D-lactate is primarily derived from carbohydrate fermentation by gut microbiota such as *Lactobacilli* (116).

Current evidence indicates that, in HCC, D-lactate activates macrophages to induce TNF- α and IL-6 production, remodeling the TME by regulating M2 TAMs into an immunosuppressive state (117,118). In ESCC, cancer cells upregulate LDHD to metabolize D-lactate into pyruvate. This metabolic adaptation meets energy demands and facilitates the evasion of D-lactate-induced ferroptosis, highlighting LDHD as a viable therapeutic target (119). Furthermore, both L- and D-lactate have been shown to facilitate DNA repair and confer resistance to anticancer therapy in CC cells via HDAC inhibition and hydroxycarboxylic acid receptor 1 activation (120). Crucially, the structural similarity between L- and D-lactate suggests a potential for crosstalk and competition. D-lactate has been observed to promote H3K18la levels (121), raising the possibility that D-lactate or its derivatives could competitively bind to the active pockets of writers, erasers or readers, thereby interfering with the regulation of L-lactylation. Whether this interaction represents a synergistic amplification of lactylation signaling or an antagonistic blockade remains to be further investigated. Given that D-lactate participates primarily via non-enzymatic routes while L-lactate relies on enzymatic transfer (4,112), precise experimental designs are required to dissect the specific contributions of lactyl-CoA-dependent vs. -independent pathways.

From a therapeutic perspective, GLO1 emerges as a potential therapeutic target (122). Existing GLO1 inhibitors, such as S-p-bromobenzylglutathione cyclopentyl diester, can potentiate the efficacy of other therapies and have shown promise in various tumor types, including soft tissue sarcoma and chronic lymphocytic leukemia (123,124), suggesting their potential value as a reference for developing interventions against lactylation.

5. Clinical translation and therapeutic potential

Targeting lactate metabolism. As lactate can be converted to lactyl-CoA, the direct substrate for lactylation, the most effective intervention strategy is to inhibit its production and transport at the source with the aim of reducing lactate accumulation in the TME, thereby diminishing the substrate supply for downstream K_{la}.

Firstly, the glycolytic inhibitor 2-deoxy-D-glucose (2-DG) suppresses hexokinase activity and blocks the glycolytic flux, leading to a reduction in site-specific lactylation. 2-DG suppresses LUAD progression (125) and restores lenvatinib sensitivity by disrupting the insulin-like growth factor 2 mRNA-binding protein 3 - phosphoenolpyruvate carboxykinase 2 - S-adenosylmethionine - m⁶A feedback loop in HCC (80). Secondly, targeting LDH directly limits the conversion of pyruvate to lactate. LDH inhibition suppresses the lactylation of DNA repair proteins such as meiotic

recombination 11-K673la (126) and Nijmegen breakage syndrome 1-K388la (34), impairing HR and enhancing chemosensitivity. The LDH inhibitor GSK2837808A blocks mitochondrial Mic60-K282la, disrupts cristae remodeling and oxidative metabolism and restores sensitivity to EGFR-tyrosine kinase inhibitors (127). Oxamate, another LDH inhibitor, reduces lactate accumulation and alleviates immunosuppression within the TME by blocking H3K18la, thereby enhancing chimeric antigen receptor T cell activity in glioblastoma (128). Combined treatment with 2-DG and oxamate further suppresses H3K18la, augments CD8⁺ T cell cytotoxicity and prevents immune evasion in non-small cell lung cancer (NSCLC) (129). Finally, blocking lactate shuttling across the plasma membrane disrupts metabolic symbiosis between tumor and stromal cells, reversing the acidic TME. The MCT4 inhibitor VB124 (130) and the glucose transporter 1 inhibitor BAY-876 (131) have shown promising prospects. The dual MCT1/4 inhibitor 7ACC1 suppresses oxaliplatin resistance by preventing lactate transfer from cancer-associated fibroblasts and inhibiting anthrax toxin receptor 1-K453la (132).

Despite encouraging preclinical evidence, the safety and efficacy of these inhibitors require validation through large-scale animal models and clinical trials. Notably, a phase I clinical trial of the MCT1 inhibitor AZD3965 for advanced solid tumors (NCT01791595) has been completed, laying the groundwork for future clinical development. Fig. 3 summarizes representative inhibitors acting on key metabolic nodes, while Table III summarizes representative inhibitors targeting enzymes involved in lactate metabolism and protein lactylation, along with their inhibitory potency and the cancer models evaluated (133-156).

Conventional inhibitors. At present, commonly used small molecule inhibitors for p300/CBP are primarily A-485 (67,86) and C646 (51). These highly selective and cell-permeable catalytic inhibitors of p300/CBP competitively bind to their HAT domain thereby inhibiting acyl transfer, and have shown good efficacy in various cancer types, including HCC, PDAC, CRC and BC (49,51,52,73).

The range of HDAC inhibitors is more extensive. By binding to Zn²⁺, they prevent HDACs from removing acetyl groups, which promotes K_{ac} and subsequently activates the expression of tumor suppressor genes, resulting in favorable antitumor effects. Several compounds, including vorinostat and romidepsin, which inhibit multiple HDACs, have been approved by the FDA due to their excellent performance in treating cutaneous (157) and peripheral (158) T-cell lymphoma. The SIRT2-specific inhibitor AGK2 enhances the METTL16 K229la-mediated m⁶A modification of FDX1 mRNA, thereby promoting cuproptosis. When combined with the copper ionophore elesclomol, this strategy effectively augments cuproptosis in GC tumors, achieving a notable therapeutic effect (40). However, the majority of deacetylation modifications generally exert a suppressive effect on cancer progression. Therefore, the use of deacetylase inhibitors alone may not achieve satisfactory therapeutic outcomes, as HDAC inhibition often leads to increased lactylation and may exacerbate tumor malignancy. Selecting HDAC activators may be a better choice. For instance, the specific SIRT1 activator SRT2104, in

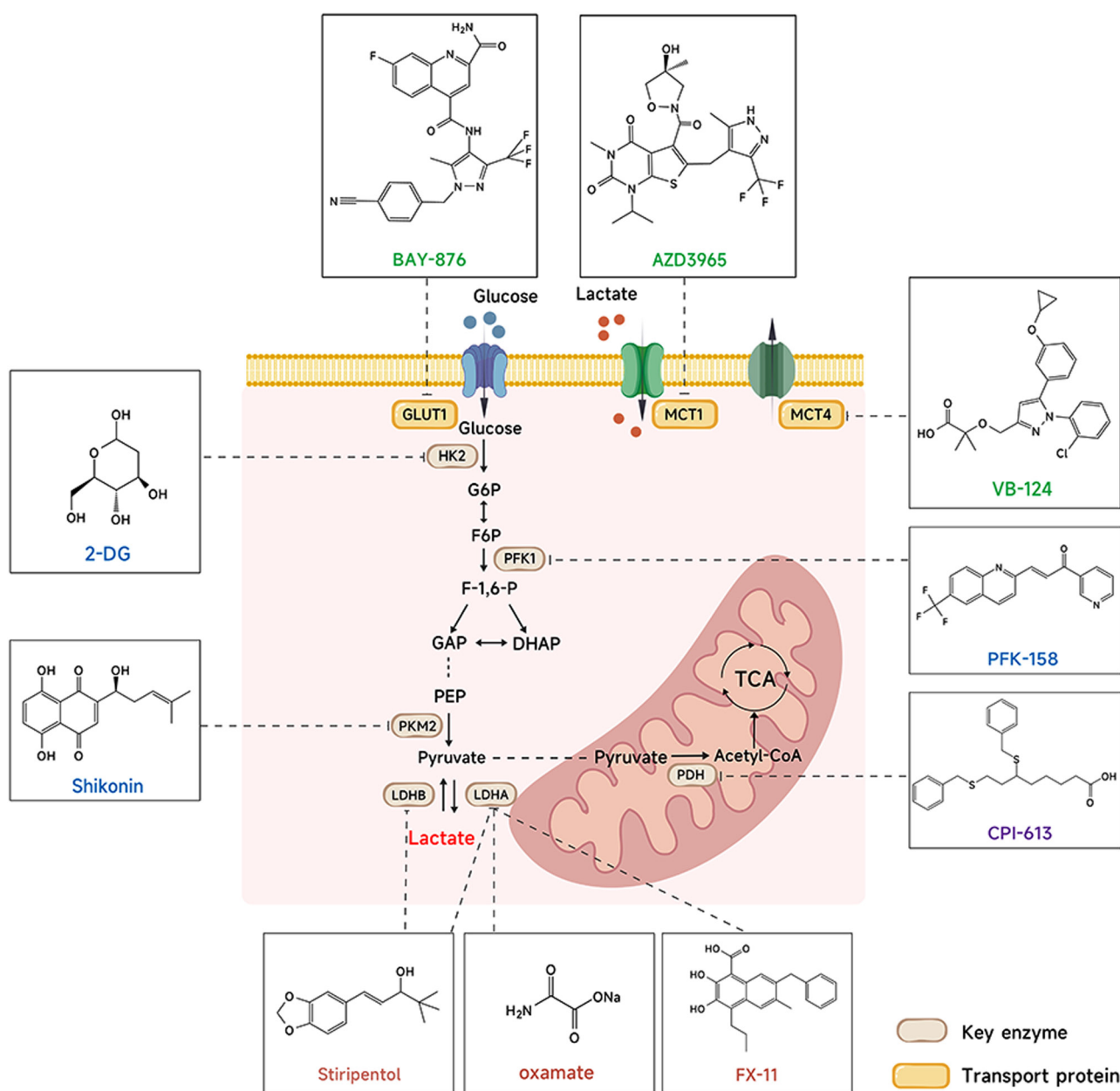


Figure 3. Therapeutic strategies targeting lactate metabolism. The small-molecule inhibitors depicted target key enzymes and transporters. Representative inhibitors are indicated alongside their molecular structures, including BAY-876 (GLUT1 inhibitor), 2-DG (HK2 inhibitor), PFK-158 (PFKFB3 inhibitor), Shikonin (PKM2 inhibitor), Stiripentol, Oxamate and FX-11 (LDHA/B inhibitors), CPI-613 (pyruvate dehydrogenase/ α -ketoglutarate dehydrogenase inhibitor), AZD3965 (MCT1 inhibitor) and VB-124 (MCT4 inhibitor). This approach seeks to reduce lactate accumulation and disrupt the metabolic-epigenetic axis that drives tumor progression. 2-DG, 2-deoxy-D-glucose; GLUT1, glucose transporter 1; HK2, hexokinase 2; MCT, monocarboxylate transporter; G6P, glucose-6-phosphate; F6P, fructose-6-phosphate; PFK1, phosphofructokinase 1; F-1,6-P, fructose-1,6-bisphosphate; GAP, glyceraldehyde-3-phosphate; DHAP, dihydroxyacetone phosphate; PEP, phosphoenolpyruvate; PKM2, pyruvate kinase M2; LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase.

combination with the LDHA inhibitor oxamate, successfully blocks the malignant progression of GC mediated by H3K18la, showing significant antitumor effects with minor adverse reactions (159). Meanwhile, by employing a platelet membrane-coated biomimetic PLGA nanodelivery system for intranasal administration, co-loading of the SIRT3 activator resveratrol and curcumin enabled targeted enrichment in lipopolysaccharide-induced inflamed lung tissue. This strategy significantly reduced the Hla levels in the lung, thereby decreasing vascular permeability and tissue injury, suppressing the expression of pro-inflammatory cytokines and promoting the polarization of pulmonary macrophages

from the M1 to the M2 phenotype (160). However, there is currently a lack of sufficient related research.

Proteolysis-targeting chimeras (PROTACs): *Precise targeting of regulatory enzymes.* Due to the challenges posed by the functional overlap and off-target effects of conventional small-molecule inhibitors, developing novel therapeutic modalities that afford high-specificity regulation has become a key research priority. In this context, targeted protein degradation technologies such as PROTACs have emerged as particularly promising strategies. PROTACs are hetero-bifunctional molecules that link a target protein to an E3 ubiquitin

Table III. Pharmacological inhibitors targeting lactate metabolism and lactylation regulatory enzymes.

A, Lactate metabolic enzyme inhibitors

First author, year	Inhibitors	Target	IC ₅₀ (μM)	Assay system	Detection method	Cancer type	(Refs.)
Wang <i>et al.</i> , 2021	BAY-876	GLUT1	24.31, 18.72, 21.62	T24, EJ, 5637	MTT	BLCA	(134)
Sołtyka-Krajewska <i>et al.</i> , 2024	2-DG	HK2	5000	U-251	MTS	GBM	(135)
Mondal <i>et al.</i> , 2019	PFK-158	PFKFB3	0.137	C13, HeyA8MDR	-	OC	(136)
Biswal <i>et al.</i> , 2025	Shikonin	PKM2	0.5, 1.25	SCC9, H357	MTT	HNSCC	(137)
Giraud <i>et al.</i> , 2006	Stiripentol	LDHA/B	1.58, 3.29	Patients with SMEI	Enzyme inhibition assay	-	(138)
Azizzadeh <i>et al.</i> , 2025	Oxamate	LDHA	8617	Mia-Paca-2, AsPc-1	MTT	PDAC	(139)
Mohammad <i>et al.</i> , 2019	FX-11	LDHA	49.27, 60.54	BxPc-3, M1a PaCa-2	MTS	PDAC	(140)
Aktepe and Yukselten, 2022	AT101	LDHA	150.5	DU-145, PC-3, LNCAP	XTT	PCa	(141)
Gao <i>et al.</i> , 2020	CPI-613	PDH, α-KGDH	200	AsPC-1, PANC-1	MTT	PDAC	(142)
Guo <i>et al.</i> , 2021	AZD3965	MCT1/2	28.37, 12.84, 23.61	A498, SLR-21, Caki-2	CCK-8	RCC	(143)
Cluntun <i>et al.</i> , 2021	VB124	MCT4	0.0086 ^a , 0.019 ^b	MDA-MB-231	Fluorescence-based activity assays	BC	(144)

B, Lactylation regulatory enzyme inhibitors

First author, year	Inhibitors	Target	IC ₅₀ (μM)	Assay system	Detection method	Cancer type	(Refs.)
Michaelides <i>et al.</i> , 2017	A-485	p300	0.067	PC-3	Radioactive enzymatic assay	PC	(146)
Liu <i>et al.</i> , 2019	C646	p300	0.23	T47D, MCF7	AlphaLISA	BC	(147)
Xiang <i>et al.</i> , 2018	SGC-CBP30	CBP/p300	0.08	LNCaP, 22Rv1	AlphaScreen assay	PCa	(148)
Biel <i>et al.</i> , 2004	MB-3	GCN5	100	-	<i>Vitro</i> enzymatic assay	-	(149)
Al-Qazzan <i>et al.</i> , 2025	β-alanine ^c TSA	AARS1 HDACs	- 14.0-27.0	- CACO2, HCT116, SW620, HT29	- SRB colorimetric assay	- CRC	- (150)
Pun <i>et al.</i> , 2022	SAHA	HDACs	0.2 ^d , 0.24 ^e , 1 ^f	HeLa recombinant enzymes	Fluorometric enzymatic assay	CC	(151)
Ning <i>et al.</i> , 2012	Tucidinostat	HDACs	0.095-0.733 ^g	Recombinant enzymes	Fluorometric enzymatic assay	-	(152)
Song <i>et al.</i> , 2025	Romidepsin	HDACs	0.000001-0.419 ^h	Recombinant enzymes	Fluorometric enzymatic assay	-	(153)
Hwang and Song, 2017	NAM	SIRT1/2	50-180	Recombinant enzymes	NAM inhibition assay	-	(154)
Spinck <i>et al.</i> , 2021	Selisistat	SIRT1	0.048, 0.5, 6.4 ⁱ	MDA-MB-231	Luminescence assay	BC	(155)

Table III. Continued.

B, Lactylation regulatory enzyme inhibitors

First author, year	Inhibitors	Target	IC ₅₀ (μM)	Assay system	Detection method	Cancer type	(Refs.)
Bai <i>et al</i> , 2018	AGK2	SIRT2	80.2, 47.6	Hs 683, U373	MTT	Glioma	(156)
Wang <i>et al</i> , 2026	Tenovin-6	SIRT2	4.84, 4.30, 5.23	OVCAR3, A2780, SKOV3	CCK8	OC	(145)
Galli <i>et al</i> , 2012	3-TYP	SIRT3	4.7	HeLa	MTT	CC ^j	(133)

^aLactate import. ^bLactate export. ^cβ-alanine acts as a structural analog of lactate, inhibiting AARS1 through competitive binding at the active site. Since it is not a classic, high-affinity inhibitor and its mechanism is substrate-dependent, an IC₅₀ value is generally not reported. ^dHDACs from HeLa cell lysate. ^eRecombinant HDAC3. ^fRecombinant HDAC8. ^gHDAC1=0.095, HDAC2=0.160, HDAC3=0.067, HDAC10=0.078, HDAC8=0.733 and HDAC11=0.432. ^hHDAC1=0.000098, HDAC2=0.000161, HDAC3=0.000104, HDAC8=0.000402 and HDAC6=0.419. ⁱSIRT1=0.048, SIRT2=0.5 and SIRT3=6.4. ^jUnder a screen of 60 tumor cell lines, 3-TYP exhibited significant growth suppression in 5 cancer cell lines (CCRF-CEM, COLO205, OVCAR-4, OVCAR-8 and SK-OV-3), while showing no notable effect on the viability of the other 45 lines. SMEI, severe myoclonic epilepsy in infancy; AlphaLISA, amplified luminescent proximity homogeneous assay; BC, breast cancer; BLCA, bladder cancer; CC, cervical cancer; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; GBM, glioblastoma; GSCs, glioma stem cells; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; LUAD, lung adenocarcinoma; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PCa, prostate cancer; PDAC, pancreatic ductal adenocarcinoma; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer; HepG2, human liver cancer cell line; NAM, nicotinamide; SAHA, suberoyl-anilide hydroxamic acid; TSA, trichostatin A; α-KGDH, α-ketoglutarate dehydrogenase; GLUT1, glucose transporter 1; HK2, hexokinase 2; LDHA/B, lactate dehydrogenase A/B; MCT1/2/4, monocarboxylate transporter 1/2/4; PDH, pyruvate dehydrogenase; PFKFB3, 6-phospho-fructo-2-kinase/fructose-2,6-biphosphatase 3; PKM2, pyruvate kinase M2.

ligase, inducing the ubiquitination of the target protein and its subsequent degradation by the proteasome. With their potential for lower toxicity and the ability to overcome drug resistance, PROTACs may represent a superior alternative to conventional small-molecule inhibitors (145,161). For instance, the PROTAC hexokinase 2 (HK2) degrader-1 has been shown to overcome the limited efficacy of the traditional glycolysis inhibitor 2-DG, which arises from substrate competition. This approach effectively inhibits glycolysis and reduces lactate levels, causing a significant decrease in downstream H3K18la levels, reversing the EndMT process and markedly alleviating the progression of atherosclerosis in a mouse model (88).

Some progress has already been made in developing PROTACs that target specific lactylated sites (54,162). For instance, the PROTAC BP3 targets tumor necrosis factor receptor-associated protein 1 degradation, thereby alleviating vascular smooth muscle cell senescence and atherosclerosis induced by H4K12la (162). In lactylation-driven tumors, this strategy focuses on degrading key downstream effector proteins to halt malignant progression. For example, H3K18la is known to upregulate aurora kinase B (65) and acetyl-CoA acetyltransferase 2 (ACAT2) (54). Consequently, PROTACs targeting these proteins could potentially enhance anti-tumor efficacy. Specifically, in PDAC, the ACAT2-targeting degrader API reverses cholesterol-linked immunosuppression driven by the H3K18la/ACAT2/mitochondrial carrier 2 axis. Furthermore, combining API with anti-programmed cell death protein 1 (anti-PD-1) therapy was shown to significantly inhibit tumor growth and restore antitumor immunity in a previous study (54).

However, extending this concept to the lactylation regulatory enzymes themselves offers a more upstream intervention

strategy. This approach allows for the elimination of the entire protein, including its non-catalytic scaffolding functions and protein-protein interaction capabilities. This is particularly important for multi-domain proteins such as p300/CBP and HDACs, achieving results that traditional small-molecule inhibitors cannot match. Notably, PROTACs targeting these enzymes have already demonstrated significant translational potential in Kac. For instance, the p300/CBP degrader dCBP-1 (163) exhibited significantly superior anti-proliferative activity in multiple myeloma cells compared with catalytic or BRD inhibitors (A-485 and GNE-781). Similarly, previous research on HDACs indicates that optimizing linkers and selecting appropriate E3 ligases can yield highly specific degraders, thus underscoring the design flexibility of this technology (161). A recent study reported the development of a series of SIRT2-directed PROTAC degraders derived from the conventional inhibitor Tenovin-6. The lead compound, W10, catalyzed target protein degradation and demonstrated potent anti-proliferative activity across multiple ovarian cancer cell lines. Notably, this approach enhanced the anticancer activity of W10 by ~53-fold compared with its parent inhibitor Tenovin-6 and no pathological organ damage was observed in mouse models (145).

Since PROTACs target the entire protein for degradation, they offer a more precise intervention than traditional inhibitors, but this approach is not without limitations. Complete removal of multifunctional enzymes that regulate multiple PTMs may result in new toxicities or off-target effects. Therefore, precisely blocking the interactions or functions necessary for the enzyme's role within the lactylation pathway may be a more sophisticated approach than completely eliminating the enzyme.

Substrate-oriented therapeutic interventions. Due to the extensive overlap between the regulatory machinery of lactylation and multiple PTMs, existing inhibitors and drugs are often non-selective. Directly regulating these regulatory enzymes can lead to broad, unpredictable changes in gene expression and potential toxic side effects. Current strategies primarily focus on targeting upstream metabolic enzymes or lactate transporters as well as on lactylation inhibitors and small-molecule peptides designed for specific modification sites (mainly n-H1a). While these methods can effectively reduce lactate and modification levels, they still lack precision or are difficult to develop (164,165). A more promising alternative may be the development of agents that can selectively inhibit the generation of key substrates and enzyme binding. For instance, by blocking the interaction between GTPSCS and p300, it is possible to inhibit local lactyl-CoA synthesis without affecting succinyl-CoA synthesis or the acetylation function of p300 (47). This has been demonstrated through site-directed mutagenesis, which can inhibit the nuclear translocation of GTPSCS and its subsequent catalytic activity for lactyl-CoA synthesis. Similarly, the nuclear translocation of ACSS2 and its function as a lactyl-CoA synthetase are regulated by phosphorylation at S267. Disrupting the ACSS2-KAT2A interaction has been shown to effectively inhibit tumor growth without altering histone acetylation levels (96). Another strategy may involve targeting the reader proteins. Once the specific recognition and binding domains of readers such as TRIM33 or DPF2 are clearly identified, drugs that block their lactylated lysine-binding pockets could be developed, offering higher specificity and drugs that are more therapeutically actionable. This highlights the need for a thorough mechanistic understanding of lactylation regulatory enzymes to rationally develop more efficient lactylation-targeted therapies (115).

The substrate-based technique is a more advanced treatment approach. Rather than blocking or degrading the entire enzyme, this method achieves targeted intervention by disrupting key molecular interactions required for lactylation. Its main advantage is its ability to selectively inhibit the lactylation pathway while keeping the other regulatory functions of the enzyme, reducing off-target consequences. However, this strategy is still mostly conceptual. To apply it effectively, the current understanding of the structural and molecular mechanisms involved needs to be enhanced.

Combination therapies. K1a promotes tumor adaptation and survival against numerous treatments by regulating DNA repair, protein stability, metabolic pathways and immune evasion (32,166-168). Table IV illustrates the role of lactylation modification in therapy resistance and the current interventions targeting it. Notably, in addition to developing highly specific tools, synergistic combination therapies could be designed (7,8,30,32,34,37,49,55-57,80,82,126,127,132,166-177). By simultaneously targeting lactate metabolism enzymes and lactylation regulatory enzymes, dual control can be achieved at both the source and the modification pathway, thus enhancing the effectiveness of tumor treatment. Blocking lactate metabolism reduces the substrate supply for K1a at its source, thereby reversing resistance to various anticancer treatments, including chemotherapy (cisplatin) resistance (34,126), oxaliplatin resistance (132) and targeted therapy (80).

As a key signaling molecule, lactate is the substrate that drives multiple immunosuppressive processes. For instance, targeting key metabolic enzymes or using glycolysis inhibitors can reduce lactate production and lactylation levels, thereby enhancing the efficacy of immune checkpoint blockade therapy, improving NK and CD8⁺ T cell infiltration and counteracting the regulatory T cell expansion caused by MOESIN-K721a (82). Through dietary interventions or metabolic inhibitors combined with anti-PD-1/PD-L1 antibodies, the immune evasion in CRC caused by KAT2A-mediated PD-L1 lactylation can be reversed (59).

Furthermore, since lactylation is intricately linked with resistance to numerous anticancer drug therapies, inhibitors targeting lactylation regulatory enzymes can restore sensitivity in therapy-resistant cases. This approach achieves an additive therapeutic effect when combined with treatments such as radiotherapy and chemotherapy. For example, using the KAT2A-targeting inhibitor MB-3 (57) and the CBP-targeting inhibitor SGC-CBP30 (126) restores sensitivity to cisplatin. The AARS1 inhibitor β -alanine reverses the poor efficacy of enfortumab vedotin therapy caused by YTHDC1 (55). Meanwhile, the HDAC2 inhibitor tucidinostat can reverse cisplatin resistance by impairing DNA damage repair (31). Another HDAC2 inhibitor, CAY-10683, in combination with terbinafine, enhances the reduction of cholesterol levels and suppresses HCC proliferation by reversing PD-L1-K1891a (29).

These interventions, aimed at altering enzymes, have reinstated resistance induced by lactylation, resulting in a more extensive antitumor effect. A dual-targeting strategy focused on lactate metabolism and lactylation regulatory enzymes offers the potential to simultaneously address immunosuppression and drug resistance, establishing a novel method for precision lactylation intervention.

K1a as a biomarker. Beyond its therapeutic implications, K1a is emerging as a critical diagnostic and prognostic biomarker. Specific K1a modifications are associated with distinct pathological states; for instance, adenylate kinase 2-K281a signals reduce p53 activity in HCC (21), while FASN-K6731a reflects lipid metabolic imbalance in NSCLC (178). Similarly, elevated H3K181a levels are clinically associated with advanced tumor stages and poor prognosis in NSCLC. Mechanistically, H3K181a drives immune evasion by activating the POM121 transmembrane nucleoporin/MYC axis to directly upregulate PD-L1 expression. Consequently, monitoring H3K181a could serve as a vital stratification tool to identify patients likely to benefit from combined metabolic and anti-PD-1 immunotherapies (129).

Crucially, integrating H1a (specifically H3K181a) with existing clinical indicators addresses current limitations in predicting immunotherapy responses. For instance, in head and neck squamous cell carcinoma, H3K181a-mediated upregulation of Related RAS viral (r-ras) oncogene homolog 2 is positively correlated with both chemoresistance and high tumor mutational burden (179). Beyond tissue analysis, the relative stability of histone modifications compared with unstable metabolites supports their utility in liquid biopsy (180). In pancreatic cancer (PC) and CRC, serum H3K181a levels show strong correlations with tumor progression and traditional markers such as CEA and CA19-9, highlighting its

Table IV. Lactylation in therapy resistance and intervention.

A, Chemotherapy				
Protein and site	Enzyme/regulator	Mechanism	Outcome	Intervention
BLM K24	AARS1	DNA end resection, HR repair ↑	Anthracycline resistance (56)	Irinotecan
RAD51 K73la	GCN5	HR repair ↑	Cisplatin resistance (57)	MB-3 + cisplatin
XLF-K288	GCN5	DSBs, NHEJ repair ↑	Chemotherapy resistance (37)	XLF-K288la, peptide inhibitor+5-FU
NBS1 K388	TIP60	HR repair enhanced	Cisplatin resistance (34)	Stiripentol, LDHA/TIP60 inhibition
MRE11 K673	CBP, LDH	DNA end resection, BRCA1-RAD51 recruitment ↑	Olaparib, cisplatin resistance (126)	CBP inhibitors, LDH inhibitors
ANTXR1 K453	RhoC/ROCK1/ SMAD5	Stemness ↑	Oxaliplatin resistance (132)	MCT1/4 inhibitor (7ACC1)
ALDOB	CEACAM6	Enhancing protein stability	5-FU resistance (166)	-
B, Radiotherapy				
Protein and site	Enzyme/regulator	Mechanism	Outcome	Intervention
XRCC1 K247	ALDH1A3/PKM2	Nuclear translocation ↑, DNA repair ↑	Chemoradiotherapy resistance (167)	D34-919
p21/HIF-1α	Glut1/LDHA	Enhanced glycolysis	Radioresistance (173)	-
TAB182	LDHA	DNA repair ↑, regulates G2/M checkpoint	Poor radiotherapy response (171,172)	TAB182 inhibition
C, Targeted therapy				
Protein and site	Enzyme/regulator	Mechanism	Outcome	Intervention
PRDX1 K67	ZNF207	NRF2 transcription ↑, ferroptosis ↓	RGF resistance (8)	ZNF207/NRF2 inhibition
Mic60 K282	Dapk2	OXPPOS ↑	Osimertinib resistance (127)	LDH inhibitor (GSK2837808A)
YAP K90	CRM1	Prevents nuclear export, stemness ↑	Sorafenib resistance (168)	Target YAP
IGF2BP3 K76	AARS1	Stabilizes PCK2/NRF2, ROS ↑	Lenvatinib resistance (80)	IGF2BP3 siRNA/2-DG
p53	NF-κB/STAT3/ SLC4A4	Warburg effect ↑	Enzalutamide resistance (174)	STAT3 inhibitor (Crizotinib)
LSD1 K503	FosL1, TFRC	TFRC, ferroptosis ↓	BRAF/MEKi resistance (175)	LSD1 inhibition
D, Immunotherapy				
Protein and site	Enzyme/regulator	Mechanism	Outcome	Intervention
APOC2 K70	P300, HDAC3	FFAs ↑, immunosuppressive TME	PD-1/PD-L1 resistance (32)	APOC2 ^{K70-lac} antibody, FX-11+anti-PD-1
ENSA K63	STAT3, CCL2/CCR2	TAM recruitment ↑, CD8 ⁺ T cell suppression	PD-1/PD-L1 resistance (49)	Targets ENSA-K63la, CCL2
YTHDC1	AARS1, RNF183, JUND	JUND mRNA stability ↓, NECTIN4 ↓	ADC (EV) resistance (55)	JUND activators/β-alanine

Table IV. Continued.

D, Immunotherapy				
Protein and site	Enzyme/regulator	Mechanism	Outcome	Intervention
MOESIN K72	TGF- β	Activates TGF- β /SMAD3, Treg $\uparrow$	ICB resistance (82)	LDHi + PD-1
METTL16 K269	CTCF	CTCF-dependent CD276/NECTIN2 $\uparrow$	CD8 ⁺ T cell, PD-1 immunotherapy $\downarrow$ (176)	Target METTL16
E, Other therapy				
Protein and site	Enzyme/regulator	Mechanism	Outcome	Intervention
NSUN2	NAA10	GSH synthesis $\uparrow$	Ferroptosis resistance (7)	Targets NSUN2/NAA10
NUDT21 K23	AARS1, HDAC2	FDX1 3' UTR extension	Cuproptosis resistance (30)	Stiripentol + elesclomol
ZMIZ1 K843	Nanog (OCT4, NPC2)	Cell stemness, cholesterol uptake $\uparrow$	Tamoxifen resistance (177)	Target ZMIZ1
GCLM K34	ACAT2	GCLC $\uparrow$, GSH synthesis $\uparrow$	Ferroptosis resistance (170)	ACAT2 inhibition + erastin
HDAC1 K412	-	FTO, ALKBH5 $\downarrow$, FSP1 $\uparrow$	Ferroptosis resistance (169)	HDACi (vorinostat, TSA)

‘-’ or unlisted residues indicate that the specific lactylation site has not yet been experimentally determined in the cited studies. 2-DG, 2-deoxy-D-glucose; 5-FU, 5-fluorouracil; AARS1, alanyl-tRNA synthetase 1; ACAT2, acetyl-CoA acetyltransferase 2; ADC, antibody-drug conjugate; ALDH1A3, aldehyde dehydrogenase 1 family member A3; ALDOB, aldolase B; ALKBH5, alkB homolog 5; ANTXR1, anthrax toxin receptor 1; APOC2, apolipoprotein C2; BLM, Bloom syndrome protein; BRCA1, breast cancer 1; CBP, CREB-binding protein; CCL2, C-C motif chemokine ligand 2; CCR2, C-C motif chemokine receptor 2; CEACAM6, carcinoembryonic antigen-related cell adhesion molecule 6; CTCF, CCCTC-binding factor; CRIZOTINIB, crizotinib; CRM1, chromosome region maintenance 1 (exportin 1); DSBs, double-strand breaks; EV, extracellular vesicle; FAS, fatty acid synthase; FDX1, ferredoxin 1; FSP1, ferroptosis suppressor protein 1; FTO, fat mass and obesity-associated protein; GCLC, glutamate-cysteine ligase catalytic subunit; GCN5, general control non-depressible 5; GSH, glutathione; Glut1, glucose transporter 1; HDAC2/3, histone deacetylase 2/3; HDACi, histone deacetylase inhibitor; HIF-1 α , hypoxia-inducible factor-1 alpha; HR, homologous recombination; IGF2BP3, insulin-like growth factor 2 mRNA-binding protein 3; ICB, immune checkpoint blockade; IL-17, interleukin-17; JUN, Jun proto-oncogene; LDH/LDHA, lactate dehydrogenase A; LSD1, lysine-specific demethylase 1; MCT1/4, monocarboxylate transporter 1/4; METTL16, methyltransferase-like 16; MRE11, meiotic recombination 11 homolog; NF- κ B, nuclear factor kappa B; NBS1, Nijmegen breakage syndrome 1; NHEJ, non-homologous end joining; NPC2, Niemann-Pick disease type C2 protein; NRF2, nuclear factor erythroid 2-related factor 2; NSUN2, NOP2/Sun RNA methyltransferase 2; OCT4, octamer-binding transcription factor 4; OXPHOS, oxidative phosphorylation; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PCK2, phosphoenolpyruvate carboxykinase 2; PKM2, pyruvate kinase M2; PRDX1, peroxiredoxin 1; RAD51, RAD51 recombinase; ROCK1, Rho-associated coiled-coil containing protein kinase 1; ROS, reactive oxygen species; SLC4A4, solute carrier family 4 member 4; SMAD3, SMAD family member 3; STAT3, signal transducer and activator of transcription 3; TAB182, tankyrase 1-binding protein 182; TAM, tumor-associated macrophage; TFR, transferrin receptor; TGF- β , transforming growth factor beta; TIP60, Tat-interactive protein 60 kDa; TSA, trichostatin A; XRCC1, X-ray repair cross-complementing protein 1; YAP, Yes-associated protein; YTHDC1, YTH domain containing 1; ZMIZ1, zinc finger MIZ-type containing 1; ZNF207, zinc finger protein 207.

potential for dynamic, non-invasive monitoring of tumor metabolism (180,181). Furthermore, H3K18la serves as an independent prognostic biomarker for PC severity (181). Combined assessment of AARS2 and its catalyzed product, H3K18la, constitutes a composite biomarker for evaluating intestinal ischemia-reperfusion injury and associated ferroptosis. This offers a novel molecular perspective for understanding and monitoring such tissue damage (182).

With the advancement of multi-omics and machine learning, lactylation-related genes and lncRNAs are being utilized to construct sophisticated prognostic models. These models demonstrate promising potential across various

cancer types by linking lactylation to immune infiltration, immunotherapy response and drug sensitivity (183,184). Such approaches efficiently narrow the scope of potential target screening, providing an effective reference framework for the precise identification of therapeutic targets and biomarkers.

6. Challenges and prospects for regulatory enzymes

Crosstalk between lactylation and other PTMs. The regulatory network of Kla is not an isolated system. It has complex and diverse interactions with other PTMs, including Kac, succinylation and crotonylation. These interactions, which use

various substrates along the same metabolic pathway and are coordinated by similar regulatory enzymes, turn metabolic activity into long-term and widespread cellular functional outputs. In this process, extensive crosstalk between distinct PTMs creates a highly tuned network defined by substrate competition and overlapping regulatory mechanisms.

Metabolic substrate competition. The competition for acyl-CoA precursors produced by various metabolic pathways is the main reason of this crosstalk. Pyruvate, a byproduct of glycolysis, is converted into lactyl-CoA and acetyl-CoA, the substrates of K1a and Kac. The Warburg effect causes the metabolic flux to be switched towards lactate, which results in a decrease in acetyl-CoA and an excess of lactoyl-CoA. The competitive and synergistic interaction between these two modifications is fueled by the difference in local substrate concentrations caused by this shift (115,185).

Notably, the role of lactate is not exclusive to K1a. Previous research has shown that lactate can also promote histone H3K27 acetylation (H3K27ac), which transcriptionally suppresses the pro-inflammatory functions of macrophages while enhancing the expression of immunosuppressive factors (186). At the same time, lactate can also mediate increases in the stemness of CD8⁺ T cells through H3K27ac (187). Since the substrates for all these modifications are tightly interconnected through glucose metabolism, a crosstalk of modification signals is inevitable.

Modification overlap and functional interaction. In M1 macrophages, H1a exhibits different temporal dynamics than Kac. During the later stages of M1 polarization, driven by lactate produced during early inflammation, K1a appears to replace Kac, activating genes involved in inflammation resolution and homeostatic repair (6). In addition, K1a and Kac can act synergistically on the same protein. For example, p300/CBP promotes high mobility group box 1 lactylation while simultaneously inhibiting SIRT1 deacetylase activity via the Hippo/YAP pathway, thereby activating acetylation and ultimately exacerbating sepsis progression (75). A competitive association exists between K1a and Kac at H3K18. HK2 expression enhances glycolytic activity and lactate production, influencing gene expression by affecting H3K181a. However, H3K18ac is suppressed during *in vitro* hepatic stellate cell (HSC) activation. Exogenous lactate supplementation improves lactylation while decreasing acetylation. Concurrently, class I HDAC inhibitors enhance H3K18ac while inhibiting H3K181a, thus reducing HSC activation (92). Due to the intricate interaction between PTMs, regulating a single modifying site cannot provide an optimal therapeutic intervention.

Dual modification systems: Shared enzymes between K1a and Kac. K1a and Kac share the same writers and erasers, which creates a complex regulatory landscape involving multiple PTMs. This is also reflected in other emerging modifications (188-190). For instance, lactylation shares regulatory systems with other modifications such as succinylation and crotonylation, including enzymes such as p300/CBP, KAT2A, HDACs and SIRT1s (188,189). Furthermore, these PTMs often need to share coenzyme synthetases (such as ACSS2) to provide the substrate acyl-CoAs, leading to substrate competition. The modification type catalyzed by p300/CBP is directly dependent on the relative concentration of available acyl-CoA

substrates at its active site. Under a high lactate environment, the p300 active site is more likely to encounter lactyl-CoA, causing its catalytic activity to switch from writing Kac to writing K1a. Secondly, lactyl-CoA synthetases produce large quantities of lactyl-CoA, creating a local environment where lactyl-CoA is dominant, and synergize with lactyl-CoA transferases to promote lactylation, such as the synergistic effect of ACSS2 and KAT2A (96). Similarly, GTPSCS translocates into the nucleus and forms a complex with p300, generating a high local concentration of lactyl-CoA, which in turn enhances H3K181a (47). Fig. 4 illustrates this integrated regulatory network, highlighting how shared enzymatic machinery and substrate competition facilitate the crosstalk between diverse PTMs.

Previous structural studies have revealed that the HAT domain of p300 contains a well-defined acyl-CoA-binding channel formed by key residues such as Y1397, W1436, Y1446 and C1438 (191,192). This hydrophobic tunnel confers selectivity toward different acyl-CoA species, enabling p300 to discriminate among acetyl-CoA, crotonyl-CoA, butyryl-CoA and other acyl donors. Due to substrate-assisted chain repositioning and the limited volume of the aliphatic back pocket, the catalytic efficiency of p300 decreases progressively as the acyl-chain length increases (191). Short and hydrophobic groups such as the acetyl moiety fit optimally into the narrow pocket, supporting highly efficient catalysis. By contrast, the lactyl group is not only bulkier, but also contains a polar hydroxyl group; its additional steric and electrostatic constraints likely require subtle conformational adjustments of the HAT domain to accommodate lactyl-CoA, ultimately reducing catalytic efficiency compared with acetyl-CoA. These structural features provide a mechanistic explanation for why p300 exhibits differential reactivity towards Kac and K1a. More notably, they highlight that competition between lactylation and acetylation may arise directly from shared catalytic machinery: When multiple acyl-CoA species coexist in the nucleus, they may compete for occupancy of the same acyl-CoA channel within p300, thereby influencing the balance between distinct PTMs. However, simulating the competitive association between the PTMs under physiological conditions remains challenging. It is difficult to replicate the complex environment faced by tumors and to exclude interference from multiple processes to precisely determine which modification is specifically regulated. At present, lysine-to-threonine site mutations are commonly used to mimic lactylation (22,74), but they still cannot fully replicate the effects of lactylation in the body. Recently developed bio-orthogonal systems based on genetic code expansion may provide improved tools for authentic simulation by directly inserting the lactyl group at target lysine sites (23,64,93).

From this perspective, compared with the MYST family, which is involved in crosstalk with multiple modifications, AARS1 appears to be a more precise therapeutic target. However, the crucial role of AARS1 in protein translation means that targeting it for inhibition would lead to notable toxicity. Indeed, mutations in AARS1 itself are associated with various diseases, such as Charcot-Marie-Tooth disease type 2N and infantile epileptic encephalopathy (193,194). β -alanine, which has a similar structure to lactate, may be a

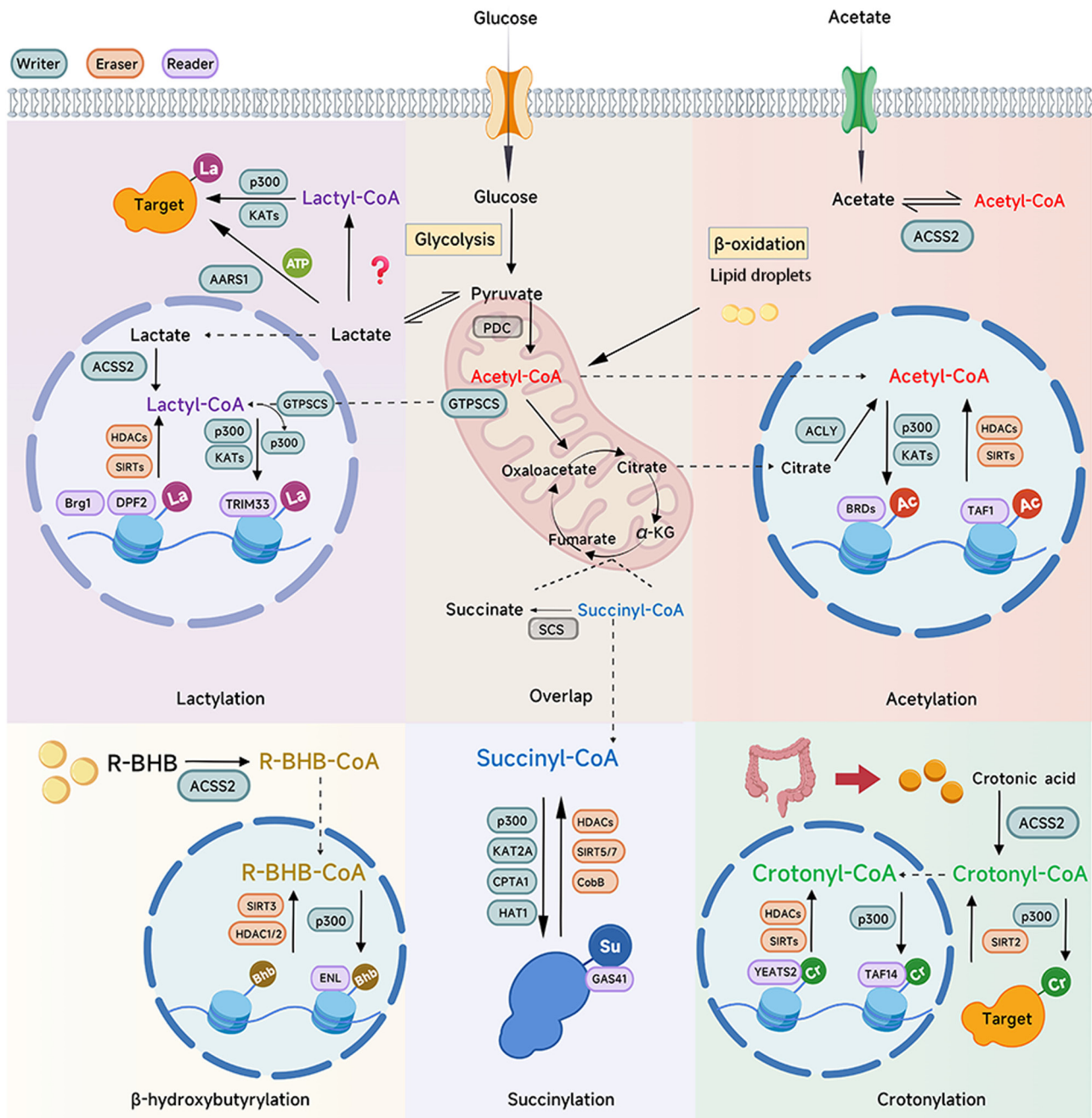


Figure 4. Crosstalk between lactylation and other PTMs. Lactylation exhibits intricate crosstalk with other acyl-based PTMs. Central metabolic pathways, including glycolysis and the TCA cycle, provide the essential acyl-CoA substrates for these modifications. The widespread sharing of enzymatic machinery provides the structural and functional basis for the acyl-mediated epigenetic regulatory network. Due to this overlap, a complex and competitive system is created in which the relative availability of each substrate and the metabolic state of the cell determine the balance between various PTMs, ultimately influencing the epigenetic and signaling landscape. PTMs, post-translational modifications; La, lactate/lactylation; KATs, lysine acetyltransferases; AARS1, alanyl-tRNA synthetase 1; ACSS2, acyl-CoA synthetase short-chain family member 2; HDACs, histone deacetylases; SIRT6, sirtuins; Brg1, Brahma-related gene-1; DPF2, double PHD fingers 2; GTPSCS, succinyl-CoA synthetase; TRIM33, tripartite motif-containing 33; PDC, pyruvate dehydrogenase complex; α -KG, α -ketoglutarate; SCS, succinyl-CoA synthetase; ACLY, ATP-citrate lyase; BRDs, bromodomain-containing proteins; TAF1, TATA-box binding protein associated factor 1; Ac, acetylation; R-BHB, R-3-hydroxybutyrate; ENL, eleven-nineteen leukemia protein; Bhb, β -hydroxybutyrylation; CPT1A, carnitine palmitoyltransferase 1A; HAT1, histone acetyltransferase 1; Su, succinylation; GAS41, glioma-amplified sequence 41; Cr, crotonylation.

theoretical candidate for developing specific interventions as it has been shown to inhibit lactylation in molecular experiments (23,55); however, further research is needed before it can become a clinical therapeutic drug. A potential therapeutic strategy could involve structural studies of AARS1 to decouple its tRNA synthetase function from its lactyltransferase function. This would enable the development of specific inhibitors

that selectively block the lactate-binding activity of AARS1 without compromising its canonical role in protein synthesis.

Limitations of current research methods. Current enzymological research on lactylation in tumors primarily focuses on a limited number of known regulatory enzymes, such as p300, HDACs or SIRT6, and often relies on chemical inhibitors or

protein-protein interaction analyses to infer their roles. This strategy is reasonable, given the availability of established inhibitors and the mechanistic overlap with Kac, but it has several limitations and risks. First, inhibitor-based studies often suffer from off-target effects, raising doubts about whether the observed changes in lactylation are direct or secondary to overall metabolic shifts. Second, protein interaction assays can reveal correlations but not causality, leaving the true enzymatic drivers uncertain. Third, focusing only on enzymes already implicated in other PTMs may overlook other writers or erasers that may be specific to lactylation (23,115). It has been shown that supplementing with exogenous sodium lactate in combination with p300 knockdown paradoxically increases Hla compared with p300 knockdown alone. This suggests that high levels of upstream lactate can override the limiting effect of p300, and it is more likely that p300 is not the sole writer of Hla and that other enzymes may be involved in this process, or even that p300 is not the primary writer for K1a (49). Finally, systemic interference with histone-modifying factors can have broad cellular effects, which can complicate the interpretation of mechanisms specific to lactylation. In conclusion, while this strategy is a necessary starting point, it needs to be combined with more precise methods such as proteomics and CRISPR screening to broaden the scope of consideration. Utilizing structural biology and the analysis of substrate-binding pockets, and possibly simulating substrates under physiological conditions (165), may be necessary to obtain more exclusive evidence to enhance the scientific rigor and reliability of enzymological research. For example, innovative methods have been successfully applied to the study of K1a erasers. Fan *et al* (45) introduced two innovative, function-oriented chemical probes. The first, an affinity-based probe named p-H4K16laAlk, allows for the UV-induced covalent capture of transiently interacting proteins directly from cell lysates. This facilitates the unbiased proteomic identification of endogenous erasers, as demonstrated by its successful capture of SIRT3. The second, a fluorogenic probe termed p-H4K16laNBD, provides a real-time readout upon the enzymatic removal of the lactyl group. Together, these tools advance the detection of lactylation regulatory enzymes from indirect inference toward direct identification and dynamic functional characterization.

Species discrepancies and translational hurdles. Despite encouraging results in preclinical studies (42,49,58), targeting lactylation regulatory enzymes faces major translational barriers due to differences in metabolic pathways and enzyme networks. LDH is highly conserved, and the lack of isoform selectivity leads to notable on-target toxicity. Unlike tumor cells, mature human erythrocytes rely entirely on LDHA-mediated NAD⁺ regeneration for ATP production, making them highly sensitive to LDH inhibition. In models such as those for Ewing sarcoma, effective antitumor doses are close to hemolytic doses, resulting in a narrow therapeutic window (195). Rodent models often underestimate this toxicity since mice better tolerate hemolysis (196) and several LDH inhibitors show rapid clearance in mice, thus preventing accurate assessment of their true pharmacological potential (197).

Crucially, species differences significantly impact AARS1-mediated lactylation. Although the lactate-dependent exposure of the NLS is a conserved mechanism, variations

in the lactate-sensing and catalytic domains suggest that sensitivity may differ between rodents and humans (36). Furthermore, downstream targets such as p53 operate within species-specific networks, implying that murine findings may not fully mirror human tumor biology (23). Therefore, rigorous validation using human-derived organoids or patient-derived xenograft models is essential to ensure preclinical findings translate effectively to clinical contexts.

Future studies should incorporate models with greater human relevance, including humanized mouse systems and patient-derived organoids, to more reliably evaluate drug exposure, toxicity and lactylation-dependent signaling.

Future outlook. Future intervention strategies for lactylation regulatory enzymes must extend beyond traditional small-molecule inhibitors to incorporate more precise approaches. First, by integrating metabolic monitoring technology, precise monitoring of lactate production, transport and the K1a process can be achieved, such as the lactate sensor FiLa (198), which can provide real-time dynamic data, thus helping to understand the role of lactylation in tumors and, in turn, guide the optimization and evaluation of subsequent intervention strategies. This, in turn, facilitates the optimization of therapeutic timing and the evaluation of intervention strategies based on real-time metabolic responses. Furthermore, by establishing biomarkers based on lactylated molecules and by developing and validating detection methods for clinical samples to assess the lactylation levels of specific sites or proteins, it may be possible to predict sensitivity to targeted metabolic or epigenetic therapies or to monitor pharmacodynamics.

Second, developing highly specific intervention tools is key to overcoming off-target effects. The vast diversity of lactylated protein substrates makes site-specific intervention complex. Although targeting and inhibiting lactylated proteins can reduce toxic side effects, the screening and validation processes still rely on high-throughput proteomics, CRISPR-based methods and custom antibodies, which are both time-consuming and technically demanding. This suggests that intervening with lactylation regulatory enzymes would be more efficient and meaningful. In addition to continuing the search for regulatory enzymes, it is important to fully elucidate the regulatory mechanisms of lactylation and, on that basis, develop inhibitors that are specific to lactylation without affecting other PTMs. Before that is achieved, another direction to consider is shifting from the traditional approach of inhibiting enzymatic catalytic activity to blocking the binding ability between regulatory enzymes and specific sites, such as the interaction between lactyl-CoA synthetase and writers. The use of potent and highly selective inhibitors, coupled with robust drug delivery systems to achieve sustained interference with regulatory enzymes, offers a promising strategy to overcome the off-target effects of conventional inhibitors and demonstrates significant translational potential.

7. Conclusion

Lactylation functions as a pivotal bridge connecting the metabolic Warburg effect to epigenetic reprogramming. The

present review summarizes the core enzymatic machinery governing this process, including writers, erasers and readers. Collectively, this regulatory network orchestrates a malignancy-associated transcriptomic profile; it drives metastasis, reshapes the immune microenvironment toward an immunosuppressive state and actively promotes resistance to chemotherapy and immunotherapy.

Despite these advances in uncovering the lactylation regulatory enzymes and identifying its diverse roles in tumor progression and therapy resistance, translating these findings into clinical therapies faces critical hurdles. First, targeting upstream metabolic enzymes often causes systemic toxicity due to off-target effects on normal tissues. Second, species-specific differences in enzyme activity limit the predictive value of conventional animal models. Third, the extensive crosstalk between lactylation and other acyl modifications creates a complex competitive landscape, complicating the identification of specific therapeutic targets. To overcome these barriers, future research must shift toward precision intervention that bypasses broad metabolic disruption in favor of selective molecular targeting. The present review highlights the need to move beyond non-selective catalytic inhibitors to advanced modalities, such as PROTACs that degrade specific enzymes or inhibitors that disrupt specific writer-reader interactions. Additionally, validating lactylation signatures as liquid biopsy biomarkers is essential for patient stratification. By resolving these structural and translational challenges, targeting the lactylation regulatory network offers a transformative strategy to reprogram tumors and overcome therapeutic resistance.

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Authors' contributions

GT conceived and designed the study. GT and HZ drafted the manuscript and provided overall supervision of the project. RL, CZ, YL, XL and JQ conducted the literature search and study selection, performed data collation from the included references, and contributed to specific sections of the manuscript. JZ contributed to the study design, provided funding support, supervised the project and offered critical revision suggestions. All authors participated in the revision of the manuscript and have read and approved the final version. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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