Role and clinical importance of lactylation in tumors (Review)

CHAOWEI ZHANG[1,2*], XINYU TANG[1,2*], YUXUAN HAN[1,2], WEIYI YAO[1,2], QING HONG[1,2], YANAN ZHU[1,2] and NA CHEN[1,2]

[1]Department of Hematology, Beijing Luhe Hospital, Capital Medical University, Beijing 101199, P.R. China; [2]Graduate School, Shandong First Medical University, Jinan, Shandong 250117, P.R. China

Received December 10, 2025; Accepted February 19, 2026

DOI: 10.3892/mmr.2026.13856

Abstract. Lactic acid was once considered a metabolic waste product of glycolysis; however, it is now know to serve a role in tumorigenesis and progression. Lactylation is a novel post-translational modification in which lactyl groups derived from lactic acid are covalently attached to lysine residues. This modification is not only present on histones but is also widely distributed among non-histone proteins, markedly impacting gene expression, protein function and cellular metabolism. Lactylation participates in the proliferation, invasion, metabolism and immune evasion of tumor cells by regulating metabolic reprogramming and epigenetic modulation. The present review comprehensively discusses the role of lactylation in the tumor microenvironment, and elucidates its relationship with tumor immune evasion and drug resistance. A deeper understanding of the mechanisms underlying lactylation, the identification of its regulatory factors and the exploration of therapeutic strategies targeting lactylation may yield novel insights into the clinical treatment of tumors.

Contents

Correspondence to: Professor Na Chen, Department of Hematology, Beijing Luhe Hospital, Capital Medical University, 82 Xinhua South Road, Tongzhou, Beijing 101199, P.R. China
E-mail: nachen1982@126.com

*Contributed equally

Key words: lactylation, tumor metabolism, tumor microenvironment, immune evasion, drug resistance

1. Introduction

Historically, lactate was dismissed as a byproduct of glycolytic metabolism, resulting in an oversight of its vital physiological contributions (1). The seminal work of Otto Warburg in the 1920s revealed that malignant cells display dysregulated glycolysis, generating surplus lactate despite the availability of oxygen (2,3). While traditionally viewed strictly as an endpoint of anaerobic respiration, research has now established that lactate serves as a crucial bridge between glycolysis and oxidative phosphorylation, and also as a versatile signaling agent (4). Consequently, this paradigm shift has redefined lactate from a metabolic remnant to a pivotal biological indicator (5).

Protein post-translational modifications (PTMs) are enzymatically mediated covalent attachments of functional groups that occur either during or after protein biosynthesis. These alterations markedly expand the proteomic landscape, generating a functional diversity that extends beyond the genomic blueprint (6). In eukaryotes, the majority of proteins are subject to terminal modifications via diverse mechanisms, including acetylation, lipidation and others (7). Crucially, PTMs are closely linked to oncogenesis, governing key carcinogenic processes such as sustained proliferation, apoptosis evasion, angiogenic induction and metastasis (8) In 2019, Zhang *et al* (9) characterized a novel PTM termed lactylation (or lysine lactylation), which was initially observed on histones. This process entails the covalent bonding of a lactyl moiety, derived from lactate, to lysine residues, thereby functioning as a mechanism for gene regulation; specifically, lactate acts as the precursor providing the essential substrate pool for this modification (9). Furthermore, subsequent investigations have revealed that lactylation is not limited to histones but also broadly affects non-histone proteins, modulating their functions through distinct regulatory pathways (10-12).

Lactylation serves as a fundamental regulator of essential physiological processes, including cardiac performance (13), embryogenesis (14) and osteoblast differentiation (15). Concurrently, this PTM is implicated in the etiology and advancement of diverse pathologies, ranging from inflammatory cascades (16) and renal tubular damage (17), to cerebral trauma (18) and pulmonary fibrosis (19). Crucially, lactylation profoundly impacts the tumor microenvironment (TME). Beyond influencing oncogenic expression, it orchestrates a complex network involving immune modulation, metabolic reprogramming, therapeutic resistance and autophagy.

By engaging with cancer-associated genes [e.g., MYC proto-oncogene (MYC), snail family transcriptional repressor 1 and programmed cell death 1 ligand 1], lactylation alters transcriptional landscapes to drive proliferation, invasiveness and immune escape (20,21). Consequently, the present review comprehensively summarizes the current knowledge on lactate metabolism and lactylation in oncology, with a specific emphasis on emerging strategies for tumor diagnosis and targeted therapy.

2. Lactic acid in cancer

Lactic acid production and metabolism. In both physiological and neoplastic contexts, glucose acts as the principal substrate for lactate generation, marking the end of the glycolytic cascade (Fig. 1) (22). Cellular uptake of glucose is predominantly mediated by glucose transporter (GLUT) proteins (23). Following internalization, glucose is metabolized to pyruvate under normoxic conditions. Subsequently, the bulk of this pyruvate enters the mitochondria via the mitochondrial pyruvate carrier, or is shuttled after conversion to undergo oxidative phosphorylation. Within the mitochondria, the tricarboxylic acid (TCA) cycle and electron transport chain drive the synthesis of ATP, releasing CO_2 and H_2O as byproducts (24) Conversely, in hypoxic or anaerobic environments, oxidative phosphorylation is compromised. To maintain redox homeostasis and sustain glycolysis, cytosolic pyruvate is reduced to lactate by lactate dehydrogenase (LDH) (25) Structurally, LDH exists as a tetramer formed by varying combinations of muscle subunits (M) and heart subunits (H), yielding five distinct isozymes: LDH-1 (4H), LDH-2 (3H1M), LDH-3 (2H2M), LDH-4 (1H3M) and LDH-5 (4M) (26). While these isoforms are bidirectional, LDHA (LDH-5) preferentially drives the reduction of pyruvate to lactate, thereby markedly fueling tumor progression, whereas LDHB (LDH-1) favors the oxidation of lactate back to pyruvate (27,28). Beyond glucose, research has highlighted glutaminolysis as an alternative metabolic route in cancer cells (29). Driven by the c-Myc proto-oncogene, glutamine enters the cytoplasm via specific transporters, including ASCT2 and SNAT2 (30). Once inside the cell, glutaminase (GLS) converts glutamine into glutamate, which is further processed into α-ketoglutarate by enzymes such as glutamate dehydrogenase to enter the TCA. Carbon derived from glutamine is then metabolized into oxaloacetate and subsequently malate, which is exported from the mitochondria. In the cytosol, malic enzyme converts malate to pyruvate, generating NADPH in the process, which is ultimately reduced to lactate by LDHA. Although this pathway typically serves as a secondary source of lactate, glutamine becomes the dominant carbon reservoir supporting cancer cell metabolism during glucose starvation (31). Furthermore, evidence suggests that under such glucose-deprived conditions, lactate enhances cell survival primarily by sustaining mitochondrial respiration through GLS1-mediated glutaminolysis (32).

Driven by metabolic reprogramming, lactate concentrations in cancer cells are markedly higher than those in the circulation or healthy parenchyma (33). Malignant tumors exhibit upregulated glycolytic flux even when oxygen availability is adequate and oxidative phosphorylation remains functional. Specifically, through aerobic glycolysis, tumor tissues generate lactate levels that are 10- to 100-fold higher than those produced via complete mitochondrial glucose oxidation (34). Characterized as the Warburg effect, this phenomenon describes the propensity of cancer cells to prioritize glycolysis and lactate synthesis over oxidative phosphorylation, despite the presence of oxygen (3). This metabolic shift is essential for meeting neoplastic requirements for bioenergetics, redox homeostasis and biosynthetic precursors, a process accompanied by extensive reprogramming of metabolic enzymes and transport proteins (35,36). Consequently, the accumulation of substantial lactic acid stands as a definitive outcome of this metabolic reconfiguration.

Following its efflux from glycolytic cells, lactate enters the systemic circulation, where, under homeostatic conditions, it functions as a vital metabolic substrate for the myocardium, brain and skeletal musculature (37-39). To avert the onset of acidosis caused by supraphysiological lactate levels, rapid metabolic clearance and irreversible elimination mediated by LDH are essential for maintaining tissue equilibrium (40). Concurrently, the accumulation of lactate stimulates hepatic gluconeogenesis, allowing the liver to recycle lactate into glucose via the Cori cycle for redistribution into the vascular system (41). In cancer, where metabolic reprogramming drives excessive lactate generation, efflux is predominantly facilitated by monocarboxylate transporters (MCTs), with MCT4 serving as a pivotal mediator of this export mechanism (42). Furthermore, in hypoxic microenvironments, MCT1 also contributes to the extracellular transport of lactate (43).

Lactic acid and tumor aggravation. The TME constitutes a complex ecosystem comprising malignant cells, stromal elements such as endothelial cells and cancer-associated fibroblasts (CAFs), and infiltrating immune populations. These cellular components are embedded within a non-neoplastic extracellular matrix rich in bioactive peptides, including cytokines, chemokines, antibodies and growth factors (44). Upon accumulation in the TME, lactate actively potentiates immune escape by dampening the functional activity of immune cells and suppressing the synthesis of inflammatory mediators (45). Beyond its metabolic function, lactate acts simultaneously as an energy substrate, a signaling messenger and a potent immunosuppressive agent, thereby orchestrating diverse cellular behaviors (46). Notably, lactate buildup sustains a chronically acidic extracellular pH; this localized acidic milieu is a critical driver of angiogenesis, therapeutic resistance, immunosuppression and metastatic dissemination (47-50). Specifically, the acidic conditions compromise cytokine secretion by monocytes (51) and impair the cytotoxic capabilities of natural killer (NK) and NKT cells (52,53), ultimately fostering an environment conducive to tumor proliferation. Furthermore, lactate stimulates the upregulation of vascular endothelial growth factor, ensuring sufficient oxygen and nutrient delivery to support neoplastic growth and neovascularization (54). In colorectal cancer (CRC), research has indicated that lactic acidosis blunts the activity of antitumor immune cells and inhibits the phagocytic capacity of tumor-associated macrophages (TAMs). Concurrently, metabolic stress and nutritional deprivation favor the differentiation of regulatory T cells (Tregs) and M2-polarized macrophages, the latter of which promote tumor expansion and metastasis (55). Collectively,

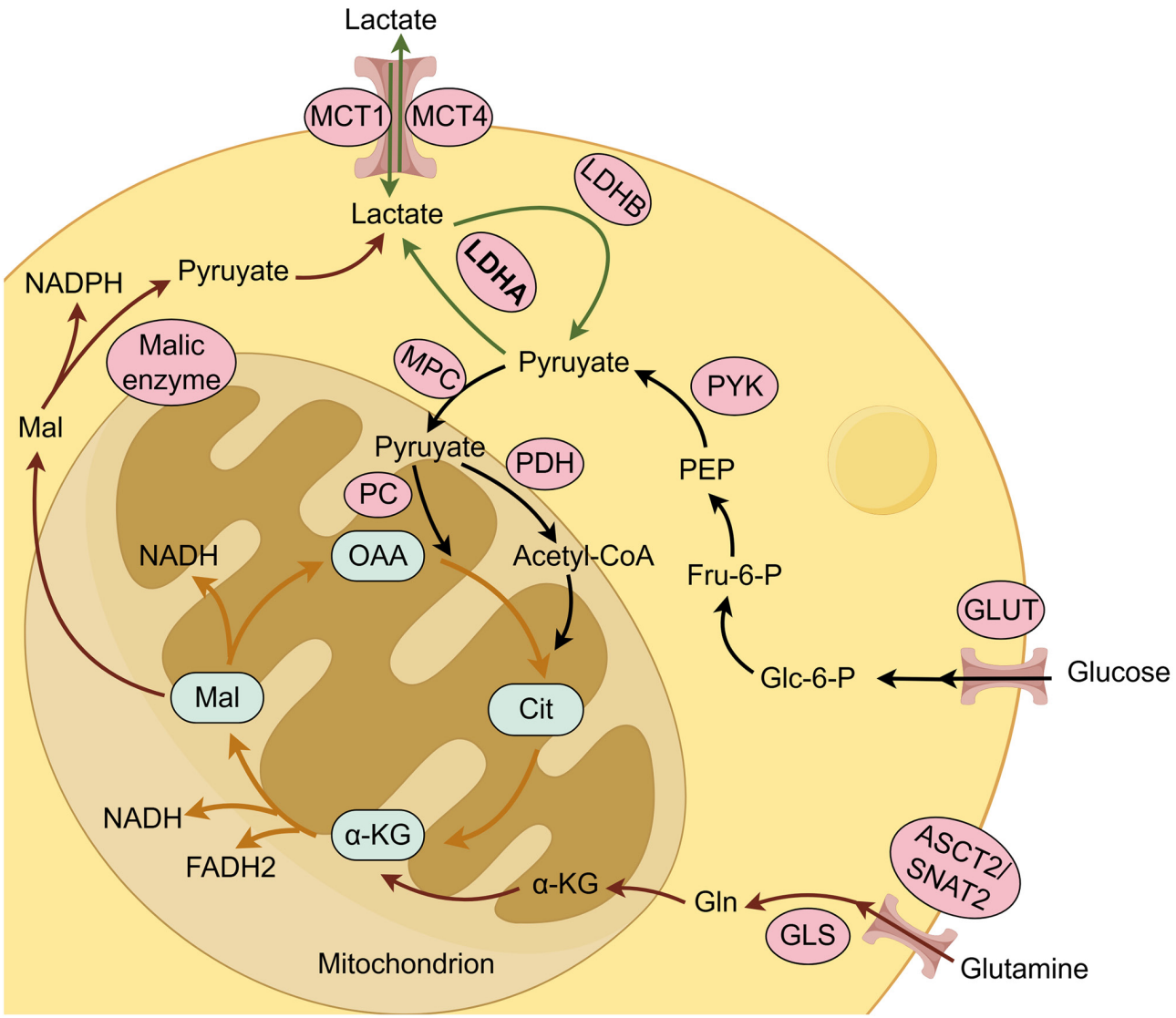

Figure 1. Schematic overview of glucose-derived lactate production, mitochondrial integration and transport mechanisms. Lactate is not merely a metabolic waste product, but a central hub in the metabolic network of both normal and malignant cells. This schematic diagram illustrates the metabolic pathways that dictate intracellular lactate availability. The glycolytic cascade and lactate synthesis: Glucose is transported into the cell via GLUTs and undergoes a series of enzymatic reactions (the glycolytic cascade, including intermediates such as Glc-6-P, Fru-6-P and PEP) to produce pyruvate. LDHA (in bold to highlight its pivotal role) preferentially catalyzes the reduction of pyruvate to lactate, marking the culmination of aerobic glycolysis. Conversely, LDHB can mediate the conversion of lactate back to pyruvate depending on the cellular redox state and metabolic demands. Lactate transport and homeostasis: Intracellular lactate levels are tightly regulated by MCTs. MCT1 primarily facilitates the influx (uptake) of exogenous lactate, whereas MCT4 is the principal transporter for lactate efflux (export), particularly in highly glycolytic tumor cells. Together, these transporters maintain the intracellular lactate homeostasis required for downstream signaling and protein modifications. Mitochondrial metabolism and alternative fluxes: Pyruvate can be imported into the mitochondrion via the MPC to feed the TCA cycle through conversion into acetyl-CoA (by PDH) or OAA (by PC). Additionally, Gln serves as a vital nitrogen and carbon source, entering the TCA cycle via glutaminolysis (ASCT1/SNAT2 and GLS1). The export of Mal from the mitochondria and its conversion to pyruvate by the malic enzyme also provides an alternative route for pyruvate/lactate generation while producing NADPH for antioxidant defense. Figure was generated by Figdraw (www.figdraw.com ID: ORPSP4a80d). Cit, citrate; Fru-6-P, fructose-6-phosphate; Glc-6-P, glucose-6-phosphate; Gln, glutamine; GLS1, glutaminase 1; GLUT, glucose transporter; LDH, lactate dehydrogenase; Mal, malate; MCT, monocarboxylate transporter; MPC, mitochondrial pyruvate carrier; OAA, oxaloacetate; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase; PEP, phosphoenolpyruvate; PYK, pyruvate kinase; TCA, tricarboxylic acid; α-KG, α-ketoglutarate.

these mechanisms orchestrate robust tumor immune evasion (56). In summary, the synergistic effects of TME acidification and sustained high lactate levels drive tumor progression by disabling immune surveillance and fortifying cancer cells against host defenses.

Mechanistic investigations have confirmed that GPR81, a lactate receptor, is a pivotal modulator of both tumor proliferation and metastatic progression (57). Evidence from *in vitro* and *in vivo* models has suggested that GPR81 regulates metabolic processes in cancer cells through autocrine loops and simultaneously drives immune escape via paracrine mechanisms (58,59). In breast cancer (BC), *in vitro* experiments have revealed elevated GPR81 levels relative to healthy mammary epithelium (60), and knockdown of GPR81 markedly suppresses BC cell proliferation (61). Furthermore, activation of GPR81 by lactate induces PD-L1 upregulation, thereby promoting immune evasion (62). Additionally, experimental findings have identified a signaling axis in which lactate activates STAT3, which subsequently binds to the GPR81 promoter to induce GPR81 transcription (57). In lung cancer (LC)

models, inhibition of GPR81 signaling reduces PD-L1 protein abundance (63). Moreover, silencing GPR81 in hypopharyngeal squamous cell carcinoma cells potentiates cisplatin-induced apoptosis (64). Preclinical studies have also demonstrated that antagonizing GPR81 augments the therapeutic efficacy of metformin (65,66). From a clinical perspective, the contribution of lactate metabolism to metastasis is corroborated by correlative analyses in patient populations (67). Driven by the Warburg effect, LDHA expression shows a direct linear relationship with lactate levels, and its depletion has been observed to inhibit metastasis in hepatocellular carcinoma (HCC) (68,69). In human BC tissues, the potassium channel KCNK1 is markedly upregulated and is associated with poor prognosis. Mechanistically, KCNK1 physically interacts with LDHA to enhance lactate production, creating a positive feedback loop that drives metastatic spread (70). Furthermore, clinical data have indicated that patients with cervical cancer (CC) exhibiting high LDH levels are at a greater risk for deep stromal invasion and nodal metastasis (71). Similarly, in cases of brain metastasis, elevated serum LDH is inversely associated with overall survival (OS) (72).

3. Lactylation and the associated regulatory mechanisms

While the pivotal role of lactate in tumor biology has long been recognized, the precise molecular machinery governing its regulatory effects remained obscure until the conceptualization of lactylation. Consequently, the identification of this modification has notably broadened the horizon of PTM research, offering a novel framework to decipher the molecular impact of lactate on key physiological and pathological events within cancer (9). Current evidence has established lactylation as a pervasive biological phenomenon that is intrinsically linked to the proliferation of diverse malignancies (20). Driven by these insights, substantial investigative efforts have been invested in this field.

Discovery of protein lactylation. Histones are fundamental chromatin proteins that compact the eukaryotic genome into nucleosomes and higher-order chromosomal structures, thereby maintaining physiological stability (73,74). PTMs of these proteins provide a crucial regulatory layer, influencing DNA-dependent processes to facilitate cellular differentiation and optimize gene function. Furthermore, sequence variants within histone families enrich the chromatin landscape, offering diverse mechanisms for signaling and regulation. While initial reports characterized histone lactylation broadly, a recent study by Zhang *et al* (75) employed chemical analysis to differentiate three distinct isomers: Lysine L-lactylation (Kl-la), N-ε-(carboxyethyl)-lysine (Kce) and D-lactyllysine (Kd-la). Notably, this investigation established Kl-la as the dominant isomer on histones, specifically induced by upregulated glycolytic flux. This distinction is particularly relevant in oncology, given that the Warburg effect drives tumor cells to generate L-lactate, the specific substrate for Kl-la. Conversely, Kd-la originates from methylglyoxal, a toxic metabolic byproduct. This suggests that Kl-la serves as the primary functional bridge connecting metabolic reprogramming to tumor epigenetics, whereas the specific roles of Kce and Kd-la within the TME warrant further independent study (75). Utilizing high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) on trypsinized core histones from human MCF-7 cells, Zhang *et al* (9) pioneered the detection of a specific 72.021 Da mass shift on lysine residues. The authors further validated the widespread occurrence of histone lysine lactylation using metabolic isotope labeling, thereby establishing a cornerstone for Kl-la research. While this work focused on characterizing histone lactylation as a novel epigenetic regulator of transcription, subsequent research broadened this perspective. Subsequently, Gaffney *et al* (76) detected lactylation on various metabolic enzymes associated with glycolysis, suggesting that this modification could exert negative feedback control on glycolytic flux. The findings of this previous study underscored the ubiquity of lactylation across human tissues, demonstrating that this modification is not confined to histones but also exerts regulatory effects on non-histone proteins.

Non-histone lactylation is increasingly recognized as a pivotal regulator of a range of cellular processes in both physiological and pathological contexts. The functional impact and enzymatic dynamics of this modification are dictated by the subcellular positioning and protein-protein interactions of the specific substrates, employing varied mechanisms to modulate target protein activity (77). Broadly, lactate-driven protein modification is markedly ubiquitous across diverse biological systems. In the context of *Toxoplasma gondii*, a prevalent parasitic pathogen, investigations have revealed that lactylated proteins are present in various subcellular organelles. These modifications are closely linked to vital processes such as mRNA splicing, glycolytic metabolism, aminoacyl-transfer RNA (tRNA) biosynthesis, RNA transport and several signaling cascades (e.g., DNA damage repair and mTOR signaling) (78). Similarly, proteomic analyses in yaks have identified 421, 308 and 650 lactylated proteins in cardiac, muscular and hepatic tissues, respectively; these modifications are integral to metabolic regulation and the maintenance of physiological homeostasis (79). Furthermore, in the plant kingdom, researchers have characterized 927 specific lactylation sites across 394 proteins in wheat (80). Furthermore, mechanistic inquiries into specific non-histone targets have yielded profound insights. For example, the lactylation of α-myosin heavy chain has been shown to maintain sarcomeric integrity and functionality in a mouse model, effectively mitigating the progression of heart failure (81). In oncology, MRE11, a key mediator of homologous recombination (HR), has been reported to undergo lactylation at residue K673, a modification that reduces tumor cell susceptibility to chemotherapy. Consequently, inhibiting MRE11 lactylation restores the sensitivity of cancer cells to agents such as cisplatin and poly(ADP-ribose) polymerase inhibitors (PARPi) (82).

Mechanisms controlling protein lactylation. Elucidating the precise regulatory machinery of lactylation necessitates a thorough characterization of its enzymatic effectors. This regulatory system is orchestrated by three distinct classes of proteins: 'Writers' that deposit lactyl moieties onto specific residues, 'erasers' that catalyze the removal of these modifications, and 'readers' that possess specialized domains to interpret site-specific epigenetic codes. Drawing parallels to the successful therapeutic targeting of acetylation enzymes in

oncology (83), it is postulated that the enzymatic regulators of lactylation hold comparable potential as precision targets for treating cancer and other pathologies.

Writers. The bromodomain-containing protein p300, traditionally recognized for catalyzing histone H3 acetylation to drive transcription (84), was established by Zhang *et al* (9) to be a dual-function enzyme also capable of mediating histone lactylation. Mechanistic studies have revealed that p300 overexpression can augment histone lactylation in 293T cells, whereas its depletion was shown to markedly diminish H3 lysine 18 lactylation (H3K18la) in both HCT116 and 293T cell lines (85,86). Subsequent investigations have broadened the functional scope of p300. For example, Minami *et al* (87) demonstrated that p300 facilitated osteoblast differentiation through lactate-induced histone modification. In cardiovascular pathology, Dong *et al* (88) reported that lipid peroxidation accelerated atherosclerosis by triggering endothelial-to-mesenchymal transition, a process driven by lactate-dependent H3K18la via the p300/ASF1A complex. Furthermore, therapeutic interventions targeting p300 have shown promise; Wang *et al* (89) reported that andrographolide alleviated aortic valve calcification by disrupting p300-mediated histone H3 lactylation. p300 also modulated inflammatory responses; its inhibition suppressed the lactylation of Yin-Yang 1, thereby mitigating microglial inflammation (90). In oncology, p300 has been characterized as the primary histone lactylation writer in pancreatic ductal adenocarcinoma (PDAC) (91). Additionally, in intrahepatic cholangiocarcinoma, p300 has been reported to catalyze the lactylation of nucleolin (NCL) at lysine (K)477, a modification that fuels tumor proliferation and invasion (92).

Beyond p300, the repertoire of lactyltransferases has expanded. Ju *et al* (93) identified alanyl-tRNA synthetase (AARS)1 as an enzyme capable of utilizing ATP and lactate to directly catalyze protein lactylation. Similarly, the acetyltransferase KAT8 has been implicated in depositing lactyl marks on numerous substrates. Notably, KAT8 deficiency has been shown to markedly impair CRC growth within lactate-rich microenvironments, highlighting its potential as a therapeutic target (94).

Recent evidence has also highlighted the role of 5-methylcytosine (m5C) in CRC progression (95,96). The m5C methyltransferase NSUN2 is frequently upregulated and drives oncogenesis in CRC. A critical signaling axis involves NSUN2 (as the writer) and YBX1 (as the reader) regulating ENO1, thereby reprogramming glucose metabolism to increase lactate production. This accumulated lactate subsequently enhances NSUN2 transcription via H3K18la and promotes NSUN2 lactylation at K356, a modification essential for RNA binding. This establishes a positive feedback loop within the NSUN2/YBX1/m5C-ENO1 axis, effectively linking metabolic shifts with epigenetic remodeling (95). Additionally, TIP60 acts as the specific writer for NBS1 lactylation at K388, a modification that facilitates HR repair (97). In hepatic stellate cell activation, hexokinase 2 (HK2) serves a requisite role in driving histone lactylation-dependent gene expression; consequently, HK2 knockdown mitigates stellate cell activation and liver fibrosis (98). Collectively, these findings underscore the pivotal roles of p300, AARS1, KAT8, NSUN2, TIP60 and HK2 as key enzymatic effectors of protein lactylation.

Erasers. The superfamily of histone lysine deacetylases (HDACs) is traditionally divided into two primary lineages: The classical zinc-dependent HDACs and the NAD^+-requiring Sirtuin (SIRT) family (99). While the classical zinc-dependent HDAC1-3 are characterized as robust deacylase complexes (100), the SIRT family generally demonstrates comparatively limited delactylase efficacy (101). Specific functional roles have been delineated for these enzymes; for example, Fan *et al* (102) reported that HDAC2 acted as a negative regulator of angiogenesis by diminishing H3K9 lactylation. Concurrently, HDAC2 has been implicated as a putative eraser of histone lactylation within PDAC cells (91). During genomic maintenance, HDAC3 serves as the specific delactylase for NBS1 during DNA repair processes (97). Furthermore, Zu *et al* (103) established SIRT2 as a proficient eraser of histone lactylation. This is exemplified by the regulation of METTL16, an atypical methyltransferase: Under copper stress, METTL16 undergoes lactylation at K229, a modification that is antagonized by SIRT2. Collectively, current evidence positions HDAC1-3 and SIRT2 as pivotal regulatory enzymes governing the removal of lactyl modifications.

Readers. During PTM, the functional execution of an epigenetic mark depends not merely on its deposition by a writer, but crucially on its subsequent recognition by specialized effector proteins. These proteins, termed readers, possess distinct structural domains engineered to identify and bind to specific site-specific modifications (104). While the characterization of readers specific to protein lactylation has historically lagged behind that of writers and erasers, the field has seen advances over the past 2 years. As aforementioned, YBX1 has been identified as a direct reader of lactylated ENO1 in CRC, serving an integral role in the NSUN2/YBX1/m5C-ENO1 signaling axis; a discovery with profound implications for understanding CRC pathogenesis. Hu *et al* (105) used proteomic profiling of H3K18la immunoprecipitates to identify the specific recruitment of Brg1 during cellular reprogramming. Their analysis demonstrated co-enrichment of H3K18la and Brg1 at the promoters of genes governing pluripotency and epithelial junction integrity. Furthermore, biochemical validation of the physical interaction between Brg1 and H3K18la effectively established Brg1 as a bona fide reader of histone lactylation (105). Despite these isolated advances, the current landscape of lactylation reader research remains nascent and limited in scope, underscoring an urgent need for more comprehensive mechanistic investigations to fully map this regulatory network.

Lactyl-CoA. Historically, lactyl-CoA was primarily recognized for its industrial utility as a foundational building block in the biosynthesis of biodegradable and biocompatible lactate-derived copolymers (106). From a biochemical perspective, the generation of this intermediate is a prerequisite for protein lactylation, a process that depends on the conversion of lactate to lactyl-CoA catalyzed by the enzyme acyl-CoA transferase. To elucidate this mechanism, Zhang *et al* (106) performed comprehensive enzymological characterization, encompassing screening, cloning and purification, of five candidate lactyl-CoA synthetases, specifically evaluating the stability profiles of the three variants that

demonstrated superior specific activity. Furthermore, the endogenous existence of this metabolite has been definitively confirmed *in vivo*, particularly in mouse liver and muscle tissues. By employing liquid chromatography-high-resolution mass spectrometry validated against synthetic standards, investigators have successfully verified the ubiquitous presence of lactyl-CoA across a range of mammalian cell lines and murine tissues (107).

Molecular pathways regulating lactylation

Glycolytic pathway. The generation of lactate serves as the fundamental nexus connecting the glycolytic pathway to protein lactylation. Generally, the abundance of lactylation modifications mirrors the extent of glycolytic reprogramming and is directly modulated by the concentration of lactate byproducts generated during this metabolic shift. In a study examining the postmortem dynamics of the broiler chicken pectoralis major muscle over 48 h, researchers observed distinct metabolic associations: Protein lactylation was inversely associated with glycogen reserves, glucose levels, glycolytic potential and pH, whereas it was positively associated with lactate accumulation. Furthermore, lactylation levels tracked consistently with the enzymatic activities of LDH and phosphofructokinase, suggesting that this modification may actively participate in the feedback regulation of glycolysis by modulating enzyme expression and function (108). In embryonic stem cells (ESCs), glycolytic metabolism is indispensable for regulating the pluripotency lifecycle, from establishment through maintenance to exit. A specific focus on Esrrb, an orphan nuclear receptor that drives pluripotency and differentiation toward extraembryonic endoderm stem cells, has revealed that it undergoes lactylation at K228 and K232. This modification potentiates the binding affinity of Esrrb for target genes, thereby reinforcing ESC self-renewal capabilities (109). In conclusion, the glycolytic cascade is a primary determinant of the lactylation landscape, positioning lactate as a critical molecular bridge linking metabolic reprogramming to post-translational signaling.

Hypoxia response pathway. In hypoxic microenvironments, the activation of hypoxia-inducible factor (HIF)-1α acts as a critical driver of malignancy, fostering tumor cell migration, invasion and metastatic spread through the promotion of epithelial-mesenchymal transition (110). Mechanistically, HIF-1α functions as a master transcriptional regulator that drives glycolytic machinery (111). By orchestrating the expression of genes essential for glycolysis, HIF-1α indirectly amplifies lactate generation, which subsequently fuels protein lactylation. This regulatory axis has been corroborated by studies utilizing PX-478, a potent HIF-1α inhibitor; inhibition of HIF-1α was shown to abrogate the surge in extracellular lactate levels, thereby confirming its modulatory role in lactylation substrate availability (112,113). Beyond indirect regulation, hypoxia may also exert direct control over lactylation-associated enzymes. Recent findings have indicated that intracellular hypoxia triggers mitochondrial protein lactylation via a distinct mechanism: It induces the accumulation of mitochondrial AARS (AARS2). Acting as a non-canonical lysine lactyltransferase, AARS2 targets and inactivates key metabolic enzymes, specifically the pyruvate dehydrogenase complex (PDC) and carnitine palmitoyltransferase 2 (114).

p53-related pathways. There is a distinct association between p53 status and the expression profile of proteins governing aerobic glycolysis in HCC cells. Functionally, the stabilization and subsequent activation of p53 effectively downregulate genes driving aerobic glycolysis and restricts glycolytic flux; this regulatory action notably diminishes lactate generation, thereby impeding the progression of HCC (115). Other studies in HCC have demonstrated that interrupting the p53/isocitrate dehydrogenase 1/HIF-1α signaling cascade shifts cellular metabolism toward mitochondrial respiration while suppressing aerobic glycolysis (116,117). This metabolic switch results in reduced lactate output, further arresting malignant advancement (116). Collectively, these findings indicate that p53 exerts its regulatory influence on lactylation primarily by indirectly modulating the glycolytic pathway.

Non-histone protein lactylation targets. While histone lactylation is recognized as a canonical epigenetic modifier, emerging proteomic landscapes have unveiled a ubiquitous role for this modification across the non-histone proteome, where it critically governs protein stability, enzymatic kinetics and interactome dynamics. These non-histone substrates primarily cluster into three functional domains: Metabolic regulation, DNA damage response and signal transduction, which together orchestrate complex networks that fuel tumorigenesis.

Metabolic enzymes are primary targets of lactylation, establishing a feed-forward mechanism that amplifies the Warburg effect. Specific examples include the lactylation of PDHX at K488 in HCC, which impairs complex assembly to block oxidative phosphorylation while boosting glycolysis (118). Furthermore, aldolase A (ALDOA) lactylation diminishes its binding to DEAD-box helicase 17 (DDX17), a molecular event that augments the stem-like properties of liver cancer cells (119). In immunometabolism, the modification of pyruvate kinase M2 (PKM2) at K62 acts as a switch for macrophage reprogramming, effectively dampening inflammatory outputs (120).

In genomic integrity, lactylation modulates DNA repair machinery, directly underpinning therapeutic resistance. The HR factor MRE11 is lactylated at K673, a modification that potentiates DNA repair efficiency, and consequently reduces cancer cell susceptibility to cisplatin and PARPi (82). Similarly, lactylation events on NBS1 (at K388) and XRCC1 (at K247) have been characterized as drivers of chemo- and radioresistance across diverse malignancies (97,121). This modification tunes critical signaling effectors governing proliferation and immune escape. For example, in Tregs, lactylation of Moesin at K72 amplifies TGF-β signaling, thereby facilitating Treg differentiation and fostering an immunosuppressive niche (122). In intrahepatic cholangiocarcinoma, p300-mediated lactylation of NCL has been shown to drive tumor expansion and invasion by regulating RNA splicing (92). For a comprehensive synthesis of these findings, the specific substrates, modification sites and downstream consequences are systematically detailed in Table I.

4. Protumor role of lactylation in tumors

Lactylation and tumor metabolism. Metabolic reprogramming has been widely recognized as a fundamental driver

Table I. Key non-histone lactylation substrates and functions.

A, Metabolic enzymes

Substrate	Site	Writer/eraser	Tumor/context	Biological function and mechanism	(Refs.)
NMNAT1	K128	Writer: p300	Pancreatic cancer	Supports nuclear NAD+ salvage pathway; promotes tumor growth	(32)
PDHX	K488	-	HCC	Disrupts PDC assembly; promotes metabolic shift to glycolysis	(118)
ALDOA	K230/K322	-	HCC (LCSCs)	Promotes cancer stemness by reducing interaction with DDX17	(119)
PKM2	K62	-	Macrophages	Regulates M1/M2 polarization; suppresses inflammatory metabolic adaptation	(120)

B, DNA repair

Substrate	Site	Writer/eraser	Tumor/context	Biological function and mechanism	(Refs.)
MRE11	K673	-	General cancer cells	Attenuates chemosensitivity to cisplatin and PARPi by promoting HR repair	(82)
NBS1	K388	Writer: TIP60; eraser: HDAC3	General cancer cells	Facilitates HR repair; contributes to resistance	(97)
XRCC1	K247	-	Glioblastoma	Promotes resistance to chemoradiotherapy	(121)

C, Signaling and regulation

Substrate	Site	Writer/eraser	Tumor/context	Biological function and mechanism	(Refs.)
Nucleolin	K477	Writer: p300	Intrahepatic cholangiocarcinoma	Promotes proliferation and invasion via RNA splicing regulation of MADD	(92)
NSUN2	K356	-	Colorectal cancer	Critical for capturing target RNAs; forms NSUN2/YBX1/m5C-ENO1 positive feedback loop	(95)
METTL16	K229	Eraser: SIRT2	-	Interaction with SIRT2 inhibits METTL16 lactylation	(103)
Moesin	K72	-	Tregs	Enhances TGF-β/SMAD3 signaling; promotes Treg generation and immune evasion	(122)
IGF1R	-	-	Lung cancer/ multiple myeloma	Stabilizes IGF1R protein; promotes glycolysis and proliferation	(132,193)

ALDOA, aldolase A; DDX17, DEAD-box helicase 17; HCC, hepatocellular carcinoma; HDAC3, histone lysine deacetylase 3; HR, homologous recombination; K, lysine; LCSCs, liver cancer stem cells; m5C, 5-methylcytosine; PARPi, poly(ADP-ribose) polymerase inhibitors; PDC, pyruvate dehydrogenase complex; PKM2, pyruvate kinase M2; SIRT2, Sirtuin 2; Tregs, regulatory T cells.

of tumorigenesis and malignant progression (123). To fuel sustained proliferation, neoplastic cells undergo profound bioenergetic restructuring (33). Lactylation has emerged as a pivotal epigenetic modulator, altering chromatin topology to influence transcriptional landscapes. Crucially, this modification creates a bidirectional regulatory axis; it not only reshapes the transcriptional and functional profiles of key glycolytic enzymes (124), but also serves as a molecular bridge connecting metabolism to epigenetics, thereby directly upregulating metabolism-associated genes (125).

As established, LDHA functions as the central enzyme catalyzing pyruvate-to-lactate conversion. Concurrently,

GLUT3 is integral to glucose uptake and glycolysis in cancer cells (126). Single-cell sequencing data have revealed the notable upregulation of GLUT3 in both primary and metastatic lesions. Notably, GLUT3 expression has been shown to be positively associated with LDHA levels and lactylation pathways; in gastric cancer, GLUT3 has been reported to modulate lactylation dynamics, thereby driving disease progression (127). In esophageal carcinoma, hypoxic conditions trigger the lactylation of Axin1 and SHMT2 proteins, a modification that further potentiates cell proliferation, metastasis and stemness features (128,129).

The landscape in non-small cell LC (NSCLC) appears multifaceted. Evidence has suggested that lactate can suppress the mRNA levels of glycolytic enzymes (HK1 and PKM) and TCA cycle enzymes (SDHA and IDH3G); chromatin immunoprecipitation assays have confirmed an enrichment of histone lactylation at the promoters of HK1 and IDH3G, indicating that lactate regulates metabolism partly through epigenetic repression (130). Conversely, hypoxia-induced lactylation of SOX9 has been reported to amplify glycolytic activity, thereby enhancing stemness and invasive potential in NSCLC cells (131). Thus, lactylation exerts complex, context-dependent effects on glycolysis within this malignancy.

In LC models, the IGF1/IGF1R axis is critical for metabolic regulation. Research has indicated that stability of the IGF1R oncogene is enhanced by lactate-mediated lactylation, establishing a positive feedback loop that further fuels glycolysis and lactate generation (132). In pancreatic adenocarcinoma, studies have linked elevated global histone lactylation to poor prognosis (91,133). Mechanistically, EP300 has been identified as the writer catalyzing lactylation at K128 of NMNAT1. This modification supports the nuclear NAD^+ salvage pathway, thereby sustaining tumor growth (32). Furthermore, in CC, lactate has been shown to upregulate and stabilize DCBLD1, a type I protein containing an LCCL domain, via lactylation. This stabilization activates the pentose phosphate pathway, ultimately promoting proliferation and metastasis (134). Collectively, these findings underscore protein lactylation as a critical nexus integrating lactate metabolism, oncogenic signaling and clinical outcomes.

Lactylation and the TME. Functionally and structurally, the TME constitutes a sophisticated ecosystem orchestrated by a heterogeneous array of cell types, including endothelial cells, CAFs, mesenchymal stromal cells and various immune cell subsets, such as macrophages, dendritic cells, NK cells, T cells and B cells. Crucially, this multicellular environment establishes a permissive niche that actively supports protein lactylation. Therefore, dissecting the crosstalk between these TME constituents and lactylation pathways, particularly their contributions to tumorigenesis, invasive behavior, and immune evasion, holds potential to advance the frontiers of cancer immunotherapy.

Lactylation in immune cells. Immune populations represent pivotal constituents of the TME; consequently, elucidating the dynamics of lactylation within these cells is of profound scientific significance (Fig. 2) (135).

T lymphocytes. Traditionally, the immune system is conceptualized as a defensive apparatus tasked with distinguishing self from non-self, orchestrating innate and adaptive responses to eliminate threats and preserve tissue homeostasis (136). Within this framework, T lymphocytes occupy a central position (137). As the linchpins of cellular immunotherapy and tumor surveillance, T cells are responsible for antigen recognition, cytokine secretion, and the coordination of broad immune responses to thwart malignant invasion. Based on their distinct surface markers and functional profiles, these lymphocytes are further categorized into specialized subsets (138).

Research highlights the notable sensitivity of T lymphocytes to the lactate-rich milieu of the TME, where lactate signaling fundamentally alters cellular signaling and therapeutic outcomes (139). Specifically, lactate accumulation drives histone lactylation, thereby compromising histone transcriptional activity in $CD4^+$ and $CD8_+$ cells. This epigenetic suppression reduces cytokine production and cytolytic efficacy, ultimately blunting lymphocyte responses and favoring tumor progression (140-142).

Quinn *et al* (143) revealed that under glucose-deprived, lactate-rich conditions, glycolytic effector T cells undergo profound metabolic inhibition. High lactate concentrations drive LDH to reduce NAD^+ to NADH, thereby disrupting the cellular redox balance. This depletion of NAD^+ impairs downstream enzymatic reactions that depend on GAPDH and PGDH, creating a bottleneck that depletes glycolytic intermediates and serine, a critical metabolite derived from 3-phosphoglycerate and essential for T-cell proliferation. Notably, serine supplementation can effectively rescue T-cell proliferation from this lactate-induced reductive stress (143). Beyond metabolic restriction, lactate impairs the T-cell redox system. Pharmacological intervention using dichloroacetate to target tumor lactate metabolism has been shown to reinvigorate T-cell antitumor immunity (144).

In head and neck squamous cell carcinoma (HNSCC), H3K9 lactylation is linked to immunotherapy resistance, activating immune checkpoints via IL-11 and causing $CD8^+$ T-cell dysfunction (142). Furthermore, GLUT10 has been implicated as a crucial GLUT for $CD8^+$ T-cell activation. Lactate accumulates in the TME and directly binds to GLUT10, blocking glucose uptake; therefore, disrupting this lactate-GLUT10 interaction offers a novel therapeutic avenue to restore $CD8^+$ cytotoxicity (145).

The clinical efficacy of PD-1 blockade hinges on the balance between effector $CD8^+$ T cells and immunosuppressive Tregs. In highly glycolytic tumors (such as MYC-amplified or hepatic cancers), Tregs exhibit higher PD-1 levels than effector T cells. This occurs because Tregs in low-glucose environments actively import lactate via MCT1, thereby driving nuclear translocation of NFAT1 and upregulating PD-1, whereas effector expression is suppressed. Thus, a lactate-rich TME selectively upregulates PD-1 on Tregs (146). Additionally, lactate fuels Treg generation through the specific lactylation of Moesin at K72. This modification strengthens the interaction between Moesin and TGF-β receptor I and activates downstream SMAD3 signaling. Consequently, combining anti-PD-1 therapy with LDH inhibitors yields superior efficacy over monotherapy (122). These findings

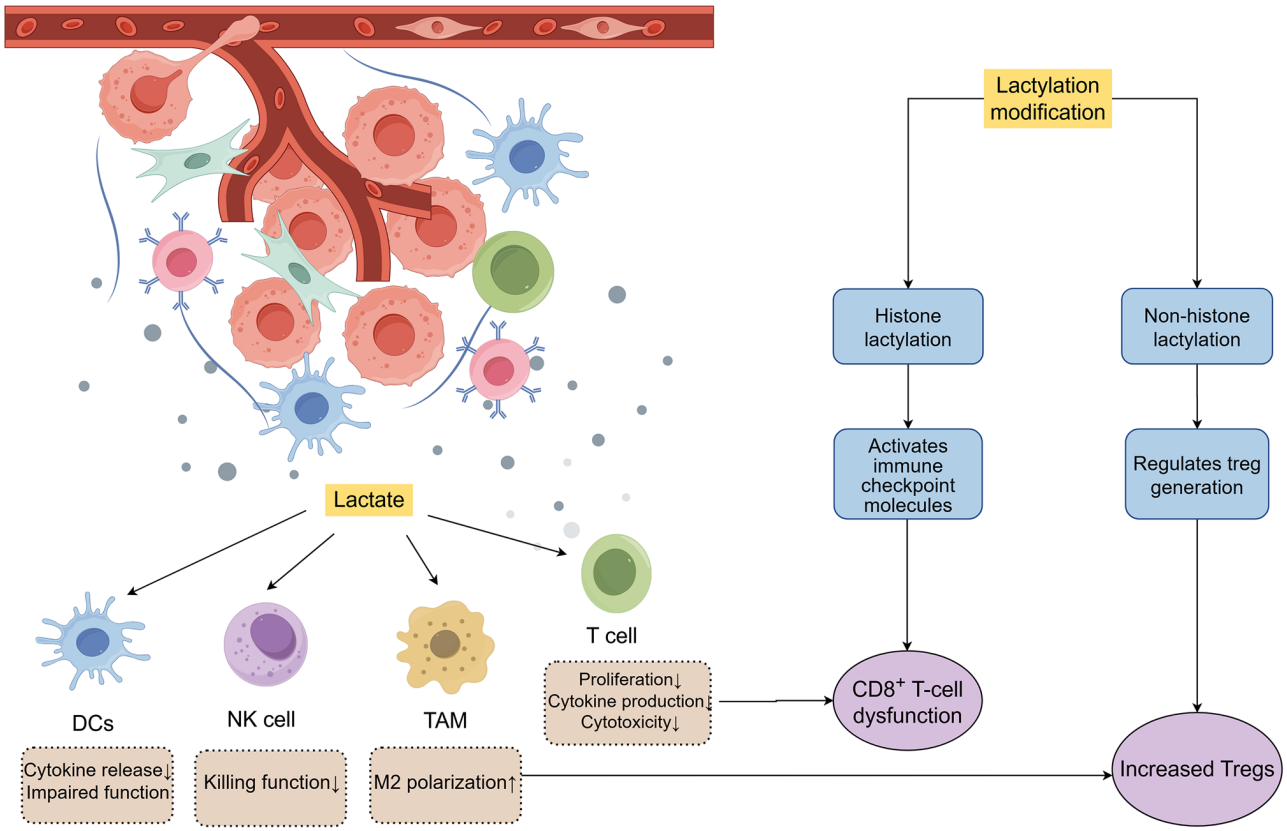

Figure 2. Impact of lactate-induced lactylation on immune cell populations within the tumor microenvironment. Lactate directly impairs the effector functions of various immune cells through multiple mechanisms: i) DCs: High lactate concentrations suppress cytokine release and cause overall functional impairment, thereby dampening the initiation of immune responses. ii) NK cells: The cytotoxic 'killing function' of NK cells is markedly suppressed, facilitating tumor immune evasion. iii) TAMs: Lactate promotes the polarization of macrophages toward the pro-tumorigenic M2 phenotype. These M2-like TAMs further contribute to the expansion of the Treg pool (indicated by the arrow). iv) T cells: Lactate exposure leads to a comprehensive reduction in T-cell fitness, characterized by diminished proliferation, decreased cytokine production and impaired cytotoxicity. The intracellular accumulation of lactate facilitates protein lactylation, which can be categorized into two major pathways: i) Histone lactylation: This epigenetic modification activates the transcription of immune checkpoint molecules ultimately driving $CD8^+$ T-cell dysfunction and exhaustion. ii) Non-histone lactylation: This modification acts as a key regulator in metabolic and signaling pathways that govern Treg generation. Increased non-histone lactylation, coupled with signals from M2 macrophages, leads to an increased Treg population. Figure was generated by Figdraw (www.figdraw.com ID: PROUR10489). NK, natural killer; TAMs, tumor-associated macrophages; Treg, regulatory T cell; DC, dentritic cell.

suggest that targeting lactylation-driven Treg differentiation constitutes a promising strategy to provide novel options in cancer treatment.

Macrophages. As cornerstones of the innate immune architecture, macrophages are defined by their marked phenotypic malleability. This high plasticity allows them to orchestrate responses to diverse physiological and pathological cues by transitioning between functional states (147,148). This heterogeneity is traditionally conceptualized as 'polarization', a spectrum often simplified into a dichotomy dictated by the microenvironment: The classically activated (M1) and alternatively activated (M2) phenotypes, which generally exhibit antagonistic roles (149). M1 macrophages are characterized by robust antigen-presenting capabilities, and the secretion of proinflammatory cytokines such as IL-12, IL-23 and TNF-α (150). Conversely, the M2 phenotype is predominantly aligned with anti-inflammatory processes, and is strongly implicated in fostering tumor proliferation and metastasis (55). Emerging evidence has suggested that metabolic rewiring is not merely a consequence but a prerequisite for this phenotypic switching (151). Specifically, the lactylation of PKM2 at K62 has been isolated as a pivotal mechanism driving the metabolic reprogramming essential for macrophage inflammatory activation (120).

In the TME, TAMs display notable heterogeneity, adapting their function in response to niche-specific signals. While it is established that metabolic shifts accompany these phenotypic changes, recent findings have argued that metabolic reprogramming actively dictates the activation state and function of macrophages (152,153). For example, in CRC, RARγ downregulation in TAMs is associated with poor clinical outcomes. Mechanistically, tumor-derived lactate drives H3K18 lactylation, which transcriptionally suppresses the RARγ gene in macrophages, thereby accelerating disease progression (154). Both bioinformatics profiling and real-world clinical data corroborate that elevated H3K18 lactylation serves as a negative prognostic indicator (155,156). Notably, the regulation is bidirectional: Macrophages can also modulate the lactylation landscape. In glioblastoma (GBM) models, monocyte-derived macrophages have been shown to actively erase histone lactylation. This erasure facilitates the intratumoral accumulation of T cells and suppresses tumor growth (157). Consequently, a reciprocal regulatory axis between macrophages and

lactylation collectively shapes the trajectory of tumor initiation and development.

Dendritic cells (DCs). In addition to macrophages and T cells, high lactate accumulation in the TME also impairs the function and cytokine release of DCs (21). In tumor-infiltrating myeloid cells (TIMs), the upregulation of lactylation enzyme METTL3 induces immunosuppressive effects in CRC (158). Lactic acid inhibits the differentiation and antigen presentation of DCs, promoting their transformation into tumor-associated DCs (TADCs), which results in a reduction of IL-12 secretion and impaired immune response (159). The transcription factor SREBP2, influenced by lactic acid, further regulates the maturation of DCs and their immunosuppressive functions, thereby inhibiting anti-tumor immune responses (160).

NK cells. Leveraging established gene signatures associated with histone lactylation, a study utilized single-sample gene set enrichment analysis to assess the cellular landscape of the TME. The analysis highlighted a clear stratification; the low-lactylation cohort was characterized by a robust infiltration of NK cells and cytotoxic lymphocytes. Conversely, the high-lactylation group exhibited a predominance of stromal elements, specifically showing enriched populations of fibroblasts and endothelial cells (125).

Lactylation in stromal cells. CAFs represent a prominent and diverse mesenchymal population within the TME, serving a pivotal role in orchestrating malignant behaviors (161). In clear cell renal cell carcinoma (ccRCC), histone lactylation in CAFs has been shown to drive tumor progression, with TIMP1 identified as a central downstream target of this epigenetic modification (162). Furthermore, in gastric cancer, the epigenetic landscape of CAFs, specifically defined by H3K18la levels, critically affects the therapeutic efficacy of immune checkpoint inhibitors by regulating PD-L1 abundance (163). Regarding the vascular component, tumor endothelial cells typically remain quiescent under physiological conditions. However, in lung adenocarcinoma (LUAD), SLC25A29 has emerged as a vital prognostic determinant linked to tumor staging. Mechanistic studies have confirmed that SLC25A29 expression is epigenetically regulated by H3K14 and H3K18 lactylation at its promoter (164,165). Functionally, downregulation of SLC25A29 promotes endothelial proliferation and migration while suppressing apoptosis, thereby accelerating LUAD progression (166).

Lactylation in cancer cells. Epigenetic dysregulation is increasingly recognized as a cornerstone of tumorigenesis. As a newly defined epigenetic modification, lactylation orchestrates tumor development by regulating both histone and non-histone substrates, while simultaneously modulating metabolic plasticity (167-169). HCC represents a highly lethal malignancy and ranks as the second leading cause of cancer mortality globally (170). Its pathogenesis is frequently preceded by chronic liver injury, stemming from hepatitis B, hepatitis C or steatohepatitis, where the risk of mortality scales exponentially with the severity of fibrosis (171). The pathogenic continuum from fibrosis to cirrhosis, and ultimately to HCC, involves complex regulatory shifts (172).

Emerging evidence has implicated lactylation, a structural analog of acetylation, as a driver of this fibrotic progression. Notably, gene signatures marked by histone lactylation in fibrotic tissues are concomitantly upregulated in HCC, suggesting a direct mechanistic link between fibrotic remodeling and hepatocarcinogenesis (173). Furthermore, liver cancer stem cells (LCSCs) underpin the phenotypic heterogeneity of HCC. Proteomic profiling has unveiled that ALDOA undergoes lactylation at residues K230 and K322; mechanistically, this modification disrupts the physical interaction between ALDOA and DDX17, thereby potentiating DDX17 function and reinforcing the stem-like phenotype of LCSCs (119).

In BC, The Cancer Genome Atlas analysis has highlighted the pivotal role of lactylation (174). Specifically in triple-negative BC (TNBC), an aggressive subtype, elevated histone H4 lysine 12 lactylation (H4K12la) is inversely associated with OS (175). This poor prognosis is driven by the H4K12la-mediated transcriptional suppression of Schlafen 5, delineating a novel oncogenic axis (176). Similarly, in ovarian cancer (OC), the chemokine CCL18 is frequently upregulated; this is epigenetically driven by H3K18 lactylation, which actively fuels tumorigenesis (177).

Uncontrolled proliferation and metastatic dissemination represent defining hallmarks of malignancy, with the latter accounting for ~90% of cases of cancer-related mortality (178,179). Against this backdrop, the rapidly expanding field of lactylation research offers novel therapeutic paradigms for the treatment of refractory tumors. In HCC, lactylation drives malignancy through dual epigenetic and metabolic mechanisms. First, pyrroline-5-carboxylate reductase 1 increases IRS1 transcriptional activity by modulating H3K18 lactylation at its promoter, thereby increasing proliferation and metastasis (180). Moreover, the metabolic shift from oxidative phosphorylation to aerobic glycolysis is cemented by inactivation of the mitochondrial PDC. Specifically, lactylation of the PDHX component at K488 impairs PDC assembly, a critical event that accelerates HCC progression (118).

In TNBC, elevated glycolytic flux initiates a specific oncogenic cascade: It promotes histone lactylation at the c-Myc promoter, leading to c-Myc upregulation. This, in turn, transcriptionally activates the splicing factor SRSF10, ultimately driving accelerated tumor growth (181). Similarly, in OC, bioinformatics profiling has linked lactylation-associated gene signatures to specific tumor subtypes and immune landscapes (156). Immunohistochemical validation has further confirmed that elevated histone lactylation serves as a robust indicator of poor prognosis in patients with OC (155).

Immune evasion constitutes a fundamental barrier in oncology. In NSCLC, elevated lactylation is associated with adverse outcomes. Mechanistically, H3K18la directly drives POM121 transcription, activating the POM121/MYC/PD-L1 signaling axis to blunt immune surveillance. Consequently, targeting this axis by combining glycolysis inhibitors with anti-PD-1 antibodies has demonstrated potent antitumor efficacy (182).

The CRC landscape reveals complex roles for lactylation in initiation, progression and therapeutic resistance (94,183). Regarding chemoresistance, SMC4 downregulation induces a 'diapause-like' quiescent state. This downregulation increases lactate production via glycolytic enzymes while suppressing

PGAM1. The resulting increase in lactate levels drives histone lactylation to upregulate ABC transporters, thereby conferring chemoresistance (184). Furthermore, the interplay between the microbiome and non-histone lactylation is critical yet underappreciated (185,186). For example, tumor-resident ' suppresses NF-κB signaling by inducing lactylation of RIG-I. This modification drives M2 macrophage polarization and facilitates colorectal liver metastasis. Targeting this pathway with a specific RIG-I lactylation inhibitor has been shown to restore sensitivity to 5-fluorouracil (187).

In ccRCC, pathogenesis is closely tied to the inactivation of von Hippel-Lindau (VHL) (188). Loss of VHL function perturbs histone lactylation dynamics, leading to the transcriptional activation of PDGFRβ. This establishes a positive feedback loop between histone lactylation and PDGFRβ signaling, presenting a viable therapeutic target (189).

Beyond solid tumors, lactylation markedly impacts hematological malignancies. In leukemia, histone lactylation promotes progression by upregulating ALKBH3, which removes m1A methylation from SP100A and consequently destabilizes the tumor suppressor PML (190). In diffuse large B-cell lymphoma, elevated lactate levels are closely linked to prognosis, immune function and drug resistance (191). Similarly, in multiple myeloma (MM), lactylation-related genes have emerged as prognostic biomarkers (192). Addressing resistance to proteasome inhibitors in MM, research indicates that Mucin20 drives resistance by modulating the MET signaling pathway through the suppression of IGF-1R lactylation (193). Despite these advances, the field remains nascent and mechanistic landscapes await further elucidation.

5. Lactylation modifications influence cancer therapy

Novel approaches to tumor therapy. Lactate serves as the primary substrate for protein lactylation and drives tumor progression through multiple molecular mechanisms. Consequently, pharmacologically intercepting the lactate axis constitutes a promising frontier in oncology (194). Current therapeutic strategies have focused extensively on blocking lactate metabolism and transport, with research directed toward LDHA/B and MCT1/4.

Regarding LDH inhibition, several potent compounds targeting LDHA have emerged. For example, ML-05 has been shown to effectively curtail cellular lactate synthesis and suppress proliferation in melanoma models (195). Furthermore, evidence suggests that LDHA inhibitors can function as valuable adjunctive agents in pancreatic cancer regimens (196). While LDHB is generally considered secondary to LDHA in tumorigenesis, it retains functional importance in modulating autophagy, apoptosis and the immune microenvironment (197,198). To date, the selective LDHB inhibitor AXKO-0046 has demonstrated competitive inhibition; however, it remains a tool for mechanistic validation in cancer metabolism rather than a clinical therapeutic (199).

AZD3965 represents a first-in-class inhibitor targeting MCT1 and MCT2 with selectivity over MCT3 and MCT4. Preclinically, it suppresses hematological tumor growth, and exhibits synergy with doxorubicin or rituximab in diffuse large B-cell and Burkitt lymphomas (200). Crucially, the 2023 publication of its Phase I trial (NCT01791595) provided pivotal clinical insights. While the drug showed a favorable safety profile, its single-agent efficacy was limited, likely due to a compensatory lactate efflux mechanism mediated by MCT4 in solid tumors. This underscores the necessity for patient stratification strategies, specifically targeting MCT4-negative tumors, or the development of combination therapies (201).

Conversely, MCT4 is essential for lactate efflux under hypoxic conditions, and its blockade can induce lethal intracellular lactate accumulation (202). In HNSCC, MCT4 inhibition has been proven to attenuate invasiveness (203). A notable advancement involves VB124, a potent MCT4 inhibitor that restricts liver tumor growth in immunocompetent models by potentiating $CD8^+$ T-cell infiltration and cytotoxicity (204). These findings position VB124 as a high-priority candidate for future clinical investigation, particularly in synergistic combinations with immunotherapy.

Lactylation promotes tumor drug resistance. Therapeutic recalcitrance represents a formidable barrier in oncology, profoundly undermining the clinical efficacy of antineoplastic regimens (205). Accumulating evidence implicates protein lactylation, which affects both histone and non-histone substrates, as a potent driver of this phenomenon, conferring resistance to radiotherapy and chemotherapy through multiple molecular mechanisms.

In GBM, clinical outcomes have revealed that patients with elevated ALDH1A3 expression derive minimal benefit from postoperative chemoradiation. To elucidate the molecular basis of this failure, proteomic profiling of lactate-rich GBM stem cells identified the lactylation of XRCC1 at K247 as a pivotal determinant of radio- and chemoresistance (121). Parallel investigations in GBM have further established that H3K9 histone lactylation drives temozolomide resistance. Notably, the repurposed antiepileptic agent stiripentol has been shown to effectively inhibit this lactylation event, offering a viable combinatorial strategy for GBM management (206).

In bladder cancer, where resistance to platinum-based agents is common, single-cell RNA sequencing has unveiled a strong association between cisplatin resistance and histone H3K18la (207). Similarly, for advanced prostate cancer, resistance to the androgen receptor signaling inhibitor enzalutamide poses a notable challenge. Mechanistic studies attribute this to the NF-κB/STAT3/SLC4A4 signaling axis, which facilitates p53 lactylation, thereby driving tumor progression and drug insensitivity (208,209).

In HCC, acquired resistance remains the primary limiting factor for molecular targeted therapies. In lenvatinib-resistant models, a lactylated IGF2BP3-PCK2-SAM-m6A feedback loop has been found to sustain high expression of PCK2 and NRF2; this upregulation bolsters the antioxidant defense system, thereby maintaining lenvatinib resistance (210). Furthermore, although bevacizumab is a cornerstone of CRC treatment, its efficacy is often compromised by resistance mechanisms linked to histone lactylation. Consequently, targeting histone lactylation in conjunction with bevacizumab represents a novel therapeutic option for overcoming resistance in advanced malignancies (183). For reference, detailed data regarding these treatment associations are compiled in Table II.

Table II. Onco-therapeutic drugs targeting lactate metabolism and lactylation.

Target	Drug name	Research status	Applications	Mechanism	(Refs.)
GPR81	Generic antagonists	Preclinical	Breast cancer	Enhances antitumor effects of metformin	(65,66)
p300	Andrographolide	Preclinical	Aortic valve calcification/cancer	Interferes with p300-mediated histone lactylation	(89)
PDK/lactate	Dichloroacetate	Clinical	Solid tumors	Inhibits lactate metabolism; enhances T-cell antitumor function	(144)
Histone H3K18la	Inhibitors	Preclinical	CRC (bevacizumab resistance)	Inhibition sensitizes tumors to anti-angiogenic therapy	(183)
LDHA	ML-05	Preclinical	Melanoma, pancreatic cancer	Inhibits lactate production; suppresses proliferation	(195,196)
LDHB	AXKO-0046	Preclinical	Cancer metabolism research	Competitively inhibits LDHB; modulates autophagy	(199)
MCT1	AZD3965	Phase I clinical trial	Lymphoma (DLBCL), solid tumors	Blocks lactate transport; exhibits synergy with chemotherapy	(200,201)
MCT4	VB124	Preclinical	HCC, HNSCC	Inhibits lactate efflux; enhances CD8+ T-cell infiltration	(204)
Lactylation	Stiripentol	Clinical (epilepsy); preclinical (GBM)	GBM	Inhibits H3K9 lactylation; overcomes temozolomide resistance	(206)

CRC, colorectal cancer; DLBCL, diffuse large B-cell lymphoma; GBM, glioblastoma; H3K18la, H3 lysine 18 lactylation; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter.

Challenges and future directions. Despite the substantial therapeutic potential of targeting lactate metabolism and lactylation, translation of these strategies into clinical practice is currently hindered by limitations in single-agent potency and pharmacological specificity.

Monotherapies frequently fail to achieve durable responses, a failure attributed to tumor metabolic flexibility and compensatory activation of alternative transport mechanisms, exemplified by the upregulation of MCT4 following MCT1 blockade. To overcome this, combinatorial regimens have been prioritized to induce synergistic antitumor activity. A particularly promising option involves coupling glycolysis or lactate inhibitors with immunotherapeutic agents (211). Given that lactate accumulation within the TME actively dampens T-cell cytotoxicity, therapeutic depletion of lactate alleviates this immunosuppression. Indeed, empirical data have demonstrated that the concurrent administration of anti-PD-1 antibodies and LDH inhibitors yields efficacy superior to that of either agent alone (212). In NSCLC, combining glycolysis inhibitors with immune checkpoint blockade has been shown to disrupt the histone lactylation-driven POM121/MYC/PD-L1 signaling axis, effectively resensitizing resistant tumors to anti-PD-1 therapy (182).

Conversely, the development of lactylation-specific inhibitors is constrained by the risk of off-target toxicity. A notable bottleneck is the functional duality of 'writer' enzymes; p300, for example, functions as both a histone acetyltransferase and a lactyltransferase (85). Consequently, indiscriminate inhibition of p300 risks suppressing physiological histone acetylation, which could catastrophically disrupt essential transcriptional programs and cellular homeostasis. Future medicinal chemistry efforts must therefore prioritize the structural delineation of domains specific to lactyl-CoA binding. The goal is to uncouple lactylation inhibition from acetylation, thereby maximizing therapeutic precision while minimizing collateral toxicity. Furthermore, recent literature positions lactylation as a central epigenetic node integrating multifactorial resistance mechanisms. This suggests that targeting downstream effectors, rather than the writers themselves, may offer a strategic bypass around compensatory metabolic adaptations (213).

6. Critical challenges in clinical translation

While the therapeutic potential of targeting lactylation is evident, translating these findings from bench to bedside

faces several critical hurdles that must be addressed in future research.

Limitations in detection and biomarkers. Currently, the identification of lactylation relies heavily on HPLC-MS/MS and isotope metabolic labeling (9). While robust for research, these methods are costly, time-consuming and impractical for routine clinical diagnosis using tissue biopsies or blood samples. Although immunohistochemistry has been used to detect lactylation in OC tissues (155), standardization of antibodies remains a challenge. Future priorities should focus on developing highly specific, lactylation-sensitive imaging agents and noninvasive liquid-biopsy biomarkers to enable real-time monitoring of lactylation dynamics in patients.

Tumor heterogeneity and patient stratification. Lactylation levels exhibit notable heterogeneity not only among patients but also within the TME. For example, single-cell analyses have revealed distinct lactylation patterns in different cell subsets, such as macrophages and cancer stem cells (119,120). This heterogeneity suggests that a 'one-size-fits-all' metabolic therapy may fail. Consequently, the construction of patient-derived xenograft models or organoids to evaluate individual sensitivity to lactylation inhibitors is essential. Furthermore, gene signatures related to lactylation, as identified in OC (156), should be validated as predictive tools for therapeutic response. Consistent with this, recent literature posits that deciphering the specific interaction networks between lactylation and immune checkpoints is critical for advancing precision oncology (214).

Safety and ethical considerations. A major ethical and safety concern is that lactate is not solely a tumor metabolite but a critical fuel for normal physiological functions, including cardiac modulation (13) and skeletal muscle metabolism (39). Broad-spectrum inhibition of lactate production or transport (via systemic LDH or MCT inhibition) carries a risk of severe systemic toxicity, including muscle fatigue and cardiac dysfunction. Therefore, developing drug delivery systems that specifically target the acidic TME or exploiting synthetic lethality to minimize off-target effects on healthy tissues is a prerequisite for clinical trials.

7. Conclusions

Lactate has long been regarded as the end product of glycolysis, but it is now recognized as a multifunctional signaling molecule that serves a central role in promoting tumor cell metabolism and immune evasion. Lactylation, a recently discovered PTM, directly affects the functions of both histones and non-histones, linking metabolic reprogramming to epigenetic regulation. Moreover, lactylation modifications, by modulating cellular metabolic pathways, markedly influence tumor progression, immune suppression and mechanisms of drug resistance across various cancer types. In tumor immunology, lactylation influences the polarization and function of immune cells, including T cells and macrophages, thereby suppressing antitumor immune responses and promoting tumor resistance and recurrence. In the future, in-depth investigation of the mechanisms underlying lactylation, identification of its regulatory factors and the development of targeted therapeutics may provide novel directions and strategies for cancer treatment. By combining metabolic inhibitors with immunotherapy, it is anticipated that the efficacy of cancer treatment can be enhanced and resistance to current therapies can be overcome. These studies will help elucidate the complex role of lactylation modifications in tumorigenesis and drive the development of innovative therapeutic approaches.

Acknowledgements

Not applicable.

Funding

The present study was supported in part by the National Natural Science Foundation of China (grant no. 62372276) and in part by the Investigator-Initiated Basic Research Project of Beijing Luhe Hospital (grant nos. LHYY2025-YJZJC0011 and LHYY2025-YJZJC0012).

Availability of data and materials

Not applicable.

Authors' contributions

All authors contributed to the study conception and design. Literature search, data extraction and literature analysis were performed by YH, WY, QH and YZ. The first draft of the manuscript was written by CZ, XT and NC, and all authors commented on previous versions of the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

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.

References

1. Dart A: Tumour metabolism: Lactic acid: Not just a waste product? Nat Rev Cancer 16: 676-677, 2016.
2. Koukourakis MI and Giatromanolaki A: Warburg effect, lactate dehydrogenase, and radio/chemo-therapy efficacy. Int J Radiat Biol 95: 408-426, 2019.
3. Warburg O, Wind F and Negelein E: The metabolism of tumors in the body. J Gen Physiol 8: 519-530, 1927.
4. Chen AN, Luo Y, Yang YH, Fu JT, Geng XM, Shi JP and Yang J: Lactylation, a novel metabolic reprogramming code: Current status and prospects. Front Immunol 12: 688910, 2021.
5. Shih CC, Lee TS, Tsuang FY, Lin PL, Cheng YJ, Cheng HL and Wu CY: Pretreatment serum lactate level as a prognostic biomarker in patients undergoing supratentorial primary brain tumor resection. Oncotarget 8: 63715-63723, 2017.

6. Wang S, Osgood AO and Chatterjee A: Uncovering post-translational modification-associated protein-protein interactions. Curr Opin Struct Biol 74: 102352, 2022.
7. Chen L and Kashina A: Post-translational modifications of the Protein Termini. Front Cell Dev Biol 9: 719590, 2021.
8. Pan S and Chen R: Pathological implication of protein post-translational modifications in cancer. Mol Aspects Med 86: 101097, 2022.
9. Zhang D, Tang Z, Huang H, Zhou G, Cui C, Weng Y, Liu W, Kim S, Lee S, Perez-Neut M, *et al*: Metabolic regulation of gene expression by histone lactylation. Nature 574: 575-580, 2019.
10. Hu Y, He Z, Li Z, Wang Y, Wu N, Sun H, Zhou Z, Hu Q and Cong X: Lactylation: The novel histone modification influence on gene expression, protein function, and disease. Clin Epigenetics 16: 72, 2024.
11. Liu W, Zhang T, Wang B and Yin H: Aerobic glycolysis promotes NLRP3 inflammasome activation via NLRP3 lactylation. Cell Chem Biol 33: 213-226.e5, 2026.
12. Zhang Y, Wang J, Li C, Lei Z, Zhao X, Xuan X, Sukocheva O, Tse E and Liu J: Protein lactylation in cancer and other pathologies: Epigenetic regulation of glycolysis and its therapeutic perspectives. Semin Cancer Biol 118: 28-43, 2026.
13. Ghosh-Choudhary S and Finkel T: Lactylation regulates cardiac function. Cell Res 33: 653-654, 2023.
14. Yang D, Zheng H, Lu W, Tian X, Sun Y and Peng H: histone lactylation is involved in mouse oocyte maturation and embryo development. Int J Mol Sci 25: 4821, 2024.
15. Nian F, Qian Y, Xu F, Yang M, Wang H and Zhang Z: LDHA promotes osteoblast differentiation through histone lactylation. Biochem Biophys Res Commun 615: 31-35, 2022.
16. Susser LI, Nguyen MA, Geoffrion M, Emerton C, Ouimet M, Khacho M and Rayner KJ: Mitochondrial fragmentation promotes inflammation resolution responses in macrophages via histone lactylation. Mol Cell Biol 43: 531-546, 2023.
17. Chen J, Feng Q, Qiao Y, Pan S, Liang L, Liu Y, Zhang X, Liu D, Liu Z and Liu Z: ACSF2 and lysine lactylation contribute to renal tubule injury in diabetes. Diabetologia 67: 1429-1443, 2024.
18. Zhou Y, Yang L, Liu X and Wang H: Lactylation may be a novel posttranslational modification in inflammation in neonatal hypoxic-ischemic encephalopathy. Front Pharmacol 13: 926802, 2022.
19. Li J, Zeng G, Zhang Z, Wang Y, Shao M, Li C, Lu Z, Zhao Y, Zhang F and Ding W: Urban airborne PM(2.5) induces pulmonary fibrosis through triggering glycolysis and subsequent modification of histone lactylation in macrophages. Ecotoxicol Environ Saf 273: 116162, 2024.
20. Yu X, Yang J, Xu J, Pan H, Wang W, Yu X and Shi S: Histone lactylation: From tumor lactate metabolism to epigenetic regulation. Int J Biol Sci 20: 1833-1854, 2024.
21. Chen J, Huang Z, Chen Y, Tian H, Chai P, Shen Y, Yao Y, Xu S, Ge S and Jia R: Lactate and lactylation in cancer. Signal Transduct Target Ther 10: 38, 2025.
22. Qiao Q, Hu S and Wang X: The regulatory roles and clinical significance of glycolysis in tumor. Cancer Commun (Lond) 44: 761-786, 2024.
23. Yadav D, Yadav A, Bhattacharya S, Dagar A, Kumar V and Rani R: GLUT and HK: Two primary and essential key players in tumor glycolysis. Semin Cancer Biol 100: 17-27, 2024.
24. Sun Q, Güven B, Wagg CS, Almeida de Oliveira A, Silver H, Zhang L, Chen B, Wei K, Ketema EB, Karwi QG, *et al*: Mitochondrial fatty acid oxidation is the major source of cardiac adenosine triphosphate production in heart failure with preserved ejection fraction. Cardiovasc Res 120: 360-371, 2024.
25. Rogatzki MJ, Ferguson BS, Goodwin ML and Gladden LB: Lactate is always the end product of glycolysis. Front Neurosci 9: 22, 2015.
26. Read JA, Winter VJ, Eszes CM, Sessions RB and Brady RL: Structural basis for altered activity of M- and H-isozyme forms of human lactate dehydrogenase. Proteins 43: 175-185, 2001.
27. Vanderlinde RE: Measurement of total lactate dehydrogenase activity. Ann Clin Lab Sci 15: 13-31, 1985.
28. Serganova I, Cohen IJ, Vemuri K, Shindo M, Maeda M, Mane M, Moroz E, Khanin R, Satagopan J, Koutcher JA and Blasberg R: LDH-A regulates the tumor microenvironment via HIF-signaling and modulates the immune response. PLoS One 13: e0203965, 2018.
29. Pérez-Escuredo J, Dadhich RK, Dhup S, Cacace A, Van Hée VF, De Saedeleer CJ, Sboarina M, Rodriguez F, Fontenille MJ, Brisson L, *et al*: Lactate promotes glutamine uptake and metabolism in oxidative cancer cells. Cell Cycle 15: 72-83, 2016.
30. Zhang Z, Liu R, Shuai Y, Huang Y, Jin R, Wang X and Luo J: ASCT2 (SLC1A5)-dependent glutamine uptake is involved in the progression of head and neck squamous cell carcinoma. Br J Cancer 122: 82-93, 2020.
31. Hensley CT, Wasti AT and DeBerardinis RJ: Glutamine and cancer: Cell biology, physiology, and clinical opportunities. J Clin Invest 123: 3678-3684, 2013.
32. Huang H, Wang S, Xia H, Zhao X, Chen K, Jin G, Zhou S, Lu Z, Chen T, Yu H, *et al*: Lactate enhances NMNAT1 lactylation to sustain nuclear NAD(+) salvage pathway and promote survival of pancreatic adenocarcinoma cells under glucose-deprived conditions. Cancer Lett 588: 216806, 2024.
33. Hanahan D and Weinberg RA: Hallmarks of cancer: The next generation. Cell 144: 646-674, 2011.
34. Liberti MV and Locasale JW: The warburg effect: How does it benefit cancer cells? Trends Biochem Sci 41: 211-218, 2016.
35. Shang RZ, Qu SB and Wang DS: Reprogramming of glucose metabolism in hepatocellular carcinoma: Progress and prospects. World J Gastroenterol 22: 9933-9943, 2016.
36. Hay N: Reprogramming glucose metabolism in cancer: can it be exploited for cancer therapy? Nat Rev Cancer 16: 635-649, 2016.
37. Dienel GA: Brain lactate metabolism: The discoveries and the controversies. J Cereb Blood Flow Metab 32: 1107-1138, 2012.
38. Dong S, Qian L, Cheng Z, Chen C, Wang K, Hu S, Zhang X and Wu T: Lactate and myocardiac energy metabolism. Front Physiol 12: 715081, 2021.
39. Bartoloni B, Mannelli M, Gamberi T and Fiaschi T: The multiple roles of lactate in the skeletal muscle. Cells 13: 1177, 2024.
40. Igah I, Ihediwa U and Uzoigwe CE: Lactic acidosis. N Engl J Med 372: 1077, 2015.
41. Manoj KM, Nirusimhan V, Parashar A, Edward J and Gideon DA: Murburn precepts for lactic-acidosis, Cori cycle, and Warburg effect: Interactive dynamics of dehydrogenases, protons, and oxygen. J Cell Physiol 237: 1902-1922, 2022.
42. Bisetto S, Wright MC, Nowak RA, Lepore AC, Khurana TS, Loro E and Philp NJ: New insights into the lactate shuttle: Role of MCT4 in the modulation of the exercise capacity. iScience 22: 507-518, 2019.
43. Hong CS, Graham NA, Gu W, Espindola Camacho C, Mah V, Maresh EL, Alavi M, Bagryanova L, Krotee PAL, Gardner BK, *et al*: MCT1 modulates cancer cell pyruvate export and growth of tumors that Co-express MCT1 and MCT4. Cell Rep 14: 1590-1601, 2016.
44. Anderson NM and Simon MC: The tumor microenvironment. Curr Biol 30: R921-R925, 2020.
45. Gao Y, Zhou H, Liu G, Wu J, Yuan Y and Shang A: Tumor microenvironment: Lactic acid promotes tumor development. J Immunol Res 2022: 3119375, 2022.
46. Apostolova P and Pearce EL: Lactic acid and lactate: Revisiting the physiological roles in the tumor microenvironment. Trends Immunol 43: 969-977, 2022.
47. Wang JX, Choi SYC, Niu X, Kang N, Xue H, Killam J and Wang Y: lactic acid and an acidic tumor microenvironment suppress anticancer immunity. Int J Mol Sci 21: 8363, 2020.
48. Choi JW, Jung SJ, Kasala D, Hwang JK, Hu J, Bae YH and Yun CO: pH-sensitive oncolytic adenovirus hybrid targeting acidic tumor microenvironment and angiogenesis. J Control Release 205: 134-143, 2015.
49. Audero MM, Prevarskaya N and Fiorio Pla A: Ca(2+) Signalling and hypoxia/acidic tumour microenvironment interplay in tumour progression. Int J Mol Sci 23: 7377, 2022.
50. Chen S, Liao C, Hu H, Liao J, Chen Z, Li S, Zeng X, Peng B, Shen S, Li D, *et al*: Hypoxia-driven tumor stromal remodeling and immunosuppressive microenvironment in scirrhous HCC. Hepatology 79: 780-797, 2024.
51. Nasi A, Fekete T, Krishnamurthy A, Snowden S, Rajnavölgyi E, Catrina AI, Wheelock CE, Vivar N and Rethi B: Dendritic cell reprogramming by endogenously produced lactic acid. J Immunol 191: 3090-3099, 2013.
52. Kumar A, Pyaram K, Yarosz EL, Hong H, Lyssiotis CA, Giri S and Chang CH: Enhanced oxidative phosphorylation in NKT cells is essential for their survival and function. Proc Natl Acad Sci USA 116: 7439-7448, 2019.
53. Xie D, Zhu S and Bai L: Lactic acid in tumor microenvironments causes dysfunction of NKT cells by interfering with mTOR signaling. Sci China Life Sci 59: 1290-1296, 2016.
54. Hirschhaeuser F, Sattler UG and Mueller-Klieser W: Lactate: A metabolic key player in cancer. Cancer Res 71: 6921-6925, 2011.

55. Yunna C, Mengru H, Lei W and Weidong C: Macrophage M1/M2 polarization. Eur J Pharmacol 877: 173090, 2020.
56. Nicolini A and Ferrari P: Involvement of tumor immune microenvironment metabolic reprogramming in colorectal cancer progression, immune escape, and response to immunotherapy. Front Immunol 15: 1353787, 2024.
57. Xie Q, Zhu Z, He Y, Zhang Z, Zhang Y, Wang Y, Luo J, Peng T, Cheng F, Gao J, *et al*: A lactate-induced Snail/STAT3 pathway drives GPR81 expression in lung cancer cells. Biochim Biophys Acta Mol Basis Dis 1866: 165576, 2020.
58. Lundø K, Trauelsen M, Pedersen SF and Schwartz TW: Why warburg works: Lactate controls immune evasion through GPR81. Cell Metab 31: 666-668, 2020.
59. Brown TP and Ganapathy V: Lactate/GPR81 signaling and proton motive force in cancer: Role in angiogenesis, immune escape, nutrition, and Warburg phenomenon. Pharmacol Ther 206: 107451, 2020.
60. Roland CL, Arumugam T, Deng D, Liu SH, Philip B, Gomez S, Burns WR, Ramachandran V, Wang H, Cruz-Monserrate Z and Logsdon CD: Cell surface lactate receptor GPR81 is crucial for cancer cell survival. Cancer Res 74: 5301-5310, 2014.
61. Ishihara S, Hata K, Hirose K, Okui T, Toyosawa S, Uzawa N, Nishimura R and Yoneda T: The lactate sensor GPR81 regulates glycolysis and tumor growth of breast cancer. Sci Rep 12: 6261, 2022.
62. Brown TP, Bhattacharjee P, Ramachandran S, Sivaprakasam S, Ristic B, Sikder MOF and Ganapathy V: The lactate receptor GPR81 promotes breast cancer growth via a paracrine mechanism involving antigen-presenting cells in the tumor microenvironment. Oncogene 39: 3292-3304, 2020.
63. Feng J, Yang H, Zhang Y, Wei H, Zhu Z, Zhu B, Yang M, Cao W, Wang L and Wu Z: Tumor cell-derived lactate induces TAZ-dependent upregulation of PD-L1 through GPR81 in human lung cancer cells. Oncogene 36: 5829-5839, 2017.
64. Jia Q, Xu O, Wang J, Dong J, Ren X, Jia X and Shan C: Effects of GPR81 silencing combined with cisplatin stimulation on biological function in hypopharyngeal squamous cell carcinoma. Mol Med Rep 22: 1727-1736, 2020.
65. Chen S, Zhou X, Yang X, Li W, Li S, Hu Z, Ling C, Shi R, Liu J, Chen G, *et al*: Dual Blockade of Lactate/GPR81 and PD-1/PD-L1 pathways enhances the anti-tumor effects of metformin. Biomolecules 11: 1373, 2021.
66. Niu Y, Hu S, Zhang Y, Yang J, Zhang J, He R, Chen L, Xu L, Zhao H, Gan B, *et al*: Lactate-activated GPR81/FARP1 signaling drives insulin-independent glucose uptake and metabolic control. Cell Res 36: 137-151, 2026.
67. Wang Y, Jia H, Lin H, Tan X, Du Z, Chen H, Xu Y, Han X, Zhang J, Zhao S, *et al*: Metastasis-associated gene, mag-1 improves tumour microenvironmental adaptation and potentiates tumour metastasis. J Cell Mol Med 16: 3037-3051, 2012.
68. Rizwan A, Serganova I, Khanin R, Karabeber H, Ni X, Thakur S, Zakian KL, Blasberg R and Koutcher JA: Relationships between LDH-A, lactate, and metastases in 4T1 breast tumors. Clin Cancer Res 19: 5158-5169, 2013.
69. Sheng SL, Liu JJ, Dai YH, Sun XG, Xiong XP and Huang G: Knockdown of lactate dehydrogenase A suppresses tumor growth and metastasis of human hepatocellular carcinoma. FEBS J 279: 3898-3910, 2012.
70. Hou X, Ouyang J, Tang L, Wu P, Deng X, Yan Q, Shi L, Fan S, Fan C, Guo C, *et al*: KCNK1 promotes proliferation and metastasis of breast cancer cells by activating lactate dehydrogenase A (LDHA) and up-regulating H3K18 lactylation. PLoS Biol 22: e3002666, 2024.
71. Huang Q, Li S, Chen X, He C, Chen Y, Huang Y, Liu Y, Wang Y and Zheng X: Association between serum lactate dehydrogenase and lymph node metastasis in cervical cancer. Oncol Lett 26: 482, 2023.
72. Ippolito L, Duatti A, Iozzo M, Comito G, Pardella E, Lorito N, Bacci M, Pranzini E, Santi A, Sandrini G, *et al*: Lactate supports cell-autonomous ECM production to sustain metastatic behavior in prostate cancer. EMBO Rep 25: 3506-3531, 2024.
73. Pham KN, Mamun Y and Fernandez-Lima F: Structural heterogeneity of human histone H2A.1. J Phys Chem B 125: 4977-4986, 2021.
74. Taylor BC and Young NL: Combinations of histone post-translational modifications. The Biochemical journal 478: 511-532, 2021.
75. Zhang D, Gao J, Zhu Z, Mao Q, Xu Z, Singh PK, Rimayi CC, Moreno-Yruela C, Xu S, Li G, *et al*: Lysine L-lactylation is the dominant lactylation isomer induced by glycolysis. Nat Chem Biol 21: 91-99, 2025.
76. Gaffney DO, Jennings EQ, Anderson CC, Marentette JO, Shi T, Schou Oxvig AM, Streeter MD, Johannsen M, Spiegel DA, Chapman E, *et al*: Non-enzymatic lysine lactoylation of glycolytic enzymes. Cell Chem Biol 27: 206-213.e6, 2020.
77. Gao X, Pang C, Fan Z, Wang Y, Duan Y and Zhan H: Regulation of newly identified lysine lactylation in cancer. Cancer Lett 587: 216680, 2024.
78. Yin D, Jiang N, Cheng C, Sang X, Feng Y, Chen R and Chen Q: Protein Lactylation and metabolic regulation of the zoonotic parasite toxoplasma gondii. Genomics Proteomics Bioinformatics 21: 1163-1181, 2023.
79. Wu Z, Chai Z, Cai X, Wang J, Wang H, Yue B, Zhang M, Wang J, Wang H, Zhong J and Xin J: Protein lactylation profiles provide insights into molecular mechanisms underlying metabolism in Yak. J Agric Food Chem: Jun 8, 2024 (Epub ahead of print).
80. Zhu J, Guo W and Lan Y: Global analysis of lysine lactylation of germinated seeds in wheat. Int J Mol Sci 24: 16195, 2023.
81. Zhang N, Zhang Y, Xu J, Wang P, Wu B, Lu S, Lu X, You S, Huang X, Li M, *et al*: α-myosin heavy chain lactylation maintains sarcomeric structure and function and alleviates the development of heart failure. Cell Res 33: 679-698, 2023.
82. Chen Y, Wu J, Zhai L, Zhang T, Yin H, Gao H, Zhao F, Wang Z, Yang X, Jin M, *et al*: Metabolic regulation of homologous recombination repair by MRE11 lactylation. Cell 187: 294-311. e21, 2024.
83. Shang X, Peng Y, Wang Y, Feng Z, Li M, Peng Z and Ren W: Profile analysis of N4-acetylcytidine (ac4C) on mRNA of human lung adenocarcinoma and paired adjacent non-tumor tissues. Biochim Biophys Acta Gen Subj 1867: 130498, 2023.
84. Wang X, Yang Y, Ren D, Xia Y, He W, Wu Q, Zhang J, Liu M, Du Y, Ren C, *et al*: JQ1, a bromodomain inhibitor, suppresses Th17 effectors by blocking p300-mediated acetylation of RORγt. Br J Pharmacol 177: 2959-2973, 2020.
85. Zong Z, Ren J, Yang B, Zhang L and Zhou F: Emerging roles of lysine lactyltransferases and lactylation. Nat Cell Biol 27: 563-574, 2025.
86. Huang H, Zhang D, Weng Y, Delaney K, Tang Z, Yan C, Qi S, Peng C, Cole PA, Roeder RG and Zhao Y: The regulatory enzymes and protein substrates for the lysine β-hydroxybutyrylation pathway. Sci Adv 7: eabe2771, 2021.
87. Minami E, Sasa K, Yamada A, Kawai R, Yoshida H, Nakano H, Maki K and Kamijo R: Lactate-induced histone lactylation by p300 promotes osteoblast differentiation. PLoS One 18: e0293676, 2023.
88. Dong M, Zhang Y, Chen M, Tan Y, Min J, He X, Liu F, Gu J, Jiang H, Zheng L, *et al*: ASF1A-dependent P300-mediated histone H3 lysine 18 lactylation promotes atherosclerosis by regulating EndMT. Acta Pharm Sin B 14: 3027-3048, 2024.
89. Wang C, Wang S, Wang Z, Han J, Jiang N, Qu L and Xu K: Andrographolide regulates H3 histone lactylation by interfering with p300 to alleviate aortic valve calcification. Br J Pharmacol 181: 1843-1856, 2024.
90. Huang J, Wang X, Li N, Fan W, Li X, Zhou Q, Liu J, Li W, Zhang Z, Liu X, *et al*: YY1 lactylation aggravates autoimmune uveitis by enhancing microglial functions via inflammatory genes. Adv Sci (Weinh) 11: e2308031, 2024.
91. Li F, Si W, Xia L, Yin D, Wei T, Tao M, Cui X, Yang J, Hong T and Wei R: Positive feedback regulation between glycolysis and histone lactylation drives oncogenesis in pancreatic ductal adenocarcinoma. Mol Cancer 23: 90, 2024.
92. Yang L, Niu K, Wang J, Shen W, Jiang R, Liu L, Song W, Wang X, Zhang X, Zhang R, *et al*: Nucleolin lactylation contributes to intrahepatic cholangiocarcinoma pathogenesis via RNA splicing regulation of MADD. J Hepatol 81: 651-666, 2024.
93. Ju J, Zhang H, Lin M, Yan Z, An L, Cao Z, Geng D, Yue J, Tang Y, Tian L, *et al*: The alanyl-tRNA synthetase AARS1 moonlights as a lactyltransferase to promote YAP signaling in gastric cancer. J Clin Invest 134: e174587, 2024.
94. Xie B, Zhang M, Li J, Cui J, Zhang P, Liu F, Wu Y, Deng W, Ma J, Li X, *et al*: KAT8-catalyzed lactylation promotes eEF1A2-mediated protein synthesis and colorectal carcinogenesis. Proc Natl Acad Sci USA 121: e2314128121, 2024.

95. Chen B, Deng Y, Hong Y, Fan L, Zhai X, Hu H, Yin S, Chen Q, Xie X, Ren X, *et al*: Metabolic recoding of NSUN2-mediated m(5)C modification promotes the progression of colorectal cancer via the NSUN2/YBX1/m(5)C-ENO1 positive feedback loop. Adv Sci (Weinh) 11: e2309840, 2024.
96. Wang J, Qi C, Wang R, Cao Y, Zhou Y and Ye G: m5C RNA modification in colorectal cancer: mechanisms and therapeutic targets. J Transl Med 23: 948, 2025.
97. Chen H, Li Y, Li H, Chen X, Fu H, Mao D, Chen W, Lan L, Wang C, Hu K, *et al*: NBS1 lactylation is required for efficient DNA repair and chemotherapy resistance. Nature 631: 663-669, 2024.
98. Rho H, Terry AR, Chronis C and Hay N: Hexokinase 2-mediated gene expression via histone lactylation is required for hepatic stellate cell activation and liver fibrosis. Cell Metab 35: 1406-1423.e8, 2023.
99. de Ruijter AJ, van Gennip AH, Caron HN, Kemp S and van Kuilenburg AB: Histone deacetylases (HDACs): Characterization of the classical HDAC family. Biochem J 370: 737-749, 2003.
100. Moreno-Yruela C, Zhang D, Wei W, Bæk M, Liu W, Gao J, Danková D, Nielsen AL, Bolding JE, Yang L, *et al*: Class I histone deacetylases (HDAC1-3) are histone lysine delactylases. Sci Adv 8: eabi6696, 2022.
101. Fan Z, Liu Z, Zhang N, Wei W, Cheng K, Sun H and Hao Q: Identification of SIRT3 as an eraser of H4K16la. iScience 26: 107757, 2023.
102. Fan W, Zeng S, Wang X, Wang G, Liao D, Li R, He S, Li W, Huang J, Li X, *et al*: A feedback loop driven by H3K9 lactylation and HDAC2 in endothelial cells regulates VEGF-induced angiogenesis. Genome Biol 25: 165, 2024.
103. Zu H, Li C, Dai C, Pan Y, Ding C, Sun H, Zhang X, Yao X, Zang J and Mo X: SIRT2 functions as a histone delactylase and inhibits the proliferation and migration of neuroblastoma cells. Cell Discov 8: 54, 2022.
104. Suskiewicz MJ: The logic of protein post-translational modifications (PTMs): Chemistry, mechanisms and evolution of protein regulation through covalent attachments. Bioessays 46: e2300178, 2024.
105. Hu X, Huang X, Yang Y, Sun Y, Zhao Y, Zhang Z, Qiu D, Wu Y, Wu G and Lei L: Dux activates metabolism-lactylation-MET network during early iPSC reprogramming with Brg1 as the histone lactylation reader. Nucleic Acids Res 52: 5529-5548, 2024.
106. Zhang X, Mao Y, Wang B, Cui Z, Zhang Z, Wang Z and Chen T: Screening, expression, purification and characterization of CoA-transferases for lactoyl-CoA generation. J Ind Microbiol Biotechnol 46: 899-909, 2019.
107. Varner EL, Trefely S, Bartee D, von Krusenstiern E, Izzo L, Bekeova C, O'Connor RS, Seifert EL, Wellen KE, Meier JL and Snyder NW: Quantification of lactoyl-CoA (lactyl-CoA) by liquid chromatography mass spectrometry in mammalian cells and tissues. Open Biol 10: 200187, 2020.
108. Wang Z, Xing T, Zhang L, Zhao L and Gao F: Dynamic changes of protein lactylation and their correlations with the glycolytic process during the postmortem acidification of broiler breast. Poult Sci 103: 104354, 2024.
109. Dong Q, Zhang Q, Yang X, Nai S, Du X and Chen L: Glycolysis-Stimulated Esrrb lactylation promotes the self-renewal and extraembryonic endoderm stem cell differentiation of embryonic stem cells. Int J Mol Sci 25: 2692, 2024.
110. Zhang M, Zhang Y, Ding Y, Huang J, Yao J, Xie Z, Lv Y and Zuo J: Regulating the expression of HIF-1alpha or lncRNA: Potential directions for cancer therapy. Cells 11: 2811, 2022.
111. Yan P, Yang K, Xu M, Zhu M, Duan Y, Li W, Liu L, Liang C, Li Z, Pan X, *et al*: CCT6A alleviates pulmonary fibrosis by inhibiting HIF-1α-mediated lactate production. J Mol Cell Biol 16: mjae021, 2024.
112. Ilegems E, Bryzgalova G, Correia J, Yesildag B, Berra E, Ruas JL, Pereira TS and Berggren PO: HIF-1α inhibitor PX-478 preserves pancreatic β cell function in diabetes. Sci Transl Med 14: eaba9112, 2022.
113. Yang Z, Su W, Wei X, Pan Y, Xing M, Niu L, Feng B, Kong W, Ren X, Huang F, *et al*: Hypoxia inducible factor-1α drives cancer resistance to cuproptosis. Cancer Cell 43: 937-954.e9, 2025.
114. Mao Y, Zhang J, Zhou Q, He X, Zheng Z, Wei Y, Zhou K, Lin Y, Yu H, Zhang H, *et al*: Hypoxia induces mitochondrial protein lactylation to limit oxidative phosphorylation. Cell Res 34: 13-30, 2024.
115. Zhou X, Wu D, Mi T, Li R, Guo T and Li W: Icaritin activates p53 and inhibits aerobic glycolysis in liver cancer cells. Chem Biol Interact 392: 110926, 2024.
116. Zhou X, Wu D, Zhu L, Li R, Yu H and Li W: Withaferin A inhibits liver cancer tumorigenesis by suppressing aerobic glycolysis through the p53/IDH1/HIF-1α signaling axis. Curr Cancer Drug Targets 24: 534-545, 2024.
117. Sobrido-Cameán D, Coulson B, Miller M, Oswald MCW, Pettini T, Bailey DMD, Baines RA and Landgraf M: Mitochondrial ROS and HIF-1α signaling mediate synaptic plasticity in the critical period. PLoS Biol 23: e3003338, 2025.
118. Jiang Z, Xiong N, Yan R, Li ST, Liu H, Mao Q, Sun Y, Shen S, Ye L, Gao P, *et al*: PDHX acetylation facilitates tumor progression by disrupting PDC assembly and activating lactylation mediated gene expression. Protein Cell 16: 49-63, 2025.
119. Feng F, Wu J, Chi Q, Wang S, Liu W, Yang L, Song G, Pan L, Xu K and Wang C: Lactylome analysis unveils lactylation-dependent mechanisms of stemness remodeling in the liver cancer stem cells. Adv Sci (Weinh) 11: e2405975, 2024.
120. Wang J, Yang P, Yu T, Gao M, Liu D, Zhang J, Lu C, Chen X, Zhang X and Liu Y: Lactylation of PKM2 suppresses inflammatory metabolic adaptation in pro-inflammatory macrophages. Int J Biol Sci 18: 6210-6225, 2022.
121. Li G, Wang D, Zhai Y, Pan C, Zhang J, Wang C, Huang R, Yu M, Li Y, Liu X, *et al*: Glycometabolic reprogramming-induced XRCC1 lactylation confers therapeutic resistance in ALDH1A3-overexpressing glioblastoma. Cell Metab 36: 1696-1710.e10, 2024.
122. Gu J, Zhou J, Chen Q, Xu X, Gao J, Li X, Shao Q, Zhou B, Zhou H, Wei S, *et al*: Tumor metabolite lactate promotes tumorigenesis by modulating MOESIN lactylation and enhancing TGF-beta signaling in regulatory T cells. Cell Rep 39: 110986, 2022.
123. Zhang X, Song W, Gao Y, Zhang Y, Zhao Y, Hao S and Ni T: The role of tumor metabolic reprogramming in tumor immunity. Int J Mol Sci 24: 17422, 2023.
124. Li Y, Cao Q, Hu Y, He B, Cao T, Tang Y, Zhou XP, Lan XP and Liu SQ: Advances in the interaction of glycolytic reprogramming with lactylation. Biomed Pharmacother 177: 116982, 2024.
125. Zhou J, Ma X, Liu X, Liu Y, Fu J, Qi Y and Liu H: The impact of histone lactylation on the tumor microenvironment and metabolic pathways and its potential in cancer therapy. Genes Genomics 46: 991-1011, 2024.
126. Masin M, Vazquez J, Rossi S, Groeneveld S, Samson N, Schwalie PC, Deplancke B, Frawley LE, Gouttenoire J, Moradpour D, *et al*: GLUT3 is induced during epithelial-mesenchymal transition and promotes tumor cell proliferation in non-small cell lung cancer. Cancer Metab 2: 11, 2014.
127. Yang H, Yang S, He J, Li W, Zhang A, Li N, Zhou G and Sun B: Glucose transporter 3 (GLUT3) promotes lactylation modifications by regulating lactate dehydrogenase A (LDHA) in gastric cancer. Cancer Cell Int 23: 303, 2023.
128. Li Q, Lin G, Zhang K, Liu X, Li Z, Bing X, Nie Z, Jin S, Guo J and Min X: Hypoxia exposure induces lactylation of Axin1 protein to promote glycolysis of esophageal carcinoma cells. Biochem Pharmacol 226: 116415, 2024.
129. Qiao Z, Li Y, Li S, Liu S and Cheng Y: Hypoxia-induced SHMT2 protein lactylation facilitates glycolysis and stemness of esophageal cancer cells. Mol Cell Biochem 479: 3063-3076, 2024.
130. Jiang J, Huang D, Jiang Y, Hou J, Tian M, Li J, Sun L, Zhang Y, Zhang T, Li Z, *et al*: Lactate modulates cellular metabolism through histone lactylation-mediated gene expression in non-small cell lung cancer. Front Oncol 11: 647559, 2021.
131. Yan F, Teng Y, Li X, Zhong Y, Li C, Yan F and He X: Hypoxia promotes non-small cell lung cancer cell stemness, migration, and invasion via promoting glycolysis by lactylation of SOX9. Cancer Biol Ther 25: 2304161, 2024.
132. Zhang R, Li L and Yu J: Lactate-induced IGF1R protein lactylation promotes proliferation and metabolic reprogramming of lung cancer cells. Open Life Sci 19: 20220874, 2024.
133. Yang J, Yu X, Xiao M, Xu H, Tan Z, Lei Y, Guo Y, Wang W, Xu J, Shi S and Yu X: Histone lactylation-driven feedback loop modulates cholesterol-linked immunosuppression in pancreatic cancer. Gut 74: 1859-1872, 2025.
134. Meng Q, Sun H, Zhang Y, Yang X, Hao S, Liu B, Zhou H, Xu ZX and Wang Y: Lactylation stabilizes DCBLD1 activating the pentose phosphate pathway to promote cervical cancer progression. J Exp Clin Cancer Res 43: 36, 2024.

135. Qu J, Li P and Sun Z: Histone lactylation regulates cancer progression by reshaping the tumor microenvironment. Front Immunol 14: 1284344, 2023.
136. Pereira MVA, Galvani RG, Gonçalves-Silva T, de Vasconcelo ZFM and Bonomo A: Tissue adaptation of CD4 T lymphocytes in homeostasis and cancer. Front Immunol 15: 1379376, 2024.
137. Khan U and Ghazanfar H: T lymphocytes and autoimmunity. Int Rev Cell Mol Biol 341: 125-168, 2018.
138. Wu Y, Yuan M, Wang C, Chen Y, Zhang Y and Zhang J: T lymphocyte cell: A pivotal player in lung cancer. Front Immunol 14: 1102778, 2023.
139. Tu VY, Ayari A and O'Connor RS: Beyond the Lactate Paradox: How Lactate and Acidity Impact T Cell Therapies against Cancer. Antibodies (Basel, Switzerland) 10: 2021.
140. Fan W, Wang X, Zeng S, Li N, Wang G, Li R, He S, Li W, Huang J, Li X, *et al*: Global lactylome reveals lactylation-dependent mechanisms underlying T(H)17 differentiation in experimental autoimmune uveitis. Sci Adv 9: eadh4655, 2023.
141. Brescia C, Audia S, Pugliano A, Scaglione F, Iuliano R, Trapasso F, Perrotti N, Chiarella E and Amato R: Metabolic drives affecting Th17/Treg gene expression changes and differentiation: Impact on immune-microenvironment regulation. APMIS 132: 1026-1045, 2024.
142. Wang R, Li C, Cheng Z, Li M, Shi J, Zhang Z, Jin S and Ma H: H3K9 lactylation in malignant cells facilitates CD8(+) T cell dysfunction and poor immunotherapy response. Cell Rep 43: 114686, 2024.
143. Quinn WJ III, Jiao J, TeSlaa T, Stadanlick J, Wang Z, Wang L, Akimova T, Angelin A, Schäfer PM, Cully MD, *et al*: Lactate limits T cell proliferation via the NAD(H) Redox State. Cell Rep 33: 108500, 2020.
144. Rostamian H, Khakpoor-Koosheh M, Jafarzadeh L, Masoumi E, Fallah-Mehrjardi K, Tavassolifar MJ, M Pawelek J, Mirzaei HR and Hadjati J: Restricting tumor lactic acid metabolism using dichloroacetate improves T cell functions. BMC Cancer 22: 39, 2022.
145. Liu Y, Wang F, Peng D, Zhang D, Liu L, Wei J, Yuan J, Zhao L, Jiang H, Zhang T, *et al*: Activation and antitumor immunity of CD8(+) T cells are supported by the glucose transporter GLUT10 and disrupted by lactic acid. Sci Transl Med 16: eadk7399, 2024.
146. Kumagai S, Koyama S, Itahashi K, Tanegashima T, Lin YT, Togashi Y, Kamada T, Irie T, Okumura G, Kono H, *et al*: Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments. Cancer Cell 40: 201-218. e9, 2022.
147. Orecchioni M, Ghosheh Y, Pramod AB and Ley K: Macrophage Polarization: Different gene signatures in M1(LPS+) vs. Classically and M2(LPS-) vs. alternatively activated macrophages. Front Immunol 10: 1084, 2019.
148. da Rocha RF, De Bastiani MA and Klamt F: Bioinformatics approach to evaluate differential gene expression of M1/M2 macrophage phenotypes and antioxidant genes in atherosclerosis. Cell Biochem Biophys 70: 831-839, 2014.
149. Wang Y, Smith W, Hao D, He B and Kong L: M1 and M2 macrophage polarization and potentially therapeutic naturally occurring compounds. Int Immunopharmacol 70: 459-466, 2019.
150. Mauro A, Russo V, Di Marcantonio L, Berardinelli P, Martelli A, Muttini A, Mattioli M and Barboni B: M1 and M2 macrophage recruitment during tendon regeneration induced by amniotic epithelial cell allotransplantation in ovine. Res Vet Sci 105: 92-102, 2016.
151. Di Conza G and Ho PC: Metabolic adaptation of macrophages in chronic diseases. Cancer Lett 414: 250-256, 2018.
152. Ammarah U, Pereira-Nunes A, Delfini M and Mazzone M: From monocyte-derived macrophages to resident macrophages-how metabolism leads their way in cancer. Mol Oncol 18: 1739-1758, 2024.
153. Xu B, Liu Y, Li N and Geng Q: Lactate and lactylation in macrophage metabolic reprogramming: current progress and outstanding issues. Front Immunol 15: 1395786, 2024.
154. Li XM, Yang Y, Jiang FQ, Hu G, Wan S, Yan WY, He XS, Xiao F, Yang XM, Guo X, *et al*: Histone lactylation inhibits RARγ expression in macrophages to promote colorectal tumorigenesis through activation of TRAF6-IL-6-STAT3 signaling. Cell Rep 43: 113688, 2024.
155. Chao J, Chen GD, Huang ST, Gu H, Liu YY, Luo Y, Lin Z, Chen ZZ, Li X, Zhang B, *et al*: High histone H3K18 lactylation level is correlated with poor prognosis in epithelial ovarian cancer. Neoplasma 71: 319-332, 2024.
156. Yu L, Jing C, Zhuang S, Ji L and Jiang L: A novel lactylation-related gene signature for effectively distinguishing and predicting the prognosis of ovarian cancer. Transl Cancer Res 13: 2497-2508, 2024.
157. De Leo A, Ugolini A, Yu X, Scirocchi F, Scocozza D, Peixoto B, Pace A, D'Angelo L, Liu JKC, Etame AB, *et al*: Glucose-driven histone lactylation promotes the immunosuppressive activity of monocyte-derived macrophages in glioblastoma. Immunity 57: 1105-1123.e8, 2024.
158. Xiong J, He J, Zhu J, Pan J, Liao W, Ye H, Wang H, Song Y, Du Y, Cui B, *et al*: Lactylation-driven METTL3-mediated RNA m(6)A modification promotes immunosuppression of tumor-infiltrating myeloid cells. Mol Cell 82: 1660-1677.e10, 2022.
159. Kumar S, Sahu N, Jawaid T, Jayasingh Chellammal HS and Upadhyay P: Dual role of lactate in human health and disease. Front Physiol 16: 1621358, 2025.
160. Plebanek MP, Xue Y, Nguyen YV, DeVito NC, Wang X, Holtzhausen A, Beasley GM, Theivanthiran B and Hanks BA: A lactate-SREBP2 signaling axis drives tolerogenic dendritic cell maturation and promotes cancer progression. Sci Immunol 9: eadi4191, 2024.
161. LeBleu VS and Kalluri R: A peek into cancer-associated fibroblasts: Origins, functions and translational impact. Dis Model Mech 11: dmm029447, 2018.
162. Kong W, He J, Zhou Q, Zhou X, Wei X, Yang Y, Mei Y, Wang S, Zhang X, Yao B, *et al*: Histone lactylation-related genes correlate with the molecular patterns and functions of cancer-associated fibroblasts and have significant clinical implications in clear cell renal cell carcinoma. Heliyon 10: e33554, 2024.
163. Li Z, Liang P, Chen Z, Chen Z, Jin T, He F, Chen X and Yang K: CAF-secreted LOX promotes PD-L1 expression via histone Lactylation and regulates tumor EMT through TGFβ/IGF1 signaling in gastric cancer. Cell Signal 124: 111462, 2024.
164. Lv M, Huang Y, Chen Y and Ding K: Lactylation modification in cancer: mechanisms, functions, and therapeutic strategies. Exp Hematol Oncol 14: 32, 2025.
165. Wei Y, Guo H, Chen S and Tang XX: Regulation of macrophage activation by lactylation in lung disease. Front Immunol 15: 1427739, 2024.
166. Zheng P, Mao Z, Luo M, Zhou L, Wang L, Liu H, Liu W and Wei S: Comprehensive bioinformatics analysis of the solute carrier family and preliminary exploration of SLC25A29 in lung adenocarcinoma. Cancer Cell Int 23: 222, 2023.
167. Crispo F, Condelli V, Lepore S, Notarangelo T, Sgambato A, Esposito F, Maddalena F and Landriscina M: Metabolic dysregulations and epigenetics: A bidirectional interplay that drives tumor Progression. Cells 8: 798, 2019.
168. Zhang X, Liang C, Wu C, Wan S, Xu L, Wang S, Wang J, Huang X and Xu L: A rising star involved in tumour immunity: Lactylation. J Cell Mol Med 28: e70146, 2024.
169. Chen L, Huang L, Gu Y, Cang W, Sun P and Xiang Y: Lactate-Lactylation Hands between Metabolic Reprogramming and Immunosuppression. Int J Mol Sci 23: 11943, 2022.
170. Fu Y and Chung FL: Oxidative stress and hepatocarcinogenesis. Hepatoma Res 4: 39, 2018.
171. Berumen J, Baglieri J, Kisseleva T and Mekeel K: Liver fibrosis: Pathophysiology and clinical implications. WIREs Mech Dis 13: e1499, 2021.
172. Šmíd V: Liver fibrosis. Vnitr Lek 66: 61-66, 2020 (In Czech).
173. Li LN, Li WW, Xiao LS and Lai WN: Lactylation signature identifies liver fibrosis phenotypes and traces fibrotic progression to hepatocellular carcinoma. Front Immunol 15: 1433393, 2024.
174. Deng J and Liao X: Lysine lactylation (Kla) might be a novel therapeutic target for breast cancer. BMC Med Genomics 16: 283, 2023.
175. Cui Z, Li Y, Lin Y, Zheng C, Luo L, Hu D, Chen Y, Xiao Z and Sun Y: Lactylproteome analysis indicates histone H4K12 lactylation as a novel biomarker in triple-negative breast cancer. Front Endocrinol (Lausanne) 15: 1328679, 2024.
176. Li J, Chen Z, Jin M, Gu X, Wang Y, Huang G, Zhao W and Lu C: Histone H4K12 lactylation promotes malignancy progression in triple-negative breast cancer through SLFN5 downregulation. Cell Signal 124: 111468, 2024.
177. Sun J, Feng Q, He Y, Wang M and Wu Y: Lactate activates CCL18 expression via H3K18 lactylation in macrophages to promote tumorigenesis of ovarian cancer. Acta Biochim Biophys Sin (Shanghai) 56: 1373-1386, 2024.

178. Wang X, Li Y, Li J, Li L, Zhu H, Chen H, Kong R, Wang G, Wang Y, Hu J and Sun B: Cell-in-cell phenomenon and its relationship with tumor microenvironment and tumor progression: A review. Front Cell Dev Biol 7: 311, 2019.
179. Zheng A, Zhang L, Yang J, Yin X, Zhang T, Wu X and Ma X: Physical activity prevents tumor metastasis through modulation of immune function. Front Pharmacol 13: 1034129, 2022.
180. Wang H, Xu M, Zhang T, Pan J, Li C, Pan B, Zhou L, Huang Y, Gao C, He M, *et al*: PYCR1 promotes liver cancer cell growth and metastasis by regulating IRS1 expression through lactylation modification. Clin Transl Med 14: e70045, 2024.
181. Pandkar MR, Sinha S, Samaiya A and Shukla S: Oncometabolite lactate enhances breast cancer progression by orchestrating histone lactylation-dependent c-Myc expression. Transl Oncol 37: 101758, 2023.
182. Zhang C, Zhou L, Zhang M, Du Y, Li C, Ren H and Zheng L: H3K18 lactylation potentiates immune escape of non-small cell lung cancer. Cancer Res 84: 3589-3601, 2024.
183. Li W, Zhou C, Yu L, Hou Z, Liu H, Kong L, Xu Y, He J, Lan J, Ou Q, *et al*: Tumor-derived lactate promotes resistance to bevacizumab treatment by facilitating autophagy enhancer protein RUBCNL expression through histone H3 lysine 18 lactylation (H3K18la) in colorectal cancer. Autophagy 20: 114-130, 2024.
184. Sun X, He L, Liu H, Thorne RF, Zeng T, Liu L, Zhang B, He M, Huang Y, Li M, *et al*: The diapause-like colorectal cancer cells induced by SMC4 attenuation are characterized by low proliferation and chemotherapy insensitivity. Cell Metab 35: 1563-1579.e8, 2023.
185. Huang H, Chen K, Zhu Y, Hu Z, Wang Y, Chen J, Li Y, Li D and Wei P: A multi-dimensional approach to unravel the intricacies of lactylation related signature for prognostic and therapeutic insight in colorectal cancer. J Transl Med 22: 211, 2024.
186. Chu YD, Cheng LC, Lim SN, Lai MW, Yeh CT and Lin WR: Aldolase B-driven lactagenesis and CEACAM6 activation promote cell renewal and chemoresistance in colorectal cancer through the Warburg effect. Cell Death Dis 14: 660, 2023.
187. Gu J, Xu X, Li X, Yue L, Zhu X, Chen Q, Gao J, Takashi M, Zhao W, Zhao B, *et al*: Tumor-resident microbiota contributes to colorectal cancer liver metastasis by lactylation and immune modulation. Oncogene 43: 2389-2404, 2024.
188. Liu J, Chen P, Zhou J, Li H and Pan Z: Prognostic impact of lactylation-associated gene modifications in clear cell renal cell carcinoma: Insights into molecular landscape and therapeutic opportunities. Environ Toxicol 39: 1360-1373, 2024.
189. Yang J, Luo L, Zhao C, Li X, Wang Z, Zeng Z, Yang X, Zheng X, Jie H, Kang L, *et al*: A positive feedback loop between Inactive VHL-Triggered Histone Lactylation and PDGFRβ signaling drives clear cell renal cell carcinoma progression. Int J Biol Sci 18: 3470-3483, 2022.
190. Gu X, Zhuang A, Yu J, Yang L, Ge S, Ruan J, Jia R, Fan X and Chai P: Histone lactylation-boosted ALKBH3 potentiates tumor progression and diminished promyelocytic leukemia protein nuclear condensates by m1A demethylation of SP100A. Nucleic Acids Res 52: 2273-2289, 2024.
191. Zhu M, Xiao Q, Cai X, Chen Z, Shi Q, Sun X, Xie X and Sun M: Predicting lymphoma prognosis using machine learning-based genes associated with lactylation. Transl Oncol 49: 102102, 2024.
192. Sun C, Zhang W, Liu H, Ding Y, Guo J, Xiong S, Zhai Z and Hu W: Identification of a novel lactylation-related gene signature predicts the prognosis of multiple myeloma and experiment verification. Sci Rep 14: 15142, 2024.
193. Wang X, Shi Y, Shi H, Liu X, Liao A, Liu Z, Orlowski RZ, Zhang R and Wang H: MUC20 regulated by extrachromosomal circular DNA attenuates proteasome inhibitor resistance of multiple myeloma by modulating cuproptosis. J Exp Clin Cancer Res 43: 68, 2024.
194. Byun JK: Tumor lactic acid: A potential target for cancer therapy. Arch Pharm Res 46: 90-110, 2023.
195. Du M, Yu T, Zhan Q, Li H, Zou Y, Geng M, Meng T and Xie Z: Development of a novel lactate dehydrogenase A inhibitor with potent antitumor activity and immune activation. Cancer Sci 113: 2974-2985, 2022.
196. Xian ZY, Liu JM, Chen QK, Chen HZ, Ye CJ, Xue J, Yang HQ, Li JL, Liu XF and Kuang SJ: Inhibition of LDHA suppresses tumor progression in prostate cancer. Tumour Biol 36: 8093-8100, 2015.
197. Zhang P, Wan Y, Ma J, Gong J, Zhong Z, Cui Y, Zhang H, Da Y, Ma J, Li C, *et al*: Epigenetic silencing of LDHB promotes hepatocellular carcinoma by remodeling the tumor microenvironment. Cancer Immunol Immunother 73: 127, 2024.
198. Urbańska K and Orzechowski A: Unappreciated Role of LDHA and LDHB to control apoptosis and autophagy in tumor cells. Int J Mol Sci 20: 2085, 2019.
199. Shibata S, Sogabe S, Miwa M, Fujimoto T, Takakura N, Naotsuka A, Kitamura S, Kawamoto T and Soga T: Identification of the first highly selective inhibitor of human lactate dehydrogenase B. Sci Rep 11: 21353, 2021.
200. Curtis NJ, Mooney L, Hopcroft L, Michopoulos F, Whalley N, Zhong H, Murray C, Logie A, Revill M, Byth KF, *et al*: Pre-clinical pharmacology of AZD3965, a selective inhibitor of MCT1: DLBCL, NHL and Burkitt's lymphoma anti-tumor activity. Oncotarget 8: 69219-69236, 2017.
201. Halford S, Veal GJ, Wedge SR, Payne GS, Bacon CM, Sloan P, Dragoni I, Heinzmann K, Potter S, Salisbury BM, *et al*: A phase I Dose-escalation Study of AZD3965, an oral monocarboxylate transporter 1 inhibitor, in patients with advanced cancer. Clin Cancer Res 29: 1429-1439, 2023.
202. Goldberg FW, Kettle JG, Lamont GM, Buttar D, Ting AKT, McGuire TM, Cook CR, Beattie D, Morentin Gutierrez P, Kavanagh SL, *et al*: Discovery of clinical candidate AZD0095, a selective inhibitor of monocarboxylate transporter 4 (MCT4) for oncology. J Med Chem 66: 384-397, 2023.
203. Bisetto S, Whitaker-Menezes D, Wilski NA, Tuluc M, Curry J, Zhan T, Snyder CM, Martinez-Outschoorn UE and Philp NJ: Monocarboxylate transporter 4 (MCT4) knockout mice have attenuated 4NQO induced carcinogenesis; A Role for MCT4 in driving oral squamous cell cancer. Front Oncol 8: 324, 2018.
204. Fang Y, Liu W, Tang Z, Ji X, Zhou Y, Song S, Tian M, Tao C, Huang R, Zhu G, *et al*: Monocarboxylate transporter 4 inhibition potentiates hepatocellular carcinoma immunotherapy through enhancing T cell infiltration and immune attack. Hepatology 77: 109-123, 2023.
205. Damia G and Garattini S: The pharmacological point of view of resistance to therapy in tumors. Cancer Treat Rev 40: 909-916, 2014.
206. Yue Q, Wang Z, Shen Y, Lan Y, Zhong X, Luo X, Yang T, Zhang M, Zuo B, Zeng T, *et al*: Histone H3K9 lactylation confers temozolomide resistance in glioblastoma via LUC7L2-Mediated MLH1 intron retention. Adv Sci (Weinh) 11: e2309290, 2024.
207. Li F, Zhang H, Huang Y, Li D, Zheng Z, Xie K, Cao C, Wang Q, Zhao X, Huang Z, *et al*: Single-cell transcriptome analysis reveals the association between histone lactylation and cisplatin resistance in bladder cancer. Drug Resist Updat 73: 101059, 2024.
208. Chen HJ, Yu MM, Huang JC, Lan FY, Liao HH, Xu ZH, Yu YJ, Huang YC and Chen F: SLC4A4 is a novel driver of enzalutamide resistance in prostate cancer. Cancer Lett 597: 217070, 2024.
209. Wang Y, Chen J, Wang Y, Zhao J, Zhang J and Wang H: Pharmacologically targeting protein lactylation to overcome cancer drug resistance. Eur J Med Chem 296: 117905, 2025.
210. Lu Y, Zhu J, Zhang Y, Li W, Xiong Y, Fan Y, Wu Y, Zhao J, Shang C, Liang H and Zhang W: Lactylation-driven IGF2BP3-mediated serine metabolism reprogramming and RNA m6A-modification promotes lenvatinib resistance in HCC. Adv Sci (Weinh) 11: e2401399, 2024.
211. Fang C, Peng Q, Li X, Qu X, Qiao Z, Yin B, Xiao L, Chen Y, Dong X, Cai L, *et al*: Multichannel immune nanoregulators suppress lactic acid metabolism and lactic acid-shaped acidic microenvironment to uproot anti-tumor immunosuppression. Adv Mater 38: e12230, 2026.
212. Wan J, Shi JH, Shi M, Huang H, Zhang Z, Li W, Guo C, Bao R, Yu X, Han Q, *et al*: Lactate dehydrogenase B facilitates disulfidptosis and exhaustion of tumour-infiltrating CD8(+) T cells. Nat Cell Biol 27: 972-982, 2025.
213. Xu K, Shou Y, Liu R, Xiong H, Dai X, Bao X, Chen X, Huang L, Sheng H, Zhang H and Lu Y: Lactylation in cancer: Advances and opportunities for treatment resistance. Clin Transl Med 15: e70478, 2025.
214. Chang D, Li D, Sun Y, Shi J, Zhang S and Wang C: Targeting lactylation for cancer: Mechanisms, effects, and therapeutic prospects. Int J Mol Sci 26: 11278, 2025.