Journal of Advanced Research 75 (2025) 229–248

Contents lists available at ScienceDirect

Journal of Advanced Research

journal homepage: www.elsevier.com/locate/jare

Review Article

Lactate-mediated lactylation in human health and diseases: Progress and remaining challenges

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HIGHLIGHTS

- Because of lactylation, lactate has gracefully transformed from an "ugly duckling" into a "beautiful swan".
- Lactate-mediated lactylation participates in the regulation of numerous physiological and pathological processes.

GRAPHICAL ABSTRACT

Lactylation is an epigenetic process catalyzed by HATs or AARS1/2 ("writers") and removed by HDACs ("erasers"). The substrates of lactylation include both histone and non-histone proteins. Histone lactylation typically regulates the transcription of downstream genes, while non-histone lactylation may have multiple effects, influencing the stability, localization, structure, interaction, or function of proteins. Due to lactylation, lactate has transformed from an "ugly duckling"into a "beautiful swan". In this review, we summarize the roles and mechanisms of lactylation in human health and disease, as well as the remaining questions regarding lactylation.

Abbreviations: 2-DG, 2-deoxy-D-glucose; AARS1/2, alanyl-tRNA synthetase 1/2; ABC, advanced breast cancer; AD, Alzheimer's disease; AEC, alveolar epithelial cell; AGK2, arginine kinase 2; AK2, adenylate kinase 2; AKR1B10, aldo-keto reductase family 1 B10; AML, acute myeloid leukemia; AMP, adenosine monophosphate; ATG14L, autophagy related 14 like; ATP, adenosine triphosphate; Bca, bladder cancer; BMSCs, bone mesenchymal stem cells; BUB1B, budding uninhibited by benzimidazoles 1 homolog beta; BZW2, basic leucine zipper and W2 domain-containing protein 2; CCNB1, cyclin B1; CCNE2, cyclin E2; ccRCC, clear cell renal cell carcinoma; CDK2, cyclin-dependent kinase 2; CENPA, centromere protein A; CHC, chlorhexidine; CI, cerebral infarction; CI/R, cerebral ischemia/reperfusion; CIK, cytokine-induced killer cells; COL1A1, collagen type I alpha 1; COL1A2, collagen type I alpha 2 chain; COMP, cartilage oligomeric matrix protein; CPT2, carnitine palmitoyltransferase 2; CRC, colorectal cancer; CXCL1/5, C-X-C motif chemokine ligand 1/5; DCA, dichloroacetate; DML, demethylzeylasteral; DR, diabetic retinopathy; EC, esophageal cancer; eEF1A2, elongation factor 1 alpha 2; EIF4G/4A/4E, eukaryotic translation initiation factor 4 gamma/4A/4E; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase family member 1; FASN, fatty acid synthase; FDX1, Fe-S cluster assembly factor 1; FGF2, fibroblast growth factor 2; FGS, fargesin; FMT, fibromyxoid transformation; FN1, fibronectin 1; FOXP-3, forkhead box P3; FTO, fat mass and obesity associated protein; GBM, glioblastoma; GCN5, general control non-depressible 5; Glis1, gli-like transcription factor 1; GLUT, glucose transporter; GPR37, G protein-coupled receptor 37; HA, hyaluronic acid; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDAC, histone deacetylase; HIF-1α, hypoxia-inducible factor 1 alpha; HK, hexokinase; HMGB1, high mobility group protein 1; HR, homologous recombination; HSC, hepatic stellate cell; HSPA6, heat shock 70kDa protein 6; IDH3G, isocitrate dehydrogenase 3, gamma; IFN-β, interferon beta; IKKε, inhibitor of nuclear factor kappa B kinase subunit epsilon; IL2/4, interleukin 2/4; IPF, idiopathic pulmonary fibrosis; JAK1, janus kinase 1; JNK, c-Jun N-terminal kinases; KAT2A, lysine acetyltransferases 2 A; KAT8, lysine acetyltransferase 8; Kcr, lysine crotonylation; Kla, lysine lactylation; KLF4/15, krüppel-like factor 4/15; LCN2, lipocalin 2; LCP1, lymphocyte cytosolic protein 1; LDH, lactate dehydrogenase; LDHi, lactate dehydrogenase inhibitor; LPS, lipopolysaccharide; LUAD, lung adenocarcinoma; MAP4K4, mitogen-activated protein kinase kinase kinase kinase 4; MAPK, mitogen-activated protein kinase; MAPK6P4, mitogen-activated protein kinase 6 pseudogene 4; MCT, monocarboxylate transporter 1; MECP2, methylated CpG-binding protein 2; METTL16, methyltransferase 16, RNA N6-adenosine; METTL3, methyltransferase-like 3; MI, myocardial infarction; MPC, mitochondrial pyruvate carrier; MRE11, meiotic recombination 11; mROS, mitochondrial reactive oxygen species; MS-275, entinostat; MTHFD1L, methylenetetrahydrofolate dehydrogenase 1-like; NAFLD, non-alcoholic fatty liver disease; NASH, ignallingic steatohepatitis; Neu2, neuraminidase 2; NK, natural killer cells; NREP, neuronal regeneration related protein; OCT4, octamer-binding transcription factor 4; P300, histone acetyltransferases p300; P53, tumor protein p53; PASMC, pulmonary artery smooth muscle cells; Pca, prostate cancer; PDGFRβ, platelet-derived growth factor receptor beta; PDH, pyruvate dehydrogenase; PDHA1, pyruvate dehydrogenase catalytic subunit 1; PD-L1, programmed death-Ligand 1; PER1, period circadian regulator 1; PFS, progression-free survival; PGK1, phosphoglycerate kinase 1; PH, pulmonary hypertension; PKM, pyruvate kinase; PLF, pulmonary lymphoid follicle; PRRSV, porcine reproductive and respiratory syndrome virus; RUBCNL, rubicon-like Autophagy Enhancer; RUNX1, runt-related transcription factor 1; SAKI, sepsis-induced acute kidney injury; SALL4, sal-like protein 4; SERPINE1, serpin family E member 1; SHMT2, serine hydroxymethyl transferase 2; SIRT, sirtuins; SMAD3, SMAD family member 3; SOX-2, SRY (Sex determining Region Y)-box 2; SRSF10, serine/arginine-rich splicing factor 10; STAT3/5, signal transducer and activator of transcription 3/5; TCA, tricarboxylic acid cycle; TCF7L2, transcription factor 7 Like 2; TEAD, transcriptional enhancer factor; TGF-β, transforming growth factor beta; TIMP1, tissue inhibitor of metalloproteinases 1; TIMs, tumor-infiltrating myeloid cells; TIP60, tat interactive protein 60kDa; TLR4, toll-like receptor 4; TME, tumor microenvironment; TRAF3, tumor necrosis factor receptor-associated factor 3; TSA, trichostatin A; TTK, twistless kinase; ULK1, UNC-51-like kinase 1; UVRAG, UV radiation resistance associated gene; VEGFA, vascular endothelial growth factor A; VEGFR2, vascular endothelial growth factor receptor 2; VHL, von hippel-lindau; VPS34, vacuolar protein sorting 34; YAP, yes associated protein; YBX1, Y-Box binding protein 1; YTHDF1, YTH N6-methyladenosine RNA binding protein 1; YTHDF2, YTH (YT521-B homology) domain 2; YY1, yin yang 1; ZGA, zygotic genome activation; α-MHC, α-myosin heavy chain; α-SMA, alpha-smooth muscle actin.

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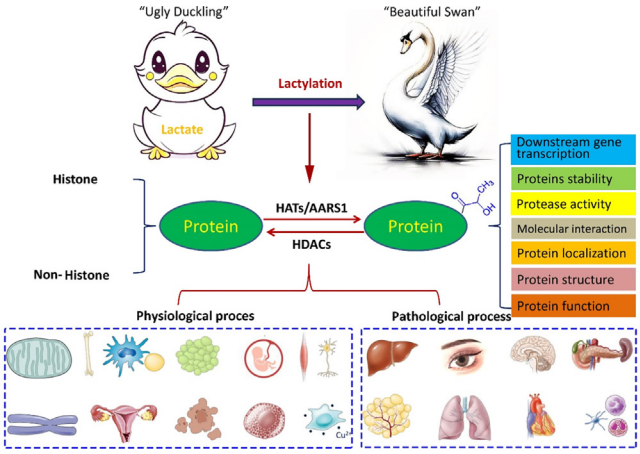
https://doi.org/10.1016/j.jare.2024.11.010
2090-1232/

- Histone lactylation alters the transcription of target genes, while nonhistone lactylation has diverse effects on proteins.
- Lactylation can be targeted for diseases treatment in two ways: ① by targeting the production or transport of lactate and ② by targeting "writers" or "erasers" of lactylation.
- Despite the significant progress made in the research of lactylation, there are still numerous challenges and issues that remain.



ARTICLE INFO

Article history:
Received 31 July 2024
Revised 5 November 2024
Accepted 7 November 2024
Available online 9 November 2024

Keywords:
Posttranslational modification
Lactate
Lactylation
Epigenetic
Metabolism

ABSTRACT

Background: Lactate was once considered as metabolic waste for a long time. In 2019, Professor Zhao Yingming's team from the University of Chicago found that lactate could also be used as a substrate to induce histone lactylation and regulate gene expression. Since then, researchers have discovered that lactate-mediated lactylation play important regulatory roles in various physiological and pathological processes.

Aim of review: In this review, we aim to discuss the roles and mechanisms of lactylation in human health and diseases, as well as the effects of lactylation on proteins and metabolic modulators targeting lactylation.

Key scientific concepts of review: In this work, we emphasize the crucial regulatory roles of lactylation in the development of numerous physiological and pathological processes. Of relevance, we discuss the current issues and challenges pertaining to lactylation. This review provides directions and a theoretical basis for future research and clinical translation of lactylation.

Contents

Introduction

Lactate, a metabolic product of cells undergoing glycolysis under anaerobic conditions, has long been considered a useless metabolic waste product. However, in the 1920 s, Otto Warburg, a German oncologist, discovered that compared to normal cells, tumor cells can absorb glucose more efficiently and still prefer to undergo glycolysis even in the presence of oxygen, producing a large amount of lactate and providing energy. This is known as the "Warburg effect" [1]. In recent years, researchers have found that lactate can not only be transported into cells as an energy source for metabolism, but is also an important ignalling molecule [2] involved in regulating important physiological and pathological processes such as angiogenesis and immune response, the mechanism of which still needs further study.

In addition to lactate, there are thousands of metabolites found in biological systems [3]. Recent studies have shown that in addition to their primary role in metabolism, these small molecules produced during cellular metabolic processes can also be covalently modified onto proteins as substrates to participate in epigenetic regulation [4,5]. Epigenetics refers to the condition in which the DNA sequence remains unchanged, while gene expression undergoes heritable changes. There are numerous patterns of epigenetic regulation, mainly including DNA methylation, RNA modification, noncoding RNA modification, and a variety of protein modifications [6]. Acetylation, ubiquitination, methylation, and phosphorylation are common types of protein modifications [7]. As the main carrier of life activities, protein modification often has a significant impact on life processes. For example, acetylation of histones typically activates downstream target gene transcription, ubiquitination can affect protein degradation, and phosphorylation can affect protease activity [8]. With the development of science and technology [9], many novel types of protein modifications have been identified, including crotonylation [10], methacrylylation [11], O-glycosylation [12], succinylation [13], β-hydroxybutylation [14], palmitoylation [15] and lactylation [16].

In 2019, Professor Zhao Yingming's team from the University of Chicago first reported in Nature that [16] lactate could serve as a substrate modified to histone lysine residues, and regulate downstream gene expression. Since then, a new epigenetic regulation pattern – lactylation – has entered the perspective of researchers. Recently, studies have shown that lactylation is an important epigenetic regulatory mode that participates in the regulation of numerous physiological and pathological processes [17,18], such as embryonic development, tumorigenesis, inflammation and many others. These studies suggest that lactate can regulate biological processes through a novel mechanism known as lactylation. Currently, research on lactate-mediated lactylation has become a hot topic. However, some unresolved problems still exist.

In this review, we summarize recent progress in lactate-mediated protein lactylation, including the regulatory roles and mechanisms of lactylation in physiological and pathological processes, the types of lactylation and their effects on proteins, and the molecules that regulate lactylation and its targets. Finally, we summarize the current questions that still exist in lactylation research. This review provides direction and a theoretical basis for the research and clinical translation of protein lactylation.

Lactate metabolism and lactylation

Lactate metabolism and lactate shuttles

Glucose is a primary source of energy for the body. Depending on whether oxygen is present, glucose metabolism can be divided into anaerobic glycolysis and oxidative phosphorylation [19]. Typically, lactate is a metabolic product of anaerobic glycolysis under hypoxic conditions. Glucose metabolism involves multiple steps and requires the participation of various enzymes [20]. Specifically, after cells take up glucose through glucose transporters (GLUTs), the conversion of intracellular glucose is catalyzed by hexokinase (HK) to glucose-6-phosphate. Furthernore, through the catalysis of several enzymes such as pyruvate kinase (PKM), glucose-6-phosphate is converted to pyruvate. Under normal aerobic conditions, the generated pyruvate enters the mitochondria and is converted to acetyl-CoA by pyruvate dehydrogenase (PDH). Acetyl-CoA then enters the TCA cycle and is completely oxidized to carbon dioxide and water, releasing a large amount of ATP to provide energy for the organism (Fig. 1), that's the so called "oxidative phosphorylation". However, under hypoxic conditions, the generated pyruvate does not enter mitochondria for oxidation but is instead converted to lactate by lactate dehydrogenase (LDH), leading to lactate accumulation within the cell, that's the so called "anaerobic glycolysis". Importantly, under certain special pathophysiological conditions, such as exercise, tumors, sepsis, trauma, and heart failure [1], even when oxygen is sufficient within the cell, glucose still primarily undergoes glycolysis and produces a large amount of lactate, which is known as "aerobic glycolysis" [21]. Apart from being produced by cellular metabolism, intracellular lactate can also originate from the extracellular microenviron-

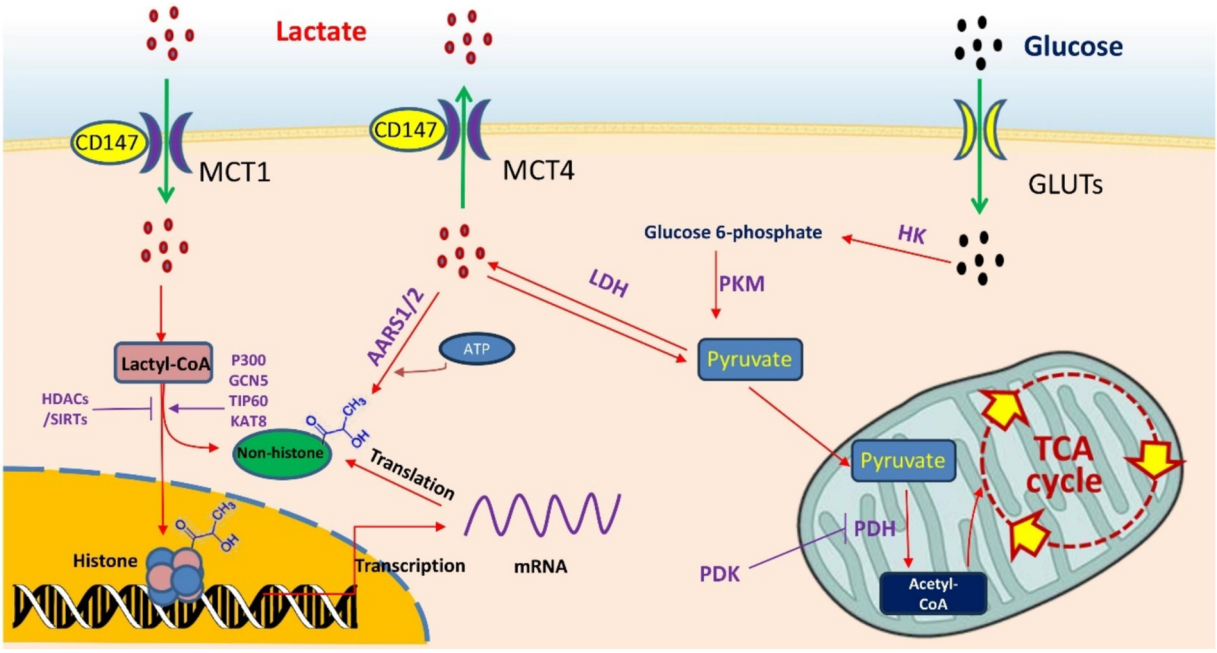


Fig. 1. Lactate metabolism and lactylation. Lactate can be divided into exogenous and endogenous lactate. Exogenous lactate is transported into cells by MCTs and then catalyzed to lactyl-CoA, which provides lactoyl groups for histone and nonhistone lactylation. Endogenous lactate is produced from glycolysis. Under aerobic conditions, the glucose metabolite pyruvate enters mitochondria and is broken down by the TCA cycle. MCTs: monocarboxylate transporters. GLUTs: glucose cotransporters. LDH: lactate dehydrogenase.HK: hexokinase. PDH: pyruvate dehydrogenase. PDK: pyruvate dehydrogenase kinase. HDACs: histone deacetylases. SIRTs: sirtuins. TCA: tricarboxylic acid. AARS 1/2: Alanyl-tRNA synthetase 1/2.

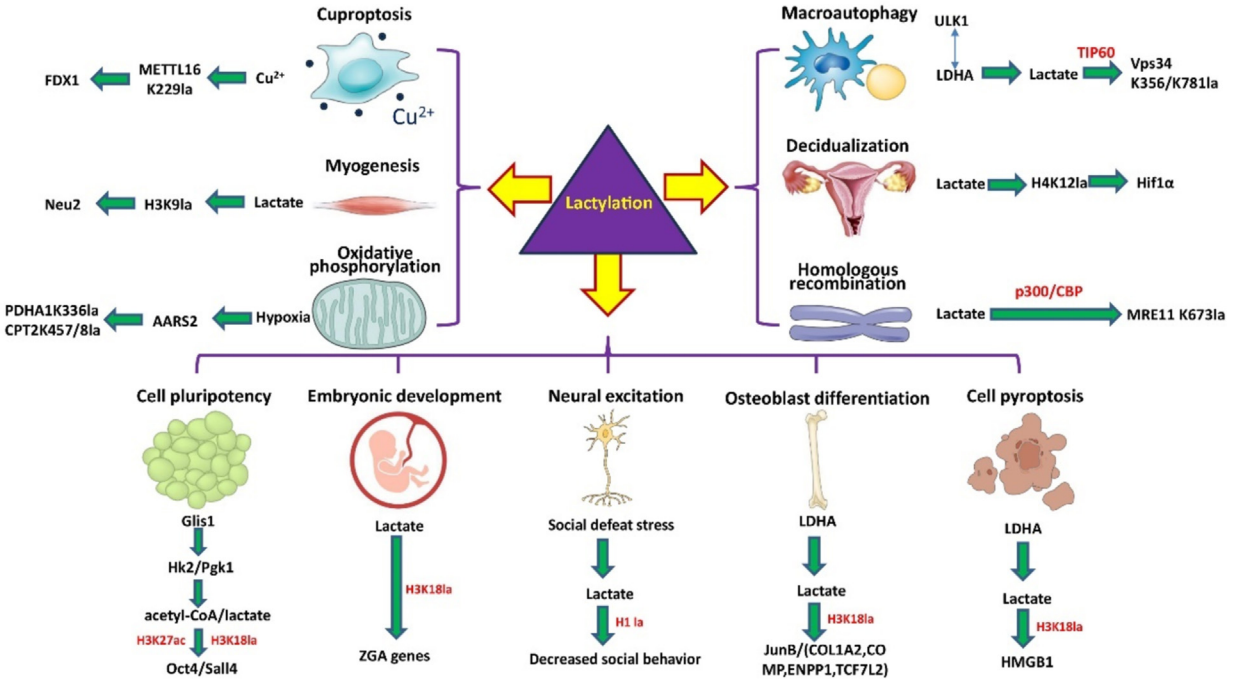


Fig. 2. Lactylation regulates various physiological processes. Lactylation regulates various physiological processes. Histone and nonhistone lactylation are involved in the regulation of cell pluripotency, embryonic development, neural excitation, osteoblast differentiation, cell pyroptosis and macroautophagy, decidualization, homologous recombination, cuproptosis, myogenesis and oxidative phosphorylation.

ment. Extracellular lactate cannot directly enter the cell but requires the involvement of the lactate transporter MCT1 and the coordination of CD147 [22]. At the same time, intracellular lactate can also be transported to the extracellular space by another lactate transporter MCT4 to perform regulatory functions such as signaling molecules [22,23].

Lactate-mediated lactylation

In addition to serving as an energy molecule and signaling molecule [2], recent studies have revealed that lactate can participate in epigenetic regulation through a novel protein modification method: lactylation [24]. Lactylation is the process of covalent modification of proteins with lactoyl groups [25]. During this process, lactate is typically first catalyzed into lactyl-CoA, which then transfers the lactoyl groups to substrate proteins under the action of ‘‘writer” proteins. The known lactylation ‘‘writer” proteins are mainly histone acetyltransferases, including P300 [16], GCN5 [26],TIP60 [27]and KAT8 [28] (Fig. 1) . Lactylation is a reversible biological process, and the known ‘‘erasers” for removing lactylation modifications are primarily histone deacetylases (HDACs or SIRTs) [29]. Moreover, scientists recently discovered a new class of lactylation ‘‘writer” proteins, alanyl-tRNA synthetase, which includes the members AARS1 [30] and AARS2 [31]. Due to the similar chemical structures of lactate and alanine, AARS1 can directly recognize lactate and, with the participation of ATP, convert it to lactyl-AMP and covalently modify it onto substrate proteins [32].

Roles of lactylation in physiological processes

The physiological activities of the body are inseparable from the participation of proteins. Changes in lactate levels can also be found in many physiological processes, indicating a close relationship between protein lactylation and physiological activities. Currently, lactylation is involved in the regulation of many physiological processes, including somatic reprogramming (Fig. 2).

Lactylation and somatic reprogramming

Changes in gene expression and the restoration of stem cell characteristics in somatic cells under the induction of various factors are known as somatic reprogramming [33]. The most well-known cell reprogramming factors are the transcription factors OCT4, KLF4, SOX2 and c-Myc [34]. Additionally, the transcription factor Glis1 is known as the ‘‘fifth reprogramming factor” [35]. A recent study [36] revealed that during fibroblasts reprogramming, the transcription factor Glis1 directly binds to the promoters of glycolysis related genes such as HK1 and PGK1, and induces their expression. These factors led to an increase in the levels of acetyl-CoA and lactate in cells, and subsequently promoted the expression of the cell stemness-related genes Oct4 and Sall4 through H3K27 acetylation and H3K18 lactylation, which ultimately transformed somatic cells into pluripotent stem cells. This research indicates that lactylation is closely associated with somatic cell reprogramming, and histone lactylation can directly regulate the expression of key genes involved in cell reprogramming.

Lactylation and development

Embryonic development is a precise and orderly process, involving lactylation. Yang *et al.* [37] first detected dynamic changes in histone lactylation during mouse embryonic development. They found that H3K18la, H3K23la, and pan-histone lactylation were abundant in oocytes, as well as in preimplantation embryos. In addition, the histone lactylation level reached its peak in the blastocyst stage. These results suggest that histone lactylation may be involved in the regulation of embryonic development. Recently, Li *et al.* [38] found that lactate is highly enriched in the nuclei of early embryos when major zygotic genome activation (ZGA) occurs in humans and mice. The inhibition of its production and uptake results in developmental arrest at the 2-cell stage, major ZGA failure, and loss of lactate-derived H3K18la, which can be rescued by the addition of lactyl-CoA and recapitulated by the overexpression of the H3K18R mutation. By profiling the landscape of H3K18la during mouse preimplantation development, they found that H3K18la is enriched in the promoter regions of most major ZGA genes and is correlated with their expression. In humans, H3K18la is also enriched in ZGA markers and temporally concomitant with their expressions. This research indicated that H3K18la regulates embryonic development. In addition, lactylation is closely related to neural development. After systematically detecting the dynamic changes in histone lysine crotonylation (Kcr) and lysine lactylation (Kla) during neural development, Dai *et al.* found [39] that histone Kcr and Kla were widespread in the brain and changed dynamically during neural development. In addition, by using the HDAC inhibitor MS-275 and an induced neural differentiation system, they demonstrated that histones Kcr and Kla play key roles in the regulation of neural development. Overall, these findings show that lactylation is an important regulatory force in organismal development, and histone lactylation can regulate the expression of genes related to development.

Lactylation and neural excitation

Elevated lactate has been found in the brain under physiological conditions, as well as cerebral ischemia. Currently, lactate is transformed from a metabolic end-product to a signaling molecule. Many studies have confirmed that lactate is an important regulator of brain behavior [40]. In addition, lactate-mediated lactylation was found to be associated with neural excitation and social stress [41]. Researchers have shown that nerve stimulation and social stress increase the levels of lactate and lactylation in brain regions, as well as the expression of the neuronal activity marker c-Fos. Furthermore, by conducting immunoprecipitation and mass spectrometry, they found that stress preferentially increased the lactylation level of H1 and that elevated histone H1 lactylation was associated with decreased social behavior. This research suggests that lactylation is closely related to brain activity and may be involved in the regulation of neuronal excitation.

Lactylation and osteoblast differentiation

During osteogenic differentiation, osteoblasts tend to metabolize glucose through aerobic glycolysis [42,43]. Lactate, the end product of aerobic glycolysis, has been found to induce osteoblast differentiation by stabilizing HIF-1α [44]. However, whether lactate-mediated lactylation is involved remains unclear. Recently [45], elevated LDHA, lactate and histone lactylation were found during the process of osteogenic differentiation. In addition, LDHA depletion significantly reduced H3K18la levels through a reduction in lactate production, thereby downregulating JunB expression, and ultimately impairing osteogenic differentiation. Moreover, another team has revealed the role and new mechanism of lactylation in osteoblast differentiation [46]. They found that the lactate produced by vascular endothelial cells can induce H3K18la in bone mesenchymal stem cells (BMSCs), which in turn upregulates the expression of osteogenic differentiation genes such as COL1A2, COMP, ENPP1 and TCF7L2, ultimately promoting osteogenic differentiation. Collectively, these researches [47] revealed the critical roles and mechanisms of histone lactylation in osteogenic differentiation.

Lactylation and cell pyroptosis

Pyroptosis is a kind of programmed cell death mediated by gasdermin [48]. When pyroptosis is initiated, the cell will continue to expand until the membrane bursts, causing the release of cell contents and activating a strong inflammatory response. Pyroptosis has been confirmed to be associated with the regulation of innate immunity and related diseases. When studying the molecular mechanisms of CI reperfusion (CI/R) injury, Yao *et al.* reported that [49] the expression of LDHA in N2a cells subjected to oxygen glucose deprivation/reoxygenation was significantly increased. Increased LDHA then promoted the levels of lactate and histone H3K18la, which upregulated the expression of high mobility group protein 1 (HMGB1), and eventually facilitated pyroptosis. The research indicates that lactate positively regulates the occurrence of pyroptosis by inducing histone lactylation.

Lactylation and macroautophagy

Macroautophagy is a conservative degradation process of lysosomes. Through the phagocytosis of cytoplasmic components in a double-membraned organelle, these components are then transported to lysosomes for degradation, which contributes to cell homeostasis and adaptation to pressure [50]. Recently, the regulatory relationship between glycolysis and autophagy has been revealed [27]. In the case of nutritional deficiency, UNC-51-like kinase 1 (ULK1) directly interacts with and activates the glycolytic enzyme LDHA, phosphorylates serine-196, and stimulates lactate generation. Lactate links autophagy and glycolysis via acyltransferase KAT5/TIP60 mediated Vps34 lactylation (K356 and K781). Specifically, Vps34 lactylation could enhance its association with Atg14L, Beclin1 and UVRAG, thereby increasing the lipid kinase activity of Vps34. The promotion of autophagic flow and endolysosomal transport could also be observed with Vps34 lactylation. The research shows that there is a close relationship between glycolysis and macroautophagy, indicating that glycolysis regulates macroautophagy through lactylation.

Lactylation and decidualization

Decidualization is an important process for establishing pregnancy [51]. The activation of glycolysis and lactate synthesis during decidualization has been known for many years [52], but their functions and mechanisms remain largely unknown. Recently, Zhao *et al* [53]. found that enhanced endometrial glycolysis is tightly coupled with H4K12la during decidualization and that inhibition of histone lactylation impaired decidualization. Mechanistically, CUT&Tag and ATAC-seq revealed HIF-1α as the target gene of H4K12la, which in turn forms an H4K12la–HIF-1α-glycolysis feedback loop to drive decidualization. The research suggests that histone lactylation is important for establishing pregnancy by promoting decidualization.

Lactylation and homologous recombination

Homologous recombination (HR) is an important form of DNA damage repair that plays a significant role in maintaining the stability of the genome [54]. Recently, a study [55]showed that lactylation is also involved in the regulation of HR. First, researchers have shown that lactate-induced lactylation promotes DNA damage repair and chemotherapeutic drug resistance in tumor cells. Furthermore, after screening key HR proteins, they found that MRE11, a crucial homologous recombination (HR) protein, is lactylated at K673 by the CBP acetyltransferase in response to DNA damage. Moreover, MRE11 lactylation enhances its binding to DNA, facilitating DNA end resection and HR. This finding clarified how the tumor metabolite lactate participates in regulating HR and chemotherapeutic drug resistance, suggesting that targeting MRE11 lactylation is a potential tumor treatment strategy.

Lactylation and cuproptosis

Cuproptosis, a type of copper ion-induced cell death, is a novel type of cell death [56]. Recently, Sun et al. [57] reported that lactylation is also involved in the regulation of cuproptosis. They discovered that copper ion stimulation in gastric cancer cells induces METTL16 lactylation at K229 and enhances its enzymatic activity, which further triggers m6A modification of the mRNA of the key cuproptosis gene FDX1, increasing the expression of FDX1 and ultimately leading to cuproptosis in gastric cancer cells. The research clarifies how lactylation participates in regulating cuproptosis, indicating that the combined use of elesclomol and AGK2, a SIRT2-specific inhibitor, is an effective method for killing tumor cells.

Lactylation and myogenesis

Muscle tissue is the main site of lactate production [58], and some studies have suggested that lactate can regulate the differentiation of myofibroblasts [59], but the underlying mechanism remains unclear. Recently, Dai *et al.* [60] reported that lactate promotes the differentiation of myofibroblasts into muscle cells by inducing histone lactylation. Specifically, using site-specific antibodies for lactylation, they discovered that lactate promotes H3K9la in myofibroblasts. Additionally, neuraminidase 2 (Neu2), a positive myogenic factor in skeletal muscle, is a downstream target gene of H3K9la. Lactate promotes myogenesis by upregulating the expression of Neu2. The research indicates that lactate promotes myogenesis by inducing histone lactylation.

Lactylation and oxidative phosphorylation

Oxidative phosphorylation and anaerobic glycolysis are the two main energy-producing pathways in the body [61]. Among them, oxidative phosphorylation completely oxidizes glucose into carbon dioxide and water, generating a large amount of ATP. However, its disadvantage is that the process is complex and the energy supply is relatively slower. Conversely, glycolysis can rapidly metabolize glucose into lactate and produce ATP, but the disadvantage is that it generates less energy. Both oxidative phosphorylation and anaerobic glycolysis are essential energy metabolism pathways in the body, and the balance between them has been unclear until recently. Recently, Mao *et al.* [31]reported that lactylation regulates the balance between oxidative phosphorylation and anaerobic glycolysis. Specifically, they found that hypoxia can induce the expression of the mitochondrial alanyl-tRNA synthetase (AARS2) protein, which acts as a novel lactyltransferase to further catalyze the mitochondrial pyruvate dehydrogenase catalytic subunit (PDHA1) K336la and carnitine palmitoyltransferase 2 (CPT2) K457/8la, leading to a decrease in the activity of these two enzymes and inhibition of oxidative phosphorylation. This finding indicates that lactylation serves as a "link" between anaerobic glycolysis and the reverse regulation of oxidative phosphorylation.

Lactylation and glycolysis

As we know, lactate is a product of glycolysis. However, interestingly, lactate can also regulate glycolysis by lactylation, thus forming a loop. For example, in Alzheimer's disease, Pan et al. [62]discovered that the levels of lactate and histone H4K12la significantly increased in brain regions of AD patients. Furthermore, they found that the key glycolytic enzyme PKM2 gene is a down-

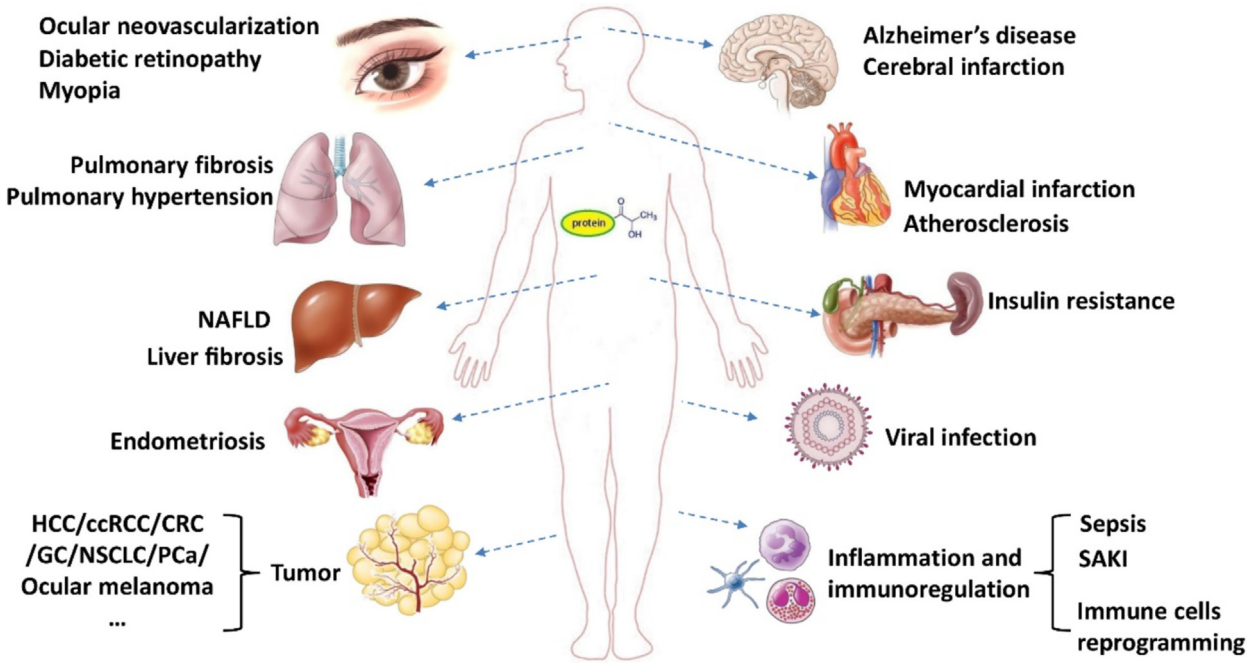


Fig. 3. Lactylation contributes to various diseases. Lactylation is involved in the regulation of cancer progression, inflammation and immune related diseases, fibrosis related diseases, Alzheimer's disease, myocardial infarction, insulin resistance, pulmonary hypertension, nonalcoholic fatty liver disease, cerebral infarction, ocular neovascularization, endometriosis, viral infection and many others. NAFLD: nonalcoholic fatty liver disease. HCC: Hepatocellular carcinoma. ccRCC: clear cell renal cell carcinoma. CRC: colorectal cancer. GC: gastric cancer. NSCLC: non-small cell lung cancer. PCa: prostate cancer. SAKI: sepsis-induced acute kidney injury.

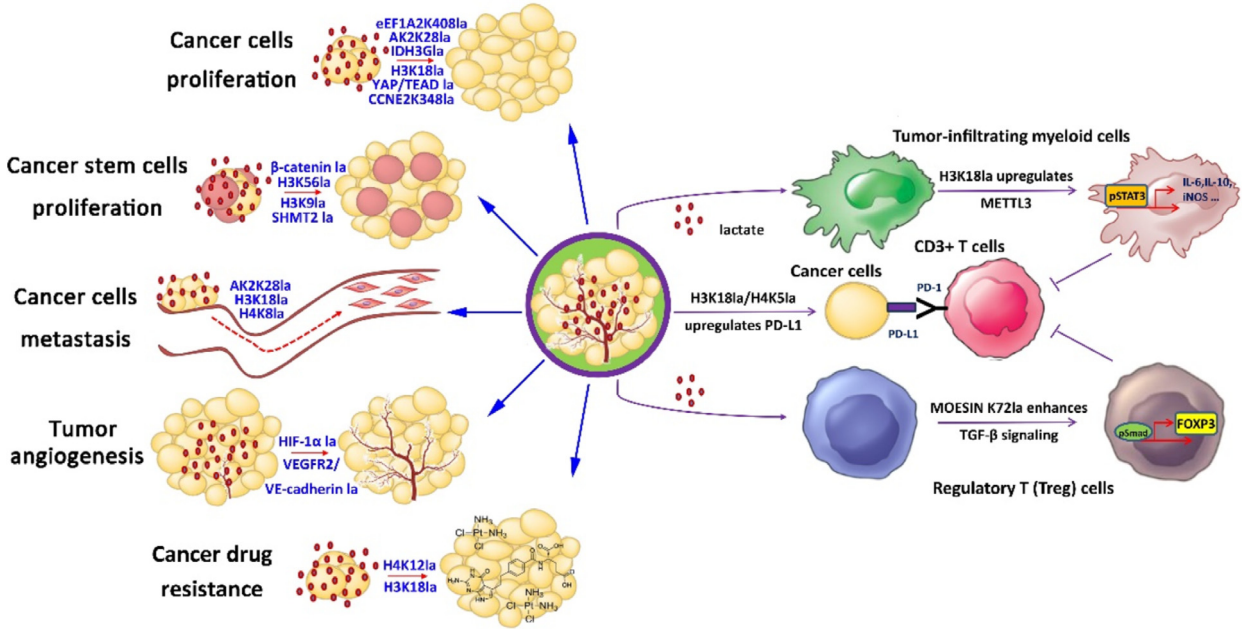


Fig. 4. Lactylation drives oncogenesis via multiple mechanisms. On the one hand, lactylation promotes cancer cell proliferation or metastasis, cancer stem cell proliferation, tumor angiogenesis and drug resistance. On the other hand, lactylation contributes to the formation of the tumor immune microenvironment by regulating tumor-infiltrating myeloid cells, Treg cells and the expression of PD-L1 in cancer cells.

stream target of H4K12la, and PKM2 promotes glycolysis through a positive feedback mechanism. Finally, they observed that pharmacological inhibition of PKM2 disrupts the glycolysis/H4K12la/PKM2 positive feedback loop and alleviates microglial dysfunction and Aβ pathology. Additionally, Zhao et al. [53]found that elevated lactate during decidualization can induce H4K12la and upregulate the transcription factor hypoxia-inducible factor 1 alpha (HIF-1α), which in turn forms an H4K12la–HIF-1α-glycolysis feedback loop to drive decidualization. Recently, Li et al. [63] discovered that lactate and histone H3K18la levels are significantly increased in pancreatic ductal adenocarcinoma and closely associated with poor prognosis of the patients. Further mechanistic studies showed that H3K18la can upregulate the expression of mitotic checkpoint regulators TTK and BUB1B. TTK and BUB1B can elevate the expression of P300, which in turn increased glycolysis. Besides, TTK activates LDHA by catalyzing its phosphorylation, thereby increasing lactate

and H3K18la levels. These findings suggest that lactate, as a product of glycolysis, can inversely regulate glycolysis via lactylation, and disruption of this loop may halt related pathological processes.

Roles of lactylation in pathological processes

Alterations in the lactate level are a typical characteristic of the occurrence and development of many diseases. Previous studies have shown that lactate is a metabolic waste [23,64]. However, recent studies have shown that lactate can regulate the progression of various diseases through lactylation (Fig. 3). Its substrates include both histones and non-histones, and the modification sites and mechanisms are also diverse.

The development of malignant tumors

High lactate is a marked feature of the tumor microenvironment [65]. There are two main reasons for its occurrence. First, compared to normal tissue, tumor tissue possesses abnormal blood vessels, which leads to insufficient blood supply and low oxygen content. Second, tumor cells still decompose glucose mainly by glycolysis even under aerobic conditions, which is called the "Warburg effect". Lactate is an inducing factor for lactylation. Currently, many studies have proposed that [32,66–68] the abundance of lactylation in tumor tissue is significantly greater than that in adjacent tissue, and is closely related to the poor prognosis of patients, indicating the potential of lactylation level as a tumor diagnostic marker. In addition, lactate mediated lactylation accelerates tumor development through various underlying mechanisms (Fig. 4).

Lactylation promotes tumor cell proliferation

Tumor cells exhibit prominent malignant proliferation properties [69], which are highly correlated with lactylation. Through in-depth lysine lactylome and proteome analysis, Yang *et al.* [70] successfully identified 9275 Kla sites and 9140 proteins from a total of 52 tumor and adjacent liver tissue samples collected from hepatitis B virus (HBV) related hepatocellular carcinoma (HCC) patients. In particular, Kla was found mainly in enzymes involved in metabolic pathways, such as the TCA cycle. The suppression of adenylate kinase 2 function by K28 lactylation has been verified as the probable mechanism for promoting the proliferation and metastasis of HCC cells. Moreover, the lactated modified "eraser" protein SIRT3 has been reported to be expressed at low levels in liver cancer tissue, and is thus unable to effectively exert its inhibitory effect on tumor cell growth in liver cancer cells by removing cyclin E2 (CCNE2) K348 lactylation [71]. Another study revealed that [67] in ocular melanoma, the level of tumor tissue lactylation was significantly increased. H3K18la upregulated the expression of the m6A reader YTHDF2 in tumor cells, while YTHDF2 recognized and facilitated the degradation of the PER1 and TP53 mRNAs, accelerating the occurrence of ocular melanoma. In addition, in ccRCC, the lactylation of inactive the VHL-triggered histone H3K18 could promote the progression of ccRCC by activating PDGFRβ mRNA transcription [72]. In addition, in lung cancer, Wang *et al.* [73]reported that BZW2 promoted the malignant progression of LUAD by promoting glycolysis-mediated lactate production and the lactylation of IDH3G. In bladder cancer, Xie *et al.* [74]reported that histone H3K18 la promotes cancer cell proliferation and migration by upregulating the expression of LCN2, while CircXRN2 functions as a tumor suppressor gene by inhibiting this process through activating the Hippo pathway. In colorectal cancer, Xie *et al.* [28]reported that protein lactylation is significantly increased in tumor tissues and is closely related to poor patient prognosis. Through lactylation proteomics analysis, the authors revealed that the translation elongation factor eEF1A2 undergoes lactylation at the K408 site. eEF1A2 K408la enhances protein translation, thereby promoting tumor cell proliferation, and KAT8 is the "writer" molecule that catalyzes eEF1A2 K408la. In breast cancer, Pandkar *et al.* [75]reported that lactate can induce histone H3K18la and upregulate the expression of c-Myc, while the increased c-Myc further promotes breast cancer cell proliferation through the c-Myc-SRSF10 axis. In gastric cancer, Ju *et al.* [30] reported that alanyl-tRNA synthetase AARS1, in addition to its classic function as an alanyl-tRNA synthetase, can also serve as a lactyltransferase. It directly utilizes lactate as a lactoyl donor to catalyze the lactylation of key components of the Hippo signaling pathway, YAP and TEAD, activating downstream gene transcription and expression, and promoting malignant proliferation of gastric cancer cells. Collectively, these studies suggest that lactylation is a positive regulatory factor for tumor cell proliferation.

Lactylation promotes the proliferation and self-renewal of tumor stem cells

Tumor stem cells are known as the "seed" cells of tumor occurrence and development, and are the "root" of continuous proliferation, metastasis, and chemotherapy resistance of tumor cells [76]. Recently, a study revealed that [77] lactate mediated lactylation could promote the proliferation and self-renewal of tumor stem cells, while demethylzeylasteral (DML) could inhibit the generation of lactate and the lactylation of histones H3K9 and H3K56 in liver tumor stem cells, thereby repressing the genesis of liver cancer. In addition, hypoxia or lactate stimulation has been shown to increase the level of the β-catenin protein in colorectal cancer (CRC) cells and increase its constancy, resulting in enhanced tumor cell stemness and proliferation ability [78]. In addition, Qiao *et al.* [79]reported in their research on esophageal cancer (EC) that the hypoxic tumor microenvironment can induce lactylation of the serine hydroxymethyl transferase 2 (SHMT2) protein, enhancing its stability. SHMT2 promotes the stemness of esophageal cancer cells by interacting with and increasing the expression of MTHFD1L. Furthermore, in glioblastoma, Li *et al.* [80]reported that histone H3K18la upregulates the expression of LINC01127, which in turn regulates MAP4K4 in a *cis*-acting manner to activate the JNK signaling pathway, thereby promoting the self-renewal of glioblastoma stem cells. Overall, these researches indicate that lactylation is a positive regulatory factor for the self-renewal of cancer stem cells.

Lactylation promotes tumor cell metastasis

Tumor metastasis is the main cause of tumor recurrence, and is also a major factor in the failure of tumor treatment [81]. Lactylation is closely related to tumor metastasis. In the colorectum, LPS derived from gut microbes has been found to induce lactylation of tumor cell histone H4K8, inhibit the binding of the transcription factor YY1 to the LINC00152 promoter and upregulate its expression, thus assisting in tumor cell invasion and migration [82]. In liver cancer, lactylation at K28 restricts the enzyme activity of AK2, and facilitates tumor cell proliferation and metastasis [70]. In addition, in a colorectal cancer liver metastasis model, Zhou *et al.* [83]reported that orphan G protein-coupled receptor 37 (GPR37) could activate the Hippo pathway, thereby promoting LDHA expression and glycolysis. This leads to increased lactylation of H3K18la, resulting in upregulation of CXCL1 and CXCL5, which promotes colorectal cancer liver metastasis. Collectively, these

studies indicate that lactylation is a positive regulatory factor for tumor cell metastasis.

Lactylation promotes angiogenesis in tumors

Intratumoral angiogenesis not only provides nutrients for cancer cell proliferation, but also provieds conditions for the development and metastasis of tumors [84]. Therefore, inhibiting angiogenesis can obviously prevent the development, diffusion, and metastasis of tumor tissue [85]. In prostate cancer [86], Luo *et al*. reported that lactate introduced into PCa cells through MCT1 stabilized HIF-1α under normal oxygen conditions via HIF-1α lactylation. Moreover, HIF-1α lactylation increased the transcription of KIAA1199, a binding protein of hyaluronic acid (HA), promoting tumor angiogenesis by increasing the secretion of VEGFA. In addition, in glioblastoma (GBM), Zhang *et al*. [87] reported that the functional peptide P4-135aa encoded by the pseudogene MAPK6P4 promotes the phosphorylation of the transcription factor KLF15 at the S238 site and stabilizes its protein expression. Subsequently, the transcription factor KLF15 enters the nucleus and upregulates the transcription level of LDHA, leading to an increase in lactate levels and promoting the lactylation of the angiogenic markers VEGFR2 and VE-cadherin. This, in turn, increases their protein expression and promotes tumor angiogenesis. Overall, these researches suggest that lactylation is a positive regulatory factor for tumor angiogenesis.

Lactylation promotes chemotherapeutic drug resistance

Drug resistance is a crucial factor in cancer recurrence and metastasis [88]. By studying the mechanisms related to pemetrexed resistance in lung cancer brain metastatic cells, Duan *et al*. [89] reported that aldo–keto reductase family 1 B10 (AKR1B10) is highly expressed in lung cancer brain metastatic cells. Knocking down AKR1B10 significantly increased the sensitivity of lung cancer brain metastasis cells to the chemotherapy drug pemetrexed. Mechanistically, the authors discovered that AKR1B10 promotes glycolysis and lactate production in lung cancer brain metastasis cells by upregulating LDHA expression, which further induces H4K12la, leading to the upregulation of the cell cycle regulatory gene CCNB1 and ultimately causing drug resistance in cells. Furthermore, in studying the mechanisms of bevacizumab resistance in colorectal cancer, Li et al. [90]found that tumor tissues from bevacizumab-resistant patients with colorectal cancer had increased levels of lactylation. The inhibition of lactylation hindered the development and progression of colorectal cancer. Mechanistically, researchers have shown that lactate in the tumor microenvironment induces histone H3K18 lactylation, upregulates the expression of the autophagy enhancer protein RUBCNL, promotes cell autophagy, and contributes to the tumorigenesis and progression of colorectal cancer. Recently, by single-cell sequencing, Li *et al*. [91] discovered that cisplatin resistance in bladder cancer (BCa) is closely related to histone lactylation. They found that cisplatin-resistant subpopulations of bladder cancer cells exhibit significant glycolytic metabolic characteristics. These cells induce H3K18 lactylation, upregulate the expression of the transcription factors YBX1 and YY1, and subsequently promote cisplatin resistance in BCa. In summary, these studies indicate that lactylation contributes to drug resistance for cancer treatment.

Lactylation promotes tumor immune evasion

In addition to directly participating in regulating the malignant phenotypes of tumor cells such as proliferation and metastasis, lactylation is also closely related to the formation of an immunosuppressive tumor microenvironment [92]. The tumor microenvironment (TME) is a complex combination of tumor cells, immune cells, and various interstitial cells [93]. Among them, CD3 + T cells, CIK cells, and NK cells are the main tumor killing cells that inhibit tumor progression. In contrast, immunosuppressive cells such as tumor-infiltrating myeloid cells (TIMs) and regulatory T (Treg) cells can inhibit the killing effect of CD3 + T cells on tumor cells, playing an important role in maintaining the immunosuppressive tumor microenvironment [94]. In CRC, H3K18la upregulated the expression of METTL3 in TIMs, which further boosted the immunosuppressive functions of myeloid cells via the m6A/JAK1/STAT3 axis, stimulating the development of CRC [95]. Lactate stimulation can also increase the maintance and function of Treg cells, whereas lactate degradation decreases Treg cell induction, increased antitumor immunity, and reduces tumor growth in mice [96]. Mechanistically, lactate promoted MOESIN K72 lactylation, which improved the interaction between MOESIN and TGF-β receptor I, and facilitated SMAD3 signal transduction, thus regulating the generation of Treg cells. In addition to regulating immune cells, in AML, Huang *et al*. [97] reported that the transcription factor STAT5 promotes glycolysis in AML by upregulating the expression of glycolysis-related genes, leading to lactate accumulation. In turn, elevated lactate upregulates PD-L1 expression by inducing the lactylation of varies histones, thereby promoting tumor immune evasion. Collectively, these studies indicate that lactylation contributes to the formation of an immunosuppressive tumor microenvironment and promotes the development of cancer by controlling the function of immunosuppressive cells or upregulating PD-L1 expression in cancer cells.

Inflammation-related diseases

Inflammation is a protective response of body tissue to harmful stimuli such as pathogenic microorganisms and dead cells, and is a complex biological process mediated by immune cells [98]. Typically, the function of inflammation is to eliminate cell damage factors and initiate tissue repair. However, excessive or prolonged inflammatory reactions are detrimental to the body and require anti-inflammatory responses to maintain homeostasis. Recent research has revealed that one of the notable features of the inflammatory microenvironment is elevated lactate, which could induce immune cell anti-inflammatory capacity by regulating their reprogramming through lactylation [99,100]. In an inflammatory microenvironment, lactate was found to induce proinflammatory Th17 cells to metabolically reprogram into regulatory T cells expressing FOXP-3 by catalyzing H3K18la [101]. In addition, the accumulation of lactate are involved in the dysregulation of CD4 + T cell differentiation. In experimental autoimmune uveitis, through in-depth lysine lactylome analysis, Fan *et al*. [102] found that transcription factor Ikzf1 k164la promoted TH17 differentiation by directly modulating the expression of TH17-related genes, including RUNX1, TLR4, interleukin-2(IL-2), and IL-4. Moreover, lactate stimulation can also promote the proinflammatory to reparative transformation of macrophages through PKM2 lactylation [103].

Inflammation regression is a necessary step in the process of heart repair after myocardial infarction (MI). The anti-inflammatory and angiogenic functions of monocyte macrophages are regulated by histone lactylation via the promotion of repair gene transcription, which is beneficial for improving the repair environment and cardiac function after MI [26]. In addition, in sepsis, an inflammation-related disease, a high circulating level of lactate is a typical feature. By comparing the collected samples from healthy and diseased populations, researchers have shown that lactylation existed in both healthy and sick people, but to different degrees. The level of H3K18la might be positively related to the severity of sepsis and infection [104]. Similarly, the significant

increase in HMGB1 lactylation might be positively correlated with the severity and mortality of sepsis. HMGB1 lactylation is mediated by macrophages ingesting extracellular lactate via MCTs through a p300/CBP-dependent mechanism. Lactylated HMGB1 is then released from macrophages via exosome secretion which increases endothelial permeability, and exacerbates sepsis [105]. Recently, researchers have shown that lactate modification is also closely related to sepsis-induced acute kidney injury (SAKI) [106]. Through a multi-modifiedomics strategy (acetylation and lactylation modification), researchers discovered that the acetylation of the α subunit of pyruvate dehydrogenase E1 (PDHA1) promotes an increase in lactate levels, which in turn promotes the lactylation of the non-histone protein Fis1 K20 and regulates mitochondrial fission to regulate the occurrence of SAKI. Taken together, these studies suggest that lactylation regulates the occurrence of inflammatory diseases and their complications through multiple mechanisms.

Fibrosis related diseases

Fibrosis is a pathological process characterized by necrotic parenchymal cells, and abnormally increased and excessively deposited extracellular matrix in tissue [107]. Progressive fibrotic processes can lead to structural damage and functional decline of organs, ultimately resulting in organ failure, which is the main cause of disability and mortality in many diseases [108]. Lactylation has also been implicated in fibrosis. In pulmonary fibrosis, myofibroblasts metabolize abnormally, producing and secreting a large amount of lactate, which further leads to the presence of histone Kla in the promoter regions of macrophage fibrogenic genes. This finding is in accordance with the upregulation of epigenetic modifications in fibrotic lung myofibroblasts [109]. In arsenite-related idiopathic pulmonary fibrosis, Wang *et al.* [110]discovered a novel mechanism by which lactylation promotes lung fibrosis. They found that lactate in the IPF microenvironment is transported into alveolar epithelial cells (AECs) through MCT1, leading to H3K18la and upregulation of YTHDF1. YTHDF1 further upregulates NREP expression through RNA m6A modification, and NREP in alveolar epithelial cells facilitates the fibromyxoid transformation (FMT) of pulmonary lymphoid follicles (PLFs) by regulating TGF-β1. In addition, compared with normal pregnant placentas, placentas from women with preeclampsia had greater lactate levels. This elevated lactate could regulate the expression of fibrosis-related genes such as FN1 and SERPINE1 through histone lactylation, thereby resulting in placental fibrosis [111]. Furthermore, recently, Rho *et al.* [112] reported that lactylation is also involved in the development of liver fibrosis. Specifically, they found that hexokinase 2 (HK2) upregulates lactate levels and induces histone H3K18la, which in turn upregulates the expression of genes such as α-SMA, COL1A1, and TIMP1, thereby governing the activation of hepatic stellate cells (HSCs) and resulting in liver fibrosis. In summary, these studies suggest that lactylation contributes to the development of fibrosis related diseases through multiple mechanisms.

Alzheimer's disease

Alzheimer's disease (AD) is characterized by the proinflammatory activation of microglia, which involves the transition from oxidative phosphorylation to glycolysis [113]. Significant increases in lactate and lactylation levels have been found in AD model mice and patient brain tissue [114,115,62]. Mechanistically, histone H4K12 lactylation activated glycolytic gene transcription in AD microglia, leading to its proinflammatory activation. This finding correlated with the generation of AD, and intervention in related signaling pathways could markedly improve the symptoms of AD mice. Overall, these studies show that lactylation contributes to the development of AD, indicating that inhibiting related signaling pathways can improve AD symptoms.

Heart related diseases

High lactate levels are positively associated with prognosis and mortality in patients with heart attack [116]. Through the MCT-dependent signaling pathway, lactate can be transported into cells and prompt Snail1 lactylation, which upregulates the endothelial-to-mesenchymal transition of the heart after MI, thereby accelerating cardiac fibrosis and aggravating cardiac dysfunction [117]. Apart from myocardial infarction, lactate and lactylation have also been implicated in regulating heart failure. Recently, by lactylation omics analysis, researchers discovered a significant decrease in lactate concentration in myocardial cells during heart failure, which further led to a decrease in the lactylation level of K1897 on the α-myosin heavy chain (α-MHC) and a significant reduction in the interaction between α-MHC and titin, ultimately resulting in heart failure [118]. Collectively, these findings indicate that lactylation is closely related to the development of cardiac-related diseases and may serve as a target for intervention.

Insulin resistance

The phenomenon of reduced sensitivity of surrounding tissue to insulin, elevated blood sugar, and islet function compensation for increased insulin secretion is called insulin resistance. Previous findings have shown that circulating lactate levels were often increased in obese and insulin resistant individuals [119,120]. A recent study indicated that [121] lactate-mediated lactylation in skeletal muscle is connected with insulin resistance in humans. The research indicates that lactate may regulate insulin resistance through lactylation, but the underlying mechanisms remain unclear.

Pulmonary hypertension

Pulmonary hypertension (PH) is a progressive disease characterized by elevated mROS and enhanced glycolysis [122]. Hypoxia is considered to induce an increase in mROS, which further restrains HIF-1α hydroxylation, and subsequently activates the HIF-1α/PDK1&2/p-PDH-E1α axis. This triggered hypoxic glycolysis in PASMCs, leading to lactate accumulation and increased histone lactylation, which upregulated downstream target genes of HIF-1α, thus promoting the proliferation of PASMCs. Furthermore, in hypoxic PH rats, drug intervention with an LDH inhibitor reduced the histone lactylation, and enhanced PASMC proliferation and vascular remodeling [123]. In summary, these studies indicate that lactylation promotes pulmonary hypertension, suggesting that targeting lactylation could be a potential therapeutic strategy for related diseases.

Nonalcoholic fatty liver disease

The mitochondrial pyruvate carrier (MPC) is a protein complex in the inner mitochondrial membrane that transports pyruvate from outside the mitochondria into the mitochondrial matrix to produce acetyl-CoA [124]. The underlying relationships between MPC1 and fibrosis, inflammation or insulin sensitivity in obese or NASH mice have been reported in a few studies [125]. However, whether MPC1 can control the levels of lactate and lactylation in NAFLD remains unclear. Recently, MPC1 was found to decrease the level of lactate in hepatocytes, and was negatively associated with lactylation of several proteins, especially fatty acid synthase (FASN). Mechanistically, high MPC1 expression decreased FASN K673 lactylation, activated FASN thereafter, and promoted liver lipid accumulation in NAFLD [126]. Overall, the research found that MPC1 promotes NAFLD through regulating FASN lactylation, indi-

cating that targeting MPC1 may be an effective treatment for non-alcoholic fatty liver disease (NAFLD).

Cerebral infarction

Cerebral infarction (CI) is associated with high morbidity and mortality. Impaired cerebral blood circulation and local tissue ischemia and hypoxia damage are commonly observed after CI. It often injures neurons, and eventually leads to paralysis, aphasia and other neurological deficit symptoms [127]. Recently, lactylation has been suggested to regulate CI progression. Lymphocyte cytosolic protein 1 (LCP1) lactylation is reduced by glycolysis inhibition, which facilitates LCP1 degradation, and ultimately relieves CI progression [128]. The research demonstrates that lactylation promotes cerebral infarction, and inhibiting lactylation can improve the condition.

Eye diseases

The eyes are the windows of the soul, and lactylation has also been found to be related to the occurrence of many eye diseases. For example, ocular neovascularization is one of the major characteristics of proliferative retinopathy [129]. Retinal microglia are tightly associated with hypoxia-induced angiogenesis and vasculopathy [130], but the potential underling mechanisms remain to be explored. Wang *et al.* [131] developed a lactylation map of microglia under normal and hypoxic conditions, via the application of 4D proteomics and lactylation omics technology. They revealed that the elevation of YY1 (K183 site) lactylation in microglia under hypoxia and the subsequent increase in FGF2 transcription and expression are ways to regulate angiogenesis in endothelial cells. These results provide a novel theoretical basis for the study of the pathogenesis and treatment of proliferative retinopathy and other critical diseases that cause blindness. In addition, lactylation is closely related to diabetic retinopathy. Recently, Chen *et al.* [132] reported that retinal lactate homeostasis is disrupted under diabetic retinopathy (DR) conditions, and that lactate-mediated H3K18la can affect the stability of CDK2 mRNA by regulating FTO expression, ultimately impacting endothelial cell function and retinal homeostasis, revealing the importance of histone lactylation in the pathogenesis of DR. Moreover, scleral hypoxia is a significant factor contributing to myopia, but how hypoxia induces myopia is poorly understood. Recently, Lin *et al.* [133] reported that a hypoxia induced glycolysis/lactate/histone lactylation cascade drives fibroblast to-myofibroblast transdifferentiation (FMT), resulting in myopia. They demonstrated that the suppression of glycolysis, lactate production, or Notch1 expression can mitigate FMT and myopia development. Taken together, these researches suggest that lactylation plays important roles in the development and progression of eye diseases.

Atherosclerosis

Atherosclerosis is a serious cardiovascular disease, and current research has shown that exercise is highly beneficial for improving cardiovascular health, but the underlying mechanisms are not entirely clear [134]. Recently, Wang *et al.* [135]reported that lactate produced during exercise can inhibit the occurrence of atherosclerosis by inducing the lactylation of methylated CpG-binding protein 2 (Mecp2) at the K271 site in vascular endothelial cells. Furthermore, through RNA-sequencing and Chip-qPCR, they found that Mecp2 k271la inhibited the expression of epiregulin (Ereg), which altered the mitogen-activated protein kinase (MAPK) signaling pathway by regulating the phosphorylation of epidermal growth factor receptors, thereby affecting the expression of Vcam-1, Icam-1, Mcp-1, IL-1β, IL-6, and Enos in ECs, which in turn promoted the regression of atherosclerosis. The research indicates that lactate-mediated lactylation is beneficial for improving atherosclerosis.

Table 1
Histone lactylation sites and biological effects.

Histone Lactylation sites	Downstream target genes	Biological processes	Reference
H1	N/A	Neural excitation	[41]
H2BK6, H4K80	miR-155-5p	Dyslipidemia	[144]
	Oct4/Sall4	Cell pluripotency	[36]
	N/A	Neural development	[39]
	JunB	Osteoblast differentiation	[45]
	HMGB1	Pyroptosis	[49]
	Foxp3	Inflammation	[101]
	Lrg1, Vegf-a, and IL-10	Myocardial infarction	[26]
	FN1 and SERPINE1	Preeclampsia	[111]
	YTHDF2	Ocular melanoma	[66]
	PDGFRβ	ccRCC	[72]
	Mettl3	Colorectal cancer	[95]
H3K18	Bmp5, Trpc5, and Kit	Hypoxic pulmonary hypertension	[123]
	RUBCNL	Chemotherapy drug resistance	[90]
	HSPA6	Viral infection	[137]
	c-Myc	Breast cancer	[75]
	LINC01127	Gliomas	[80]
	ALKBH3	Ocular melanoma	[147]
	HMGB1	Endometriosis	[139]
	α-SMA、Col1a1 and Timp 1	Liver fibrosis	[112]
	Ythdf1	Arsenite-related idiopathic pulmonary fibrosis	[110]
	CXCL1 and CXCL5	Colorectal cancer liver metastases	[83]
	HIF-1α	Prostate cancer	[146]
	YBX1 and YY1	Cisplatin resistance	[91]
	FTO	Diabetic retinopathy	[132]
	ZGA genes	Zygotic genome activation	[38]
	Notch1	Myopia	[133]
H3K18/H4K5	PD-L1	Immunosuppression	[97]
H3K23/ H3K18	N/A	Embryonic development	[37]
H3K9	Neu2	Myogenesis	[60]
H3K9/H3K56	N/A	Liver cancer	[77]
	PKM2	Alzheimer's disease	[62]
H4K12	CCNB1	Chemotherapy drug resistance	[89]
	HIF-1α	Decidualization	[53]
H4K18	LINC00152	Colorectal cancer	[82]
H4K8	HK-1 and IDH3G	NSCLC	[68]
Histone	ARG1,PDGFA, THBS1 and VEGFA	Lung fibrosis	[109]

Viral infection

Porcine reproductive and respiratory syndrome virus (PRRSV) is an arterivirus that has devastated the swine industry worldwide for more than 30 years [136]. Previous studies have found that cells infected with this virus exhibit high lactic acid levels, but the specific role and mechanism are unclear. Recently, Pang *et al.* [137] reported that infection with PRRSV can induce the lactylation of histone H3K18, which upregulates the expression of HSPA6. In turn, HSPA6 reduces IFN-β induction by hindering the interaction between TRAF3 and IKKε, ultimately leading to increased viral replication. The research suggests that lactylation promotes viral infection.

Endometriosis

The molecular mechanisms of endometriosis have long been unclear [138]. Recently, Chen *et al.* [139] reported that compared

Table 2
Nonhistone lactylation sites and biological effects.

Nonhistone lactylation site	Biological effects	Biological processes	Reference
PKM2 K62	The lactylation of PKM2 inhibits its tetramer-to-dimer transition, promotes its pyruvate kinase activity and reduces nuclear distribution	Macrophage phenotype transition	[103]
AK2 K18	Lactylation at K28 inhibits the function of adenylate kinase 2	Liver cancer	[70]
CCNE2 K348	Lactylated CCNE2 promotes HCC cell growth	Liver cancer	[71]
β-catenin site:N/A	β-catenin lactylation enhanced the protein stability and expression of β-catenin	Colorectal cancer	[78]
HIF-1α site:N/A	HIF-1α lactylation stabilizes HIF-1α under normoxia	Prostate cancer	[86]
METTL3 K281/K345	Lactylation on zinc-finger domain of METTL3 enhances its capture of m6A-modified RNA	Colorectal cancer	[95]
MOESIN K72	Lactylation of Lys72 in MOESIN improves MOESIN interaction with transforming growth factor b (TGF-b) receptor and downstream SMAD3 signaling	Tumorigenesis	[96]
HMGB1 Site:N/A	HMGB1 lactylation promotes its exosomal release in polymicrobial sepsis	Sepsis	[105]
Snail1 Site:N/A	Lactylation of Snail1, a TGF-β transcription factor, activates TGF-β/Smad2 signal after hypoxia/MI.	Myocardial infarction	[117]
FASN K673	Lactylation at the K673 site of FASN inhibited FASN activity	NAFLD	[126]
LCP1 Site:N/A	Inhibiting the glycolysis decreased the lactylation levels of LCP1 and resulted in the degradation of LCP1	Cerebral infarction	[128]
YY1 K183	YY1 lactylation in microglia plays an important role in retinal neovascularization by upregulating FGF2 expression	Ocular neovascularization	[131]
α-MHC K1897	α-MHC K1897la enhanced the interaction of α-MHC with Titin	Heart failure	[118]
Fis1 K20	Fis1 K20la promoted excessive mitochondrial fission	Sepsis-induced acute kidney injury	[106]
eEF1A2 K408	eEF1A2K408la boosted translation elongation and enhanced protein synthesis	Colorectal cancer	[28]
Ikzf1 K164	Ikzf1 K164la promoted TH17 differentiation by directly modulating the expression of TH17-related genes	TH17 differentiation	[102]
VEGFR2/VE-cadherin Site:N/A	VEGFR2 and VE-cadherin lactylation increased their protein expression	Vasculogenic mimicry	[87]
PFKP K688	Lactylation of PFKP attenuates its enzyme activity	Colorectal cancer	[150]
Mecp2 k271	Mecp2 k271la repressed the expression of epiregulin (Ereg) to inhibit atherosclerosis	Atherosclerosis	[135]
MRE11 K673	MRE11 lactylation promotes its binding to DNA	Homologous recombination	[55]
METTL16 K229	METTL16 lactylation at site K229 promotes FDX1 accumulation via m6A modification on FDX1 mRNA	Cuproptosis	[57]
SHMT2 Site:N/A	Hypoxia triggered lactylation of the SHMT2 protein and enhanced its stability	Esophageal cancer	[79]
PDHA1 K336 CPT2 K456/7	PDHA1 K336la and CPT2 K456/7 la inhibit the activity of these two enzymes	Oxidative phosphorylation	[31]
YAP K90 TEAD1 K108	Lactylation of YAP 85 at K90 and TEAD1 at K108 activate downstream target gene expression	Gastric cancer	[30]
p53 K120 /K139	Lactylation of p53 impairs p53 LLPS and DNA binding	Tumorigenesis	[32]
Vps34 K356/k781	Vps34 lactylation enhance its association with Atg14L, Beclin1 and UVRAG, thereby increasing the lipid kinase activity of Vps34	Macroautophagy	[27]
CENPA K124	The lactylation of CENPA at K124 promotes CENPA activation	Hepatocellular carcinoma	[156]

with normal endometrial tissue and stromal cells, endometriotic tissue and stromal cells exhibit increased LDHA expression and lactate levels. Furthermore, they discovered that lactate promotes the proliferation, invasion, and migration of endometrial stromal cells by inducing histone H3K18 lactylation, which upregulates the expression of HMGB1, ultimately promoting the progression of endometriosis. This research indicates that lactylation contributes to the development and progression of endometriosis.

Effects of lactylation on proteins

From the above, we can see that lactylation plays important regulatory roles in various pathological and physiological processes. Now, through lactylome and proteome analysis, researchers have found that lactylation occurs widely in proteins [140,141]. According to the kind of substrate proteins, lactylation can be divided into histone and nonhistone lactylation. The effects of lactylation on different proteins vary. Generally, histone lactylation mostly alters the transcription of target genes, while nonhistone lactylation has diverse effects on proteins.

Histone lactylation regulates gene transcription

The basic unit of chromatin is the nucleosome, an octamer formed by DNA winding histones. Histones are among the main components of chromatin, and their chemical modification after

translation is one of the important epigenetic modifications. Common histone modifications include acetylation, butyrylation, methylation, and phosphorylation [142]. These modifications change the relationship between histones, and between histones and DNA, controlling the opening and compression of chromatin, and allowing gene expression or silencing [143]. Current research has shown that the primary effect of histone lactylation is to activate chromatin and stimulate the transcription of downstream target genes.

Histones are mainly classified into five categories based on their amino acid composition and molecular weight: H1, H2A, H2B, H3, and H4. Among them, histones H1, H2B, H3 and H4 can be lactylated (Table 1). Elevated histone H1 lactylation has been correlated with stress-associated neural excitation stimulation and reduced social behavior [41]. However, its specific lactylation sites have yet not been reported. For histone H2B, the only identified site of lactylation is K6. H2BK6la and H4K80la cooperatively regulate the expression of miR-155-5p, playing an important role in dyslipidaemia [144]. For histone H3, many lactylation sites,including K9, K18, K23, and K56, [37,77] have been discovered. Among them, H3K18 is the most common and extensively studied site in histone lactylation, and has the most diverse regulatory target genes [145]. At present, the downstream target genes activated by H3K18la transcription include reparative genes Lrg1, Vegf-a, and IL-10 [26], pluripotency genes Oct4, Sall4, and Mycn [36];the transcription factors JunB [45], FOXP3 [101],c-MYC [75],HIF-1α [146],YBX1 and YY1 [91];the proinflammatory factor HMGB1 [49,139]; the m6A-related regulatory proteins METTL3 [95],YTHDF2 [66],ALKBH3 [147],YTHDF1 [110]and FTO [132],the fibrosis-related genes FN1, SERPINE1 [111],α-SMA、Col1a1 and Timp 1 [112];the signaling pathway key proteins Notch1 [133];the chemokine CXCL1 and CXCL5 [83];the non-coding RNA LINC01127 [80];the autophagy enhancer protein RUBCNL [90]; the PASMC proliferation genes Bmp5, Trpc5, and Kit [123],PDGFRβ [72], HSPA6 [137] and ZGA genes [38]. In addition, by exerting synergistic effects with H4K5la, H3K18la can also regulate the expression of PD-L1, playing a significant role in immunosuppression in AML [97]. Interestingly, the underlying mechanism by which H3K18la regulates the expression of so many genes remain unclear, and the special characteristics of the H3K18 site are still unknown. H3K9 and H3K56 lactylation have been suggested to promote the hyperplasia in liver cancer cells, but their downstream target genes have not yet been identified [77]. Individually, H3K9la upregulates Neu2 expression to play a role in myogenesis [60]. K8, K12, and K18 are the lactylation sites of histone H4. Among them, H4K8 lactylation regulates the expression of the metabolism-related genes HK-1 and IDH3G in lung cancer cells [68], H4K12 lactylation activates the transcription of the glycolytic genes HIF-1α [53], PKM2 [62] and CCNB1 [89], and H4K18 lactylation reduces the binding efficiency of the repressor YY1 with the LINC00152 promoter [82].

Nonhistone lactylation has diverse effects on proteins

Apart from histone lactylation, researchers have also found that many important functional nonhistone proteins exhibit lactylation. There are various effects of lactylation on nonhistone proteins (Table 2). In summary, lactylation can affect nonhistone proteins in six ways.

(1) Affects the stability of proteins. Protein stability is regulated by various factors, and lactylation is one of them [148]. The effect of lactylation on protein stability is not fixed, as it may either increase [79,87] or decrease protein stability. For example, hypoxia induced glycolysis was shown to stimulate β-catenin lactylation, and further enhance its stability and expression, thus exacerbating the malignancy of CRC [78]. In addition, under normoxia, HIF-1α could be stabilized through lactylation via the import of lactate into PCa cells by MCT1 [86]. However, research has shown that the inhibition of glycolysis lessened LCP1 lactylation, which increases its degradation, and eventually alleviates CI progression [128].

(2) Affects the catalytic activity of proteases. Most enzymes are proteins. When lactylation occurs precisely at the active sites of an enzyme, its activity may be affected accordingly [149]. Similarly, lactylation may either increase [57] or inhibit the activity of proteases [31,150]. For example, PKM2 lactylation at the K62 site facilitates the function of pyruvate kinase [103], while lactylation at the K28 site inhibits adenylate kinase 2 activity [70]. Additionally, MPC1 knockout could mediate the lactylation of FASN at the K673 site, which suppressed FASN activity, and downregulated liver lipid accumulation [126,151], while Vps34 lactylation (K356 and K781) has been suggested to increase its own integration with Beclin1, Atg14L, and UVRAG, thereby promoting the lipid kinase activity of Vps34 [27].

(3) Affects the interactions between proteins and other molecules. Interactions between molecules are influenced by various factors [152], and lactylation has been shown to affect interaction between proteins and other biological macromolecules [32,55]. For example, the interaction between METTL3 and m6A modified RNA was found to be enhanced by METTL3 lactylation on the zinc-finger domain at the K281 and K345 sites [95]. Additionally, MOESIN lactylation at Lys72 could strengthen its association with TGF-β receptor I and activate downstream SMAD3 signaling, which further modulates Treg cell generation [96]. Moreover, α-MHC K1897la was found to enhance the interaction of α-MHC with Titin, which alleviated heart failure [118].

(4) Affects the distribution of proteins. Proteins are known to be the bearers of life activities, and for proteins to perform their corresponding functions, they must reach their designated locations [153]. Lactylation also regulates the localization and distribution of proteins. For example, researchers found that PKM2 nuclear distribution is decreased due to lactylation at the K62 site. [103] In addition, in polymicrobial sepsis, lactate can promote the exosomal release of macrophage HMGB1 [105].

(5) Affects the structure of proteins. The structure of a protein determines its biological function [154], and research has shown that lactylation can also alter protein structure. For example, the transformation of PKM2 from a tetramer to a dimer occurs through PKM2 lactylation at the K62 site [103], which promotes its pyruvate kinase activity and reduces its nuclear distribution.

(6) Affects the function of proteins. Transcription factors are a class of protein molecules with special structures that regulate gene expression [155]. Various transcription factors can be lactylated [30 102,135], which affects their functions. For example, lactylation of Snail1 via interaction with CBP/p300 could induce the transformation of cardiac endothelial cells into mesenchymal cells after MI [117]. Moreover, increased YY1 lactylation in microglia under hypoxia accelerated angiogenesis [131]. In addition, the lactylation of mitochondrial fission 1 protein (Fis1) lysine 20 (Fis1 K20la) was found to promote excessive mitochondrial fission, thereby enhancing SAKI [106]. In addition to those of transcription factors, the functions of some other proteins are also enhanced after lactylation [28,57]. For example, CCNE2 lactylation at the K348 site could promote the malignant proliferation of HCC cells [71]. In addition, Liao *et al.* [156] found that CENPA can be lactylated at lysine 124 (K124), which promotes CENPA activation, leading to enhanced expression of its target genes.

Targeting lactylation by metabolic modulators for disease therapy

Overall, we can see that lactylation plays an important regulatory role in various pathophysiological processes, with diverse tar-

Table 3
Metabolic modulators regulating lactate-mediated lactylation.

Target	Metabolic modulators	Drug dosage	Effects on lactylation	Biological processes	Reference
MCTS	CHC	N/A	Down	Myocardial infarction	[117]
	AZD3965	0.5 μM		Myocardial infarction	[26]
CD147	MEM-M6/1	1.25–10 μg/ml	Down	Cancer progression	[158]
LDH	Oxamate	20 mM	Down	Insulin resistance	[121]
		8 mM		ccRCC	[72]
		50 μM		Hypoxic pulmonary hypertension	[123]
		20 m M		Sepsis	[105]
	GSK2837808A	100 pM		Embryonic development	[37]
	FX-11	N/A		Myocardial Infarction	[26]
	LDHi	20 mg/kg		Cancer progress	[96]
PDH	Rotenone	5 nM	Up	Myocardial Infarction	[26]
		500 nM		Colorectal cancer	[95]
		1.5 mg/kg		Ocular neovascularization	[131]
PDK	DCA	5 mM	Down	Inflammation	[101]
		5 mM		Myocardial Infarction	[26]
		20 mM		Ocular neovascularization	[131]
PKM2	FGS	10–50 μM	Down	NSCLC	[157]
HK	2-DG	5 mM	Down	Insulin resistance	[121]
		10 mM			
		20 mM		Cerebral Infarction	[128]
		1 mM		Inflammation	[101]
		4 mM		ccRCC	[72]
P300	C646	100 μ M	Down	Colorectal cancer	[95]
		5 μM		sepsis	[105]
	A485	20 μM		Ocular neovascularization	[131]
TIP60	MG149	20 μM	Down	Autophagy	[27]
HDACs	TSA	1 μM	Up	Colorectal cancer	[95]
	MS-275	1 μM		Neural development	[39]
SIRT3	Honokiol	10 mg/kg	Down	hepatocellular carcinoma	[71]
AARS1	β-alanine	1.2 %β-alanine	Down	Tumorigenesis	[32]

get proteins and biological effects. Targeting lactylation might be a novel therapeutic strategy for related diseases. Studies (Table 3) have indicated that lactylation is regulated by numerous metabolic modulators (Fig. 5). According to different mechanisms, lactylation targeting can be divided into two main categories:

Targeting lactylation by inhibiting the production or transport of lactate

Typically, lactate is a donor of lactyl-CoA and a promoting factor of lactylation. Therefore, targeted regulation of intracellular lactate production or transportation can control the process of lactylation. The production of intracellular lactate is a complex physiological process catalyzed by multiple enzymes and involves multiple steps. Stimulation of cells with the HK inhibitor 2-DG or the PKM inhibitor FGS [157] commonly leads to reduced glycolysis, lactate levels, and lactylation, since HK and PKM are considered the critical enzymes that promote the conversion of glucose to pyruvate, the upstream substance of lactate [72,101,128]. Under anaerobic conditions, LDH participates in the translation of pyruvate to lactate, and the LDH inhibitors oxamate [72], LDHi [96], FX-11 [26] and GSK2837808A [37] were found to significantly reduce intracellular lactate and lactylation levels. In contrast, under aerobic conditions, pyruvate is usually converted to acetyl-CoA via PDH, while the use of rotenone, an inhibitor of PDH, blocks this process, causing pyruvate metabolism in the direction of lactate, thus promoting lactylation [26,95]. Pyruvate dehydrogenase kinases (PDKs) can also restrict the activity of PDH. The PDK inhibitor DCA was therefore effective in facilitating acetyl-CoA production from pyruvate, leading to a decrease in the levels of lactate and lactylation [26,101,131].

In addition, exogenous lactate plays a vital role in inducing lactylation. These findings indicate that MCT1 is necessary for the entry of exogenous lactate into cells. CD147 was also involved in the regulation of lactate transport, as it coexists with MCTs on the cell membrane and controls their expression. Accordingly, the application of the MCT inhibitors CHC [117] and AZD3965 [26], as well as the CD147 antibody MEM-M6/1 [158] could reduce intracellular lactate and lactylation levels.

Targeting lactylation by "writers" or "erasers" regulators

In addition to requiring the participation of lactate, lactylation itself is also a reversible enzymatic reaction. Therefore, modulating enzyme activity can also target lactylation. The enzymes that catalyze protein lactylation are known as "writers", and the acetyltransferases P300, GCN5, TIP60 and KAT8 [28] were recently discovered. Both the P300 inhibitors C646 [95,105] and A485 [131], and the TIP60 inhibitor MG149 [27] can suppress lactylation. Excitingly, the alanyl-t RNA synthetase,AARS1 was recently found to act as a lactyl-transferase to promote lactylation [30,32], while β-alanine could disrupt lactate binding to AARS1 and inhibit global lactylation. In contrast, "erasers" refer to enzymes that erase protein lactylation. Histone deacetylases (HDACs and SIRTs) are "erasers" identified at present, and the use of the HDAC inhibitors TSA [95] and MS-275 [39] stimulates lactylation, while the SIRT3 activator honokiol [71] reinforces delactylation.

The possibility of clinical applications for drugs targeting lactylation

Before applying drugs to clinical disease treatments, the primary considerations must be their efficacy and safety. Among the aforementioned drugs targeting lactylation, MCT inhibitor AZD3965 is an anti-tumor candidate drug that has entered phase I clinical trials. Current clinical results indicate that it is safe and well-tolerated [159], while in vitro and animal experiments have demonstrated its effectiveness in treating tumors [160], indicating that AZD3965 is a highly promising anti-tumor drug. Additionally, HDAC inhibitor MS-275 (entinostat) is a candidate anti-cancer drug that has entered phase III clinical trials. Previous phase I and II clinical trials have shown that MS-275, either alone or in combination with other drugs, is safe and effective for treating

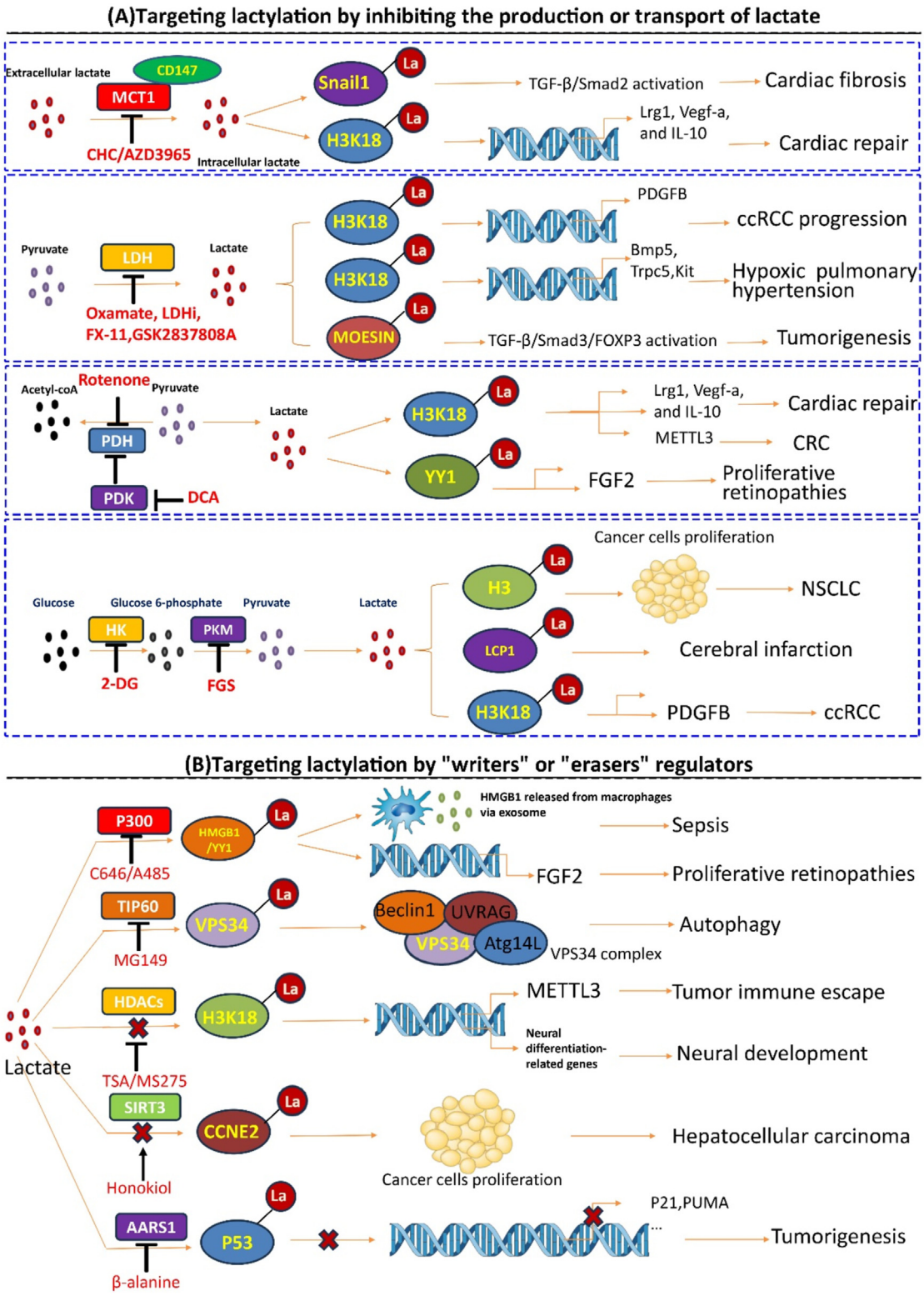


Fig. 5. Metabolic modulators and their targets in the regulation of lactylation. Lactylation can be targeted in two ways: ① by targeting the production or transport of lactate and ② by targeting "writers" or "erasers" of lactylation. The production or transport of lactate relies on many enzymes or functional proteins, which can be targeted by drugs. Lactylation is catalyzed by "writers" and removed by "erasers". The "writers" or "erasers" of lactylation can also be targeted by drugs.

solid tumors and lymphomas [161–164]. Excitingly, recent phase III results showed that entinostat combined with exemestane significantly enhanced progression-free survival (PFS) compared to exemestane monotherapy in patients with $HR^{+}/HER2^{-}$ advanced breast cancer (ABC) who progressed following endocrine therapy [165]. This combination could represent a novel treatment option for Chinese patients with ABC. In contrast to AZD3965 and entinostat, honokiol, an activator of SIRT-3 [166], is a natural compound derived from the Chinese and Japanese traditional medicine Magnolia officinalis, which has been used for thousands of years. In

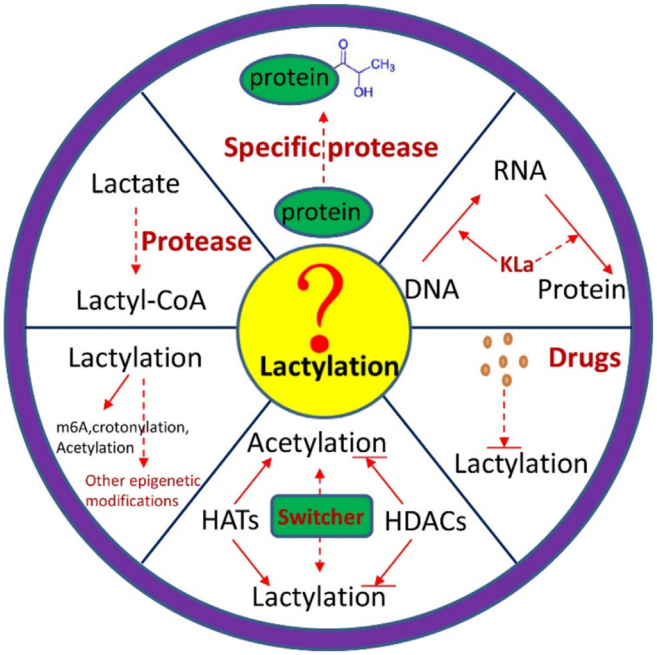


Fig. 6. The remaining questions related to lactylation. Despite the progress in our understanding of lactylation in recent years, many questions remain regarding basic aspects, such as whether there is an enzyme that specifically catalyzes lactylation and whether lactylation can regulate gene expression beyond histone lactylation. Solid arrows: reported biological processes; Dashed arrows: physiological processes that may exist but have not yet been reported.

recent years, various food safety authorities have evaluated honokiol and deemed it safe [167]. Honokiol possesses multiple pharmacological effects, including anti-infective, anxiolytic, and antioxidant properties [168]. It has also been found to have antitumor activity in recent years, making it a potential anti-cancer drug [169]. Besides these, other lactylation regulatory molecules also exhibited certain pharmaceutical activities in in vitro and animal trials [167–169]. However, their safety, efficacy, and indications still require further research.

Concluding remarks and future perspectives

Due to the existence of lactylation, lactate, a primary product of glycolysis in mammals, has gracefully transformed from an "ugly duckling" into a "beautiful swan." Currently, lactate-mediated lactylation participates in the regulation of numerous pathophysiological processes, including cell pluripotency, embryonic development, neural excitation, cancer, inflammation and immune related diseases, and fibrosis related diseases. Lactylation substrate proteins and sites are diverse, and their biological effects are varied. Generally, histone lactylation mostly alters the transcription of target genes, while nonhistone lactylation affects protein functions. Considering the important role of lactylation in the development of diseases, targeting lactylation may be a promising therapeutic strategy for treating diseases.

In general, the physiological and pathological processes regulated by lactylation are accompanied by abnormal lactate levels. However, is this a necessary condition for lactylation to participate in the regulation of biological processes? We believe the answer is no. For example, in the process of cuproptosis, the upstream condition that triggers METTL16 lactylation is Cu^{2+}, but not lactate [57]. However, due to the network of signal regulatory pathways in organisms [170], we cannot rule out the existence of unknown signaling pathways linking copper ion and lactate metabolism. This also means that some physiological or pathological processes may still be regulated by lactylation even if there is no change in the lactate level. As a novel epigenetic regulation way, lactylation is becoming a hotspot and leading edge of research, and its functions and mechanisms under other physiological and pathological conditions are being revealed gradually. However, the remaining questions related to lactylation are still numerous (Fig. 6):

(1) Do dedicated "writers" or "erasers" that catalyze or erase lactylation exist? At present, the discovered "writers" of lactylation include histone acetyltransferases and alanyl-tRNA synthetase, while the "writers" of lactylation are mainly histone deacetylases. The enzymes that specifically catalyze or clear protein lactylation are still unknown. (2) HATs and HDACs act as "writers" and "erasers" of lactylation respectively. What are the factors that regulate their role switching? In other words, when a HAT (histone acetyltransferase) or HDAC (histone deacetylase) encounters a protein, what factors determine whether that protein will undergo acetylation or lactylation? The existence of competition between acetylation and lactoylation and its underlying mechanism are still unclear. (3) The key enzyme that catalyzes the conversion of lactate to lactyl-CoA has been found in prokaryotes [171,172], but has not been detected in animals or humans. Excitingly, AARS1, an alanyl-t RNA synthetase, was recently found to moonlights as a lactate sensor and lactyltransferase to promote P53 lactylation and tumorigenesis. In this process, AARS1 directly recognizes lactate and catalyzes the lactylation of P53, without the involvement of lactyl-CoA. Instead, it utilizes lactyl-AMP [32]. However, the proportions of protein lactylation mediated by histone acetyltransferases and AARS1/2 respectively are still unclear. (4) Histone lactylation may modulate the transcription of downstream genes. However, could lactylation control gene expression at nontranscriptional level, such as protein translation? Gene expression regulation is complex and multilayered and occurs at both the RNA and the protein levels [173]. Typically, histone lactylation regulates gene transcription. However, the regulatory role and mechanisms of lactylation in protein translation remain poorly understood. Excitingly, recent research has revealed evidence that lactylation regulats protein translation. Researchers have shown that the translation elongation factor eEF1A2 undergoes lactylation at the K408 site, which enhances protein translation and thereby promotes tumor cell proliferation [28]. Apart from eEF1A2, protein translation also involves the participation of various other regulators [174], such as the translation initiation complex composed of EIF4G, EIF4A, and EIF4E. It is still unclear whether these proteins can undergo lactylation and affect protein translation. (5) The regulation of intracellular gene expression is a network structure, and research has discovered the associations of lactylation with RNA m6A modification [95] and other acylations [175]. Among these, the link between acetylation and lactylation is the most common. In polymicrobial sepsis, Yang et al. [105] found that macrophages can uptake extracellular lactate to promote both HMGB1 lactylation and acetylation, which promotes the release of HMGB1 via exosome secretion and increases endothelium permeability. Moreover, Li L et al. [36] showed that transcription factor Gli-like transcription factor 1 (Glis1) can enhance both the levels of acetyl-CoA and lactate and synergistically drove histone acetylation and lactylation to induce pluripotency. Additionally, under low-temperature conditions, Lu et al. [176] found that mitochondrial damage in macrophages leads to metabolic reprogramming, which induces histone acetylation and promotes M1 proinflammatory differentiation. At the same time, metabolic reprogramming results in increased histone lactylation mediated by lactate in M1 macrophages, which initiates repair gene expression. In addition to acetylation, other post-translational acylations, such as crotonylation, have also been reported to crosstalk with lactylation. During neural development, Dai et al. [39] found that histone lysine

crotonylation (Kcr) and lysine lactylation (Kla) are widely distributed in the brain, which promote cell-fate transitions in the developing telencephalon. In addition, lactylation may also be linked with succinylation. In gastric cancer, Zhang et al. [177]found that lysine acetyltransferases 2 A (KAT2A) promotes the succinylation of PKM2 at K475 site and accelerate glycolysis, which may induces lysine lactylation in cancer cells. However, what is the "cross talk" between lactylation and other types of gene expression regulation modes? Given the extensive and intricate spectrum of target genes and biological processes regulated by lactylation, it is reasonable to speculate that lactylation engages in "cross-talk" with other types of regulatory modes. However, the precise underlying mechanisms remain to be elucidated. (6) Lactylation plays a prominent regulatory role in various pathological processes, and studies have shown that inhibiting lactate mediated lactylation has antitumor effects [77,157]. Nevertheless, no specific therapeutic drugs have been developed for diseases specifically targeting lactylation. At present, we can target lactylation via two approaches: by inhibiting lactate production or its uptake into cells, and by suppressing the "writers" that catalyze lactylation. However, the specificity and efficacy of these two approaches pose a challenge, as these targets are involved not only in lactylation but also in other vital physiological processes [178]. The key enzymes that catalyze the conversion of lactate to lactyl-CoA and AARS1/2 may be good targets for targeting lactylation in the treatment of related diseases.

Lactylation has opened up new avenues for epigenetic research, and has also revealed new biological functions and molecular mechanisms related to the role of lactate. Here, we reviewed the roles and mechanisms of lactate-mediated lactylation in human health and diseases, as well as the effects of lactylation on proteins and the strategies for targeting lactylation in the treatment of diseases. Finally, we raised the current issues and challenges surrounding the study of lactylation. With further research, it is believed that in the near future, unsolved questions related to lactylation will be unraveled by researchers, and these studies will provide new ideas and approaches for the diagnosis and treatment of related diseases.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study was supported by the China Postdoctoral Science Foundation under Grant Number 2024M754253, the Chongqing Postdoctoral Science Foundation (CSTB2023NSCQ-BHX0015), National Natural Science Foundation of China (NSFC, NO. 82372529) and was sponsored by the Science and Technology Innovation Enhancement Project of Army Medical University (2022XQN45).

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