Review article

The role of nonhistone lactylation in disease

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ABSTRACT

In 2019, a novel post-translational modification termed lactylation was identified, which established a connection among lactate, transcriptional regulation and epigenetics. Lactate, which is traditionally viewed as a metabolic byproduct, is now recognized for its significant functional role, including modulating the tumor microenvironment, engaging in signaling and interfering in immune regulation. While research on lactylation (KLA) is advancing, the focus has primarily been on histone lactylation. This paper aims to explore the less-studied area of nonhistone lactylation, highlighting its involvement in certain diseases and physiological processes. Additionally, the clinical relevance and potential implications of nonhistone lactylation will be discussed.

1. Introduction

Since its discovery in 1780, lactic acid has been considered a byproduct of metabolism, a metabolic waste product produced by strenuous exercise or hypoxic conditions [1]. However, with decades of research, there has been a fundamental change in the way we think about lactate. The lactate shuttle hypothesis suggests that lactate acts as a bridge molecule that coordinates signaling between different cells, tissues, and organs [2]. Lactate can act as a metabolic substance that is autonomously taken up by tumors, thereby altering the tumor microenvironment [3,4]. Lactic acid can act as a signaling molecule and participate in signaling pathways to regulate gene expression and functional changes in immune cells, macrophages, cancer cells, fibroblasts, etc., which play indispensable roles in tumors, inflammation and metabolism [5–8].

A new protein post-translational modification (PTM), lysine lactylation (Kla), discovered by Zhang et al., in 2019, has provided new research ideas on the physiopathological functions of lactate [9]. Many studies on histone lactylation have been carried out. Stimulation of histone lactylation can promote macrophage polarization, which is involved in tumor development [10]. It also directly drives the expression of downstream genes, such as Arg1 and YTHDF2, to regulate the glycolytic pathway, Jak-STAT pathway and PI3K-Akt-GSK pathway [9,11,12]. In 2020, researchers used high-throughput sequencing to sequence the lactating sites of botrytis cinerea and found that there were a large number of lacylation sites [13]. In a further investigation of the human proteome, the

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researchers determined that lacylation exists not only in histones, but also widely in non-histones [14,15]. The discovery of nonhistone lactylation has expanded the understanding of lactylation, allowing us to move away from viewing it solely as a modification of chromatin. Like histone lactylation, nonhistone lactonization exhibits spatiotemporal dynamics [16]. We hope that the lactylation of nonhistone proteins can be a target for disease treatment and provide therapeutic assistance.

2. Lactic acid and nonhistone modifications

Warburg noted that even in the presence of an adequate supply of oxygen, tumor cells still prefer glycolysis for energy over oxidative phosphorylation (OXPHOS), which provides a more efficient energy supply. This phenomenon is known as the Warburg effect [17]. The Warburg effect, in addition to providing tumor cells with large amounts of adenine nucleoside triphosphate needed for growth and proliferation, also provides large amounts of lactate. Lactate, an inevitable product of the glycolytic pathway, is a regulatory molecule for metabolism, the immune response and intercellular communication [18].Lactate metabolism in glycolytic and oxidizing tumor cells is shown in Fig. 1.

Lactic acid is partially transferred from lactoyl glutathione (LGSH) to protein lysine residues to form lactylation modifications.The production process of nonhistone lactylation is shown in Table 2.Although not at the same levels, sequencing of lactylation in the plants Funga pathogen Botrytis cinerea, rice, Trypanosoma brucei and humans demonstrated the evolutionary conservation and biological consistency of lactylation (see Fig. 2). In humans, researchers have characterized the lactylproteome of the human body through the cyclic imposition of lactyllysine via tandem mass spectrometry, revealing that outside of histones, lactylation occurs widely in the human proteome and is enriched in the glycolytic pathway [14]. In the genomic lactate group analysis for hepatitis-associated hepatocellular carcinoma (HCC), a total of 9275 Kla sites were identified, of which 9256 were located in nonhistone proteins. Researchers further clarified that PKM2 lactylation can regulate hepatocellular carcinoma cell proliferation and metastasis and determined that nonhistone protein lactylation can promote the proliferation and migration of tumors [15]. In acute ischemic stroke (AIS), researchers identified a total of 1003 Kla sites on 469 proteins in the cerebral cortex of a mouse model of cerebral ischemia/reperfusion injury (CIRI), and these sites were associated with the mitochondrial apoptotic pathway and mediated neuronal death [21].Lactylation content determined by genome sequencing ispresented in Table 1.The study of the lactylation of nonhistone proteins extends the mechanistic study of lactic acid in human diseases, as lactic acid functions not only as a metabolite or signaling
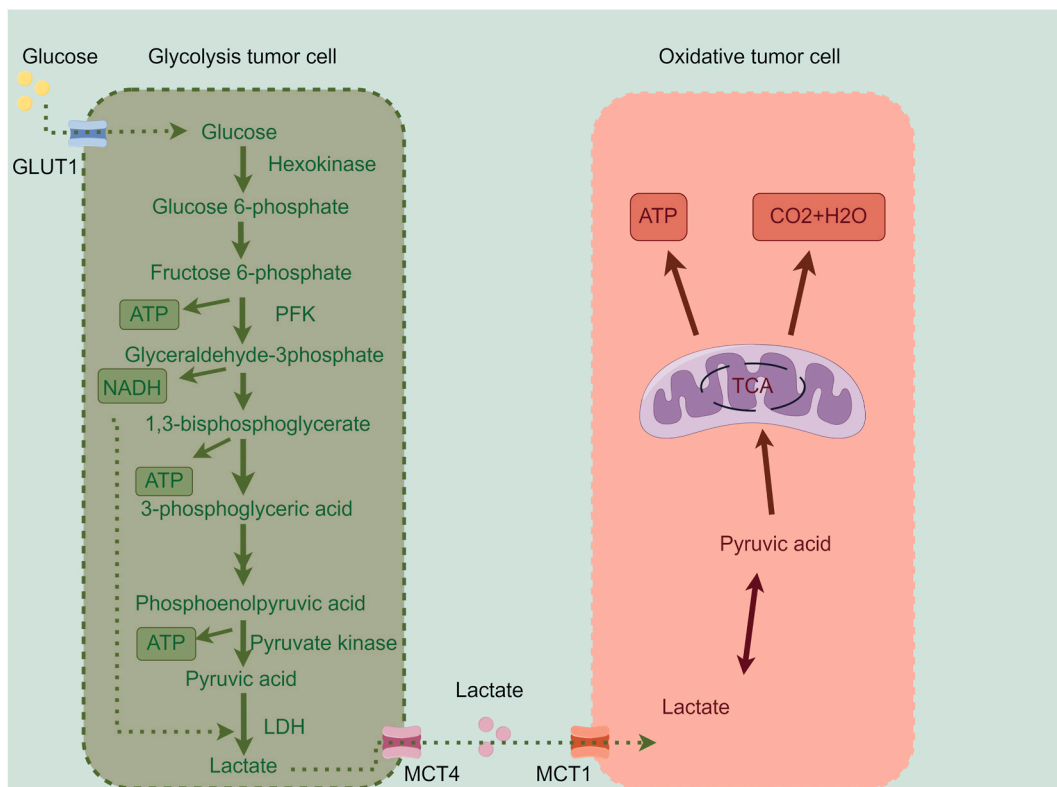

Fig. 1. Lactate metabolism in glycolytic tumor cells and oxidative tumor cells.
Under hypoxia, NADH and pyruvate are reduced to lactate, and ultimately, one molecule of glucose will produce two ATP molecules and two lactate molecules. Glycolytic tumor cells transport lactate into EMT via mct4, whereas oxidative tumor cells take up lactate via mct1 and generate energy via OXPHOS.
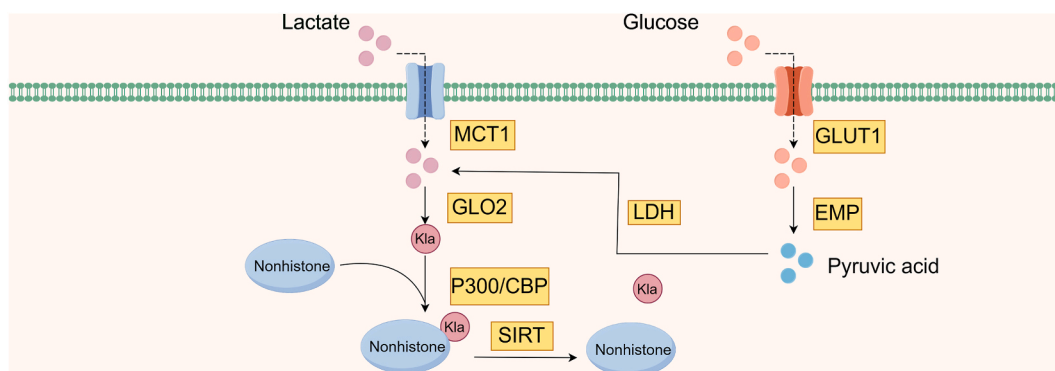
Fig. 2. Production of non-histone lactylations.
Lactate enters cells via MCT1 and later becomes Kla via GLO2. Glucose enters the cell via GLUT1 and later becomes pyruvate via the EMP pathway, eventually pyruvate becomes lactate through LDH.P300/CBP lactylates nonhistone proteins and SIRT can de-lactylated it.

molecule but also as a modifying molecule that plays different roles in proteins.

3. Functions of nonhistone lactylation

3.1. Nonhistone lactylation and metabolic regulation

Lactate is not only a metabolite but also an energy substrate [25]. Under aerobic conditions, pyruvate produced by glycolysis generates carbon dioxide and oxygen through OXPHOS. However, under hypoxia, nicotinamide adenine dinucleotide (NADH) and pyruvate are reduced to lactate, and ultimately, one molecule of glucose will produce two adenosine triphosphates (ATP) and two lactate molecules [26,27]. However, in the determination of circulating metabolites in mice, it was determined that lactate can also be a major source of carbon for the TCA cycle and thus becomes a major source of energy [28]. The role of lactate in metabolic regulation deserves to be explored in depth, and lactylation provides a new direction for research. In 2020, James et al. identified 350 Kla proteins, which were mainly enriched in the glycolytic pathway, after analysis using the Database for Annotation, Visualization, and Integrated Discovery (DAVID) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) databases in a nonenzymatic lactylation study [29]. Researchers further determined from glycolytic enzymes that lactate is partially transferred from LGSH to protein lysine residues to undergo lactylation, a process regulated by glyoxalase 2 (GLO2). This suggests that lactylation is enriched in glycolytic enzymes and can lead to reduced glycolytic output. In contrast, another study showed that hypoxia promotes the expression of mitochondrial alanyl-tRNA synthetase (AARS2), which lactylates PDHA1 K336 and carnitine palmitoyltransferase 2 (CPT2) K457/8 in the pyruvate dehydrogenase complex, leading to their inactivation and inhibition of OXPHOS by restricting the influx of acetyl-CoA for the oxidation of pyruvate and fatty acids. Moreover, SIRT3, which is an essential part of the pyruvate dehydrogenase complex, is a key component of OXPHOS. SIRT3, in turn, reverses PDHA1 and CPT2 lactylation, thereby activating OXPHOS [30]. This suggests that intracellular nonhistone lactonation plays a key regulatory role between aerobic and anaerobic metabolism and plays a critical role in the adaptation of cells to different energy demands and environmental conditions, providing a flexible and fine-grained means of regulating metabolic homeostasis in the cell.

3.2. Nonhistone lactylation and cell signaling

Lactate can function as a signaling molecule in the regulation of cancer and cardiovascular disease-related diseases [31,32]. Lactate causes a decrease in cAMP levels by activating G protein-coupled receptor 81 (GPR81) [33]. This pathway includes autocrine and paracrine pathways that can ultimately promote angiogenesis, immune evasion, the inflammatory response, and neurodevelopment

Table 1
Lactylation content determined by genome sequencing.

Source	Number	Sites	Enrich
HCC [15]	9140	9275	Metabolic pathways
FHC/SW480 [22]	444	637	glycolysis pathway
Cerebral Endothelium of CIRI Rats [21]	469	1003	Mitochondrial apoptosis pathway
Botrytis cinerea [13]	166	273	Protein synthesis
Rice [20]	342	638	Central carbon metabolism and protein biosynthesis
Protozoan Parasite Trypanosoma brucei [19]	257	387	Glucose metabolism
mouse prefrontal cortex [23]	63	N/A	Nucleosome-and histone-related biological processes
human lungs [24]	451	724	RNA splicing, actin filament organization, and neutrophil degranulation

N/A:Not Available.

Table 2
The regulation of nonhistone lactylation in cell lines and diseases.

Gene	Cell lines	Lactylation protein(s)/site(s)	Function and mechanism	Writer/Eraser	Disease
METTL16 [61]	HGC-27	K229	Cuproptosis	SIRT2	Gastric cancer
YY1 [39]	HMC3	K183	Neovascularizationupregulate FGF2	P300	Retinopathy of premary
PKM2 [46]	293T	K62	Inflammation Wound healing	N/A	Inflammatory
Snail1 [71]	HUVEC	N/A	EndoMT upregulate Cdh5,Kdr downregulate Acta2,Fn1,S100a4	MCT1	Myocardial infarction
FASN [73]	AML-12	K673	hepatocyte lipid accumulation	MPC1	NAFLD
Vps34 [74]	HEK293T; H1299	K356 K781	Autophagic flux endolysosomal trafficking skeletal muscle homeostasis	KAT5/TIP60	lung cancer gastric cancer
α-MHC [70]	H9c2	K1897	Reduces α-MHC-Titin interaction	p300; SIRT1; LDHA	Heart failur
METTL3 [55]	293T	K281 K345	m6A modification immunosuppression	N/A	Colon cancer
HMGB1 [48, 49]	RAW 264.7	N/A	Downregulate VE-cadherin,Claudin 5 upregulate ICAM1	P300/CBP HSPA12A	Sepsis LI/R
MOESIN [50]	Treg	K72	Regulates Treg cells enhances TGF-β signaling anti-PD-1 treatment	N/A	Liver cancer
Fis1 [58]	N/A	K20	Mitochondrial apoptosis	PDHA1	SAKI
Mecp2 [69]	MAECs	k271	Downregulate Ereg inflammation repair	N/A	ASCVD
HIF-1α [40, 75]	N/A	N/A	downregulate sema3A upregulate VEGFA VE-cadherin	MCT1; MCT4	Prostate cancer
PFKP [22]	SW480	K688	The glycolysis pathway	N/A	Colorectal cancer
CCNE2 [38]	Huh7	K348	Tumor cell proliferation migration invasion	SIRT3	HCC
PDHA1 [30]	N/A	K336	Inhibiting OXPHOS	AARS2; SIRT3	endurance exercise
CPT2 [30]	N/A	K457/8	Inhibiting OXPHOS	AARS2; SIRT3	endurance exercise
MRE11 [60]	N/A	K673	Homologous recombination chemoresistance	CBP/LDH	N/A
IDH3G [62]	H1975	N/A	Glycolytic pathway	BZW2	Lung Adenocarcinoma
LCP1 [67]	PC12	N/A	Cell viability	N/A	Cerebral infarction
DCBLD1 [65]	SiHa	K172	active pentose phosphate pathway autophagic degradation	N/A	Cervical cancer
METTL3 [55]	293T	N/A	enhance the capture of m6A-modified RNA	N/A	colon tumor

N/A:Not Available.

[34–37].

JIN et al. studied the role of SIRT3 in lactylation in HCC and reported that SIRT3 regulates lactylation and that the main lactylation proteins regulated are related to the cell cycle. For example, the cell cycle protein E2 (CCNE2) and lactylation of this protein are clearly associated with apoptosis in HCC [38].

The significant overlap of nonhistone lactylation sites with key nodes of several signaling pathways, including TGF-β and autophagy, suggests an important regulatory role for this form of modification in signaling [7,39,40]. Among them, PIK3C3/VPS34 lactylation can promote autophagy through the degradation of epidermal growth factor receptor (EGFR) and decreased hydrolytic maturation of cathepsin D (CTSD) [7]. Future studies need to further elucidate the regulatory mechanisms involved in nonhistone lactylation and signaling pathways, as well as their roles in disease development, which will help reveal potential therapeutic targets and biological mechanisms involved.

3.3. Nonhistone lactylation and immunomodulation

The expression of key proteins in immune cells, such as T cells, B cells and macrophages, is affected by lactate, which has been determined to be closely linked to immune cell function [25,27,41,42]. By regulating the level of lactylation of these proteins, nonhistone lactylation can be involved in key processes such as activation, proliferation and differentiation of immune cells [23,43].

In the immune system, macrophages, as important immune cells, are involved in the clearance of pathogens and immunoregulation. Macrophages require large amounts of energy to maintain their active state during infection and inflammatory states, and nonhistone lactylation has been associated with the regulation of macrophage energy metabolism. PKM2 is a key enzyme in glycolysis and plays a critical role in the regulation of the Warburg effect. PKM2 can promote macrophage differentiation through the exosomal pathway or regulate inflammatory vesicle activation in macrophages by mediating glycolysis [44,45]. Wang et al. identified PKM2 lactylation by mass spectrometry, and lactate revealed the role of PKM2 lactylation in the adaptation to inflammatory metabolism in proinflammatory macrophages by increasing PKM2 lactylation and inhibiting its tetramer-to-dimer transition, which inhibits the Warburg effect and facilitates inflammatory metabolic adaptation in proinflammatory macrophages [46].

Nonhistone lactylation also modulates key proteins involved in inflammatory regulation in macrophages, such as high mobility group protein B1 (HMGB1). HMGB1 is a chromatin-associated nuclear protein that is a key regulatory protein for cell survival [47]. In

sepsis, researchers have shown that lactate can drive HMGB1 lactylation in macrophages and that this process is regulated by the p300/CBP pathway, which in turn impairs the nuclear recruitment of p300/CBP via GPR81, ultimately leading to the release of HMGB1 from macrophages via the exosomal pathway, resulting in damage to vascular endothelial integrity [48]. In contrast, in hepatic ischemia–reperfusion (LI/R), HSPA12A, a novel regulator, can inhibit macrophage chemotaxis and inflammatory activation by inhibiting glycolysis-mediated lactylation and secretion of HMGB1 from hepatocytes, ultimately inhibiting macrophage chemotaxis and inflammatory activation [49].

Regulatory T (Treg) cells play a crucial role in maintaining the immunosuppressive tumor microenvironment. Lactate modulates Treg cell production through MOESIN Lys72 lactylation, thereby improving the interaction of MOESIN with TGF-β receptor I and SMAD3 signaling [50]. In microglia, YY1 lactylation activates FGF2 upregulation to promote angiogenesis, leading to proliferative retinopathy [39].

Different subtypes of CD4 T cells are closely related to immunity, and metabolic reprogramming of OXPHOS and glycolysis can regulate the activation and differentiation of CD4 T cells [51,52]. In autoimmune uveitis, the lacylation of Ikzf1 regulates its binding to TH17-related genes, a process that occurs at lys164 [53]. Lacylation of lys164 directly regulates TH17 related genes, including Runx1, Tlr4, IL-2, and IL-4.

Tumor-infiltrating myeloid cells (TIMs) are key regulators of tumor progression, including monocytes, macrophages, dendritic cells, and neutrophils [54].Researchers found that methyltransferase-like 3 (METTL3) in TIMs can promote Jak1 translation through mode of RNA N^6-methyladenosine (m^{6}A), thus activating STAT3 signal transduction. The METTL3/m^{6}A/JAK1/STAT3 axis resulted in enhanced immunosuppressive function of myeloid cells. It is noteworthy that both histone lacylation and non-histone lacylation occur in this process. H3K18 lacylation increased Mettl3 expression in tumor-infiltrating myeloid cells, and Mettl3 lacylation increased the ability to capture m6A modified RNA [55].

These studies highlight the multilevel regulation of nonhistone lactylation in immune cells and provide new molecular mechanisms for immune regulation.

4. Nonhistone lactylation and disease

4.1. Nonhistone lactylation and inflammation

Inflammation is one of the most intensively studied areas of lactylation. During inflammation, high lactate is a sign of poor prognosis [56]. Lactate influences the onset and progression of the inflammatory response by affecting the production of inflammatory mediators, the activation of immune cells and the regulation of inflammatory signaling pathways [57]. In sepsis, lactate inhibits the Warburg effect through activation of PKM2 and promotes the shift of proinflammatory macrophages to a reparative phenotype [46]. In turn, macrophages can take up extracellular lactate via monocarboxylic acid transporter protein (MCT), and secrete HMGB1 lacty-lation through exosomes to destroy the integrity of endothelial cells and increase vascular permeability [48]. In a subsequent study targeting LI/R, investigators determined that heat shock protein A12A (HSPA12A) protects the liver from LI/R injury by inhibiting macrophage chemotaxis and inflammatory activation through inhibition of glycolysis-mediated lactylation and secretion of HMGB1 from hepatocytes [49]. This provides the basis for targeting lactate/lactate-related signaling to combat sepsis. Furthermore, in sepsis-induced acute kidney injury (SAKI), researchers found that hyperacetylation and inactivation of pyruvate dehydrogenase E1 subunit alpha 1 (PDHA1) enhanced lactate overproduction, which mediated Fis1 lactylation and exacerbated SAKI, whereas lowering lactate levels and lactylation of Fis1 attenuated SAKI [58].

4.2. Nonhistone lactylation and cancer

Lactate is highly expressed in tumor cells and is associated with cancer progression [59]. Nonhistone lactylation has been demonstrated to be associated with key processes involved in tumor metabolism, proliferation, and invasion in gastric, liver, lung, colorectal, and prostate cancers [22,38,60–62]. In HCC, cyclin E2 (CCNE2) lactylation promotes HCC cell growth, and SIRT3 regulates the lactylation of CCNE2 to act as a cancer suppressor [38]. Another study revealed that lactylation of MOESIN Lys72 in HCC cells could be used to regulate Treg cells in the microenvironment and, in this way, enhance downstream TGF-β signaling to counteract anti-PD-1 [50]. In addition, researchers have also found that Glypican-3 can inhibit cancer progression by regulating overall lacty-lation of HCC cells and c-myc lactylation [63]. In colorectal cancer, hypoxia significantly increased the protein level and the level of lactylated β-catenin in CRC cells, and knockdown of this protein significantly inhibited the growth and stemness of CRC cells [64]. In prostate cancer, hypoxia-inducible factor 1a (HIF-1a) lactylation promotes the transcription of KIAA (ahyaluronic acid binding pro-tein), which in turn promotes angiogenesis [40]. In gastric cancer, researchers have shown that METTL16 lactylation is associated with copper-induced death due to high copper concentrations. Copper stress promotes METTL16 lactylation at K229, followed by cuproptosis. Elevated levels of METTL16 significantly improved the therapeutic efficacy of the copper ionophore elesclomol, which, in combination with the SIRT2 inhibitor AGK2, induces cuproptosis in gastric cancer cells both in vitro and in vivo, thus providing a novel approach for the treatment of gastric cance [61]. In cervical cancer, emulsification of CUB and LCCL structural domain-containing type I (DCBLD1) maintains DCBLD1 stability through a mechanism involving increased enrichment of HIF-1 in the DCBLD1 promoter region. Ultimately, it activates the pentose phosphate pathway (PPP) by inhibiting the autophagic degradation of G6PD, thereby promoting cancer progression [65].These studies suggest that lactylation is deeply involved in key protein modifications in tumors, thus impacting tumor development, and studies targeting lactylation can aid in tumor therapy.

4.3. Nonhistone lactylation and neurological disorders

Lactate, a metabolic substance, is a source of energy for neurons and is responsible for regulating neuronal signaling functions and promoting nervous system stability [66]. Altered levels of lactate and lactylation have been shown to potentially be associated with social stress and stress-related neuroexcitation [23]. Lymphocyte cytoplasmic protein 1 (LCP1), a major cytoskeletal binding protein associated with the control of cell motility, is thought to be associated with LI/R [67,68]. Researchers have shown that LCP1 lactylation promotes the progression of cerebral infarction, and the glycolysis inhibitor 2-DG may help reduce the level of LCP1 lactylation and induce cellular damage [67].

4.4. Nonhistone lactylation and diseases of the cardiovascular system

Lactate is an important energy support for cardiac metabolism. Lactate is associated with cardiovascular system diseases such as cardiac hypertrophy, myocardial injury, heart failure, and atherosclerosis[69–72]. Using a high-fat diet-induced apolipoprotein-deficient mouse model of ASCVD, researchers found that an exercise-induced increase in lactylation promotes Mecp2 K271 lactylation, which inhibits the expression of Eregs, leading to alterations in the downstream MAPK pathway, resulting in the inhibition of atherosclerosis progression [69]. In heart failure, the sarcomeric interaction of a-MHC with Titin is critical for cardiac structure and contraction. Zhang et al. reported that a-MHC K1897 lactylation directly modulates the interaction between a-MHC and Tinin, thereby alleviating heart failure [70]. In myocardial infarction, lactylation in turn induces cardiac fibrosis and exacerbates cardiac dysfunction, which results from increased Snail1 lactylation, and Snail lactylation induction leads to endothelial mesenchymal transition (EndoMT) and TGF-β/Smad2 activation [71]. These studies demonstrate the complex role of lactate in the cardiovascular system.

4.5. Nonhistone lactylation and other diseases

In nonalcoholic fatty liver disease, researchers have shown that fatty acid synthase K673 lactylation leads to a decrease in enzyme activity in the regulation of hepatic lipids by MPC1, which mediates hepatic lipid synthesis via MPC1 [73]. In addition to disease, Mao et al. reported that exercise-induced intracellular hypoxia induced lactylation and that PDHA1 and CPT2 lactylation could limit OXPHOS to balance the duration of fatigue during high-intensity endurance exercise [30].The currently known regulation of nonhistone lactylation in cell lines and diseases is shown in Table 2.

5. Lacylation and other modifications

Lacylation and acetylation are types of post-translational modifications on lysine. Zhang et al. employed M1 macrophages to demonstrate that histone lacylation and acetylation exhibit distinct temporal dynamics [9]. Nevertheless, there exists an interaction between acetylation and lacylation in diseases. In sepsis, lactic acid promotes the lacylation and acetylation of HMGB1, thereby enhancing endothelial permeability [48]. In acute kidney injury, excessive lactate mediated by PDHA1 acetylation can increase the lacylation of Fis1 and ultimately exacerbate the progression of the disease [58].

M6A modification is the most abundant RNA modification in eukaryotic cells and plays a pivotal role in tumorigenesis [76]. The METTL family represens a category of proteins that transfer methyl groups to nucleic acids, proteins, lipids, and other small molecules [77]. In gastric cancer, METTL16 lacylation promotes m^{6}A modification on FDX1 mRNA, ultimately facilitating cuproptosis. In colon tumors, METTL3 lacylation promotes m6A modification on Jak1 mRNA, promoting the immunosuppression of tumor-infiltrating myeloid cells [55,61]. Additionally, by seeking different lacylation-related genes between normal tissues and tumor tissues, researchers identified the genes related to m^{6}A through correlation analysis and ultimately successfully constructed a risk model associated with clear cell renal cell carcinoma [78].

Nevertheless, further studies are required on the connection between lacylation and methylation, acetylation or other modifications.

6. Drug development and therapeutic potential

Cellular metabolic programming in cancer is regulated by a variety of oncogenes, such as HIF-1, Myc, p53, and the PI3K/Akt/mTOR pathway [79,80]. The efficacy of cancer therapy can be improved by the use of glycolysis inhibitors or the combination of glycolysis inhibitors and other drugs [81]. Currently, inhibition of the glycolytic enzymes hexokinase (HK), pyruvate kinase (PK), lactate dehydrogenase (LDH), and glucose transporter protein (GLUT) has been shown to inhibit tumors [82]. In addition to the above therapeutic targets, therapeutic modalities targeting lactylation transporter proteins or lactylated writing or erasing proteins, such as MCT1, MCT4, P300/CBP, and the sirtuin (SIRT) family, have also shown tumor potential [27,83].

LDH is a key enzyme that catalyzes the final step of glycolysis, converting pyruvate to lactate. LDH expression is elevated in a variety of malignant tumors, is associated with the prognosis of liver, lung, and pancreatic cancers, and is considered to be a potent target for targeted cancer therapies[84–88]. Oxamic acid sodium (OXA), a well-defined inhibitor of LDHA, can reduce lactylation levels. Decreased cell migration in esophageal cancer; increased cytotoxic effects on docetaxel; induced apoptosis in prostate cancer; and increased the sensitivity of colon cancer cells to cisplatin, olaparib or etoposide [60,89,90].

2 Deoxy-D-glucose (2-DG) is an inhibitor of glucose metabolism that induces apoptosis by inhibiting the functions of hexokinase and glucose-6-phosphate isomerase [91]. 2-DG inhibits the glycolytic pathway, inhibiting the generation of a variety of malignant tumors[92–94]. 2-DG has been subjected to phase I clinical trials [95]. In myocardial infarction, 2-DG has also been shown to reduce lactate levels, thereby alleviating myocardial infarction [71].

The transmembrane transport of lactate is controlled by a family of MCTs, particularly MCT1 and MCT4, which are important factors in tumor invasion through the transport of lactate [83]. α-Cyano-4-hydroxycinnamate (α CHC), an inhibitor of MCT1/2 that inhibits the ability of lactate to be transported, can regulate lactate content [96]. CHC has been shown to be involved in the treatment of dry breast, pancreatic, and gastric cancers[97–99]. Fan et al. reported that α CHC could be used to attenuate lactate-induced cardiac insufficiency and EndoMT after MI in a study of myocardial infarction [71]. The SIRT family has also been shown to undergo delactylation. AGK2, a selective SIRT2 inhibitor, has been shown in ex vivo assays to increase the sensitivity of gastric cancers, particularly in mucinous adenocarcinomas, to elesclomol [61]. Honokiol, a naturally occurring agent and activator of SIRT3, was shown to increase the sensitivity of gastric cancers, particularly in mucinous adenocarcinomas, to Elesclomol by investigators who determined that Honokiol increased SIRT3 expression in a dose-dependent manner, leading to a decrease in lactylation levels, and this process was shown to reduce HCC growth and promote apoptosis in HCC cells in ex vivo assays [38].

In addition to the therapeutic use of lactylation proteins as targets of action, analysis of the lactylation profile of tumors through datasets can be used to determine the therapeutic efficacy and prognosis of tumors [100]. For example, lactylation-related models of gastric cancer can be constructed to identify individual tumors with different immune evasion risks [100]. Similarly, the construction of lactylation models for hepatocellular carcinoma and breast cancer renal cancer has successfully predicted the effect of drugs on tumor response and prognosis[78,101–105]. Drugs that target lactic acid production and transport are summarized in Table 3.

7. Conclusions and perspectives

Lactylation is involved in a variety of biological processes, including gene expression regulation, cell signaling, and inflammatory responses, which have a significant impact on disease occurrence and progression [106]. Specifically, in the field of oncology, lactate is involved in key processes such as tumor cell proliferation, metastasis, and drug resistance by modifying key proteins [107]. On the one hand, lactylation can regulate metabolic reprogramming within tumor cells, enabling tumor cells to adapt to harsh microenvironments and maintain their survival and proliferation advantages [18]. On the other hand, lactylation can also affect the acid–base balance of EMT and promote acidification of the tumor microenvironment, thereby promoting tumor cell invasion and metastasis [108,109]. In addition, proteins involved in lactylation can act as immunomodulators and participate in the regulation of signal transduction pathways in tumor cells [110]. Lactylation mediates TGF-β, Hippo, MAPK and other pathways that affect tumor cell proliferation and survival signaling [50,100,111,112]. In neurological disorders, lactate, a metabolite, not only is a source of energy for neurons in the nervous system but also participates in the regulation of neuronal signaling functions and promotes the stability of the nervous system [113,114]. In the cardiovascular system, nonhistone lactylation has been found to be closely associated with the onset and progression of cardiovascular diseases such as atherosclerosis, myocardial infarction, and heart failure. This form of modification is involved in physiological processes such as the regulation of vascular endothelial cell function, the modulation of inflammatory responses in the vascular wall, and vasoconstriction and dilation, which have important implications for cardiovascular health [115,116]. Moreover, nonhistone lactylation is also widely involved in the inflammatory process, participating in key steps such as the production of inflammatory mediators, the activation of immune cells, and the regulation of inflammatory signaling pathways [46,48]. Further studies have shown that the regulation of targets in the lactate metabolic pathway, such as MCT, GLUT, LDH, and SIRT, may positively affect the treatment of related diseases [27]. The prediction of the characteristics of lactylation-related genes can help to identify potential targets for tumor therapy [117].

In summary, there is a close relationship between nonhistone lactylation and diseases, and in-depth study of the mechanism of action of this form of modification is highly important for revealing the pathogenesis of diseases, understanding the progression of diseases, and developing new therapeutic approaches.

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Table 3
Drugs that target the production and transport of lactate.

Drug	Type	Effect
AGK2	SIRT2 inhibitor	effectively inhibit gastric cancer progression With Elesclomol
Honokiol	SIRT3 activator	Induction of apoptosis in HCC cells
C646	P300/CBP inhibitor	Attenuated levels of lactate-promoted lactylation in macrophages
2-DG	HK inhibitor	Reduction of lactate-induced cardiac insufficiency and EndoMT after MI
Oxamic acid sodium	LDHA inhibitor	Increased sensitivity of HCT116 and RKO colon cancer cells to cisplatin, olaparib, or etoposide
α-cyano-4-hydroxycinnamate	MCT1/2 inhibitor	Reduction of lactate-induced cardiac insufficiency and EndoMT after MI
GSK2837808A	LDHA inhibitor	Decrease SAKI

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CRediT authorship contribution statement

Hao Yu: Writing – review & editing, Writing – original draft. **Tingting Zhu:** Writing – original draft. **Dongwen Ma:** Data curation. **Xiaohan Cheng:** Resources. **Shengjia Wang:** Formal analysis. **Yongzhong Yao:** Conceptualization.

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.

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All the figures in the manuscript were drawn in Figdraw.

Abbreviations

The following abbreviations are used in this manuscript:

PTM	Posttranslational modification
Kla	Lysine lactylation
OXPHOS	Oxidative phosphorylation
PPP	Pentose phosphate pathway
HR	Homologous recombination
HCC	Hepatocellular carcinoma
AIS	Acute ischemic stroke
LGSH	Lactoyl glutathione
CIRI	Cerebral ischemia/reperfusion injury
NADH	Nicotinamide adenine dinucleotide
ATP	Adenosine triphosphate
Arg1	Arginase 1
YTHDF2	YTH N6-Methyladenosine RNA Binding Protein F2
GLO2	Glyoxalase 2
CPT2	Carnitine palmitoyltransferase 2
AlaRS	Alanyl-tRNA synthetase
cAMP	Cyclic adenosine monophosphate
GPR81	G protein-coupled receptor 81
CTSD	Cathepsin D
PKM2	Pyruvate kinase M2
CCNE2	Cyclin E2
SIRT	Sirtuin
HIF-1a	Hypoxia-inducible factor 1a
HMGB1	High mobility group protein B1
LI/R	Ischemia–reperfusion
TGF-β	Transforming growth factor
SMAD3	Mothers against decapentaplegic homolog 3
Treg	Regulatory T
MCT	Monocarboxylic acid transporter protein

(*continued*)

PTM	Posttranslational modification
HSPA12A	Heat shock protein A12A
SAKI	Sepsis-induced acute kidney injury
PDHA1	Pyruvate Dehydrogenase E1 Subunit Alpha 1
Mecp2	Methyl-CpG Binding Protein 2
Fis1	Fission, Mitochondrial 1
Snail1	Snail Family Transcriptional Repressor 1
FASN	Fatty acid synthase
Vps34	Phosphatidylinositol 3-Kinase Catalytic Subunit Type 3Vps34
METTL3	Methyltransferase 3, N6-Adenosine-Methyltransferase Complex Catalytic Subunit
PFKP	Phosphofructokinase, Platelet
CCNE2	Cyclin E2
CPT2	Carnitine Palmitoyltransferase 2
IDH3G	Isocitrate Dehydrogenase (NAD(+)) 3 Non-Catalytic Subunit Gamma
LCP1	Lymphocyte Cytosolic Protein 1
DCBLD1	Discoidin, CUB And LCCL Domain Containing 1
Ikzf1	IKAROS Family Zinc Finger 1
TIM	Tumor-infiltrating myeloid cells
m^6A	N^6-methyladenosine

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