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Lactylation and human disease

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Abstract

Background: Lactylation, a new epigenetic modification, is an important way in which lactate exerts physiological functions. There is a close relationship between increased lactylations caused by lactate and glycolysis, which can interact and play a role in disease through lactate as an intermediate mediator. Current research on lactylations has focused on histone lactylation, but non-histone lactylation also has greater research potential. Due to the ubiquity of lactate modifications in mammalian cells, an increasing number of studies have found that lactate modifications play important roles in tumour cell metabolism, gene transcription and immunity.
Methods: A systematic literature search was carried out using search key terms and synonyms. Full-paper screening was performed based on specific inclusion and exclusion criteria.
Results: Many literatures have reported that the lactylation of protein plays an important role in human diseases and is involved in the occurrence and development of human diseases.
Conclusions: This article summary the correlation between lactylation and glycolysis, histones and non-histone proteins; the relationship between lactonation modifications and tumour development; and the current existence of lactylation-related inhibitors, with a view to provide new basic research ideas and clinical therapeutic tools for lactylation-related diseases.

Introduction

Lactylation modification is a phenomenon in which cells modify lysine residues on histones during metabolism, resulting in excessive accumulation of lactate (Ref. 1). Lactylation modification is mainly classified into non-enzymatic regulated lactylation and enzyme-regulated lactylation. Non-enzymatic regulated lactylation mainly aggregates through the glycolytic pathway, whereas enzyme-regulated lactylation is mainly enriched in the inflammatory pathway, which is associated with intracellular inflammatory homeostasis (Ref. 2). As a newly discovered epigenetic modification, lactate modification involves molecules and its effects on organisms have attracted attention. With the deepening of research, it was found that lactate modification occurs in both histones and non-histone proteins and is widely present in the human body. p300 and AARS1 act as lactate 'Writer' and participate in lactate modification, while HDACs and SIRTs act as 'Eraser' of lactate modification and play a de-lactate role in the cell. (Refs 3–5). Due to the covalent and reversible nature of histone modifications mediated by Writer and Eraser, their associated proteins are ideal drug targets. Lactated modifications have been reported to be involved in the regulation of gene expression and are highly associated with a wide range of human diseases (Refs 1, 2). Investigating the mechanism of lactate modification in human diseases and designing molecularly targeted drugs against it is expected to be a new and promising therapeutic approach.

Glycolysis and lactylation

Since its discovery, lactic acid has often been regarded as a metabolic waste produced by anaerobic cellular respiration, which has many unfavourable effects on human cells (Ref. 6). However, with the deeper study of lactate, it has been gradually discovered that lactate also has favourable biological effects on cells, including energy regulation, redox, fatty acid metabolism and so on (Ref. 2). In the cell, lactate is produced mainly through two pathways: glycolysis and glutamine metabolism (Refs 7, 8). Glycolysis is the predominant mode of lactic acid production, which occurs mainly in the cytoplasm and is a common stage of glucose catabolism in all organisms (Ref. 7). Cells produce adenosine triphosphate (ATP) under aerobic conditions mainly by the tricarboxylic acid cycle (TCA), when the cells are in hypoxic conditions, the TCA will be inhibited and activate the glycolysis pathway to produce ATP, glucose after a series of catalytic reactions produced by pyruvic acid will be further reacted to generate ATP and

nicotinamide adenine dinucleotide (NADH), and finally, in a hypoxic environment, the NADH and pyruvate are reduced to lactate. Anoxic environment NADH and pyruvate are reduced to lactate (Refs 7, 9). Glycolysis is the main mode of anaerobic cellular respiration. In the 1920s, Otto Warburg et al. found that tumour cells preferred glycolysis for energy production even under aerobic conditions, rather than oxidative phosphorylation, which is more efficient in supplying energy, for energy acquisition as normal cells do under aerobic conditions, a phenomenon known as the Warburg effect (Ref. 10). In this process, lactate accumulates in large quantities in tumour cells, so it has been identified as an important metabolic marker for cancer cells, and the Warburg effect has been referred to as aerobic glycolysis or metabolic reprogramming (Refs 11–13). Glutamine metabolism is another way of lactate production. Glutamine-derived carbon is transported from the mitochondria to the cytoplasm by a series of catalytic reactions and converted to NADPH and pyruvate, of which pyruvate is the main raw material for lactate production, so glutamine can be produced from lactate by this metabolic way (Ref. 8). There are two main routes for lactate to go in the cell, on the one hand, lactate is converted to pyruvate by pyruvate dehydrogenase (PDH) to enter the TCA cycle for irreversible clearance of lactate from the cell, and on the other hand, lactate is converted to lactate coenzyme A to participate in the lactate modification of both histones and non-histone proteins (Refs 2, 14).

Lactylation is a new epigenetic modification first discovered by Zhang et al. (Ref. 1) using four orthogonal methods, which plays an important role in various physiological and pathological processes of cells along with methylation, acetylation and crotonylation, which are epigenetic modifications. The main known lactylation modifications include non-enzymatically regulated lactylation and enzymatically regulated lactylation (Refs 1, 15). Non-enzymatically regulated lactic acidification is mediated primarily by the glycolytic pathway, which inhibits enzyme activity and reduces the metabolites of glycolysis (Ref. 16). Enzymatically regulated lactylation occurs primarily in the inflammatory pathway and is associated with intracellular inflammatory homeostasis (Ref. 2). Lactylation is closely linked to enzyme activity during glycolysis, and recent studies have found that the level of lactylation is positively correlated with the intensity of intracellular glycolysis (Refs 1, 17). The three key rate-limiting enzymes in the glycolytic pathway are hexokinase II (HK2), phosphofructokinase (PFK) and pyruvate kinase 2 (PKM2; Ref. 18). Currently, research has found that three key enzymes affecting the glycolytic process can influence the level of lactylations, and Nissim Hay's team found that high expression of HK2 accelerates the glycolytic process to promote lactate production, affects the expression of histone H3 lysine 18 (H3K18la) and increases lactylations in the cell, which can affect stellate cell activation and lead to liver fibrosis (Ref. 19). Wang et al. found for the first time that PKM2 is lactated modified and has an important role in macrophage regulation, with the 62nd lysine site being its major modification site. In macrophages, lactated modification enhances the pyruvate kinase activity of PKM2, inhibits M1 macrophage glycolysis and promotes the transition of pro-inflammatory phenotypic macrophages to a reparative phenotype (Ref. 20). In addition, Michael et al. (Ref. 21) found that sAKZ692 in the Keap1-Nrf2-ARE signalling pathway causes non-enzymatic *S*-lactate modification of KEAP1 through activation of PKM2 leading to accumulation of Ga3P metabolites in the glycolytic pathway. In addition to affecting lactylation by regulating the activity of three key enzymes in glycolysis, lactate dehydrogenase A (LDHA) catalysis the conversion of pyruvate to lactate, and affecting its activity also affects lactate levels. LDHA was found to interact directly with UNC-51-like kinase 1 (ULK1), which promotes lactate production and then mediates Vps34 lactylation (at lysine-356 and lysine-781) via the acyltransferase KAT5/TIP 60, which could link glycolysis and cellular autophagy (Ref. 22). Inhibition of LDHA activity decreases lactate concentration, which can directly affect the level of lactate modification at the K1897 site of α-MHC (Ref. 23). Taken together, these studies suggest that once the activity of enzymes in glycolysis is affected, lactate modification can be further influenced by altering lactate production or metabolites in glycolysis, which can then play a role in cellular bioprocesses.

Glycolysis as the main mode of anaerobic cellular respiration plays an important role in cellular life activities, once glycolysis is affected, then it will affect the level of lactate modification in the cell, lactate, as an important post-translational modification of proteins, the modification level is related to many diseases. Cerebral infarction (CI) has high morbidity and mortality, it was found that inhibition of glycolysis level can reduce the level of lymphocyte cytosolic protein 1 (LCP1) lactylation, and promote the degradation of LCP1 to further alleviate the progression of CI (Ref. 24). Myocardial ischemia/reperfusion (MI/R) injury is closely associated with poor revascularization after myocardial infarction, and high expression of heat shock protein A12A (HSPA12A) promotes glycolysis and attenuates MI/R injury by maintaining the lactylation level of H3 during reperfusion (Ref. 25). Mitochondrial reactive oxygen species (mROS) will have promoted pulmonary artery smooth muscle cell (PASMC) proliferation in hypoxic environments by triggering glycolysis in hypoxic PASMCs and enhancing the level of associated histone lactylation modifications (Ref. 26). Elevated levels of hypoxic glycolysis in the sclera leading to increased lactate will promote myofibroblast trans differentiation (FMT) and myopia (Ref. 27). Accumulation of lactate in cells will trigger lactylation, and glycolysis, as the main pathway of lactate production in cells, is the most important way to influence lactylation in cells; in addition, the current study also found that changes in the level of lactylation can also negatively feedback regulate glycolysis. For example, in microglia, high levels of cGAS lactylation are associated with cGAS-mediated neuronal damage, but knockdown of cGAS in oxygen–glucose deprived microglia inhibited glycolysis, whereas microglial levels of pan leucine lactylation (Pan-Kla) and cGAS lactylation were upregulated, which suggests that lactic acid reverses the cGAS deficiency caused by the lack of altered glycolysis (Ref. 28). In oesophageal cancer (EC) cells, hypoxia will induce serine hydroxy methyltransferase 2 (SHMT2) lactylation, which further promotes glycolysis in EC cells, and in this way, accelerates the deterioration process of EC cells (Ref. 29). It has been found that high levels of histone lactylation are present in brain samples from patients with Alzheimer's disease (AD), and that lactylation modifications enriched in the promoter regions of glycolytic genes activate transcriptional processes, promote glycolysis levels and exacerbate microglial dysfunction in AD through a positive feedback loop of glycolysis/H4K12la/PKM2 (Ref. 30). In summary, there is a close link between glycolysis and lactylation, and the two can regulate each other or play important roles in many diseases through synergistic effects.

Histones and lactylation

Histone is a basic protein in the chromatin of eukaryotic body cells and contains five components, which are, from largest to smallest in terms of molecular weight, H1, H3, H2A, H2B and H4 (Ref. 31).

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Histone binds and wraps around 1.7 loops of DNA and about 146 base pairs to form the nucleosome, the basic unit of chromatin (Ref. 31). Histone modification is the process of epigenetic modification of the N-terminus (tail) of histones such as methylation, acetylation, phosphorylation, succinylation, SUMOylation and ubiquitination by the action of relevant enzymes (Ref. 32). Histone modification is one of the most important epigenetic modes of regulation of gene expression in eukaryotes and plays an important role in the process of physiological activities in eukaryotes by affecting the compactness of chromatin and thus gene expression (Ref. 33). As an important epigenetic regulation, histone modification may directly affect the structure of histones by changing the nature of the substrate amino acid residues. Currently, such types of epigenetic marks as H3K27me3 and H3K9me3 have been found to have hereditary properties, but there are unknown hereditary properties in some epigenetic marks, such as H3K36me3 and acetylation modification, and the study of histone epigenetic marks still has a large amount of research. Genetic marks are still of great research depth and value (Ref. 32).

Histone lactylation is a new epigenetic modification that has been identified in recent years. Zhang et al. used high-performance liquid chromatography (HPLC)-tandem mass spectrometry (MS) to examine core histones in MCF7 human breast cancer cells and found that the mass shifts of lysine residues in three protein hydrolysed peptides were the same as those induced by the addition of lactylation groups to the ε-amino group of lysine residues, a phenomenon that demonstrates for the first time the existence of histone lactylation (Kla) and suggests that Kla is a newly identified post-translational modification of the protein (Figure 1; Ref. 1). They further demonstrated the presence of lysine lactylation in proteins by using four orthogonal methods and found that three histone peptides with Kla modifications were produced: H3 K23-QLATKlaAAR, H2BK5-PELAKlaSAPAPK and H4K8-GGKlaGLGK (Ref. 1). The process of lactylation modification is currently thought to involve mainly lactyl coenzyme A or *S*-D-lactoylglutathione as substrates involved, and in eukaryotes, the lactoyl group on lactoyl coenzyme A is attached to lysine residues by an enzymatic reaction mediated by the acetyltransferase p300, which effectively neutralises the positive charge of the lysine side chain (Ref. 34). In prokaryotes, Dong et al. (Ref. 35) showed that YdiF catalyses the formation of a lactyl coenzyme A as a means of providing a lactoyl group to Kla. Lactoyl coenzyme A is involved in lactylation modification in both eukaryotes and prokaryotes, but the enzyme that catalyses the formation of lactoyl coenzyme A from lactic acid has not yet been reported in studies and needs to be further explored. In addition, the lactoyl group of *S*-D-lactoylglutathione (LGSH) can also be attached to residues of lysine by a non-enzymatic reaction (Ref. 34). Both lactoyl coenzyme A and lactoyl glutathione are involved in the process of lactylation, and lactylation is more likely to occur with lactoyl coenzyme A than with LGSH (Ref. 34). However, there is no specific article explaining which of the two is the direct substrate for lactylation (Ref. 35). Li et al. (Ref. 36) have found that LGSH is the main driver of intracellular promotion of histone lactylation, not lactate. In their study of histones, they found that LGSH was the main driver of lactylation in histones (Ref. 37). In their study of histones, they found that LGSH was the major driver of lactylation in histones (Ref. 34). It was found that there is an abundance of lactated modifications in histones, and Wang et al. (Ref. 36) found that cyclic imine ions produced by lysine polypeptides modified by lactate have high sensitivity and specificity for lactylation by affinity-enriched analysis of lactated proteomes and large-scale informatics evaluation of non-lactated spectral libraries. In recent years, more and more histone emulsification modification sites have been identified, among which H3K18la exists in a variety of primary human tissues and a variety of high basal metabolic tissues, especially in cancer tissues, such as most ocular melanoma tissues, and the level of H3K18la in colorectal cancer tissues is elevated (Refs 37, 38). Eva Galle et al. (Ref. 39) found that H3K18 was lactonated in samples with different developmental stages and differential mitotic activity, such as mESC-ser (primed mouse embryonic stem cells), mESC-2i (naïve mouse embryonic stem cells) and MB (myogenic cells), and found that H3K18 could serve as a biomarker in activation promoters and tissue-specific activity enhancers.

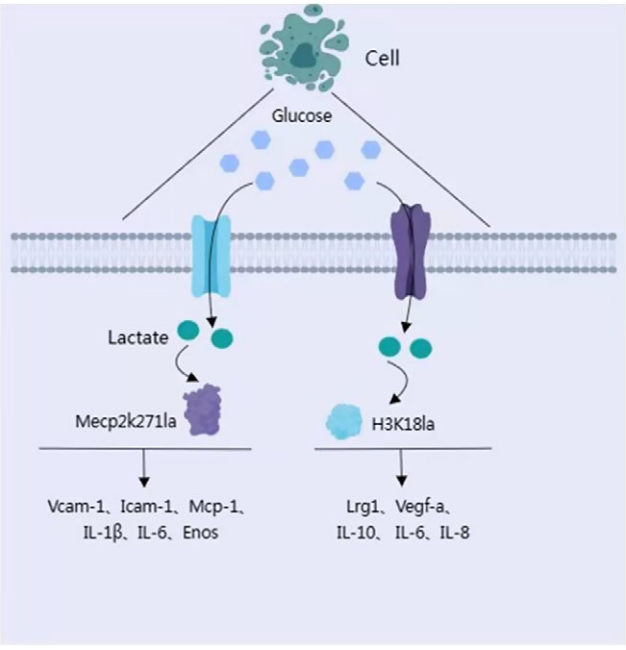


Figure 1. Possible intracellular modifications of histone lactylation.

As a post-translational modification of proteins, histone lactonisation modification influences the course of disease development by regulating gene expression. Histone lactylation promotes early remote activation of reparative transcriptional responses in monocytes and is critical for immune homeostasis remodelling and timely activation of cardiac repair processes after myocardial infarction (Ref. 20). Mecp2 lysine lactonylation (Mecp2k271la) levels are elevated after exercise, and Mecp2k271la will repress its downstream Ereg gene expression by binding to chromatin, which can affect Vcam-1, Icam-1, Mcp-1, IL-1β, IL-6 and Enos expression in ECs, thereby inhibiting the progression of atherosclerosis (Ref. 40). In addition, Wang et al. (Ref. 41) found that in bone marrow and circulating monocytes, gene repair was activated at an early stage with elevated levels of histone H3K18 lactonisation, and demonstrated that IL-1β-dependent GCN5 recruitment as an upstream regulatory element could catalyse the lactonisation of histone H3K18, in which Lrg1, Vegf-a and IL-10 were histone H3K18 lactonisation target genes, which suggests that histone lactylation can promote monocyte repair transcriptional response. Histone lactylation inhibits the development of myocardial infarction through transcriptional response regulation, and the downstream target genes affected by lactylation modification of histones may become new targets for clinical therapy. Cellular senescence can drive the development of the neurodegenerative disease AD, although the role of senescent microglia in AD remains unclear,

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Wei et al. found that elevated levels of histone H3K18 lactylation in senescent microglia and hippocampal tissues from naturally senescent mice and AD-modelled mice increased binding to the promoters of Rela (p65) and NFκB1(p50). Binding to the promoters of Rela (p65) and NFκB1 (p50) promotes senescence and AD by directly stimulating the NFκB signalling pathway to upregulate the senescence-associated secretory phenotype (SASP) components IL-6 and IL-8 (Ref. 42). Elevated FTO expression is present in vitreous fibrovascular membranes of patients with proliferative diabetic retinopathy (DR), and FTO promotes angiogenesis and induces retinal inflammation and neurodegeneration in DR, whereas histone lactylation drives upregulation of FTO in diabetic conditions, and FTO-targeted regulation of mRNA stability of CDK2 exacerbates microvascular abnormalities in DR (Ref. 43). FTO has an important role in DR, and the regulatory effect of histone lactate modification on FTO may provide more reference value for the clinical treatment of DR. Histone lactylation plays an important role in cardiovascular diseases, neurodegenerative diseases and metabolic diseases through gene regulation, in short, lactylation modification is involved in the occurrence and development of each disease with a key regulatory role, and the study of the effect of transcriptional regulation on disease not only explored how histone lactylation, a post-translational modification of proteins, affects the regulation of gene expression but also revealed the changes in different diseases and their potential pathologies.

In addition to the strong association with disease, histone lactonation is involved in cell differentiation and self-renewal. Inhibition of LDH in undifferentiated osteoblasts will reduce osteoblast differentiation as well as lactylation levels, but it was found that p300 can induce histone lactylation and promote osteoblast differentiation, suggesting that histone lactylation can promote osteoblast differentiation (Ref. 3). Li et al. (Ref. 44) found in glioma cells (GBM) that lncRNAs associated with the NF-κB signalling pathway, e.g., LINC01127, could promote the Warburg effect, inducing histone H3 to undergo lactate modification and promoting the self-renewal process in GBM cells. In addition, dynamic changes in histone post-translational modifications are important features of epigenetic reprogramming of embryonic development (Ref. 45). Yang et al. (Ref. 46) cultured in vitro fertilised oocytes at different oxygen concentrations and found that the lactate content in embryonic cells was reduced after inhibition of LDHA activity, and embryo development was inhibited after the levels of H3K23la and H3K18la were reduced. In mammals, lactate content is high in the preimplantation microenvironment, but the mechanism of this phenomenon has not been reported. Li et al. found that lactate is highly enriched in the nucleus of early embryos, and H3K18lac is mainly enriched in the promoter region of genes, which suggests that lactate plays an important role in early embryonic development, and that an understanding of the mechanism of lactate metabolism may be the basis for ensuring the normal development of preimplantation embryos in mammals (Ref. 47). The dynamic changes of histone lactate have an important impact on cell cycle and development, but there is still a gap in the study of histone lactate in many human diseases, and there is still a great potential for the study of histone lactate.

Lactated modification of non-histone proteins

Lactate modification was first discovered on histones, and early studies on lactate mainly focused on the epigenetic regulatory role played by lactate modification on histones, but as a novel post-translational modification of proteins, with deeper research it was speculated whether lactate modification would epigenetically alter the human non-histone protein proteome in the same way as acetylation, methylation, phosphorylation and other epigenetic modifications. High mobility group protein B1 (HMGB1) in macrophages was the first non-histone protein found to be lactylated modified, and lactate would promote HMGB1 lactylation by mediating a p300/CREB-binding protein (CBP)-dependent mechanism (Ref. 48). Wang et al. identified the CymIm ion in lactate-modified peptides, which is capable of characterising lactate modification sensitivity and specificity. Using this ion, they mined a large number of novel lactate-modified proteins and sites from non-enriched human proteomic data resources, including 87 lactate-modified peptides of 36 non-histone human proteins, 80 lactate-modified sites and 14 histones (Ref. 36). This suggests that the use of CymIm ions can help researchers mine more reliable novel sites for lactylations from proteomic databases. With deeper research, it has been found that lactylations are widely present in the human proteome and are mainly distributed in non-histone proteins (Refs 35, 49). Yang et al. (Ref. 50) performed an overall analysis of lactonation in human lungs under normal physiological conditions by LC–MS/MS and identified 724 Kla sites in 451 proteins. This further expands the database of lactate modification sites in human somatic cells, but as a novel post-translational modification of proteins, non-histone lactate modification sites still have a sustainable depth of development. In addition to being widely distributed in human cells, non-histone lactate modifications have been found to be distributed in fungi and plants. Gao et al. (Ref. 51) performed a global lysine-lactate motif analysis by LC–MS/MS in gracillin ashwagandha and finally identified 273 Kla sites from 166 proteins, with a wide distribution of proteins with lactylation, including the nucleus (36%), mitochondria (27%) and cytoplasm (25%). An et al. (Ref. 52) identified 638 modification sites on 342 proteins in immature grains 15 days after fertilization and, following a comparison of the lactonation groups of rice and the fungal plant pathogen *Botrytis cinerea*, found that lactonation was highly conserved between species on both histones and non-histone proteins. In summary, lactate modification is also very abundant in non-histone proteins, with a large number of modification sites to be discovered, and the existing proteomic database is a rich resource for mining such sites. However, although a certain number of non-histone lactate modification sites have been identified, the extent of lactate modification in these non-histone proteins needs to be further investigated. Secondly, whether the discovery of lactylation sites in fungi indicates that they can play an important role in disease progression involving different fungal groups. In addition, in recent years, there has been direct evidence that histone and non-histone lactylation occurs in vivo, particularly in primary human tissues and preclinical models. For example, Wu collected three normal liver samples, three HCC samples without metastasis and three HCC samples with lung metastasis and performed the analysis of the lactate group. A total of 2045 Kla sites located on 960 proteins were identified, and these lactated proteins exhibited varying Kla levels in the three groups of samples and were involved in a variety of biological processes such as amino acid metabolism, fatty acid metabolism and ribosomal protein synthesis (Ref. 53). In addition, Yuan Lin et al. (Ref. 54) also analysed tendon samples from patients with rotator cuff tendinopathy and found that 872 Kla sites were found in 284 proteins, with 136 sites upregulated for 77 proteins and 56 downregulated sites for 32 proteins compared to healthy tendons. In acute ischemic stroke, the researchers identified a total of 1003 Kla sites on 469 proteins in the cerebral cortex of a mouse model of cerebral ischemia/reperfusion injury that are

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associated with mitochondrial apoptosis pathways and mediated neuronal death (Ref. 55). Although lactation modifications have been found to exist in a variety of cell types and biological processes, their prevalence and specificity in different tissues and diseases still need to be further explored. Particularly in primary human tissues, the distribution and function of lactated modifications may vary depending on tissue type, disease state and other factors.

The discovery of non-histone lactation modifications and the identification of more loci have expanded the understanding of lactation, which, like histone lactation modifications, is involved in several physiological processes and functions in organisms. For example, non-histone lactic modifications play a crucial regulatory role in signalling, and there is significant overlap between the modification sites and important nodes of a variety of key signalling pathways, such as TGF-β pathway and autophagy (Refs 52, 56, 57). Among them, PIK3C3/VPS34 lactation enhances the binding of PIK3C3/VPS3 to BECN1, ATG14 and UVRAG; increases PIK3C3/VPS34 lipid kinase activity; promotes autophagy and promotes end lysosomal degradation pathway (Ref. 56). In addition, non-histone lactation can also be involved in key processes such as activation, proliferation and differentiation of immune cells. During infection and inflammation, macrophages need to expend a lot of energy in order to maintain their highly active state, and the regulation of this energy is closely related to the lactation of non-histone proteins. PKM2 lactation inhibits the Warburg effect and promotes the transition of pro-inflammatory macrophages to a reparative phenotype (Ref. 9). Lactate promotes the lactation of macrophage HMGB1, which is regulated by the p300/CBP pathway, which in turn hinders its nuclear recruitment, resulting in the release of HMGB1 through exosomes and the destruction of vascular endothelium (Ref. 20). Regulatory T (Treg) cells play a crucial role in maintaining the immunosuppressive tumour microenvironment. Lactate regulates the production of Treg cells by acting on the Lys72 locus of MOESIN protein, thereby enhancing the interaction between MOESIN and TGF-β receptor I and SMAD3 signalling pathways (Ref. 48). The discovery of non-histone lactation in immune cells exhibits a multi-layered and complex regulatory mechanism, which opens up new perspectives for in-depth understanding of immunomodulatory processes and provides a valuable molecular basis for the development of innovative immunomodulatory strategies.

Inflammation is the most deeply studied field of lactation modification, and lactate affects the occurrence and progression of inflammatory response by affecting the production of inflammatory mediators, the activation of immune cells and the regulation of inflammatory signalling pathways (Ref. 9). These include influencing the transition of pro-inflammatory macrophages to a repair phenotype, endothelial cell integrity and vascular permeability (Refs 20, 48). There is evidence that changes in lactate and lactation are associated with social stress and the resulting neuroexcitatory state (Ref. 58). Studies have shown that the lactation modification of LCP1 protein can accelerate the progression of CI, and the inhibitor of glycolysis process 2-DG may be able to effectively reduce the lactation level of LCP1, thereby exerting a protective effect on cells and reducing damage (Ref. 24). In addition, lactic acid, as an important energy support for cardio metabolism, has been linked to a variety of cardiovascular system diseases, such as cardiac hypertrophy, myocardial damage, heart failure and atherosclerosis (Refs 23, 40, 59, 60). Increased lactation of MECP2 K271 can inhibit atherosclerosis progression, and lactation of A-MHC K1897 can alleviate heart failure (Refs 23, 40). These studies suggest that increased the lactylation of non-histone can inhibit the development of cardiovascular diseases, but some studies show that increased lactation of Snail1 induces cardiac fibrosis and exacerbates cardiac dysfunction, and the mechanism is that Snail lactation induces EndoMT and TGF-β/Smad2 activation (Ref. 59). In conclusion, non-histone lactated modifications exhibit complex roles in cardiovascular diseases.

Cells contain higher levels of non-histone proteins than histones, and the link between lactate-modified non-histone proteins and the development of disease and tumours need to be urgently explored. High lactate and HMGB1 correlate with sepsis severity and mortality, and survival in polymicrobial sepsis could be increased by lowering lactate and thus inhibiting lactylation of the non-histone protein HMGB1 (Ref. 48). Ocular neovascularization leads to blindness. The non-histone protein Yin Yang-1 (YY1) undergoes lactated modification at lysine 183 (K183), and hyper lactated YY1 enhances FGF2 transcription and promotes retinal neovascularization (Figure 2; Ref. 52). Taken together, non-histone lactylation may promote disease progression, which may suggest new therapeutic strategies for the clinical treatment of related diseases; is it possible to control disease progression by inhibiting the associated non-histone lactylation in the disease? For example, in non-alcoholic fatty liver disease (NAFLD), mitochondrial pyruvate carrier 1 (MPC1) heterozygous knockdown would promote FASN-K673 lactylation modification, which in turn would ameliorate lipid deposition (Ref. 61). This reveals a novel mechanism of lipid accumulation in NAFLD and also suggests that MPC1-influenced lactylation of FASN-K673 occurs may be a molecular target for the treatment of NAFLD.

With the deepening research on non-histone lactate modifications and tumours, more and more studies have shown that non-histone lactate modifications are crucial for tumour progression and migration. Some studies have shown that post-translational modification (PTM) can facilitate the understanding of hepatocellular carcinoma (HCC) and the identification of therapeutic targets, although the mechanism of lactonisation modification in HCC has not been elucidated (Ref. 62). Yang et al. (Ref. 49) identified 9256 lactylation sites in HBV-associated HCC patients by proteomics and lactylation histology and found that lactylation of the K28 position of the AK2 protein was upregulated in HCC patients, which promotes

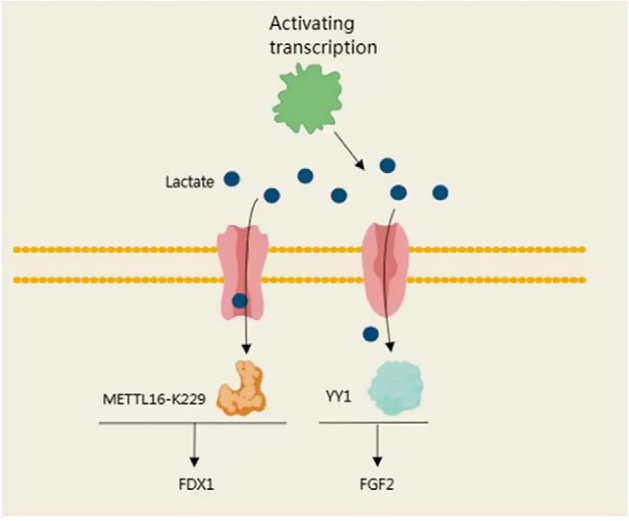


Figure 2. Possible intracellular modifications of non-histone lactonylated proteins.

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the proliferation and migration of tumour cells, and thus promotes the progression of HCC. However, the mechanism of non-histone AK2 lactylation level alteration to promote the development of HCC has not yet been clearly confirmed. In this study, the level of AK2 Kla was negatively correlated with the level of p53 pathway (Ref. 49), which also suggests that AK2 Kla may affect the development of HCC by regulating the p53 pathway, and it also proposes a potential target for HCC treatment. In addition, it has been found that in hepatocellular carcinoma (HCC), the activity of CCNE2 is enhanced after lactation modification, which in turn accelerates the proliferation of HCC cells and tumour development (Ref. 63). In colorectal cancer, both p53 expression and lactylation levels are elevated, and studies have confirmed that lactylation can alter the subcellular localization of p53 protein, which may reduce its expression in the nucleus and thus reduce its cancer inhibitory function, thereby promoting the value-adding, migration and invasion of colorectal cancer (Ref. 64). Another study showed that hypoxia significantly increased the expression of lactated β-catenin protein in CRC cells, and when the protein was knocked out, the growth of CRC cells was significantly inhibited, and their stem cell properties were significantly reduced (Ref. 65). During the development of cervical cancer, lactation of CUB and LCCL domain-containing I (DCBLD1) maintain the stability of DCBLD1 by involving mechanisms of increased HIF-1 enrichment in the DCBLD1 promoter region. As a result, DCBLD1 inhibits the autophagic degradation of G6PD (glucose-6-phosphate dehydrogenase), which in turn activates the pentose phosphate pathway (PPP). This series of reactions ultimately promotes the progression of the cancer (Ref. 66). In EC, hypoxia triggers the lactation of SHMT2 protein and enhances its stability, which in turn enhances MTHFD1L expression and accelerates the malignant progression of EC cells (Ref. 29). In glioma stem cells, PTBP1 lactation enhances its RNA-binding capacity and promotes PFKFB4 mRNA stabilization, promoting tumour progression by stimulating glycolysis (Ref. 67).

Non-histone lactylation can affect tumour migration and proliferation, although there are still more gaps in research on tumours, which provides more new directions for researchers. Clarifying the causes of alterations in tumours that affect their lactylation levels could help to discover more target cells and methods for clinical treatment. Some studies have elucidated the reasons affecting the altered levels of non-histone lactated modifications in tumour cells. Jin et al. found that elevated copper levels in gastric cancer could promote the lactylation of non-histone METTL16-K229 by promoting the interaction of glucosyltransferases AARS1/AARS2 with METTL16, which in turn promotes the m6A modification of FDX1 leading to copper death (Ref. 64). This not only reveals a new mechanism for the occurrence of copper death, but also provides a new therapeutic strategy for the treatment of GC (Ref. 64). In addition, in hepatocellular carcinoma, glypican-3 can not only affect tumour progression by regulating the overall lactation level of HCC cells, but also directly act on the proto-oncogene c-myc to inhibit tumour growth by regulating its lactation modification (Ref. 68). This discovery further enriches our understanding of the mechanism of lactation modification in HCC and provides new targets for future therapeutic strategies. In pancreatic cancer (PC), RHOF plays a carcinogenic role. It upregulates the levels of c-Myc, which further promotes transcription of pyruvate kinase M2 type (PKM2). The increase of PKM2 induces the acceleration of the glycolysis process, and the lactic acid produced in this process leads to the lactation of Snail1, which ultimately promotes the epithelial-mesenchymal transition (EMT; Ref. 69).

In summary, non-histone lactylation is widespread in humans and studies in recent years seem to indicate that non-histone lactylation plays a key role in the regulation of both diseases and tumours, which suggests newer and more promising ideas for clinical treatment. Although most studies have focused on histone lactylation, non-histone lactylation also shows greater research potential.

Lactylation and tumours

The biological function of lactate as an end product of glycolysis has been extensively studied due to the Warburg effect that occurs in tumour cells (Ref. 10). Lactate has also been shown to act as a signalling molecule to regulate intracellular signalling, where lactate will either signal through its specific receptor, G protein-coupled receptor 81 (GPR81), or be transported into the cell via the monocarboxylic acid transporter protein (MCT; Refs 70, 71). As research on tumour metabolism intensifies, more and more studies have shown that lactate is crucial to the process of tumour development. Lactate modifications mediated by lactate also play an important role in tumours, and elevated levels of lactate modifications can promote certain tumour processes (Table 1).

Lactylations mediate altered signalling pathways in tumours

Lactylation affects the process of tumour development, and clarifying the mechanism of action may provide clues for finding new therapeutic targets for tumours. Lactylations can affect tumour progression by modulating relevant signalling pathways in tumour cells. Colorectal cancer liver metastasis (CRLM) is one of the major causes of colorectal cancer development (Ref. 72). Increased expression of GPR37 in CRLM activates the Hippo pathway to promote H3K18la lactylation, leading to upregulation of CXCL1 and CXCL5, which in turn promotes the CRLM (Ref. 73). DCBLD1 lactylation in cervical cancer stabilizes DCBLD1 expression and promotes the activation of the PPP through inhibition of the autophagic degradation of G6PD. Cervical cancer development (Ref. 74). LncRNAs are involved in glioma (GBM) cell self-renewal as regulatory molecules. Li et al. (Ref. 44) found that histone lactylation in GBM increased the expression of LINC01127 (NF-κB pathway-associated LncRNA), which activated the JNK pathway by increasing the expression of MAP4K4 and increased the proliferation capacity of GBM cells. Furthermore, in tumour cells when lysine at position K72 of the MOESIN protein is lactated, it increases the interaction of MOESIN with TGF-β receptor I and its downstream SMAD3 protein, accelerating signalling and increasing the production of Treg cells, which in turn promotes tumorigenesis (Ref. 75).

Altered levels of lactate modification can form feedback regulation in cells to influence tumour progression. High expression of NUSAP1 is associated with poor prognosis in pancreatic ductal adenocarcinoma (PDAC). Chen et al. found that NUSAP1 can affect LDHA-mediated glycolysis, which increases histone lactate modification and further stabilizes NUSAP1, forming a NUSAP1–LDHA–glycolysis–lactate feed-forward loop in PDAC cells to promote its metastasis, so it seems that NUSAP1 is expected to be a new target for the treatment of PDAC (Ref. 76). In gastric cancer, H3K18 lactylation will promote VCAM1 expression, and

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Table 1. Correlation between lactylations and the occurrence of disease in humans

Type of disease	Signal pathways	Modified proteins	References
Liver fibrosis	Non	H3K18	(Ref. 96)
Inflammatory	Non	PKM2	(Ref. 20)
Cerebral infarction	Non	LCP1	(Ref. 24)
Anoxic-ischemic encephalopathy	Non	cGAS	(Ref. 28)
Esophageal cancer	Non	SHMT2	(Ref. 29)
Alzheimer's disease	NF-kB	H4K12/ H3K18	(Refs 30, 40)
Atherosclerosis	Ereg/MAPK	Mecp2k271	(Ref. 40)
Diabetic retinopathy	Non	H3K18	(Ref. 43)
Glioma	JNK	H3	(Ref. 44)
Septicemia	Non	HMGB1	(Ref. 48)
Vascular disease	Non	YY1	(Ref. 57)
Nonalcoholic fatty liver disease	Non	FNSA-K673	(Ref. 62)
Hepatocellular carcinoma	Non	AK2-K28	(Ref. 49)
Gastric cancer	AKT–mTOR	METTL16, H3K18	(Refs 65, 77)
Colorectal cancer	Hippo	H3K18	(Ref. 74)
Cervix	Pentose phosphate-related pathways	DCBLD1-K172	(Ref. 67)
Pancreatic ductal adenocarcinoma	Non	NUSAP1-LDHA	(Ref. 76)
Melanoma of the eyes	Non	H3K18	(Ref. 37)
Clear cell renal cell carcinoma	PDGFRβ	H3K18	(Ref. 81)
Prostate cancer	Non	HIF1a	(Ref. 58)
Bladder cancer	Hippo	H3K18	(Ref. 82)
Acute myeloid leukaemia	Non	H3K18, H4K5, H4K8, H4K12	(Ref. 94)

VCAM1 will activate AKT–mTOR signalling pathway-mediated CXCL1 expression, by enhancing immunosuppression and accelerating cancer progression (Ref. 77).

In addition, alterations in lactate modification can affect the outcome of tumour therapy. In ocular melanoma, increased levels of histone lactate will cause high expression of ALKBH3, which promotes the malignant transformation of cancer by attenuating the formation of PML condensate *N*1-methyladenosine SP100A methylation, and silencing of ALKBH3 can improve the therapeutic outcome of melanoma (Ref. 78). Most studies have shown that lactate modification level is a key link between lactate and tumour progression (Ref. 78). Lactate modification is a key link between lactate and tumour, and most studies have shown that the level of lactate modification is positively correlated with tumour progression. Understanding the mechanism of lactate modification can help clinics to find more molecular targets, which will provide greater possibilities for tumour therapy.

Lactylations mediate transcriptional effects on tumours

Lactylations have been known to exert gene transcriptional regulation since their discovery (Ref. 1). A growing number of studies have shown that elevated levels of lactylations in tumour cells will affect tumour progression as well as therapeutic outcome through regulation of gene transcription. In non-small cell carcinoma, H3K18la directly activates the transcription of pore membrane protein 121, which in turn promotes the nuclear transport of MYC and enables direct binding of MYC to the promoter region of CD274. Enhance immune escape in NSCLC cells by inducing the expression of PD-L1 (Ref. 79). This provides insight into the role of post-translational modifications in carcinogenesis and provides a rationale for the development of epigenetic targeting strategies for the treatment of NSCLC. The upregulation of histone lactylation in ocular melanoma can promote the transcription of YTH *N*6-methyladenosine RNA-binding protein 2 (YTHDF2), which recognizes the RNA modification sites of the two oncogenes of m6A, and promotes their degradation, thereby accelerating the development of ocular melanoma (Ref. 37). Von Hippel–Lindau (VHL) mutations play a key role in clear cell renal carcinoma (ccRCC; Ref. 80). It was found that inactive VHL actively triggers histone lactylation, which activates platelet-derived growth factor receptor β (PDGFRβ) transcription and thus promotes ccRCC progression (Ref. 81). In turn, PDGFRβ signalling can stimulate histone lactylation, thus creating a positive feedback loop in ccRCC to promote its progression (Ref. 81). Blocking this feedback loop may be a means of treating ccRCC. Prostate cancer (PCa) is resistant to anti-angiogenic therapies, and increased KIAA1199 expression in PCa tissues is positively correlated with hypoxia-inducible factor (HIF)-1α overexpression and angiogenic markers (Ref. 58). Lactylation of hypoxia-inducible factor (HIF)-1α enhances KIAA1199 transcription and promotes prostate cancer angiogenesis by increasing hyaluronic acid (Ref. 58). CircXRN2 inhibits the proliferation and migration of tumour cells, and it was found that CircXRN2 was aberrantly down-regulated in bladder cancer (BCa). CircXRN2 inhibits tumour progression driven by H3K18 lactylation through activation of the Hippo signalling pathway, which provides a new strategy for clinical interventional therapy in bladder cancer (Ref. 82).

Lactated modifications occurring in promoter regions in tumour cells can promote tumour progression. High expression of LINC00152 promotes migration and invasion of colorectal cancer cells, and the occurrence of histone lactylation on the promoter of intestinal bacterial lipopolysaccharide can affect the interaction with YY1 to upregulate the expression of LINC00152 (Ref. 83). Madhura et al. (Ref. 84) found in lactate metabolism-deficient breast cancer cell lines that elevated levels of histone lactylation promoted c-Myc expression, which further upregulated the transcription factor serine/arginine splicing factor 10 (SRSF10), which affects selective splicing in breast cancer cells to promote breast cancer progression.

Lactylation affects immunosuppression

The presence of innate and adaptive immune cells of the tumour microenvironment (TME) is involved in the recognition and

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control of tumour cells, which influences the response of tumour patients to immunotherapy (Refs 85, 86). Lactate, as a pro-tumour metabolite, affects TME homeostasis by creating an acidic environment in the organism that favours the growth of tumour cells and promotes immunosuppression through multiple pathways, leading to increased tumour immune escape (Ref. 87). Lactate accumulation inhibits T-cell function by suppressing T-cell antigen receptor-triggered production of IFN-γ, tumour necrosis factor alpha (TNF-α) and IL-2, as well as p38 protein phosphorylation (Ref. 88) Lactate can inhibit the nuclear factor of activated T cells (NFAT) in NK cells, thus inhibiting the production of IFN-γ (Ref. 89). Treg cells play an important role in maintaining immune homeostasis and preventing autoimmunity (Ref. 89). Treg cells play an important role in the maintenance of immune homeostasis and the prevention of autoimmunity, and are a potent immunosuppressive factor, and high lactate can affect the immunosuppressive activity of tumour-infiltrating Treg cells through MCT1-mediated metabolism (Ref. 87). High lactate can promote immunosuppressive cytokine expression and Treg amplification in tumour-infiltrating DCs, thereby promoting tumour immune escape (Refs 90, 91). In conclusion, lactate can promote tumour immune escape by regulating TME to inhibit immune cell activity, and so forth Lactylation, as a novel post-translational modification of proteins, expands a new horizon for the role of lactate in TME and its mechanism.

Tumour-infiltrating myeloid cells (TIMs) can accumulate at the tumour site to form an immunosuppressive TME, and lactylation can regulate TIMs activation to help tumour cells undergo immune escape (Ref. 92). Wang et al. (Ref. 93) found that high expression of METTL3 in TIMs was associated with their poor prognosis in tissue samples from colon cancer patients, METTL3 recognized the m6A modification of Jak1 in TIMs, and H3K18 lactylation modification of TIMs would induce upregulation of METTL3 expression. In addition, increased lactate can help the zinc finger structural domain of METTL3 to produce lactate modification, which increases the transcriptional activity of downstream genes through activation of the JAK1-STAT3 signalling pathway, and thus produces immunosuppression, which provides a reliable basis for targeted therapy in myeloid cells (Ref. 93). STAT5 is highly expressed in acute myeloid leukaemia, leading to excessive accumulation of intracellular lactate, promoting histone lactylation and inducing PD-L1 transcriptional activation, which drives immunosuppression, which provides a new idea to increase the effect of PD-L1 immunotherapy response (Ref. 94). The above studies have shown that lactylation can affect the immune escape of tumour cells by increasing gene transcriptional activity. Currently, more studies have focused on lactic acid as a metabolite affecting immune escape through TME, and studies on lactylation as a node in lactic acid and immune escape are still relatively scarce, so revealing the correlation between lactylation and immunity in tumours may provide basic information for the use of immunosuppressants that have been emerged in the clinic. Basic information.

Crosstalk between lactation and acetylation

Acetylation and lactation are two important post-translational modifications of proteins, both of which tend to occur on lysine residues. When both modifications occur on histones, the two may compete for the same modification site. Studies have reported that when macrophages are stimulated by bacteria, the level of acetylation gradually decreases, while the level of emulsion increases (Ref. 95). In addition, in hepatic stellate cells, exogenous lactic acid inhibits acetylation when it promotes lactation (Ref. 96). This process is known as the 'lactate clock' and is maintained in homeostasis by macrophages. Both modifications play an important role in protein function, and when competitive inhibition occurs, organism dysfunction is likely to occur, and it is of great significance to explore the competition between the two in different environments. Studies have shown that the concentration of lactyl-CoA in tumour cells is about 1/1000 of that of acetyl-CoA, and the time for acetylation to reach a steady state (24 h) is significantly shorter than that of acetylation (6 h; Refs 1, 97). This evidence seems to suggest that, in most cases, emulsion is less competitive than acetylation. This crosstalk between acetylation and lactation allows them to interact with each other to synergistically regulate the structure, function and activity of proteins. Studies have found that when acetylation levels rise and the PDHA1 enzyme becomes inactive, lactic acid accumulates in the body. This accumulation of lactate in turn promotes lactation of mitochondrial fission protein 1, a process that may exacerbate damage to renal tubular epithelial cells, thereby worsening the condition of acute kidney injury (Ref. 98). In conclusion, the interaction and competition between acetylation and lactation is a complex and very important topic, but there are still many gaps in the study of the competition sites between the two, the main factors affecting the competition, and the results.

However, the balance between acetylation and lactation may be modulated through metabolic pathways. Lactation relies primarily on lactic acid as a substrate, while acetylation primarily uses acetyl-CoA as a substrate. Both substrates can be generated from pyruvate, a common precursor, through different metabolic pathways. Any factor affecting these metabolic activities may disturb the original equilibrium between lactation and acetylation. This imbalance may have a profound impact on the signalling and functional regulation of cells, as well as the feedback mechanisms of metabolic activity, which in turn can play a decisive role in the survival and fate of cells.

Lactated modifications and their inhibitors

As a novel post-translational modification of proteins, lactate modification plays an important role in a variety of diseases and tumours, accelerating disease or tumour progression, and the search for lactate inhibitors may provide more options for the clinical treatment of diseases and tumours mediated by lactate. Histone modification is a reversible covalent modification that is mainly performed by histone-modifying enzymes and their associated cofactors in concert. Histone modifying enzymes consist of three main classes, Writer, Eraser and Reader (Ref. 99). Writer catalyses the addition of chemical groups to histones to modify them, Eraser removes these modifications from histones and Reader is a protein or protein complex that recognizes and binds specifically to the substrate of a particular post-translational modification (Ref. 99). Together, the three major modifying enzymes form a complex regulatory network that precisely controls gene expression and thus affects cell fate and function. The study of enzymes related to lactylation can help to find inhibitors of lactylation and provide more molecular targets for clinical therapy. At present, the mechanism of action of lactylation is still in the research stage, and lactylation 'Reader' has not been reported, but lactylation 'Writer' and 'Eraser' have been found. 'Writer' and 'Eraser' have been found.

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Acetyltransferase p300 and its congener, CBP, are generally considered to be the 'writers' of lactylation, but the concentration of its acetyl donor, acetyl coenzyme A, is about 1000-fold lower than that of acetyl coenzyme A in the cell (Refs 3, 48). Therefore, it still needs to be investigated in depth whether p300 is a true acetyltransferase or not. Both alanine-tRNA synthetase 1 (AARS1) and alanine-tRNA synthetase 2 (AARS2) have lactylated transferase activity, which can directly convert lactic acid and ATP to lactate-AMP, and then the lactylated group is transferred to the lysine residue on the substrate protein, resulting in lactation modification, so that both AARS1 and AARS2 are true 'writers' of lactation (Ref. 100). AARS1 mainly functions in the cytoplasm, whereas AARS2 is mostly located in the mitochondria. AARS1 and AARS2 exert their transferase activity mainly by sensing lactate changes, and recent studies have reported that AARS1 and AARS2 inactivate cGAS by sensing L-lactate, thereby mediating the lactation of proteins (Ref. 101). And it was confirmed in another study that Zhi Zong et al. (Ref. 102) used β-alanine to disrupt the binding of lactate to AARS1, resulting in a decrease in p53 lacylation, which attenuated tumourigenesis. There is a strong relationship between lactate transferase activity and lactate, but recent studies have reported that the activity of lactate transferase HDAC6 in the process of lactation α-tubulin depends not only on lactate concentration but also on its deacetylase activity (Ref. 103). In summary, there is a link between lactated transferase and lactate metabolism, which suggests that lactylated transferase may also be related to other metabolic processes. Lysine [K] acetyltransferase 8 (KAT8) and HBO1 have also been shown to be lactylated transferases, which are predominantly present in the nucleus and have been implicated in tumour progression. KAT8 promotes tumour progression by improving protein translation efficiency by lactylation of eEF1A2 at K408, and HBO1 promotes key signalling pathways and tumourigenesis by catalysing H3K9la lactation (Refs 104, 105). However, p300 is still closely associated with lactylation and it has been found that p300 can be used as a molecular target to influence tumour progression. In TIMs, researchers have found that after treating C646 cells with p300 inhibitors, the level of protein lactylation and the expression of METTL3 were reduced, which can inhibit the function of immunosuppression and impede the occurrence of immune escape of tumour cells (Figure 3; Ref. 93). Lactylation 'Eraser' can play the role of dehydrogenation, and the 'Eraser' found so far are mainly the deacetylases HDAC1–3 and SIRT1–3. Carlos et al. found that common deacetylases HDAC1–3 and SIRT1–3 can play the role of dehydrogenation, and they can be used to inhibit the immunosuppressive function of tumour cells. Carlos et al. (Ref. 5) found that the common deacetylases HDAC1–3 and SIRT1–3 exerted a demilitarizing effect in cells, but HDACs (HDAC 1–3) appeared to be the most potent lysine-lactate-modifying 'Eraser' in vitro. Treatment of Hela cells with HDAC inhibitors (sodium butyrate/TSA) and apocynin, a specific inhibitor of HDAC1–3, elevated the level of lactylation, which further supports the idea that HDAC1 and 3 are intracellular 'Erasers' of lactylation. Previous studies have found that class I HDAC can promote hepatic stellate cell (HSC) activation, and HSC activation in liver fibrosis is associated with lactylation. Hyunsoo et al. (Ref. 96) treated primary HSC in mice with the class I HDAC inhibitors Apocynin and MS275 (entinostat), and found that the class I HDAC inhibitors reduced lactylation of H3K18, which inhibited HSC activation. Inhibit HSC activation. This suggests that HDAC inhibitors reduce the level of lactylation and thus affect disease progression. In summary, lactylation enzymes may act as drug targets to influence disease progression, so the discovery of more lactylation-related enzymes could help to clinically propose more therapeutic options for lactylation-related diseases and tumours.

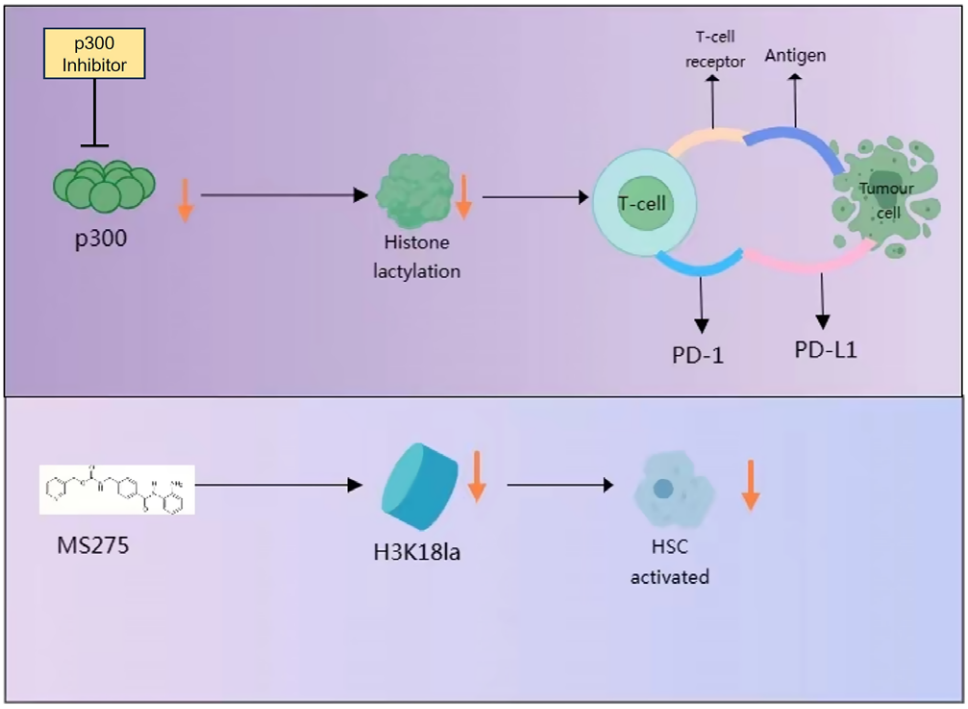


Figure 3. Current status of research on possible molecular targets of intracellular lactate modification and their inhibitors.

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In addition to lactate modification-related enzymes that may act as drug targets, a number of compounds have now been identified that can also act as lactate modification inhibitors to influence tumour progression. In hepatocellular carcinoma, demethylated elastomer of oxidation (DML) is a triterpenoid antitumour compound, and DML inhibits H3 histone lactylation to suppress hepatocellular carcinoma stem cell-induced tumourigenicity, suggesting that DML as an inhibitor may be a potential strategy for the treatment of hepatocellular carcinoma (Figure 3; Ref. 106). In addition, Xu et al. (Ref. 107) found that royal jelly acid could inhibit the lactylation of H3 histone H3K9la and H3K14la sites and thus inhibit the progression of hepatocellular carcinoma evodiamine is a natural alkaloid compound derived from the fruit of Evodia fructus, which can inhibit the level of HIF-1α lactylation in PCa cells and thus inhibit the progression of PCa, and at the same time, increase the expression of Sema3A to impede angiogenesis, so Evodiamines can be used as an adjuvant therapeutic drug for the anti-angiogenesis of PCa (Ref. 108). Glycolysis and lactylation are closely related, Li et al. (Ref. 109) found that glycolysis inhibitors 2-DG and oxalate could reduce the overall lactylation level in bladder cancer. Currently, there are fewer research reports on lactylation inhibitors, which have a greater potential for development.

Conclusion

Lactate, as the end product of cellular glycolytic metabolism, plays an important role in the tumour micro-environment, transcriptional regulation and immunosuppression. Lactate modification as a substrate, as a newly discovered epigenetic regulation, is closely related to the development of various diseases and tumours. Although there have been some studies on lactate modification in terms of modification sites and regulatory mechanisms, there are still many gaps in the basic research field. For example, whether the direct substrate of lactate modification is lactate coenzyme A or lactate glutathione, whether lactate modification occurs on residues other than lysine, and the mechanism of lactate modification in diseases and tumours are still unclear. Lactate-modified conjugating and decodifying enzymes still have great potential for development, especially 'Reader', which has not yet been reported. Inhibitors targeting lactate modification have not been studied yet, which makes the clinical treatment of its related diseases and tumours limited, and also becomes a great challenge for the development of molecularly targeted drugs. In conclusion, lactate modification as a new type of post-translational modification of proteins is involved in various important physiological activities of the organism, but it is still in its infancy, so it is urgent to reveal the mechanism of lactate modification in human diseases, and we need to have more basic theoretical knowledge to support the treatment of the diseases associated with it in the clinic.

Data citation. All references are from the PUBMED public database, and all references can be cited.

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