Am J Physiol Endocrinol Metab 324: E330–E338, 2023.
First published March 1, 2023; doi:10.1152/ajpendo.00159.2022

american physiological society

AMERICAN JOURNAL OF PHYSIOLOGY
ENDOCRINOLOGY AND METABOLISM

REVIEW

Immunometabolism

Lactylation: novel epigenetic regulatory and therapeutic opportunities

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Abstract

Lactate, which is an end product of glycolysis, has traditionally been considered a metabolic waste. However, numerous studies have demonstrated that lactate serves metabolic and nonmetabolic functions in physiological processes and multiple diseases. Cancer and pulmonary arterial hypertension have been shown to undergo metabolic reprogramming, which is accompanied by increased lactate production. Metabolic reprogramming and epigenetic modifications have been extensively linked; furthermore, posttranslational modifications of histones caused by metabolites play a vital role in epigenetic alterations. In this paper, we reviewed recent research on lactate-induced histone modifications and provided a new vision about the metabolic effect of glycolysis. Based on our review, the cross talk between the metabolome and epigenome induced by glycolysis may indicate novel epigenetic regulatory and therapeutic opportunities. There is a magnificent progress in the interaction between metabolomics and epigenomics in recent decades, but many questions still remained to be investigated. Lactylation is found in different pathophysiological states and leads to diverse biological effects; however, only a few mechanisms of lactylation have been illustrated. Further research on lactylation would provide us with a better understanding of the cross talk between metabolomics and epigenomics.

epigenetic regulatory; glycolysis; lactylation

INTRODUCTION

Glycolysis and oxidative phosphorylation (OXPHOS) not only provide essential energy sources for cellular activities but also generate a number of intermediate products coupled with metabolic processes. Lactate, the predominant end product of glycolysis, has long been regarded as metabolic waste; however, in the past 3 decades, increasing evidence has indicated its extraordinary metabolic and nonmetabolic functions (1).

The switch in gene expression based on nongenetic sequence alterations known as epigenetics, especially posttranslational modifications (PTMs), has become a research hotspot. Various histone PTMs, such as acetylation, methylation, glycosylation, ubiquitination, and phosphorylation, have been suggested to function by altering contacts between nucleosomes or recruiting nonhistone (2, 3). Most of these modification substrates are derived from metabolic processes; for instance, acetyl-CoA is a substrate that participates in the acetylation of core histones (4), and S-adenosyl methionine is capable of providing methyl groups to regulate the methylation of histones and DNA (5). Moreover, many diseases, such as cancer and pulmonary arterial hypertension (PAH), are associated with metabolic disorders and epigenetic modifications (6, 7).

Recently, lactylation, a novel epigenetic modification induced by lactate, was first demonstrated by Di Zhang et al. (8). In this review, we summarized the classic and advanced opinions of lactate, as well as the latest research progress on histone lactylation, and proposed a hypothesis for a relation between histone lactylation and PAH.

LACTATE: THE CLASSIC AND NEW PERSPECTIVES OF METABOLISM

Glucose, the predominant nutrient and circulating carbon carrier, produces energy through two metabolic pathways: glycolysis and OXPHOS. Both pathways begin with glucose being catabolized into two molecular pyruvates, which is accompanied by the production of two ATP molecules and two NADH molecules. When oxygen is available, pyruvate and NADH electrons generated by glycolysis are shuttled into mitochondria, where they turn into acetyl-CoA, subsequently entering the tricarboxylic acid cycle and producing

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Submitted 7 July 2022 / Revised 17 January 2023 / Accepted 17 February 2023

a quantity of energy. During this process, the electrons of NADH can be quickly utilized by mitochondria via α glycerol phosphate shuttle or malate aspartic acid shuttle (9, 10), on the other hand, aerobic glycolysis can still generate lactate during rest as well as stressful conditions such as exercise, trauma, sepsis, and heart failure (11, 12); however, in the absence of oxygen, electrons cannot shuttle into mitochondria, so pyruvate transformation to lactate by lactate dehydrogenase (LDH) is the only metabolic pathway in which lactate is the end product (13). Thus, under some high-demand conditions, glycolysis provides a way to generate energy rapidly and lactate is released as a metabolic waste.

Lactate has traditionally been considered a metabolic waste, but it is still unclear how lactate is catabolized. Typically, liver removes lactate via the gluconeogenic pathway and subsequently produces glucose; however, this idea has gradually changed. Researchers examined metabolomics in the arterial blood and draining veins of fasted pigs, and the results showed that lactate had higher circulatory turnover flux than glucose (14). This study demonstrated that many organs and tissues both produced and consumed circulating lactate, and higher circulatory lactate indicated the expression of LDH and monocarboxylic acid transporters (MCT) were more prevalent than the expression of glucose transporters. Furthermore, lactate and pyruvate can be interconverted by LDH in cells, and both glycolysis and lactate consumption require NADH as the electron carrier. Because of the widespread expression of the MCT and LDH, the intracellular pyruvate to lactate ratio can represent the NAD to NADH ratio (15); moreover, the mutual transformation of pyruvate and lactate can maintain the redox homeostasis in tissues and cells by balancing the NAD to NADH ratio. Characterization of this universal fuel of lactate, which is generated even in aerobic conditions, makes lactate become a metabolic benefit rather than a waste.

In some pathophysiological processes, glycolysis has been more intensively studied. Even when oxygen is available, pyruvate still produces large amounts of lactate in tissues, which is known as aerobic glycolysis, especially in diseases such as cancer, immune-mediated inflammatory diseases, and PAH, which are characterized by highly proliferative and antiapoptotic phenotypes (16). With increased glycolysis and decreased OXPHOS, aerobic glycolysis promotes a highly proliferative phenotype in cells by disturbing the pyruvate/lactate and glutamine/glutathione balance, upregulating the pentose phosphate pathway and increasing the synthesis of one-carbon units, which lead to the synthesis of amino acids, lipids, and nucleotides (17). In the meantime, the lactate balance is severely broken and forms a microacidic environment around cells, which drives immunosuppression and facilitates cell proliferation (18).

LACTYLATION: A NOVEL EPIGENETIC MODIFICATION

In addition to serving as energy sources, some metabolites have other important functions, such as the PTM of proteins. Acetylation and methylation are common PTMs, both of which alter the molecular structure of nucleosomes, influencing the recruitment of various effectors or directly stimulating or repressing target gene transcription (19). In a recent study, lactate was verified to act as a donor for the lactylation of histone lysine residues (Fig. 1), which then affected epigenetics by stimulating gene transcription from chromatin (8).

Zhang et al. identified lysine lactylation modification sites in the histone core proteins H3 and H4 in mouse bone marrow-derived macrophages (BMDMs) and human HeLa cells by liquid chromatography-mass spectrometry, which were named H3K18la and H4K5la, respectively. Under conditions of elevated endogenous lactate due to the hypoxic environment and pathogen invasion, the intracellular level of histone lactylation significantly increased and directly stimulated the expression of target genes in response to hypoxia or inflammation in M1 macrophages derived from BMDMs. In addition, exogenous inhibition of glycolysis or LDH knockdown downregulated cellular histone lactylation, indicating that histone lactylation was directly bound to cellular glycolysis. Moreover, under the late stage of hypoxia or lipopolysaccharide challenge, the dynamic change in histone lactylation correlates with the expression of genes associated with wound healing, which is an M2-like phenotype, rather than those involved in the early inflammation stage in BMDMs. Why does histone lactylation promote the M2-like macrophage phenotype in response to inflammatory stimuli? Mechanistically, the authors showed that histone lactylation could directly activate the transcription of relevant genes in a p53-dependent and histone acetyltransferase p300-mediated manner (8).

Metabolic processes and corresponding histone modifications are widely and importantly connected with physiological processes; moreover, dysregulated histone modifications can disturb the transcriptional balance and thus play an important role in the development of diseases (20–22), which have been gradually verified by studies. For example, the deletion of histone lysine 27 acetylation in renal clear cell carcinoma induced tumorigenesis by suppressing the expression of PAX8 (23), and histone lysine 27 methylation promoted myelodysplastic syndrome by mutating ASXL1 (24), the discovery of histone lactylation expands our understanding of metabolic programming and epigenetic modification. Interestingly, researchers reported a cyclic immonium ion of lactyllysine formed during tandem mass spectrometry and validated the sensitivity and specificity of this ion for lactylation (25), which shed a light on a wide landscape in human proteome beyond histones and confirmed the potential of lactylation for PTM cross talk and interaction.

LACTYLATION IS A DYNAMIC PROCESS

Recently, the mechanism of lactylation modification is studied, which reveals that lactylation is a dynamic process. Zhang et al. (8) identified p300, an acetylase, as also a lactylation writer protein, which transferred L-lactyl on histones to form histone lactylation, and overexpression of p300 remarkably increased lactylation level. Histone deacetylases (HDACs) consist of HDAC1-11 and SIRT1-7, which possess deacetylase activity. Research found that HDACs were also histone lysine delactylase. In vitro experiments HDAC1-3 substantially reduced the H3K18la and H4K5la, whereas SIRT1-3 slightly reduced H3K18la and H4K5la. However, in

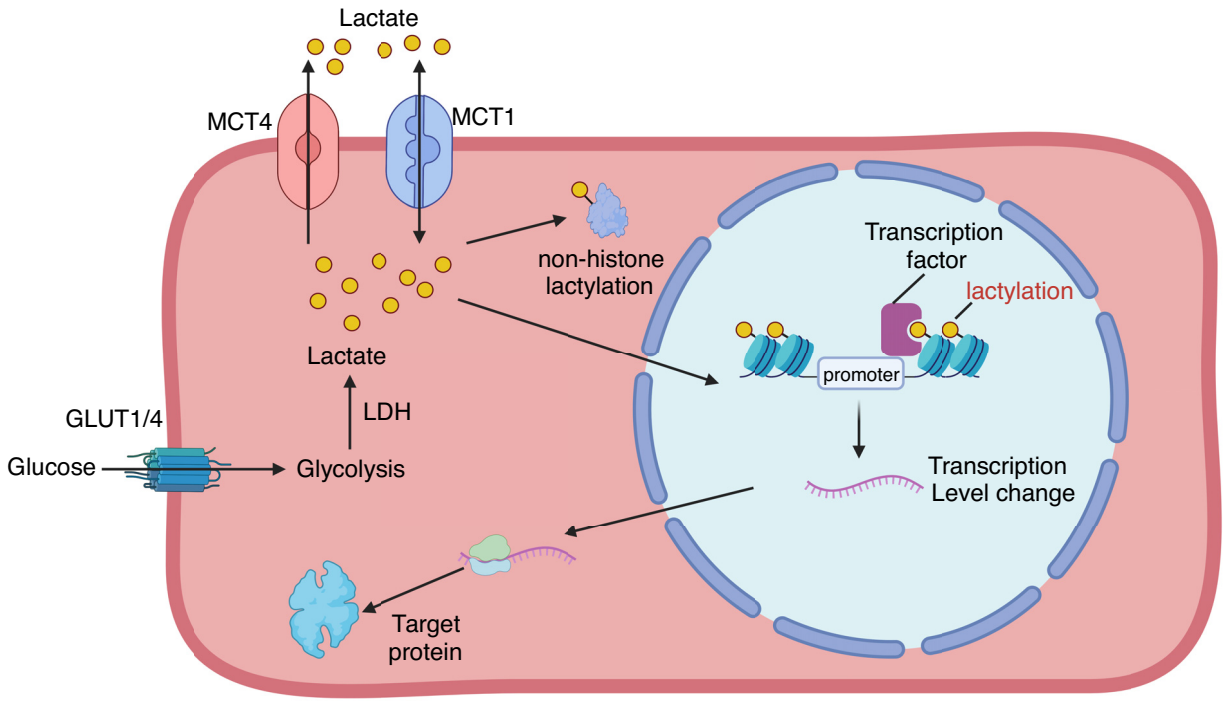

Figure 1. Lactate from extracellular plasma or glycolysis resulted in lactylation. Created using BioRender.com. GLUT1/4, glucose transporter1/4; LDH, lactate dehydrogenase; MCT1, monocarboxylate transporter 1; MCT4, monocarboxylate transporter 4.

vivo experiments, only HDAC1-3 inhibitors elevated pan Kla level, and sirtuin inhibitors failed to affect lactylation. Furthermore, knockdown of HDAC1 and HDAC3 but not HDAC2 in HeLa cells resulted in increase of H4K5la, but pan Kla and H3K18la remained unchanged, and triple knockdown of HDAC1–3 led to a stronger effect on H4K5 lactylation (26). The differences between in vitro and in vivo experiments suggested the existence of cofactors that enable the site-specific delactylation activity of HDACs. Unfortunately, there is currently no research on cofactors so far.

LACTYLATION REGULATES GENE EXPRESSION IN MULTIPLE PATHOPHYSIOLOGICAL PROCESSES

The Role of Lactylation in the Generation of Induced Pluripotent Stem Cells

Induced pluripotent stem cells (iPSCs) are generated from somatic cells by ectopically overexpressing Yamanaka factors, including Oct4, Sox2, Klf4, and c-Myc, and enhanced glycolysis was observed during the transition. However, how metabolic reprogramming affects the fate of iPSCs remains unknown. Recently, it has been reported that Gli-like transcription factor 1 (Glis1), a replacement of c-Myc in the original formula of Yamanaka factors, binds to glycolysis genes to promote their expression and elevates glycolysis levels without affecting OXPHOS in iPSCs, which leads to the accumulation of the substrates of acetylation and lactylation, including acetyl-CoA and lactate. Then, under the regulation of the "writer protein" p300, the levels of H3K9Ac, Pan Kla, and H3K18la were elevated, and these factors were mainly located at the transcription start sites of pluripotency genes and promoted their expression (Fig. 2). Thus, the iPSCs shifted from a somatic phenotype to a pluripotency phenotype (27). These results suggested that lactylation may be a key epigenetic change in the generation of iPSCs.

Lactylation Promotes Cancer Progression

Cancer cells undergo metabolic reprogramming, which is known as the Warburg effect, resulting in a boost in lactate levels and lactylation. A recent study on ocular melanoma indicated that high histone lactylation correlated with poor patient prognosis, whereas the inhibition of lactylation suppressed the proliferation of ocular melanoma cells in vitro. Further research showed that H3K18la promoted the transcription of YTHDF2, an N6-methyladenosine (m^6A) reader

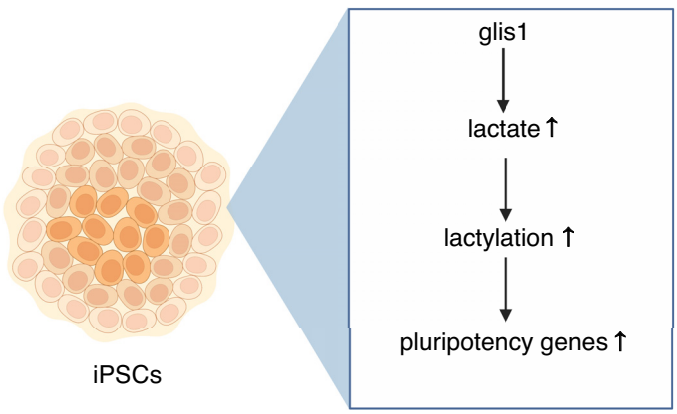

Figure 2. Lactatylation promotes pluripotency in iPSCs. Created using BioRender.com. iPSCs, induced pluripotent stem cells.

that degraded mRNAs with the m^{6}A modification. In ocular melanoma, increased YTHDF2 downregulated PER1 and TP53, which resulted in increased proliferation and migration in ocular melanoma cells (28). In another study, p300-mediated H3K18la increased the expression of METTL3, which lead to the activation of the JAK1-STAT3 signal pathway in tumor-infiltrating myeloid cells (TIMs). Besides, lactylation also took place on K281 and K345 of METTL3, which enhanced the capture of Jak1 by METTL3. The lactylation of TIMs promoted the infiltration and growth of cancer cells (29). However, lactylation might play different roles in other kinds of cancers. Research on nonsmall-cell lung cancer (NSCLC) showed that higher expression of LDHA and LDHB was correlated with poor prognosis of NSCLC; nevertheless, increased lactate levels inhibited glycolysis and the proliferation and migration of NSCLC cells (30). Furthermore, NSCLC cells treated with lactate showed upregulated *SDH, IDH*, and *HIF1A* transcription accompanied by elevated lactylation and downregulated transcription of glycolysis enzymes, including *HK-1, G6PD*, and *PKM*. ChIP assay showed that lactylated histone H4 was enriched at the promoters of *HK-1* and *IDH3G*, which suggested that the transcription of these genes was regulated by histone H4 lactylation; however, the detailed mechanism of how lactylation influenced NSCLC was not elucidated in this study. In addition, histone H4 lactylation suppressed NSCLC progression by inhibiting glycolysis, which was contradictory to the results in ocular melanoma and TIMs, raising the question of whether lactylation promotes or inhibits cancer progression (Fig. 3). Diverse answers may exist depending on circumstances.

Lactylation in Neural Excitation

One of the major functions of neurons is generating and conducting excitation, during which a large amount of lactate is produced (31). In a recent study, the depolarization of neurons facilitated the accumulation of lactate and increased in lactylation, which was attenuated by LDH inhibitors. This study also showed that lactylation was higher in the brains of mice treated with lactate. Repeated social defeat stress increased brain activity accompanied by increased lactylation in a mouse model. These findings demonstrated that increased brain activity resulted in lactylation (Fig. 4). However, how lactylation affects neural excitation remains unknown and needs further investigation.

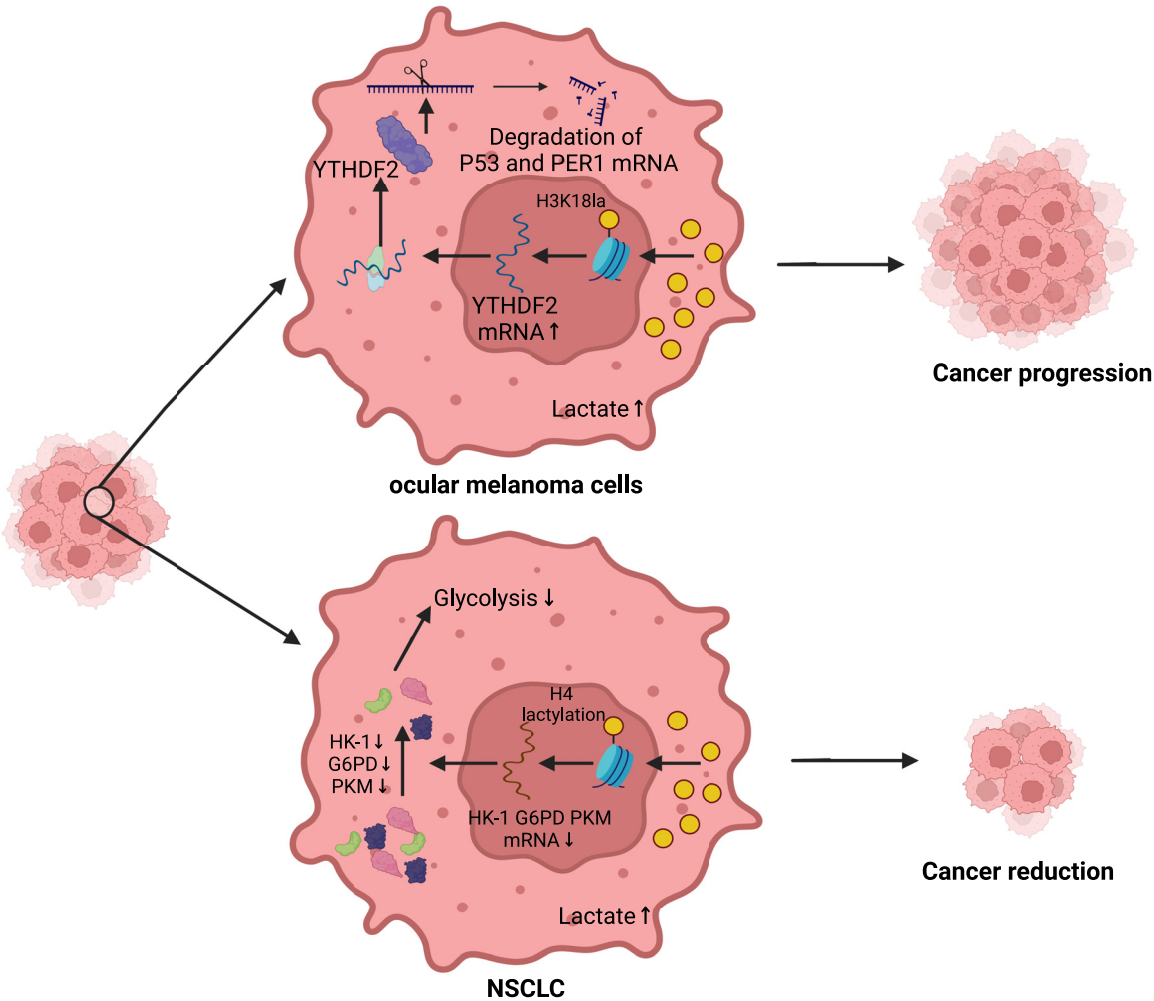

Figure 3. Lactylation regulates ocular melanoma cells and NSCLC. Created using BioRender.com. G6PD, 6-phosphoglucose dehydrogenase; HK-1, hexokinase 1; NSCLC, nonsmall-cell lung cancer; PKM, pyruvate kinase.

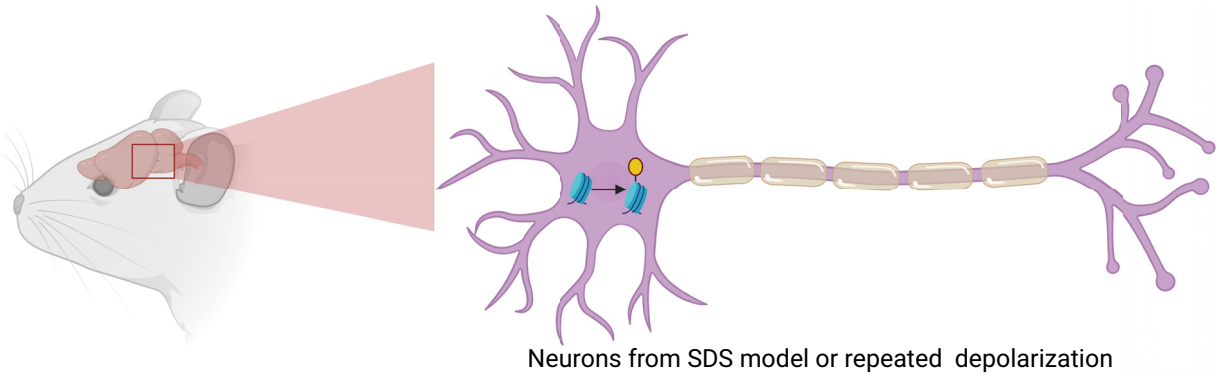

Figure 4. Lactylation is upregulated during neural excitation. Created using BioRender.com. SDS, social defeat stress.

Lactylation Promotes Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of neurodegenerative disease, and study found that lactate and H4K12 lactylation levels were upregulated in 5XFAD mice and patients with AD. Further exploration revealed that H4K12 lactylation was enriched in *PKM2*'s promoter region which upregulated the expression of PKM2. PKM2 was a glycolysis key enzyme and caused the production of lactate, the substrate of H4K12 lactylation. Thus, glycolysis, H4K12la, and PKM2 formed a positive feedback loop, and the broke of the loop inhibited microglial activation in 5XFAD mice, which alleviated AD's symptoms (32).

Lactylation Affects Macrophage Polarization

Macrophage polarization refers to the acquisition of an activation state in macrophages. Based on their functions and gene expression, activated macrophages are divided into proinflammatory M1 macrophages and anti-inflammatory M2 cells (33). BMDMs challenged with LPS and IFN-γ showed an M1 phenotype and elevated lactylation levels. After 24–48 h of M1 polarization, BMDMs started to express M2-like phenotype-related genes, such as *ARG1* and *VEGFA*. However, BMDMs treated with lactate only showed an M2-like phenotype and elevated lactylation without an early M1 polarization stage. These findings suggested that lactylation induced an M2-like phenotype and restored BMDMs to homeostasis in the late stage of M1 polarization (8). There was another study that had the opposite results, which showed that lactate and the expression of Arg1 were uncoupled. In this study, Arg1 was regulated by IL6, whereas NO and multiple cell death pathways were responsible for the accumulation of lactate and development of lactylation (Fig. 5). Their results suggested that lactate and lactylation were not coupled with macrophage activation and polarization (34). Hence, the effect of lactylation on macrophage polarization remains unclear.

Lactylation in Pulmonary Fibrosis

Pulmonary fibrosis is a chronic progressive disease that is believed to be affected by the dysregulation of multiple cell types, including alveolar endothelial cells, macrophages (35), and fibroblasts (36). Research has shown high expression of profibrotic factors, including Arg1, PDGFA, THBS1, and VEGFA, in alveolar macrophages from TGF-β1-induced pulmonary fibrosis mice. Moreover, alveolar macrophages treated directly with lactate showed high levels of protein lactylation, especially histone lactylation, which bound to the promotor regions of *ARG1, PDGFA, THBS1*, and *VEGFA* and then promoted their expression (37). Interestingly, Arg1 and VEGFA are not only profibrotic factors but also biomarkers of M2-like macrophages, and the lactylation of these factors has been shown (8) to promote the development of pulmonary fibrosis in other studies (38).

Lactylation Might Promote the Development of PAH

PAH is a fatal disease that is characterized by a cancer-like increase in cell proliferation and resistance to apoptosis (39). Strong evidence has shown that acquired abnormities in cellular metabolism and epigenetic dysregulation contributed to the pathogenesis of PAH (40, 41). Although there has been no study of lactylation in PAH, previous research suggested a high possibility that lactylation induced the development of PAH. Lactylation has been detected in pulmonary fibrosis, which is a potential etiological factor of hypoxic PAH, and the results showed enriched histone lactylation accompanied by increased PDGFA and VEGFA expression, both of which play vital roles in PAH progression by promoting pulmonary artery smooth muscle cells (PASMCs) and endothelial cells dysfunction (42).

In the lactate-enriched microenvironment, macrophages have elevated levels of lactylation and underwent similar polarization toward the M2 phenotype. M1/M2 ratio imbalance is a key mechanism of PAH, a study showed enhancement of M2 macrophage markers in the lung tissue of patients with idiopathic PAH (43). Perivascular macrophages from patients with PAH show high expression of the M2 polarization marker mannose receptor (MRC1) (44). In another experiment, macrophage low (MacLow)-induced PAH mice exhibited a decreased M1/M2 ratio, and the culture media of MacLow macrophages promoted the proliferation of PASMCs (45). M2 macrophages secreted PDGF-BB and MMP9 (46), which stimulated PASMCs proliferation and migration. Thus, there is a hypothesis that lactylation promotes macrophage M2 polarization, which induces the proliferation and migration of PASMCs and the development of PAH.

YTHDF2 and METTL3 are m^6A reorganization proteins that are upregulated by histone lactylation and promote the degradation of *TP53* and *PER1* mRNA in ocular melanoma (28). Our research revealed a high level of m^6A methylation

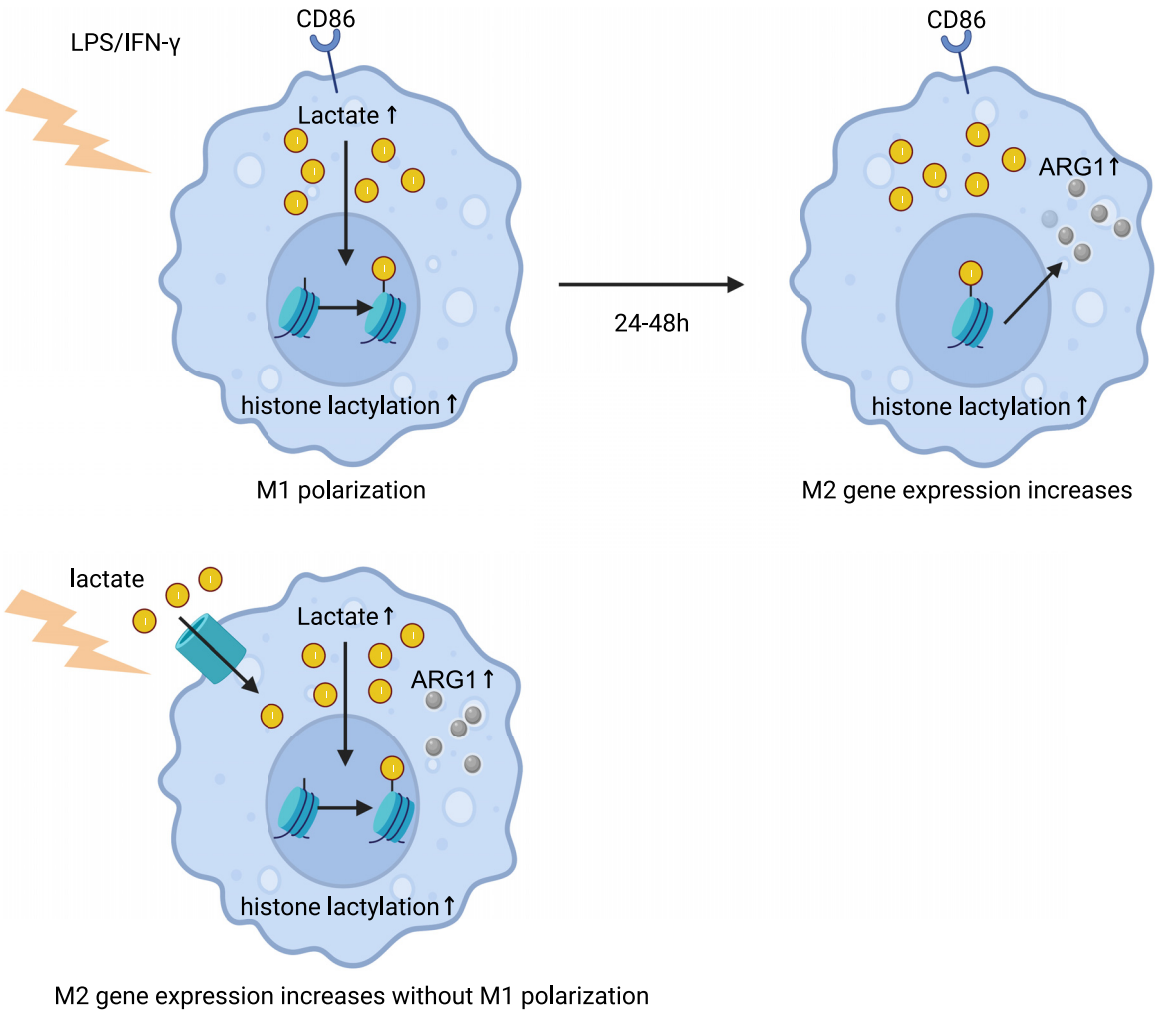

Figure 5. Lactylation influences the fate of macrophage polarization. Created using BioRender.com. ARG1, arginase 1; IFN-γ, interferon-γ; LPS, lipopolysaccharide.

and altered levels of key enzymes in monocrotaline-PAH rats (47). YTHDF2 and METTL3 were also overexpressed in PAH induced by hypoxia and led to the hyperproliferation of PASMCs (48). However, the mechanism of YTHDF2 overexpression remains unknown. PASMCs share features of cancer cells, such as a high level of the Warburg effect (49) and downregulated TP53 expression (50). It is possible that lactylation promotes PASMCs by regulating the expression of key m^6A enzymes. Thus, studying lactylation might identify a new regulatory target in PAH.

POTENTIAL THERAPEUTIC TARGET

Lactate has been increasingly considered as a novel potential therapeutic target in many diseases, especially in cancer, and till now, most treatments are targeted MCT1 and MCT4. For instance, tumor cells are characterized by antioxidation in tumor microenvironment (TME) and drugs can inhibit MCT4-mediated lactate efflux, inducing tumor acidosis and promoting reactive oxygen species production, and further collapsing the antioxidant system of tumor cells (51, 52). In addition, drugs targeting MCT1 and MCT4 are also being investigated in clinical developments (53, 54). However, metabolic reprogramming in TME that can cause impeding immune surveillance and promote cancer growth, making their resistance to traditional chemotherapeutic agents or targeted agents a major problem in cancer treatment (55, 56).

Surprisingly, studies have determined that lactylation plays an important role in cancer progression, there were several studies targeting lactate or lactylation to treat cancers and showed that lactylation would become a new therapeutic opportunity. Researchers reported a triterpene antitumor compound, demethylzeylasteral (DML), suppressed tumorigenesis of liver cancer stem cells (LCSCs) in vitro and in vivo and verified that DML inhibited LCSCs by regulating lactate and lactylation of a metabolic stress-related histone (57); further researches showed two lactylation modification sites, H3K9la and H3K56la, were associated with oncogenicity of LCSCs. Another study revealed that lactate regulated Treg cells by enhancing TGF-β signaling via TGF-βRI in TME through lactylation of MOESIN at the Lys72 residue (58). In addition, researchers found cotreatment with anti-PD-1 and a lactate dehydrogenase inhibitor had a stronger antitumor effect than anti-PD-1 alone in mice. These studies indicated lactylation was a potential candidate target for cancer treatment and proposed a new

thinking of targeting tumor cells in the treatment strategies, which provided theoretical experience for the clinical intervention of tumor recurrence.

In general, targeting lactate and lactylation metabolism are becoming a potential and prospective therapeutic strategy. The discovery of lactylation enriches the biological function and underlying mechanisms of glucose metabolism, which provide a novel idea for exploring biological functions and developing treatment strategies.

CONCLUSIONS AND PERSPECTIVES

Lactate, which is an end product of glycolysis, is produced through multiple physiological and pathological processes, such as hypoxia, inflammation, and tumor progression. However, lactate is more than a metabolic waste product and regulates multiple bioprocesses. Since 1970s, the recognition of lactate has transformed, notably, from the ATP production is faster and more efficient than aerobic oxidation of glucose to the lactate is a common fuel and as a redox buffer that maintains a balanced cellular redox state. Subsequent researchers gradually demonstrated the roles of lactate as a distinct metabolic signaling molecule and preliminarily explored the functions of lactylation as a novel acylation PTMs form in certain pathophysiological process, including directly regulating oncogenes expression, inducing anti-inflammatory phenotype in TMEs, and adjusting neuronal excitation.

The study of epigenetic regulation modified by lactylation is still at the infancy stage; however, this discovery makes the probe of epigenetic mechanisms more prospective. Researchers revealed that lactylation because of lactate accumulation could inhibit the feedback mechanism of glycolysis by covalently modifying the upstream metabolic enzymes in the glycolysis pathway (25), and demonstrated that lactylation on K147 inhibited enzyme activity. Another research by Yang et al. (59) reported a global lactylome profiling on a hepatocellular carcinoma cohort and found the lactylation of adenylate kinase 2 significantly affected the function and biological behavior of cancer cells. These two discoveries provided direct evidence for the functional importance of lactylation on nonhistone proteins, which complemented the existing regulatory model of "end product inhibition" and suggested the lactylation may be an important hub of lactate and tumor metabolism. Histone and nonhistone modification of lactylation elucidated the causal relationship between lactylation and the occurrence and development of chronic diseases such as inflammation and tumor. Exploring the regulation of lactylation is expected to be a potential and promising therapeutic target.

The discovery of lactylation will no doubt expand our visions for realizing the implications of lactate itself and the Warburg effect in human diseases. However, there are still many scientific questions to be illustrated. First, almost all lactylation research today revolves around lysine residues, however, does lactylation occurs only at lysine residues? Second, considering the function and effect of lactate itself in TME and tumor, studies of lactate-mediated lactylation should be more thorough. Xin et al. (60) proposed lactylation may just be caused only by lactate accumulation and had no specific functions. In GO and KEGG analysis, the lactate function of different organs had some differences (61). Therefore, lactate-mediated lactylation in histone and nonhistone should be more explored. Finally, the enzymes of producing and regulating lactylation modification remain to be demonstrated. For histone delactylases, as described earlier, lactyl can be transferred from lacty-CoA to histones via p300, and HDAC1–3 are histone lactylation removal enzymes. For nonhistone delactylases, Sun et al. (62) found sirtuin 1 as a potential nonhistone delactylase. Interestingly, Dong et al. (63) reported the lactylation regulatory system in prokaryotes and demonstrated that YiaC and CobB were respectively "writers" and "erasers" of lactylation proteins in vitro and intracellularly. These works showed that lactylayion regulation mechanism exists not only in eukaryotes but also in prokaryotes, which presented a new perspective for studying the mechanism of lactylation regulation metabolism in bacteria.

Here, we reviewed a novel means by which metabolic reprogramming influenced gene expression. In conclusion, there are two possible ways that lactylation regulates protein functions: *1*) Histone lactylation directly binds to the promoter region, which promotes or inhibits the transcription of certain genes and *2*) Lactylation directly modifies proteins, which regulates their bioactivities. Studies have shown that lactylation was present in multiple diseases, associated with prognosis and resulted in the alteration of gene expression. Only a few mechanisms have been illustrated, and most of the cross talk between glucose metabolism and epigenetics remains unknown. Further research on lactylation would provide us with a better understanding of the cross talk between the metabolome and epigenome.

ACKNOWLEDGMENTS

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GRANTS

This work was supported by the Hunan Provincial Health Commission Project (No. 20200483), Project of Hunan Provincial Research on Chinese Medicine (No. 201914), and 2019 National Medical Service and Support Capacity Improvement Project: Children's Difficult Diagnosis and Treatment Center.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

H.F., F.Y., and H.C. drafted manuscript; H.F., F.Y., and Y.X. edited and revised manuscript; H.F., F.Y., Z.X., H.L., H.C., Z.C., Q.L., and Y.X. approved final version of manuscript.

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