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The Regulatory Mechanisms of Lactic Acid and Protein Lactylation Modifications in Cellular Life Activities: A Review of Recent Advances

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Abstract: Historically, lactic acid, as a byproduct of glycolysis, was considered a metabolic waste product in skeletal muscle and energy metabolism. It wasn't until 1920 that scientist Warburg first discovered that even in the presence of oxygen, cells undergo glycolysis when metabolism is heightened, a phenomenon now known as the Warburg effect. The ultimate outcome of this effect is an increase in lactate production both inside and outside of the cell. Recent studies have further confirmed that lactate not only acts as a signaling molecule via G-protein-coupled receptors, but also enters cells through membrane-associated monocarboxylate transporters, where it participates in post-translational modifications of proteins. This regulates metabolism and influences epigenetic mechanisms. This review summarizes the regulatory role of lactylation in cellular metabolism based on previous research.

1. Background

Post-translational modification (PTM) refers to the covalent alterations of proteins after their synthesis, which regulate a broad spectrum of cellular processes including protein activity, localization, folding, and interactions with other macromolecules. PTMs have emerged as critical regulators of cellular functions and play pivotal roles in the pathogenesis of various diseases. Increasing evidence suggests that the regulation of cellular functions is not solely determined by the abundance of proteins, but is also profoundly influenced by the diverse range of PTMs. Proteomics, through the comprehensive analysis of PTM profiles, offers valuable insights into the molecular mechanisms underlying biological processes, facilitates the identification of disease biomarkers, and aids in the discovery of therapeutic targets.

Lactylation, a recently identified PTM, involves the covalent conjugation of a lactyl group to the lysine residue of proteins, thereby modulating gene expression and cellular processes. This

modification, also known as lysine lactylation (Kla), is implicated in the regulation of cellular metabolism and gene transcription. Lactate, a central metabolite in glycolysis, has long been recognized as a byproduct of anaerobic metabolism[17]. However, recent studies have highlighted its role as a signaling molecule that can modulate the expression of downstream target genes. Despite its recognized importance, the precise mechanisms by which lactate influences gene expression through lactylation of specific proteins remain an area of ongoing investigation. This review aims to summarize the current understanding of lactate and lactylation in the context of metabolic regulation, with the goal of providing a comprehensive framework for future studies on the functional implications of lactate in cellular and organismal physiology.

2. Lactate Production and Removal

Under anaerobic conditions, glucose is metabolized through the glycolytic pathway to generate pyruvate, which is then converted to lactate by lactate dehydrogenase A (LDHA). Furthermore, even under aerobic conditions, tumor cells or cells with enhanced metabolic activity continue to rely on glycolysis for lactate production, a phenomenon referred to as the Warburg effect. [1].In the cytoplasm, lactate is transported into the cell via Monocarboxylate Transporters (MCTs), or it can be produced through glycolysis and glutamine catabolism .Lactate undergoes catabolism within the cell through two distinct pathways. In one pathway, lactate is oxidized to pyruvate by lactate dehydrogenase B (LDHB), which then enters the mitochondria and is metabolized via the tricarboxylic acid (TCA) cycle[12]. In the other pathway, lactate is converted into glucose through gluconeogenesis. Additionally, recent studies have revealed that lactate can maintain intercellular lactate balance through a process known as the "lactate shuttle" between different tissues and cells[24]. Within the cell, lactate can be exchanged between the cytoplasm and mitochondria, as well as between the cytoplasm and peroxisomes. The shuttle of lactate between cells and recipient cells is driven by the concentration gradient generated by the mitochondrial respiratory apparatus of the recipient cells, which facilitates the oxidation of lactate.[2]Under both fully aerobic resting and exercise conditions, the body can share the same carbon source, lactate, through a mechanism known as the lactate shuttle[8]. Additionally, this study confirms that postprandial states and food absorption lead to a significant increase in lactate production. Furthermore, as exercise intensity increases, lactate generation also rises, and the circulating levels of catecholamines in the blood influence lactate metabolism. Lactate is transported across the plasma membrane via multiple monocarboxylate transporters (MCTs), primarily MCT1 and MCT4.[6]The primary physiological function of MCT1 is the uptake of lactate, whereas MCT4 primarily facilitates lactate efflux. Additionally, the direction of lactate transport through MCTs in the body is determined by the concentration gradients of lactate and protons. [11]. CD147 is a chaperone molecule of MCTs, promoting the proper expression and localization of MCT1 and MCT4 on the cell surface. Additionally, studies have shown that thyroid-stimulating hormone (TSH) stimulates the promoter activity of MCT1, thereby regulating lactate levels.

3. The Impact of Lactate and Lactylation on Cellular Life Activities

3.1 Regulatory Mechanisms of Lactylation Modification

Lactylation refers to the protein modification induced by the accumulation of lactate. This modification alters the protein's spatial conformation, influencing gene transcription and regulating the expression of relevant genes. Recent studies, combining analytical chemistry and mass spectrometry methods, have identified several lactylation modification isomers, including L-lysine lactylation (KL-la), D-lysine lactylation (KD-la), and N-ε-lysine (carboxyethyl) lactylation (Kce). These studies have also revealed that L-lactylation is the predominant form of lactylation

modification[18]Lactylation modification encompasses a comprehensive regulatory system that involves "writer" proteins, acyltransferases, and other enzymatic components to facilitate the precise capture of lactate molecules, the synthesis of lactoyl-CoA, the identification of modification sites, and the modulation of modification levels. Prominent "writer" proteins include TIP60, P300, CBP, AARS2, and others. Additionally, the SIRT family of proteins has been implicated in the regulation of de-lactylation processes. The extent of lactylation is tissue-specific and is directly influenced by the local concentration of lactate. Under high lactate conditions, lactate is converted to lactoyl-CoA, which is subsequently recognized by "writer" proteins. These proteins then transfer the lactoyl group to lysine residues on target proteins, thereby inducing covalent lactylation modifications. Such modifications alter the protein's native activity and subsequently influence its biological function. Recent investigations have unveiled a novel "writer" protein, ACSS2, which directly recognizes lactate molecules, catalyzes their conversion into lactoyl-CoA, and facilitates the subsequent lactylation process. This discovery underscores the direct interplay between glucose metabolism and post-translational protein modifications, linking metabolic pathways with cellular regulatory mechanisms[29].

3.2 Affects the synthesis and breakdown of fat

Studies have found that lactate can act as a signaling molecule within cells through autocrine signaling, binding to the G protein-coupled receptor (GPCR) GPR81 to mediate the inhibition of insulin-dependent lipolysis. This research indicates that lactate can activate GPR81, a GPCR expressed in adipocytes, and inhibit adenylate cyclase activity through a Gi-dependent pathway, resulting in anti-lipolytic effects[4]. These findings suggest that lactate functions in a hormone-like manner, directly regulating metabolic processes, and reveal a new mechanism for the insulin-mediated inhibition of lipolysis.[3]Furthermore, lactate is a major gluconeogenic precursor that increases glucose production, thereby elevating blood glucose levels. Additionally, lactate exerts its effects by binding to GPR81, which influences cAMP levels and the cAMP response element-binding protein (CREB), ultimately inhibiting lipolysis in white adipose tissue and reducing the circulating levels of free fatty acids.[5]During muscle contraction, as glycolysis is accelerated, the ratio of lactate to pyruvate (L/P) increases. When the intracellular lactate concentration rises, lactate is transported into the mitochondria and endoplasmic reticulum via monocarboxylate transporters (MCTs).Lactate is converted into acetyl-CoA, which then forms malonyl-CoA. The elevated levels of malonyl-CoA inhibit the carnitine palmitoyltransferase 1 (CPT1) enzyme, thereby suppressing the entry of free fatty acids into the mitochondrial matrix.[7]At the same time, the accumulation of acetyl-CoA can downregulate the activity of the rate-limiting enzyme β-ketothiolase in the mitochondrial β-oxidation pathway, thereby inhibiting fat breakdown.

Mitochondrial pyruvate carrier 1 (MPC1) can mediate the treatment of non-alcoholic fatty liver disease (NAFLD) by regulating the lactylation of fatty acid synthase.[23]MPC1 gene knockout regulates lactate levels in hepatocytes, thereby modulating the lactylation of fatty acid synthase. Lactylation at the K673 site of fatty acid synthase inhibits its activity and alleviates hepatic lipid accumulation.Other studies have confirmed that lactylation of Vps34 links autophagy and glycolysis, a process mediated by the lactosyltransferase KAT5/Tip60. Lactylation of Vps34 enhances its interaction with Beclin1, Atg14L, and UVRAG, thereby increasing the lipid kinase activity of Vps34. This lactylation of Vps34 promotes the transport of autophagosomes to lysosomes and endosomes, enhancing autophagic flux.[22]Exercise training promotes the lactylation of Mecp2 at lysine 271 (Mecp2k271la)[26], which reduces the expression of vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), monocyte chemoattractant protein-1 (MCP-1), interleukin (IL)-1β, and IL-6. Additionally, it increases the levels of endothelial nitric oxide synthase

(eNOS) in the aorta of mice, reduces lipid deposition in the arterial wall, and subsequently ameliorates the development of atherosclerosis.[27]Moreover, exogenous lactate can increase the lactylation level of Mecp2k271 in vivo, thereby suppressing the expression of Ereg and the activity of MAPK in endothelial cells (ECs), which inhibits the progression of atherosclerosis. High-intensity interval training (HIIT) is an important method for fat reduction; however, this effect is diminished when lactate production is inhibited. Studies have confirmed that in inguinal white adipose tissue (IWAT), HIIT significantly upregulates protein lactylation levels. Furthermore, lactate treatment via mass spectrometry increased the lactylation level of FASN in 3T3-L1 cells, inhibiting FASN activity and reducing the synthesis of palmitic acid and triglycerides.[28]This study demonstrates that lactate produced during high-intensity interval training (HIIT) increases the global protein lactylation levels in inguinal white adipose tissue (IWAT). The lactylation of FASN inhibits de novo lipogenesis, which may be an important mechanism underlying fat reduction induced by HIIT. In a global protein analysis study of skeletal muscle, it was pointed out that enhanced protein lactylation may be associated with tendon damage and cholesterol metabolism disorders.After performing high-intensity interval training (HIIT) on mice, an analysis of lactylation modification levels in different tissues revealed that lactylation was significantly upregulated in white adipose tissue (iWAT) and influenced the gene expression of downstream glycolytic pathways.

3.3 Affects glucose metabolism

Lactate as one of the important products of glycolysis, can, on one hand, inhibit glycolysis through its own concentration in a feedback manner. On the other hand, studies have confirmed that the absence of lactate membrane transporters, such as MCTs, leads to dysfunction of pancreatic β-cells, disrupting glucose-insulin signaling and the insulin signaling pathway.[9]In addition, under hyperglycemic conditions, excessive lactate generated in cells is converted into lactoyl-CoA and, through the acyltransferase P300, binds to proteins, thereby participating in post-translational modifications, specifically lactylation. A study from the United States confirmed that the global lactylation level in skeletal muscle is positively correlated with insulin resistance levels. Moreover, lactylation can influence mitochondrial oxidative respiration, participate in mitochondrial energy metabolism, and regulate circulating blood components involved in the development of insulin resistance.[10]Additionally, studies have found that Glis1, an important regulator of the cell cycle, can promote protein lactylation. Furthermore, Glis1 interacts with downstream glycolytic genes, thereby regulating the cell growth cycle.[11]Although current research on protein lactylation is primarily focused on tumors and immune evasion, various lines of evidence suggest that protein lactylation is not only an indicator of lactate levels and glycolysis but also closely linked to cellular metabolism. As a novel epigenetic mark, it influences cell fate. Yang et al. discovered that H3K18la is involved in the remodeling of endometrial receptivity, serving as a reflection of histone lactylation in the endometrium.[25]A study on embryonic development found that histone lactylation leads to changes in the expression of glycolysis-related genes, including upregulation of Hk2, Pgk1, Pfk1, Pkm, Eno1, and Ldha.[23]Another study demonstrated that the accumulation of H3K18la on genes of the germline and cleavage-stage embryos promotes transcriptional elongation.[25]The above evidence suggests that lactylation may influence embryo implantation and development by regulating embryonic cell metabolism during embryonic development. Lactate, through the acyltransferase KAT5/TIP60, mediates the lactylation of PIK3C3/VPS34 at lysine residues 356 and 781. Lactylation of PIK3C3/VPS34 enhances its association with BECN1 (beclin 1, an autophagy-related protein), ATG14, and UVRAG, increasing the lipid kinase activity of PIK3C3/VPS34 and promoting macroautophagy/autophagy, which facilitates the lysosomal degradation pathway. High lactylation

of PIK3C3/VPS34 induces autophagy and plays a crucial role in skeletal muscle homeostasis and tumor development.

4. The key role of lactylation modification of histones

Histones are unique compounds composed of proteins (known as the nucleosome core) and DNA in chromatin. Various post-translational modifications (PTMs) of histones regulate gene expression. Classical PTMs, such as acetylation, butyrylation, and succinylation, alter the spatial structure of proteins, thereby regulating numerous cellular physiological and biochemical processes.In 2019, histone lactylation modifications were first proposed. It was observed that histone lactylation could loosen the physical structure of nucleosomes, thereby promoting downstream transcription and translation processes. This, in turn, regulates gene expression and influences changes in epigenetics.[13]Histone lactylation modifications were first discovered in the metabolism of macrophages. After histone lactylation, it can promote the M1 to M2 macrophage polarization, regulate the expression of inflammatory genes, and affect the expression of Agr1, thereby playing a role in wound repair and healing.[15]In addition, histone lactylation modifications are involved in the pathogenesis of various diseases. For example, in melanoma, histone lactylation drives tumorigenesis by promoting the expression of the m6A reader protein YTHDF2[14,16].It is well known that lactate, as an important energy source, plays a crucial role in the metabolism and energy supply within the central nervous system. As a target organ rich in lactate, recent studies have confirmed that lactylation is involved in the occurrence and progression of neurological diseases.The lactate shuttle between astrocytes and neurons elucidates the crucial role of lactate in maintaining neuronal metabolism and neurotransmitter signaling[16].

In addition, lactate also plays a role in metabolic reprogramming、Lactate plays a role in the pathogenesis of neuroinflammatory diseases such as Alzheimer's disease and other neurodegenerative disorders.[18]Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, and Huntington's diseaseAdditionally, a significant amount of research on lactate has focused on immune regulation, particularly in the immune evasion of tumor cells. Increasing evidence suggests that lactate-mediated immune cell reprogramming and enhanced cellular plasticity contribute to the establishment of disease-specific immune states.

5. The key role of non histone lactylation modification

Lactylation modifications can occur not only in histones but also in non-histone proteins. However, lysine residues in non-histone proteins are more difficult to undergo lactylation substitution.In a study on macrophage inflammation regulation, it was found that macrophages can take up extracellular lactate through monocarboxylate transporters (MCTs) and, via a p300/CBP-dependent mechanism, promote the lactylation of HMGB1. This, in turn, increases endothelial cell permeability and promotes the release of macrophage exosomes, improving inflammatory outcomes.[19]Furthermore, another study found that pyruvate kinase (PKM2), a key enzyme in cellular energy metabolism, can undergo lactylation via a lactate-dependent mechanism. PKM2 is a substrate for lactylation, and it was confirmed that lactylation primarily occurs at the K62 site. Lactate increases the lactylation level of PKM2, thereby inhibiting its transition from tetramer to dimer, promoting its pyruvate kinase activity and reducing its nuclear distribution, thus regulating cellular metabolism.Similarly, data also indicate that lactylation of α-MHCK1897 in cardiomyocytes can regulate cardiomyocyte metabolism and intervene in the onset of heart failure.Most key enzymes involved in glycolysis can undergo lactylation, including aldolase, phosphoglycerate kinase, and pyruvate kinase, among others. Additionally, lactylation of poly(ADP-ribose) polymerase 1 (PARP1) can regulate its ADP-ribosylation activity, potentially contributing to DNA repair.[21] Lactylation modification can also

directly occur in the CCCH-type zinc finger domain of the METTL3 protein[20], mediating tumor immune evasion. Lactylation modification primarily occurs on proteins with a molecular weight of 25 kDa

6. Conclusion

Lactylation, as a newly recognized post-translational modification, has been extensively studied in various diseases in recent years. As an important intermediate metabolite in cellular metabolism, lactate not only acts as a signaling molecule to regulate the cell life cycle but also participates in post-translational modifications to regulate the biological functions of target proteins, thereby influencing gene expression and contributing to various cellular processes such as metabolism, proliferation, migration, and apoptosis. This review, building on previous research, introduces lactate's role in regulating cellular metabolism, summarizes the processes of lactylation modification, research methods, and its pathophysiological mechanisms in diseases. Lactylation modification, as a crucial metabolic regulatory mechanism within the cell, is widely involved in processes like metabolic regulation, immune response, proliferation, aging, and oxidative stress. It not only alters protein functions and structures but also plays a significant role in various physiological and pathological processes, particularly in tumor immune evasion and metabolic reprogramming. With further research into lactylation modification, it is anticipated that more biological functions will be revealed, providing new insights and strategies for clinical treatment.

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