Recent Advances in Lactylation Research in Age-Related Diseases: Postprint

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Date: 2025-01-07T00:00:00+00:00

Abstract

Lactylation modification is a novel regulatory mechanism of protein post-translational modification formed by the covalent coupling of lactate produced by glycolysis with lysine residues, primarily comprising histone lactylation and non-histone protein lactylation. Current studies have revealed that it participates in intracellular biological processes mainly by regulating gene transcription, protein expression, and subcellular localization. With advancing age, lactate metabolism becomes dysregulated in multiple organs, and recent research has discovered that the resulting lactylation modification can contribute to the pathogenesis and progression of various age-related diseases. Therefore, this article aims to review the functional and mechanistic studies of lactylation modification in age-related diseases.

Full Text

Preamble

Research Progress of Lactylation in Age-Related Diseases

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Abstract Lactylation is a novel mechanism of protein post-translational modification formed by the covalent coupling of lactate produced through glycolysis with lysine residues, primarily including histone lactylation and non-histone lactylation. Current research indicates that lactylation mainly participates in intracellular life processes by regulating gene transcription, protein expression, and subcellular localization. With advancing age, lactate metabolism becomes dysregulated in multiple organs, and recent studies have revealed that lactylation mediated by lactate can contribute to the pathogenesis of various age-related diseases. Therefore, this review aims to summarize the functional and mechanistic studies of lactylation in age-related diseases.

[**Key words**] Lactylation; Lactic acid; Age-related diseases; Histone lactylation; Non-histone lactylation

For a long time, lactate has been regarded as a metabolic byproduct and energy source that affects intracellular acid-base balance and metabolic pathways. Recent studies have discovered that lactate can serve as a donor for lactylation modification of protein lysine residues [1]. Currently, research on lactylation has focused primarily on two major types: histone and non-histone lactylation, which have been reported to participate in the pathogenesis of various diseases, including age-related diseases and tumors [2]. Studies have found that with aging, senescent cells undergo metabolic reprogramming, leading to a sharp increase in intracellular lactate content [3]. Multiple studies have confirmed that elevated lactate further promotes the formation of protein lactylation modifications, which influence protein expression and function, thereby participating in the development of age-related diseases [4-9]. Therefore, this review primarily summarizes the specific research progress of lactylation in age-related diseases.

1 Literature Search Strategy

A computerized search was conducted in PubMed, Web of Science, and other databases from inception to July 2024. English search terms included "Lactylation," "Lactate," "aging," "age-related diseases," "Histone lactylation," and "Non-histone lactylation." Inclusion criteria comprised studies on the effects of lactylation on age-related diseases, as well as research on the types and influencing factors of lactylation. Exclusion criteria included literature unrelated to the topic and articles without full-text availability. A total of 115 articles were ultimately included.

2 Lactate Metabolism

Lactate exists in three common isomeric forms in nature: D-lactate, L-lactate, and racemic DL-lactate. However, due to carbon atom asymmetry, L-lactate is the predominant form [2]. Lactate is a classic byproduct of glucose metabolism, primarily produced through glycolysis [2,10]. Under physiological conditions, glucose is transported from the extracellular matrix to the cytoplasm and converted by various glycolytic enzymes into pyruvate and two molecules of adeno-

sine triphosphate (ATP). Depending on oxygen availability, two scenarios occur: in aerobic environments, pyruvate is transported to mitochondria for the tricarboxylic acid cycle and oxidative phosphorylation (OXPHOS), generating approximately 36 ATP molecules [11-12]; in hypoxic environments, OXPHOS is blocked, and pyruvate is catalyzed by lactate dehydrogenase A (LDHA) to produce lactate and 2 molecules of ATP. However, in tumor cells and some proliferating cells, even under oxygen-rich conditions, there is a preference for producing large amounts of lactate through glycolysis to obtain energy, a phenomenon known as the "Warburg effect" [13]. In summary, lactate production is influenced by intracellular oxygen content, mitochondrial oxidative phosphorylation, and the glycolytic pathway.

The maintenance of lactate homeostasis in cells also depends on the solute carrier family 16, composed of monocarboxylate transporters (MCTs). Currently, 14 MCT family proteins have been identified, which are expressed in various tissues and play important roles in nutrient transport, cellular metabolism, and pH regulation. Among them, MCT1-4 are the main lactate transporters that maintain intracellular lactate balance through coordinated shuttle between glycolytic and oxidative cells, while the roles of other MCTs in lactate transport remain to be determined [14-16].

3.1 Histone Lactylation

Histones, composed of H2A, H2B, H3, and H4 core histones that form nucleosomes, are important components of chromatin and play crucial roles in regulating gene expression [17]. Histone post-translational modifications are essential for regulating gene expression and chromatin structure [18-19]. For example, histone acetylation and methylation modifications are often associated with gene activation or silencing [20-23]. In 2019, Professor Yingming Zhao' s team first proposed histone lactylation as a novel post-translational modification, discovering that it can promote gene transcription. Using proteomics, they identified 28 core histone lactylation modification sites in human and mouse macrophages, primarily including H2BK5, H3K18, H3K23, H4K5, H4K8, and H4K12 [10]. Recently, additional histone modification sites have been discovered, including H3K9, H3K56, H3K14, H2BK6, H4K80, and H2AK4 [24-28].

Furthermore, studies have investigated the upstream regulatory mechanisms of histone lactylation as follows: (1) Inflammation, hypoxia, and fine particulate matter in air (PM2.5) can stimulate the activation of the glycolytic pathway, promoting lactate production and leading to histone lactylation in gene promoter regions [29-31]; (2) Glycolysis-activating proteins (GBM-derived factors, NR4A3, HSPA12A, IGF2BP2, GLUT3, STAT5, etc.) can increase the glycolytic rate and accelerate lactate production, thereby increasing histone lactylation [32-37]; (3) The Dux protein can affect histone lactylation by interacting with lactylation enzymes [38]. In summary, histone lactylation modification sites are relatively abundant and can influence the transcriptional activity of target genes, participating in cellular life activities.

3.2 Non-Histone Lactylation

Lactylation modification occurs not only in histones but also in non-histone proteins. One study reported the first lactylation proteomic analysis in the fungus *Botrytis cinerea*, identifying 273 lactylation modification sites across 166 proteins, with 62% of proteins containing only one lactylation site and 38% having multiple sites. Subcellular localization analysis revealed that most lactylated proteins were distributed in the nucleus (36%), with similar proportions in mitochondria (27%) and cytoplasm (25%) [39]. Additionally, in *Trypanosoma brucei*, 257 lactylated proteins with 387 modification sites were detected, with 76% of proteins having one lactylation site, 14% having two sites, and 10% having three or more sites. Subcellular localization showed distribution in the nucleus (38%) and cytoplasm (35%), with a smaller portion in mitochondria (11%) [40]. Similar results were found in *Toxoplasma gondii* [41].

Beyond pathogenic microorganisms, non-histone lactylation has also been identified in mammalian cells. In human kidney epithelial 293T cells, 114 lactylation sites were found across 62 proteins, with 63% containing a single lactylation site and 37% having multiple sites. Subcellular localization analysis indicated that these proteins were primarily identified in the cytoplasmic fraction, with most likely having dual subcellular localization [28]. In summary, in both eukaryotic and prokaryotic organisms, most lactylated proteins possess a single lactylation site, while the subcellular distribution of modified proteins is diverse. Prokaryotic lactylated proteins are mainly distributed in the nucleus, whereas eukaryotic proteins are predominantly cytoplasmic (Table 1).

Multiple studies have demonstrated that lactylation modification participates in various cellular functions by regulating protein expression and functional activity, such as energy metabolism, gene regulation, protein biosynthesis, RNA splicing, nucleosome assembly, and DNA damage repair [28,39-42]. Additionally, research has found that lactylation can alter protein subcellular localization, causing translocation from the nucleus to the cytoplasm to exert different regulatory functions, and it exhibits competitive crosstalk with multiple post-translational modifications [43-45]. Another study showed that lactylation can enhance the activity of transcription factors in promoting embryonic stem cell self-renewal by increasing their binding to target genes [46]. In summary, the mechanisms of lactylation remain to be further validated and explored.

4 Factors Influencing Lactylation

Lactylation is regulated by multiple factors, primarily including glycolysis, acyltransferases that provide lactyl groups, and crosstalk between protein post-translational modifications.

4.1 Glycolysis

Lactate is the product of glycolysis. Studies have reported that in vitro activation and inhibition of glycolysis using oxidative phosphorylation inhibitor

rotenone and glucose analog 2-deoxy-D-glucose (2-DG) can intervene in intracellular lactate production, thereby affecting lactylation [9-10,47-48]. Lactate dehydrogenase is also a key oxidoreductase in the glycolytic pathway that catalyzes the conversion of pyruvate to lactate, mainly including LDHA and LDHB [49-50]. Inhibition of their protein expression and functional activity significantly suppresses lactate and lactylation levels [5,10,40,51]. One study reported that in human clear cell renal adenocarcinoma and human renal carcinoma cells, inhibiting LDHA and LDHB expression decreased histone lactylation levels, with LDHA inhibition showing the most significant effect [51], indicating that lactate dehydrogenase sensitivity and specificity to intracellular lactylation vary across different diseases.

Moreover, lactate not only plays a key role in the glycolytic pathway but also negatively feeds back to regulate glycolysis. In 2022, a study first reported that in neurodegenerative disease patients and animal models, activated glycolysis promoted massive lactate production [4]. Subsequently, it was discovered that lactate promoted histone H4 lactylation, which upregulated the expression of the glycolytic key enzyme pyruvate kinase isozyme type M2 (PKM2), ultimately creating a positive feedback loop that further activated glycolysis. In summary, lactate and lactylation are directly influenced by the intracellular glycolytic pathway, and targeted intervention of key glycolytic enzymes can regulate lactylation and its mechanistic control.

4.2 Lactylation Enzymes and De-modification Enzymes

As a dynamically changing post-translational modification, identifying the "writer" and "eraser" enzymes for lactylation remains a research priority. Currently, widely validated modification enzymes include histone acetyltransferases (HAT) and histone deacetylases (HDAC) [10,52]. The HAT family proteins that promote lactylation mainly include the p300/CBP family, GNAT family, and KAT family.

The p300/CREB-binding protein (p300/CBP) primarily exerts modification effects. In human colon cancer HCT116 cells and HEK293T cells, overexpression or knockout of p300 protein significantly altered intracellular histone lactylation levels [10]. Similarly, using the p300 inhibitor C646 could eliminate the upregulation of lactylation caused by p300 overexpression [43,53]. These experiments demonstrate that p300 is a "writer" protein for lactylation. However, recent research has found that the lactyl donor provided by p300 is approximately 1,000 times lower than acetyl-CoA, raising questions about whether p300 is a genuine lactyltransferase [54].

In recent years, studies have identified additional lactyltransferases. Through analysis of lactylation proteomics in *Escherichia coli*, the GNAT family member YiaC protein was found to possess lysine lactyltransferase activity [55]. Furthermore, recent studies have identified KAT family proteins HBO1 (KAT7) and MOF (KAT8) as lactyltransferases that catalyze histone lactylation. HBO1 pri-

marily catalyzes lactylation at the H3K9 site and requires auxiliary proteins including JADE1 and BRPF2 to enhance histone lactylation enzyme activity [56]. Additionally, MOF promotes intracellular protein translation rates by facilitating lactylation of translation initiation growth factor (eEF1A2), ultimately leading to tumorigenesis [57].

As an emerging research field, many unknown lactyltransferases remain to be explored. Moreover, a mitochondrial lactylation "writer" enzyme—mitochondrial alanyl-tRNA synthetase 2 (AARS2)—has been discovered. AARS2 is a protein lysine lactyltransferase whose accumulation under hypoxia induces lactylation of pyruvate dehydrogenase complex and carnitine palmitoyltransferase 2 (CPT2) at lysine sites [58]. Another study found that alanyl-tRNA synthetase 1 (AARS1), a homolog of AARS2, also possesses lactyltransferase activity. It can directly utilize lactate and ATP to catalyze lactylation of the Hippo signaling pathway key complex YAP/TEAD. As a lactate sensor and lactyltransferase, AARS1 binds to lactate and catalyzes the formation of lactate-AMP, subsequently transferring lactate to lysine receptor residues. Whether it can mediate mitochondrial protein lactylation requires further investigation [54,59].

Lactylation "eraser" proteins were first reported in 2019 by Professor Yingming Zhao' s team [60], mainly including Class I histone deacetylases (HDAC1-3) and Class III histone deacetylases (sirtuin 1-3, SIRT1-3), which are currently the most effective lactylation "eraser" proteins in vitro [60]. Recent studies have found that CobB functions as a delactylase in *E. coli* [55]. Undoubtedly, more potential lactylation enzymes remain to be discovered by researchers.

4.3 Post-Translational Modification Crosstalk

Proteins undergo various post-translational modifications, such as ubiquitination, methylation, and acetylation. These modifications influence each other, with one modification either interfering with the formation of another or functioning synergistically, a phenomenon known as post-translational modification crosstalk [61]. Current research has confirmed that histone lactylation is closely related to acetylation [10,43,62]. During periods of increased histone lactylation, histone acetylation levels decrease. The high distributional similarity between histone lactylation and acetylation suggests a potential competitive relationship [10], and they regulate the expression of specific gene sets by competing for binding to lysine residues on histone H3 [63]. Additionally, downregulation of lactylation increases protein phosphorylation in that region, leading to disease development [44]. Studies have also shown that lactylation can competitively bind with ubiquitination: lactylation of E3 ubiquitin ligase NEDD4 affects Caspase-11 ubiquitination and degradation by altering its binding affinity to substrate protein Caspase-11 [45]. Furthermore, research has reported crosstalk between histone lactylation and RNA m6A methylation in the pathogenesis of ocular melanoma [48,64]. In summary, lactylation exhibits modification crosstalk, with specific mechanisms requiring further exploration.

5.1 Lactylation and Neurodegenerative Diseases

Neurodegenerative diseases include Alzheimer' s disease (AD), Parkinson' s disease, Huntington' s disease, among others. AD is the most common age-related neurodegenerative brain disease, with amyloid-β (Aβ) plaques and tau neurofibrillary tangles being its two typical pathological features [65]. Microglia are resident immune cells in the central nervous system that provide immune protection under pathophysiological conditions. With the progression of neurodegenerative diseases, the monitoring and clearance functions of microglia gradually decline [66], though the causes of this dysfunction remain poorly understood. The inflammatory activation process of microglia may be involved [67-68].

Recent studies have found that pro-inflammatory activation of microglia is a hallmark of AD, involving a switch from OXPHOS to glycolysis [69-70]. Research has reported significantly increased levels of glycolytic metabolite lactate in the cerebrospinal fluid and hippocampus of AD mice [71]. Additionally, studies have found that with lactate accumulation, histone H4K12la modification levels significantly increase in brain tissues of AD patients and mice. Further investigation revealed that H4K12la can activate transcription of the glycolysis-related gene PKM2 in microglia, forming a glycolysis/H4K12la/PKM2/glycolysis feedback loop that exacerbates glucose metabolism disorders in AD patients and ultimately leads to microglial dysfunction. Inhibition of this loop significantly reduced Aβ accumulation and improved spatial learning and memory in AD mice [4]. Therefore, H4K12la lactylation resulting from abnormal microglial glycolysis may be a key factor causing pro-inflammatory activation and dysfunction of microglia.

Furthermore, senescent microglia also play an important role in AD pathogenesis, though the exact mechanisms remain unclear. Studies have shown that in naturally aged mice and AD mice, proteomic modification analysis detected increased histone H3K18la modification levels in microglia and hippocampal tissues. Upregulated H3K18la promoted aging and AD phenotypes by increasing binding to RelA (p65) and NF B1 promoter (p50), activating the NF B signaling pathway, and upregulating senescence-associated secretory phenotype components interleukin (IL)-6 and IL-8 [72]. In summary, histone lactylation participates in AD development by regulating gene transcriptional activity and influencing microglial functional status.

5.2 Lactylation and Cerebrovascular Diseases

Ischemic stroke (cerebral infarction, CI) is a common vascular disease caused by sudden reduction or blockage of cerebral blood flow [73]. With aging, blood vessels become increasingly fragile and susceptible to damage, significantly increasing stroke risk [74-76]. Multiple studies have shown that cerebral ischemia-reperfusion injury (CI/R) is associated with energy metabolism disorders [77-78]. Under physiological conditions, neuronal glycolysis is low, but when CI occurs,

aerobic respiration is inhibited and glycolysis increases, exacerbating disease progression [78]. Further studies have found that increased lactate from glycolysis promotes lactylation of lymphocyte cytosolic protein 1 (LCP1). LCP1 is an actin-binding protein significantly upregulated in CI/R models [79]. In both in vivo and in vitro CI models, LCP1 lactylation levels were significantly elevated, and inhibiting glycolysis could reduce LCP1 lactylation, leading to LCP1 degradation and alleviating cerebral infarction progression [80]. Additionally, research has shown that in middle cerebral artery occlusion rats and oxygen-glucose deprivation/reoxygenation-treated N2a cells, lactate modification enzyme LDHA increased H3K18la enrichment in the promoter region of HMGB1, regulating HMGB1 transcription and expression and inducing pyroptosis, leading to CI/R injury [81]. These studies reveal that lactylation may be a potential mechanism underlying CI exacerbation and warrants further investigation.

5.3 Lactylation and Cardiovascular Diseases

Myocardial infarction (MI) is a common condition caused by persistent ischemia of the heart or coronary arteries, with high mortality rates [82]. Its end-stage pathological manifestation is ventricular remodeling, with myocardial fibrosis being the core process. Myocardial fibrosis involves pathological extracellular matrix remodeling and fibroblast activation and is an important feature of cardiac aging, leading to disordered myocardial structure and cardiac dysfunction. Endothelial-to-mesenchymal transition (EndoMT) is a key mechanism driving the differentiation of vascular endothelial cells into fibroblasts.

EndoMT is a process that endothelial cells undergo, involving a series of cellular and molecular changes that lead to phenotypic transformation into mesenchymal cells (such as myofibroblasts) [83]. Cardiac hypoxia after MI promotes EndoMT, resulting in myocardial fibrosis [84]. Transforming growth factor-β (TGF-β) has been widely reported to play a critical role in EndoMT [85], with TGF-β signaling activation promoting the expression of EndoMT-related transcription factors [86]. Additionally, studies have found that high lactate levels are positively correlated with prognosis and mortality in heart disease patients [87-88]. Further research shows that in MI mouse models, lactate modification enzyme CBP/p300 binds to Snail1 and induces Snail1 lactylation through MCT-dependent signaling, mediating EndoMT after MI and exacerbating myocardial fibrosis [9].

MI also triggers a complex inflammatory cascade that is crucial for acute injury and post-infarction repair [89]. Persistent excessive inflammatory responses after MI aggravate myocardial injury and dysfunction, while monocyte-macrophages characterized by reparative genes can counteract inflammation and promote cardiac repair [90]. Studies have found that during early MI, monocytes undergo metabolic reprogramming, with glycolysis and MCT1-mediated histone H3K18la promoting transcription of repair genes (including Lrg1, Vegf-a, and IL-10) to counteract the dual anti-inflammatory and pro-angiogenic

activities of monocytes, facilitating post-MI cardiac repair [91]. Furthermore, lactate is a key energy substrate for the heart [92-93], with increasing evidence highlighting its protective role in cardiac hypertrophy, myocardial injury, and heart failure [94-98]. Recent studies found that intervening with modification enzymes p300, SIRT1, and LDHA in heart failure rat models revealed that exogenous lactate addition or inhibition of lactate efflux could increase α-MHC K1897 lactylation, regulating cardiac structure and function and significantly improving heart failure [5]. In summary, lactylation regulates cardiac function through mechanisms including EndoMT modulation, anti-inflammation, and pro-angiogenesis.

5.4 Lactylation and Osteoporosis

Osteoporosis results from the imbalance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption [99]. With aging, the differentiation capacity of bone marrow mesenchymal stem cells (BMSCs) into osteoblasts gradually declines, ultimately leading to osteoporosis [100]. The transformation between bone cells relies on the oxygen and nutrient supply from endothelial cells (ECs) [101]. Compared with other cells, ECs produce large amounts of ATP through glycolysis, with angiogenic stimuli further upregulating EC glycolysis to maintain angiogenesis [102]. Metabolomic analysis of 86 serum samples from osteoporosis and non-osteoporosis patients confirmed decreased serum lactate levels in osteoporosis patients, suggesting that lactate may be a biomarker for osteoporosis diagnosis and treatment. Further studies found that BMSCs isolated from osteoporosis patients showed reduced histone H3K18la lactylation and decreased expression of target genes collagen type I alpha 2 chain (COL1A2), cartilage oligomeric matrix protein (COMP), ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), and transcription factor 7-like 2 (TCF7L2), thereby inhibiting osteoblast differentiation. Subsequent lactate administration restored target gene expression and improved osteoporosis symptoms [7]. These results further elucidate the mechanism by which ECs mediate osteoblast differentiation through histone H3K18la lactylation, while identifying lactate as a potential biomarker for osteoporosis diagnosis and treatment. Future targeting of histone H3K18la lactylation activation may improve symptoms in osteoporosis patients.

5.5 Lactylation and Age-Related Lung Diseases

Idiopathic pulmonary fibrosis (IPF) is an age-related interstitial lung disease characterized by progressive scarring of lung tissue, reduced gas exchange, and ultimately impaired lung function [103-106]. Its pathological mechanism primarily involves fibroblast-to-myofibroblast transition (FMT) [107]. Current research indicates that metabolic reprogramming plays an important regulatory role in IPF FMT [108-109]. Studies have reported significantly elevated lactate in lung extracts from mouse and cellular IPF models. Increased lactate from glycolysis promotes H3K18 lactylation, which upregulates the expression of pul-

monary fibrosis-related genes, including ARG1, PDGFA, THBS1, and VEGFA, further exacerbating IPF [53]. Additionally, research has explored the specific mechanisms of lactylation-induced pulmonary fibrosis, finding that extracellular lactate from myofibroblasts increases overall lactylation and H3K18la levels through MCT1. Subsequent studies revealed that H3K18la promotes FMT and pulmonary fibrosis by crosstalk with RNA m6A methylation to increase TGF-$ $1 secretion levels [106]. Therefore, upregulated lactylation modification through metabolic reprogramming in pulmonary myofibroblasts is a potential pathogenic mechanism of IPF, and intervention in its occurrence and regulatory mechanisms may represent a future therapeutic target.

5.6 Lactylation and Age-Related Liver Diseases

Aging is a major risk factor for chronic liver diseases such as hepatitis, fibrosis, and cirrhosis [110]. Liver fibrosis (LF) refers to massive deposition of intrahepatic extracellular matrix (ECM) occurring in most chronic liver diseases. With aging, dysfunction of hepatic stellate cells (HSC) and macrophages is closely related to LF development [111]. Under physiological conditions, HSCs are quiescent; after pathogenic stimulation, HSCs are activated to produce large amounts of ECM, leading to LF. Therefore, inhibiting HSC activation is a feasible strategy for improving LF [112-114]. Studies have shown that aerobic glycolysis is a key feature of HSC activation, and inhibiting glycolysis can significantly suppress HSC activation in vitro [115]. Further research found that enhanced glycolysis during HSC activation increases lactate production, causing H3K18la enrichment at promoters of HSC activation-induced genes α-SMA and COL1A1, thereby controlling HSC activation and leading to LF. Moreover, adding lactylation enzyme inhibitors to reduce H3K18la levels significantly inhibited HSC activation and LF [6], suggesting that histone lactylation plays an important role in HSC activation, though the specific target genes require further investigation. Additionally, in in vivo and in vitro liver ischemia-reperfusion (LI/R) injury models, reducing protein lactylation levels of HMGB1 in hepatocytes significantly inhibited HMGB1-mediated macrophage chemotaxis and inflammatory activation, thereby attenuating LI/R injury [8]. Therefore, lactylation is closely associated with age-related liver diseases and warrants further exploration.

6 Summary and Outlook

With deepening research on lactylation, protein lactylation modification has attracted increasing attention from researchers. Lactate production and metabolic abnormalities, gene expression, and modification crosstalk influence the dynamic balance of lactylation. Lactylation not only plays important roles in normal cellular activities but also participates in regulating the pathogenesis of age-related diseases. Histone lactylation primarily affects cellular functional status by regulating related gene transcription and expression, while non-histone lactylation can lead to age-related disease occurrence and development by promoting EndoMT, activating signaling pathways, altering subcellular localization, and

crosstalk with other post-translational modifications. However, research on the regulatory mechanisms of lactylation is still in its infancy, with many unknown functions and new modification enzymes awaiting discovery. Current studies help reveal the distribution and regulatory mechanisms of lactylation and its effects in various age-related diseases. Translating these findings into clinically applicable therapeutic approaches remains an urgent challenge.

Author Contributions: MIAOMIAO Wu and PENGFEI Li conceived the research idea and proposition, retrieved literature, collected and organized data, drafted and wrote the manuscript, and prepared figures and tables. LINHUI Xu and LIHUA Kang revised the manuscript, controlled quality, and reviewed the article, taking overall responsibility. MIN Ji, HUAIJIN Guan, and YONG Wang supervised and managed the project, and finalized the manuscript.

Conflicts of Interest: None.

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Figure 1. Pattern diagram of the progress of lactylation in age-related diseases

Note: Panel a shows factors influencing lactate production, panel b shows protein lactylation and modification enzymes in different compartments, and panel c shows the mechanisms of lactylation in various age-related diseases. GLUT = glucose transporter, MCT = monocarboxylate transporter, TCA = tricarboxylic acid cycle, LA = lactic acid, SIRT1 = sirtuin 1, SIRT3 = sirtuin 3, AARS1 = alanyl-tRNA synthetase 1, AARS2 = alanyl-tRNA synthetase 2, CobB = Sir2 family deacetylase, KAT7 = lysine acetyltransferase 7, KAT8 = lysine acetyltransferase 8, YiaC = protein lysine lactyltransferase, HDAC = Class I histone deacetylase, P300 = histone acetyltransferase.

Table 1. Lactylation of proteins from different species

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