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Microglia lactylation in relation to central nervous system diseases

Hui Yang[1], Nan Mo[2], Le Tong[3], Jianhong Dong[1], Ziwei Fan[4], Mengxian Jia[4], Juanqing Yue[5,*], Ying Wang[6,*]

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From the Contents

Abstract

The development of neurodegenerative diseases is closely related to the disruption of central nervous system homeostasis. Microglia, as innate immune cells, play important roles in the maintenance of central nervous system homeostasis, injury response, and neurodegenerative diseases. Lactate has been considered a metabolic waste product, but recent studies are revealing ever more of the physiological functions of lactate. Lactylation is an important pathway in lactate function and is involved in glycolysis-related functions, macrophage polarization, neuromodulation, and angiogenesis and has also been implicated in the development of various diseases. This review provides an overview of the lactate metabolic and homeostatic regulatory processes involved in microglia lactylation, histone *versus* non-histone lactylation, and therapeutic approaches targeting lactate. Finally, we summarize the current research on microglia lactylation in central nervous system diseases. A deeper understanding of the metabolic regulatory mechanisms of microglia lactylation will provide more options for the treatment of central nervous system diseases.

Key Words: brain; central nervous system; glycolysis; immune response; inflammation; lactate metabolism; lactate; lactylation; microglia; neurodegenerative diseases

Introduction

Neuroglia are abundant in the central nervous system (CNS) and play key roles in brain development and homeostasis *in vivo* (Salter and Stevens, 2017). As innate immune cells of the CNS, microglia, similar to macrophages, are involved in inflammatory responses, homeostatic regulation, and the development of CNS diseases, and interact with other cells in the brain such as astrocytes and oligodendrocytes (Kabba et al., 2018). The immune surveillance function of microglia is gradually lost with age and the progression of CNS diseases, and damage to microglia can lead to neuroinflammation and neurodegeneration.

Lactate is a byproduct of glycolysis in normal cells when they are starved of oxygen and has long been considered simply a metabolic waste product (Zhu et al., 2023; Cai et al., 2024). However, in recent years, research has gradually revealed the biological functions of lactate. Lactate can be transported into cells to be metabolized as an energy substance (Schurr, 2006, 2008; van Hall et al., 2009; Hashimoto et al., 2018). In addition, it can mediate intracellular or intercellular signaling as a signaling molecule (Brooks, 2018) and plays a role in regulating innate immune signaling (Zhang et al., 2019b). Studies of tumors have found that lactate can promote tumor angiogenesis (Végran et al., 2011) and assist tumor immune escape (Gottfried et al., 2006; Fischer et al., 2007; Brand et al., 2016). However, the molecular mechanisms underlying these biological functions remain to be explored. Lactate, as a small molecule produced in a metabolic process, is not only a primary output of metabolism but can also be covalently modified to histone to participate in important epigenetic regulation. In 2019, it was found that lactate could be used as a substrate to covalently generate histone lysine residues in a process known as lactylation, opening a new field of the study: protein lactylation. Lactylation is an important way for lactate to perform its functions and is involved in important life activities such as glycolysis-related cell functions, macrophage polarization, neuromodulation, and angiogenesis (Cluntun et al., 2015). It also has strong links to a variety of diseases, such as tumor proliferation, anxiety and depression, hypoxic-ischemic diseases, and anaerobic exercise metabolism (Li et al., 2022b). Increased histone lactylation can also

[1]School of Pharmacy, Hangzhou Normal University, Hangzhou, Zhejiang Province, China; [2]Department of Clinical Laboratory, The Fourth Clinical Medical College of Zhejiang University of Traditional Chinese Medicine (Hangzhou First People's Hospital), Hangzhou, Zhejiang Province, China; [3]College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK; [4]Department of Orthopedics (Spine Surgery), the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang Province, China; [5]Department of Pathology, Affiliated Hangzhou First People's Hospital, Westlake University School of Medicine, Hangzhou, Zhejiang Province, China; [6]Department of Clinical Research Center, Affiliated Hangzhou First People's Hospital, Westlake University School of Medicine, Hangzhou, Zhejiang Province, China

***Correspondence to:** Ying Wang, PhD, nancywangying@163.com; Juanqing Yue, MS, lolayue@foxmail.com.
https://orcid.org/0000-0003-2121-7025 (Ying Wang)

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promote the expression of homeostatic genes involved in the damage repair process. Since the concept of lactylation was proposed in 2019, it has become a key research hot spot, with more than 100 related studies conducted. The discovery of lactylation has revealed new pathways in the post-translational modification of proteins and enriched the study of lactate's role in diseases (Pålsson-McDermott and O'Neill, 2020).

This review summarizes the concepts and mechanisms of microglia lactylation, including the lactate metabolism and homeostatic regulation involved in microglia lactylation, histone *vs*. non-histone lactylation, therapeutic approaches to targeting lactylation, and the role of lactylation in CNS diseases. A better understanding of microglia lactylation should provide ideas for the development of targeted therapies and drugs for CNS diseases, particularly with regard to neurodegenerative diseases and other neuropsychiatric diseases.

Search Strategy

The articles used in this review were retrieved by copying the search terms from Zhang et al. (2019), including lactylation, glycolysis, immune response, inflammation, lactate metabolism, lactate, and glycolysis. An electronic search of the PubMed database for science citation index (SCI) literature from 1996 to 2023 was performed using the following criteria: SCI (MeSH terms) and animal experimentation (MeSH terms), and the results were further filtered according to title and abstract.

The Role of Microglia in the Central Nervous System

Microglia are derived from red myeloid progenitor cells in the yolk sac and are the resident immune cells of the CNS, accounting for approximately 10%–15% of the total number of cells in the brain. Microglia are primarily dependent on colony-stimulating factor 1 receptor-dependent and dependent on transcription factor Spi-1 proto-oncogene (PU.1) and interferon regulatory factor 8 signaling (Gogoleva et al., 2019; Sierra et al., 2019). Microglia are involved in a range of biological processes, including neuronal synaptic pruning, injury repair, myelin formation, cellular debris, and the removal of misfolded proteins (Prinz et al., 2019; Zhou et al., 2020). Microglia sense extracellular signals, monitor the presence of substances in the CNS, and influence cell clearance, neuronal excitability, neurogenesis, and synaptic activity in the healthy brain (Mahan, 2021; Huo et al., 2024). The cells play important roles in the neurogenesis of the developing brain and in the maintenance of homeostasis *in vivo*. The neuroimmune responses driven by microglia and diseases of whole-brain metabolism are two key components of neurodegenerative diseases (Bernier et al., 2020; Yang et al., 2024). Microglia dysfunction can disrupt the CNS, leading to the development of diseases, including Alzheimer's disease (AD), Parkinson's disease, multiple sclerosis (MS), epilepsy, and stroke.

Microglia activation in the CNS is heterogeneous. Depending on their activation status, they can be divided into pro-inflammatory M1 type (classical activation) and neuroprotective M2 type (alternative activation) cells, which respond to changes in brain homeostasis through phenotypic alterations. Pro-inflammatory microglia are activated by nuclear factor kappa-B (NF-κB) and signal transducer and activator of transcription 1 (STAT1) and secrete pro-inflammatory cytokines such as interleukin (IL)-1β and IL-6. The pro-inflammatory phenotype is neurotoxic and can have pathogenic effects (Kwon and Koh, 2020). Neuroprotective microglia are involved in immunosuppression, neuroprotection, and tissue healing by activating STAT3 and STAT6; secreting anti-inflammatory factors, such as IL-4, IL-10, and IL-13; inhibiting the production of pro-inflammatory factors; and reducing nitric oxide release (Sica and Mantovani, 2012; Kwon and Koh, 2020).

Under resting conditions, microglia maintain a dynamic pro-inflammatory-anti-inflammatory balance. While under neuroinflammatory conditions, microglia undergo metabolic reprogramming, microglia homeostasis is disrupted, and the neurotoxic phenotype (M1 phenotype) predominates (Li et al., 2022a). Microglia dysfunction causes neuroinflammatory diseases, and the neuroinflammatory environment associated with the diseases can stimulate microglia Toll-like receptors through signaling by various ILs, cytokines, and chemokines, which trigger transcriptional and functional changes in the microglia (Bernier et al., 2020). In contrast, microglia of type M2, which exhibit neuroprotective properties, typically induce multiple anti-inflammatory factors and enhance the phagocytosis of cellular debris or protein aggregates to promote neuronal survival and improve memory and cognitive function. In addition, pharmacological treatment or genetic modification may polarize microglia, changing them to a pro-inflammatory to a neuroprotective phenotype and thus reducing pro-inflammation and neuronal loss (Tang and Le, 2016). Microglia are also capable of interacting with other neuronal cells. Neuroinflammatory microglia induce A1 astrocytes through the secretion of IL-1α, tumor necrosis factor, and C1q (the initiating molecule of the classical pathway), which transform into a neurotoxic phenotype, leading to neurodegenerative and neuroinflammatory diseases (Liddelow et al., 2017). Astrocytes can also activate microglia (Louveau et al., 2015) and upregulate the expression of the anti-inflammatory molecule arginase 1 and brain-derived neurotrophic factor (Li et al., 2020).

Research has found that epigenetic mechanisms are involved in the development of the CNS (Chen et al., 2016), including methylation, acetylation, phosphorylation, glycosylation, and ubiquitination. Various diseases are often associated with epigenetic modifications and the dysregulation of metabolic activity (Egger et al., 2004), and the resulting phenotypic shifts also play important roles in microglia. The metabolism of microglia adapts to changes in the brain energy balance, and metabolic reprogramming affects the pathological inflammatory responses of the brain by regulating the polarization of microglia. Under steady-state conditions, microglia largely rely on the oxidative metabolism of glucose. In the absence of glucose, other substrates, such as lactate and glutamine, can be rapidly employed to maintain adenosine triphosphate (ATP) production and homeostasis

monitoring (Masuda et al., 2020). Studies on the mechanisms of N6-methyladenosin modifications, non-coding RNAs, and histone lactylation in microglia activation suggest that targeted regulation of the microglia phenotype has the potential to mitigate the progression of neuroinflammatory and degenerative diseases (Ayata et al., 2018; Li et al., 2022a).

Lactylation

Discovery of lactylation

Normal cells metabolize glucose through glycolysis, mitochondrial oxidative phosphorylation, and the pentose phosphate pathway. Under aerobic conditions, the pyruvate produced by glycolysis produces carbon dioxide and oxygen by oxidative phosphorylation (OXPHOS). However, under hypoxia, glucose can be decomposed into two pyruvate molecules by glycolysis (**Figure 1**). They then produce two ATP and nicotinamide adenine dinucleotide molecules at the same time. In the process of glycolysis, nicotinamide adenine dinucleotide and pyruvate are reduced to lactate and then excreted. Finally, each glucose molecule produces two ATP molecules and two lactate molecules without consuming oxygen.

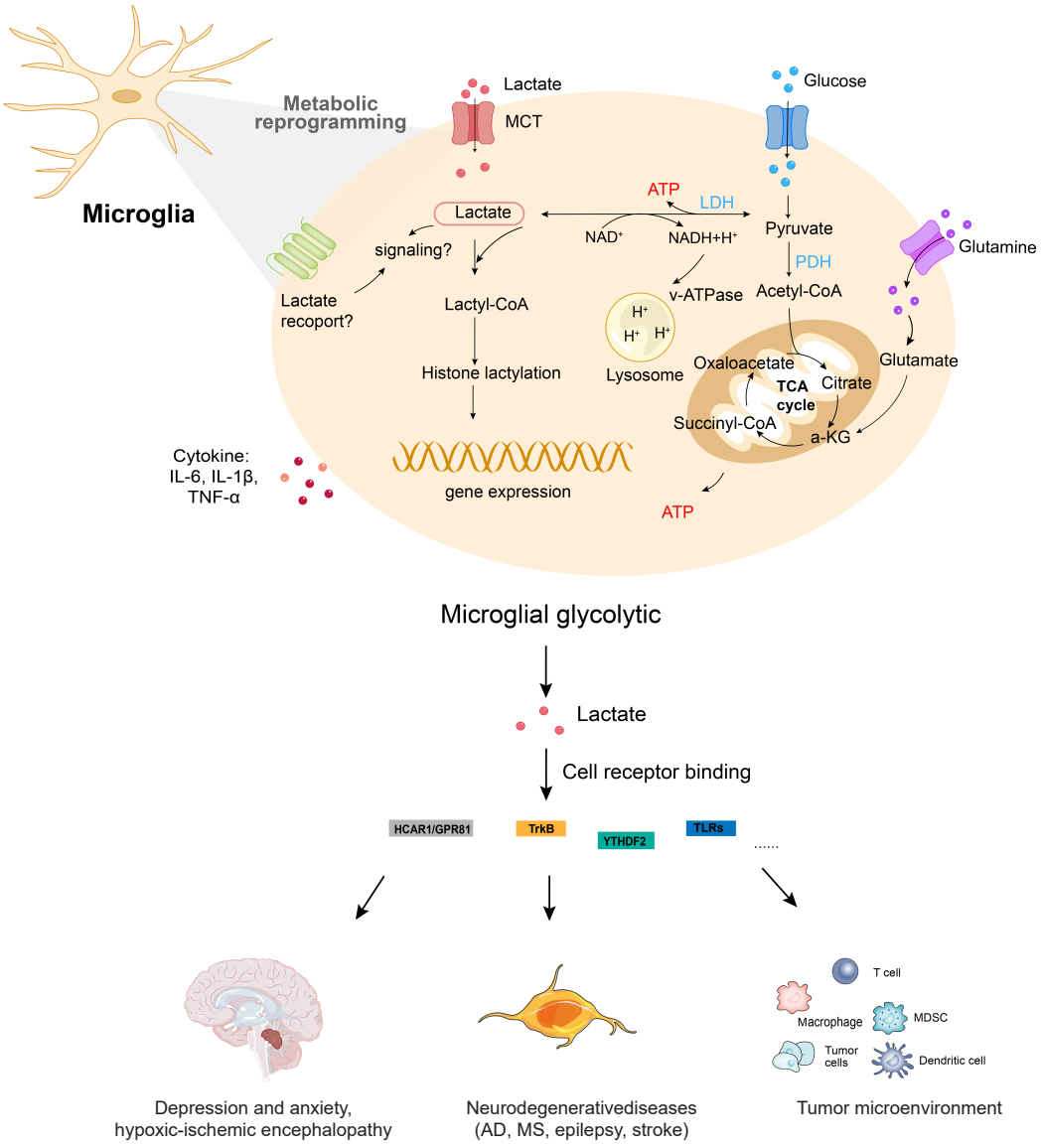

Figure 1 | **Mechanisms of microglia lactylation in relation to disease regulation.**
Lactate is transported into microglia via MCT and is metabolized by glycolysis or glutamine catabolism. Lactate acts as a signaling molecule, binding to cell surface receptors and mediating intracellular or intercellular communication. Lactate is involved in microglia metabolic reprogramming, intracellular signaling and immune functions, and phagocytosis and inhibits inflammatory responses as well as immune cell killing functions in the TME. Lactate is involved in the lactylation of both histones and non-histones. Lactylation directly promotes the expression of oncogenes and affects the function of immune cells in the TME, leading to immunosuppression and immune evasion by tumor cells. Microglia emulsification plays a crucial role in central nervous system disorders, including AD, MS, Parkinson's disease, epilepsy, stroke, depression and anxiety, and hypoxic-ischemic encephalopathy. Created with Adobe Illustrator 2022. AD: Alzheimer's disease; ATP: adenosine triphosphate; CoA: coenzyme A; GPR81: G protein-coupled receptor 81; HCAR1: hydroxycarboxylic acid receptor 1; IL: interleukin; LDH: lactate dehydrogenase; MCT: monocarboxylate transporter; MDSC: myeloid-derived suppressor cells; MS: multiple sclerosis; NAD+: nicotinamide adenine dinucleotide; NADH: reduced nicotinamide adenine dinucleotide; PDH: pyruvate dehydrogenase; TCA: tricarboxylic acid; TLR: Toll-like receptor; TME: tumor microenvironment; TNF-α: tumor necrosis factor α; TrkB: tyrosine kinase receptor B; YTHDF2: YTH N6-methyladenosine RNA binding protein 2; α-KG: α-ketoglutarate.

Lactate has long been regarded as a kind of metabolic waste, but with increasingly more in-depth research, more physiological functions of lactate have been revealed. The existing evidence shows that lactate is an indispensable substance for various physiological cell functions and plays a regulatory role in different aspects of energy metabolism and signal transduction. Lactate can provide energy as an oxidizing substrate of energy metabolism and plays an important role in aerobic energy metabolism in the brain, heart, skeletal muscle, and many other tissues and organs (Schurr, 2006). Lactate can promote angiogenesis and is actively involved in the process of wound healing by activating several molecular pathways that jointly promote angiogenesis. Lactate can stimulate endothelial cell migration and angiogenesis *in vitro*, while *in vivo* experiments have confirmed that it can recruit circulating vascular progenitor cells and promote vascular morphogenesis (Porporato et al., 2012), and similar results have been observed in tumors. Végran et al. (2011) found that lactate can enter endothelial cells through monocarboxylate transporter (MCT) 1, triggering the phosphorylation/degradation of IκBα and stimulating endothelial cells to follow the autocrine NF-κB/IL-8 pathway that drives cell migration and angiogenesis. The authors identified the lactate/NF-κB/IL-8 pathway as an important link between tumor metabolism and angiogenesis (Végran et al., 2011). In addition, lactate can regulate immune cell function and the tumor immune microenvironment, inhibiting the killing effect of immune cells in the tumor immune microenvironment and assisting tumor cell immune escape by contributing to tumor escape mechanisms (Gottfried et al., 2006; Fischer et al., 2007; Brand et al., 2016; Zhang et al., 2019b). In addition, lactate can function as a signal molecule to mediate intracellular or intercellular communication (Brooks, 2018).

In 2019, Professor Yingming Zhao's team (Zhang et al., 2019a) first discovered and proved that lactate accumulation can promote the lactylation of histone lysine residues, and this epigenetic modification can directly promote gene transcription. Zhang et al. (2019a) first showed by mass spectrometry that a mass shift of 72.021 Da occurred to a lysine residue in histone and verified the widespread occurrence of the lactylation of histone lysine residues via an isotope metabolic labeling technique and a variety of *in vitro* and *in vivo* experiments. Subsequently, Galligan's research team (Gaffney et al., 2020) also proved, using mass spectrometry, that proteins can be modified by lactate. It is worth noting that the two independent research groups have their own views on the properties of lactylation, the source of the substrate, and the modified target protein. First, Zhang et al. (2019a) believe that lactylation is an active enzymatic post-translational modification process that uses lactyl-coenzyme A as a substrate. Recently, the presence of lactyl-coenzyme A in mammalian cells and tissues has been detected by liquid chromatography-tandem mass spectrometry (Varner et al., 2020). Galligan et al. (2020), however, believe that lactylation is a passive non-enzymatic acyl transfer process based on lactyl glutathione, and glyoxalase II in cells regulates the level of lactyl-coenzyme A (lactyl glutathione). Second, Zhang et al. (2019a) have mainly focused on the lactylation of histone, and clarified that histone lactylation can be used as a new epigenetic regulator of gene transcription. Additionally, Galligan et al. (2020) found that many metabolic enzymes are also modified by lactate, and the lactylation of related enzymes could be used in negative-feedback regulation of the glycolysis pathway. Lactylation has been observed on histone and many non-histone proteins in follow-up studies. Although there are still some discrepancies, the discovery of protein lactylation has made people realize that lactate is not simply a byproduct of metabolism, and its accumulation can apparently affect functions of the body. At the same time, the new epigenetic modification of lactate has been brought into mainstream research, as it provides a link between cell metabolism and epigenetic regulation.

Writers and erasers of lactylation

The addition and removal of histone lactylation are controlled by specific enzymes or enzyme complexes called "writers" and "erasers," respectively. The modification is then read by effector proteins called "readers" to influence downstream signaling pathways and a range of biological effects. Assuming that the cell has a "lactate clock," when a certain amount of endogenous or exogenous lactate accumulates in the cell, the lactate clock is activated, initiating histone lysine lactylation (KlaThen, relevant enzymes start the process (Xie et al., 2022). The lactate clock hypothesis was established using acetylation as a model, and more tests are needed. Although the exact mechanism of histone lactylation is unknown, Zhang et al. (2019a) identified 26 and 16 histone lactylation sites in mouse bone-marrow–derived macrophages and human HeLa cells, respectively, where glucose is the major source of intracellular lactate. Both lactate production and histone lactylation levels were elevated by glucose in a dose-dependent manner, which demonstrated the presence of an endogenous lactate clock in M1 macrophages. It has been found that histone acetyltransferase and histone deacetylase (HDAC) are involved in the dynamic regulation of protein lactylation. Lactyl-coenzyme A synthase is controlled by writer, eraser, and reader enzymes and, once activated, converts lactate to lactyl-coenzyme A and further induces histone lactylation at the promoter (Irizarry-Caro et al., 2020). In another study, macrophages were found to promote high mobility group box protein 1 (HMGB1) lactylation through a histone acetyltransferase CREb-binding protein and p300 protein (CBP/p300)-dependent mechanism, and HMGB1 lactylation in macrophages was attenuated by either inhibiting endogenous lactate production or blocking extracellular lactate uptake (Yang et al., 2022b). These findings suggest that CBP/p300 acetylase is an important writer of HMGB1 lactylation in macrophages and is involved in the lactylation of proteins. In addition, class I HDAC HDAC1-3 and class III HDAC sirtuin 1–3 were found to be Kla erasure proteins, and overexpression and knockdown experiments in cervical cancer cells (HeLa cells) and in human embryonic kidney cells (HEK293T cells) have also indicated that HDAC1 and HDAC3 play roles in lactylation within cells (Moreno-Yruela et al., 2022).

Histone and non-histone lactylation and its relationship to disease and mechanisms

Histone lactylation

Studies on lactylation have focused on both histones and non-

histones. Histone lactylation is an epigenetic modification that directly stimulates gene transcription from chromatin and is also involved in regulating the M1/2 polarization of macrophages (Brooks, 2020), somatic reprogramming, and tumorigenesis (Kulkarni et al., 2019; Zhang et al., 2019a). Increased glycolysis promotes myofibroblast differentiation. It was found that, in lung fibroblasts, lipopolysaccharides may mediate their aerobic glycolytic processes by activating the phosphatidylinositol 3-kinases (PI3K)–protein kinase B (Akt)–mTOR/6-phosphofructo-2-kinase (PFKFB3) pathway (Hu et al., 2020). Lactate induces histone lactylation in the promoter of pro-fibrotic genes in macrophages and plays a key role in the pathogenesis of pulmonary fibrosis (Cui et al., 2021). Lactate activates gene expression by inducing the histone lactylation of the promoter of a pro-fibrosis mediator gene. Its regulation of cellular metabolism through histone lactylation-mediated gene expression suggests Kla has an important role in the regulation of pluripotency and tumorigenesis. B cell adapter for PI3K, which mediates the activation of the PI3K-Akt pathway following Toll-like receptor ligation, is a central regulator of macrophages and can effectively regulate their transition from an inflammatory to a reparative state by promoting lactate-induced histone lactylation (Irizarry-Caro et al., 2020). Lactate promotes HMGB1 lactylation/acetylation and release via macrophage exocytosis, and reducing lactate production *in vivo* and/or inhibiting G protein-coupled receptor 81 (GPR81 or hydroxycarboxylic acid receptor 1, HCAR1)–mediated signaling can reduce circulating exosomal HMGB1 levels and improve sepsis in a variety of microorganisms (Yang et al., 2022b). In ocular melanoma, histone lactylation promotes tumorigenesis through the expression of the N6-methyladenosine reader YTH N6-methyladenosine RNA binding protein 2, which recognizes N6-methyladenosine-modified period 1 and tumor protein p53 mRNAs and promotes their degradation, thereby accelerating the development of ocular melanoma (Yu et al., 2021). The lactic-acid–producing probiotic Saccharomyces cerevisiae significantly increased histone H3K9 acetylation and histone H3 lysine 18 lactylation (H3K18) in macrophages, inhibited macrophage scorching, regulated intestinal microbiota, and reduced DSS-induced colitis in mice (Sun et al., 2021). In addition, in non-small cell lung cancer cells, lactate attenuated glycolysis and glucose uptake, maintained mitochondrial homeostasis, down-regulated the glycolytic enzymes HK-1 and PKM, and up-regulated the mRNA levels of tricarboxylic acid cycle enzymes (SDHA, IDH3G) (Jiang et al., 2021a). Studies on histone lactylation are relatively scarce, and further research is needed to reveal how histone lactylation is written in a gene-specific manner, regulates transcriptional patterns, and precisely regulates the biochemical processing of histones (Liberti and Locasale, 2020).

Non-histone lactylation

In addition to histone lactylation, non-histone emulsification has also been conclusively found in fungal, plant, and mammalian cells. Non-histones are acidic proteins other than histones in the cell nucleus. A recent study used liquid chromatography (LC-MS/MS) to analyze the global Kla of Mycobacterium griseum (Gao et al., 2020), a destructive necrotrophic fungal pathogen with a wide multi-host distribution. Within 166 proteins, 273 Kla loci were identified, and the majority of lactylation proteins were found in the nucleus (36%), mitochondria (27%), and cytoplasm (25%), and evidence showed lactylation may influence fungal virulence by regulating protein synthesis (Gao et al., 2020). In addition, 638 Kla sites were identified in 342 proteins in rice (Meng et al., 2021), suggesting that Kla is enriched in proteins and that proteins are targeted by lactylation, with possible crosstalk with other types of acylation. In addition to fungi and plants, 2375 Kla sites were identified among 1014 lactate proteins expressed in a human gastric adenocarcinoma cell line (Yang et al., 2022a). Moreover, the content of lactylation in gastric cancer tissues is higher than that in adjacent tissues and is associated with poor prognosis, suggesting that lactylation can be used to judge the prognosis of gastric cancer. However, the modified functions of non-histone lactylation, including regulation of gene transcription, DNA damage repair, signaling, and metabolic functions, need further investigation.

Identification of protein lactylation modification sites

Lactylation modifications and regulation were also found on individual proteins. Using mass spectrometry, researchers identified for the first time in HEK293T cells two lysine residue sites of methyltransferase-like 3 (METTL3) that undergo lactylation, lysine 281 (K281) and K345, and confirmed their importance for METTL3 function (Xiong et al., 2022). In addition to histones, a variety of proteins in the nucleus, cytoplasm, mitochondria, endoplasmic reticulum, and cell membrane are lactonized, suggesting that protein lactylation may be closely related to the regulation of various life activities. The identification of Kla substrates and their precise sites is crucial for understanding the molecular mechanisms and regulation of lactylation. Fortunately, researchers have now designed a predictor called FSL-Kla (Jiang et al., 2021b), which is not only a predictive tool for Kla sites but also generates candidates for further experimental approaches, making the computational prediction of protein lactylation modification sites more convenient and efficient than traditional experimental approaches.

Lactate Homeostasis and Lactylation in the Central Nervous System under Normal Physiological Conditions

Lactate is a metabolite of systemic metabolism that is required for normal CNS function and is an effective signaling molecule and hormone in the CNS, essential for maintaining CNS excitability, plasticity, and memory (Mahan, 2021; Yang et al., 2024). Lactate can act as a signal through its specific receptor GPR81 and can also be transported to cells via MCTs (Hadzic et al., 2020) to maintain lactate homeostasis in different genes (Sun et al., 2020). Lactate in the brain is mainly produced by astrocyte glycolysis and is transported to the astrocyte-neuron cell gap via MCT1 and MCT4. Lactate enters neurons via MCT2, where it is catalyzed into pyruvate and acetyl-coenzyme A, and generates large amounts of ATP via OXPHOS to maintain synaptic transmission and neuroexcitability (Descalzi et al., 2019). This is the cell–cell lactate shuttle hypothesis proposed in neurological studies:

the astrocyte-neuron lactate shuttle hypothesis (Bittar et al., 1996). This hypothesis has been further supported by subsequent experiments (Bolaños et al., 2010; Barros and Weber, 2018). Subsequent studies have found that lactate is also present in neuronal cells, such as microglia, neurons, and oligodendrocytes, and is produced through pathways such as gluconeogenesis/glycolysis. Whether such shuttle mechanisms exist in astrocytes-microglia and microglia-neurons needs to be further investigated (Kong et al., 2019).

Lactate is shuttled between cells in a manner subject to concentration gradients, pH gradients, and redox states, and enters the plasma membrane via several MCTs, including MCT1, MCT2, and MCT4. The distribution of MCTs varies among different cells of the brain. MCT1 is expressed predominantly in endothelial cells, microglia, astrocytes, oligodendrocytes, ectodermal cells, and choroid plexus cells. MCT2 is expressed only in neurons, while MCT4 is expressed only in astrocytes. Lactate maintains metabolic co-operation and symbiosis, as well as metabolic and pro-angiogenic signaling through MCT. Widespread expression of MCT1 can further promote cancer metastasis independently of its transporter activity (Halestrap, 2012). Therefore, high expression of MCT is usually associated with poor prognosis in cancer patients. In neurons, MCT2 utilizes the lactate produced by astrocytes to promote mitochondrial respiration and is involved in memory-related metabolism (Suzuki et al., 2011). In the CNS, glycolytic astrocytes and oligodendrocytes expressing MCT1 and MCT4 supply lactate to oxidizing neurons that express MCT2. MCT1 and MCT2 promote the influx of lactate from the extracellular compartment, while MCT4 promotes the efflux of lactate from the intracellular efflux, and the lactate concentration gradient is an important factor in determining the direction of transport. However, since high-affinity transporter proteins capture low concentrations of extracellular substrates, independently of the lactate concentration, when transport is saturated, the intracellular concentration of lactate is usually higher than the extracellular one. MCT1 has moderate to high affinity for lactate, and the transporter protein MCT2 has high affinity for lactate. MCT4 has also been shown in recent studies to be a high-affinity transporter protein that promotes the flow of lactate mainly from glycolytic cells (Contreras-Baeza et al., 2019; Li et al., 2023). Lactate homeostasis has been shown to be closely linked to normal brain activity (Bergersen, 2015; Magistretti and Allaman, 2018). Brain cells respond to lactate levels by regulating lactate levels to maintain a healthy metabolic environment, directly influencing adult neural stem cells (Scandella and Knobloch, 2019). Lactate homeostasis emphasizes the importance of lactate in regulating cellular metabolism and energy balance.

Under physiological conditions, accumulated lactate can become oxidized in the brain to produce pyruvate, which enters the tricarboxylic acid cycle and is involved in inflammatory injury, immune energy metabolism, and the activation of cellular signaling pathways that regulate inflammatory progression and tumor immune tolerance (García-Cañaveras et al., 2019; Greenhalgh et al., 2020). During macrophage activation, exogenous lactate enhances Arg1 expression while promoting the expression of anti-inflammatory and pro-angiogenic genes that contribute to wound healing and repair by stimulating the release of vascular endothelial growth factor (Brooks, 2018). This was also confirmed by the increase in lactate levels in the promoter regions of genes primarily involved in biological processes. Lactate was shown to inhibit inflammatory cytokine production and mast cell degranulation through GPR81-mediated YAP inactivation, reduce nuclear NF-κB accumulation, and interrupt YAP and NF-κB interactions and nuclear translocation in macrophages (Yang et al., 2020). Furthermore, NF-κB coordinates with the nuclear factor E2-related factor (Nrf-2) pathway to regulate microglia in health and disease. Epigallocatechin gallate has protective antioxidant and anti-inflammatory effects against neuroinflammation. Studies found that epigallocatechin gallate increased Nrf-2 and heme oxygenase-1 (HO-1) levels in the presence of cobalt chloride ($CoCl_2$), attenuated the expression of hypoxia-inducible factor 1α and the production of ROS in hypoxic microglial cells, and protected microglial cells from hypoxia-induced inflammation by inhibiting the NF-κB pathway, as well as activating the Nrf-2/HO-1 pathway, in cells under hypoxia-induced inflammation and oxidative stress. This prevents hypoxia-induced encephalopathy as well as neurological damage and neuronal disease (Kim et al., 2022).

Synaptic plasticity refers to activity-dependent changes in the intensity of neuronal connections and is vital to learning and memory (Magee and Grienberger, 2020). By binding to the GPR81 receptor on the cell membrane, lactate reduces cyclic adenosine monophosphate levels, which, in turn, inhibits lipolysis and promotes the storage of high-energy metabolites (Lauritzen et al., 2014). Lactate in the physiological concentration range in the brain activates GPR81, down-regulates the brain's cyclic adenosine monophosphate levels, and participates in the regulation of a number of physiological processes in the CNS (Morland et al., 2015; Li et al., 2022b). It was found that pyruvate did not rescue the memory deficits caused by neuronal MCT2 downregulation, but learning-induced mRNA translation in excitatory and inhibitory neurons and ARC/ARG3.1 expression were positively correlated with lactate levels, suggesting a key role for lactate as fuel for the neuronal responses required for long-term memory (Descalzi et al., 2019). Reduced lactate levels normalize hippocampal neurogenesis and cognitive function in phosphatase and tensin homolog mutant mice (Wang et al., 2019), and maintaining lactate homeostasis contributes to improved hippocampal neurogenesis and cognitive function in adults (Pötzsch et al., 2021).

Role of Microglia Lactylation in the Development of Central Nervous System Disease

Microglia, as immune cells of the CNS, have similar functions to macrophages. Microglia can be used to influence the physiology and pathology of the brain by adapting and regulating lactate metabolism, phagocytosis, and inflammatory responses for therapeutic purposes. Microglia undergo energy

metabolism through glycolysis and OXPHOS. Resting microglia rely primarily on OXPHOS for ATP production, whereas activated microglia undergo a phenotypic and metabolic switch from OXPHOS to glycolysis (Zhao and Xu, 2022). This metabolic mechanism has been observed in a variety of CNS diseases (**Table 1**).

Microglia lactylation and AD

AD is one of the most common neurodegenerative diseases. The deposition of amyloid-β plaques and tau neurogenic fiber tangles are the two main pathological features of AD and are accompanied by neuronal loss and eventual cognitive decline. In AD mouse models and patients, microglia exhibited higher glucose uptake compared to astrocytes and neurons, and glucose metabolism was influenced by microglia activation. This suggests that disturbed glucose metabolism and the pro-inflammatory activation of microglia are closely related to the pathogenesis of AD (Xiang et al., 2021; Zhao and Xu, 2022).

With aging or AD progression, microglia pro-inflammatory activation and the shift from OXPHOS to oxygenated glycolysis lead to abnormally elevated lactate levels and histone lactylation. Intracellular lactate is translocated to the nucleus, leading to histone lactylation, which, in turn, promotes glycolytic activity through the transcriptional activation of glycolytic genes and exacerbates AD pathogenesis; lactate is released into the extracellular space, altering extracellular acidity and alkalinity and leading to neuronal damage (Baik et al., 2019; Pan et al., 2019). MCT transporter protein expression is reduced in AD as well as in aging (Ding et al., 2013), and several studies have reported age-related increases in CNS lactate levels (Datta and Chakrabarti, 2018).

AD has recently been shown to be associated with histone lactylation. Pan et al. (2022) detected for the first time high levels of histone lactylation in brain tissue samples from AD model mice and AD patients, and determined that the elevation of histone H4 lysine 12 lactylation (H4K12la) levels mainly occurred in microglia adjacent to amyloid β plaques. Their study demonstrated that H4K12la was enriched at the promoter of glycolysis genes, such as pyruvate kinase M2 (PKM2), in microglia and activated their transcription, thereby increasing glycolysis activity and lactate production, exacerbating microglia dysfunction in AD, and ultimately forming a regulatory positive-feedback loop of glycolysis/H4K12la/PKM2. This positive-feedback loop exacerbates the imbalance in microglia homeostasis and the occurrence of neuroinflammation, thereby promoting the development of AD. Targeted inhibition of PKM2 by small molecules such as shikonin can significantly block the positive-feedback regulatory loop, effectively reducing the number of amyloid β plaques in AD model mice and improving the learning and cognitive ability of mice. This result also suggests that inhibiting this vicious cycle may be an effective strategy to treat AD (Pan et al., 2022).

However, the main cell types involved in the disruption of lactate metabolism and the gene expression and other mechanisms involved in lactate regulation during the development of AD are not clear. Targeting the metabolic reprogramming of senescent microglia may be a new strategy for AD intervention and treatment. The links between microglia lactylation and metabolic regulation and aging need further investigation.

Microglia lactylation and depression and anxiety

Hagihara et al. (2021) found that the degree of lactylation and amount of lactate were correlated and that neuronal excitation and social defeat stress up-regulated lactate and lactylation levels in brain cells. The lactylation of 12 proteins, including histone H1, were shown to be related to social defeat stress. Up-regulated protein lactylation levels were positively correlated with the expression level of the Fos proto-oncogene (c-Fos), a marker of neuronal activity, and decreased social behavior and increased anxiety-like behavior in mice in a stress model. Their study confirmed the presence of protein lactylation in the brain and found evidence that lactate may play an important role in the regulation of neuronal activity (Hagihara et al., 2021).

Table 1 | **Relationship between lactylation modifications and CNS disease**

Disease	Study result	Reference
AD	Treats AD by inhibiting the glycolytic/H4K12la/PKM2 vicious cycle formed by disrupted microglia metabolism; sodium rutin affects microglia metabolism and function and delays the pathological state of AD. Promotes a metabolic shift from anaerobic glycolysis to mitochondrial OXPHOS; CNS lactate levels also correlate with aging.	Pan et al., 2019, 2022
Depression and anxiety	Neuronal excitation and social defeat stress upregulate lactate levels and lactylation in brain cells and are associated with anxiety and depression-like behaviors.	Hagihara et al., 2021
Multiple sclerosis	The new antidepressant (R)-ketamine significantly improved demyelination and activated microglia in the brain, affected the gut microbiota and lactate levels, improved demyelination in the mouse brain through TrkB activation, and may have a therapeutic effect by affecting gut-microbiota-microglia crosstalk.	Wentling et al., 2019; Wang et al., 2022
Hypoxic-ischemic encephalopathy	HCAR1 is a key transcriptional regulator of brain tissue response to ischemic injury. Activation of HCAR1 by elevated lactate stimulates transcriptional responses involving pathways responsible for tissue repair during and after the ischemic injury response.	Kennedy et al., 2022
Epilepsy	The absence of MCT1 and MCT2 expression in microvessels observed in epileptic patients better explains the elevated extracellular lactate concentration in brain tissue.	Li et al., 2023
Stroke	Intracerebral lactate was found in CIRI rat brain endothelial cells at lactylation sites. Higher concentrations of lactate increased the lactylated levels of H3K18la in Th17 cells and decreased the production of the pro-inflammatory cytokine IL-17A.	Dong et al., 2023; Li et al., 2023

AD: Alzheimer's disease; CIRI: cerebral ischemia/reperfusion injury; CNS: central nervous system; glycolytic/H4K12la/PKM2: glycolytic/histone H4 lysine 12 lactylation/pyruvate kinase M2; HCAR1: G protein-coupled receptor 81 (GPR81); IL-17A: interleukin-17A; MCT: monocarboxylate transporter; OXPHOS: oxidative phosphorylation; TrkB: tyrosine kinase receptor B.

Microglia lactylation and cerebrovascular disease

Lactylation also has an important role in cerebrovascular diseases. In the context of ischemia, the lactate-induced modulation of microglia clearance may accelerate cellular debris removal and promote tissue repair while attenuating the inflammatory response. Hypoxic-ischemic encephalopathy is one of the leading causes of death and disability in newborns (Tassinari and de Fraga, 2022). Histone lactylation regulates inflammation by affecting macrophage activation, and the lactate receptor HCAR1, a key transcriptional regulator promoting tissue regeneration after ischemia, contributes to brain recovery after cerebral hypoxia-ischemia in neonatal mice (Kennedy et al., 2022). Retinal microglia are associated with hypoxia-induced angiogenesis and vasculopathy, and the non-histone protein Yin Yang-1, a transcription factor, is lactylated at K183, a process that is regulated by p300 (Wang et al., 2023). Yin Yang-1 lactylation in microglia plays an important role in retinal neovascularization through the upregulation of recombinant fibroblast growth factor 2 expression. During ischemic stroke, when the brain has a reduced supply of glucose and oxygen, neuroprotection can be achieved by exogenous injections of lactate, while higher doses are toxic. Another study into lactate transport inhibitors found that the endogenous production of lactate during ischemia improved neurological outcomes (Schurr et al., 2001).

Microglia lactylation and other neurodegenerative diseases

Ceramide levels in the cerebrospinal fluid of patients with progressive MS impair mitochondrial respiration and reduce glucose bioavailability through increased glucose uptake, while exogenous supplementation with glucose or lactate can rescue the neurotoxic effects of cerebrospinal fluid treatment (Wentling et al., 2019). Ketamine, an antidepressant, has been found to significantly improve the demyelination and activation of microglia in the brain, affect gut microbiota and lactate levels, improve demyelination in the mouse brain through tyrosine kinase receptor B activation, and treat MS by affecting gut–microbiota–microglia crosstalk (Wang et al., 2022). Epilepsy is a neurological disease caused by sudden abnormal discharges of neurons in the brain and is associated with astrocyte dysfunction and diseases of glial metabolism. In the sclerotic epileptogenic hippocampus of patients with drug-refractory temporal lobe epilepsy, MCT1 expression was absent in microvessels and up-regulated in astrocytes, and MCT2 expression was absent in perivascular astrocytes. Extracellular lactate concentrations in brain tissue are elevated during epilepsy, so investigating lactate receptor signaling could provide ideas for antiepileptic drug development. Whether the increased lactylation of proteins is caused by elevated lactate levels requires further investigation (Li et al., 2023). When stroke occurs, brain tissue is in an ischemic and hypoxic state, and energy metabolism shifts from aerobic to anaerobic glycolysis, resulting in the accumulation of large amounts of lactate in the cells. Yao et al. (2023) measured the levels of protein lactylation in the endothelial cells of the brain of rats with cerebral ischemia/reperfusion injury, detecting 54 up-regulated and 54 down-regulated sites, and found that the main functions of proteins with high levels of lactylation in the brain were related to brain development, neuronal damage and regeneration, and energy transfer. In addition, damage-associated molecules released by stroke-damaged cells recognize and bind Toll-like receptors on the surface of microglia, activate immune cells (e.g., macrophages), and induce the synthesis of inflammatory cytokines. Higher concentrations of lactate increased the level of lactylation of histone H3K18 in Th17 cells and decreased the production of the pro-inflammatory cytokine IL-17A. Thus, there is a potential link between lactate-induced histone lactylation and a shift in the T cell phenotype, and further investigations of the association between lactate-histone lactylation and stroke involving the interference of the polarization of immune cells, such as macrophages, may yield interesting findings (Li et al., 2023).

Microglia lactylation and tumors

Microglia emulsification plays a crucial role in the treatment of various CNS diseases and is a promising therapeutic strategy. However, current research has focused more on the role of microglia protein lactylation in non-tumor diseases of the CNS and less on CNS tumors. Insulin-like growth-factor-binding protein 6 is involved in immune escape and inflammatory regulation during tumor development. A study found that microglia exposed to lactate or insulin-like growth-factor-binding protein 6 significantly increased the expression of MCT1 and genes involved in mitochondrial metabolism (Longhitano et al., 2023). Microglia display a pro-tumor phenotype associated with the M2-like phenotype of macrophages (Li and Graeber, 2012), demonstrating that lactate can regulate microglia polarization and reshape the tumor microenvironment in glioblastomas through insulin-like growth-factor-binding protein 6 expression (Longhitano et al., 2023), which may affect tumor progression and resistance to treatment. In the CNS, metastatic cancer cells use the activity of different non-tumor cell types in the brain microenvironment to create new ecological niches and support their proliferation and survival, and future studies based on this should lead to interesting findings. The study of the interaction between lactylation and the CNS is fascinating and crucial, yet there is a dearth of related research, with the specific mechanisms requiring further experimental validation. Moreover, while this review primarily focuses on CNS diseases, it is important to note that the peripheral nervous system and other tumor-related disorders may also be influenced by microglia lactylation, necessitating further in-depth investigations in the future.

Therapeutics Targeting Lactate

Increased glycolysis and lactate accumulation is a common feature in various types of cancer (Yang et al., 2023). Tumors mediate the regression of inflammation in the nonmalignant environment through various metabolic pathways, including lactylation (Chen et al., 2021). In tumors and inflammatory diseases, the metabolic state of the tissue microenvironment is characterized by elevated levels of lactate and other metabolic byproducts (Certo et al., 2021). However, a previous study has targeted Warburg (Ždralević et al., 2018). Lactate dehydrogenase (LDH)-A is one of the most common structures responsible for Warburg effects, but only double-knockdown of

LDH-A and LDH-B can completely block lactate secretion, and only a few have been investigated in preclinical or clinical trials. Thankfully, a number of targeted therapeutic approaches have been developed as our understanding of the role of lactate production and immunomodulation in tumors has increased. Two strategies are used to modulate the metabolic profile of tumors by regulating lactate. The first involves LDH inhibition; the nonsteroidal anti-inflammatory drug diclofenac has been shown to regulate glycolysis independently of COX inhibition and can be used to improve anti-PD-1 immunotherapy. The second is to reduce the amount of lactate within the tumor microenvironment by targeting its export via MCT, and drugs targeting MCT1 and MCT4 are currently in the preclinical study stage (Marchiq et al., 2015; Felmlee et al., 2020). For example, in a preclinical study, AstraZeneca's MCT1 inhibitor AZD3956 (NCT01791595) was shown to reduce lactate secretion into the tumor microenvironment and increase tumor immune cell infiltration by blocking MCT4 (Sasaki et al., 2016). The nonsteroidal anti-inflammatory drug diclofenac acts as an MCT4 inhibitor, reducing lactate secretion by blocking MCT4 (Sasaki et al., 2016).

Immunomodulatory drugs (IMiDs), such as thalidomide and its derivatives lenalidomide and pomalidomide, are well known for their destructive teratogenic effects. In fact, IMiDs also have a variety of antitumor effects (including antiangiogenic and anti-invasive). CD147 (a transmembrane glycoprotein) forms a complex with MCT1 that is involved in the regulation of cellular metabolism, especially glycolysis. It has been demonstrated that IMiDs (including thalidomide, lenalidomide, and pomalidomide) can compete with CD147 and MCT1 for binding to CRBN (the main target of IMiD-mediated anticancer and teratogenesis), leading to destabilization of the CD147–MCT1 complex and destabilizing CD147 and MCT1, thus exerting antitumor effects. Microenvironmental hypoxia is a major feature of myeloid malignancies, which require anaerobic glycolysis for energy production, thus lactate output is critical. Eichner et al. (2016) suggested that the IMiD-induced destabilization of CD147 and subsequent inhibition of T cell negative regulation may contribute to IMiD-induced immune cell activation.

In addition, highly glycolytic tumor metabolism has been associated with resistance to therapy in multiple myeloma and non-small cell lung cancer. Tumors in an acidic environment create a protective barrier that prevents the passage of drugs through the cell membrane (Siska et al., 2020). In hypoxia or acidosis, P-glycoprotein (P-gp) is elevated, pumping chemotherapeutic drugs out of the cell. P-gp is recognized as a selective gatekeeper of the blood–brain barrier, preventing toxins or harmful substances from entering the brain. Studies have shown that P-gp is involved in the immune-inflammatory response in CNS diseases by regulating microglia activation and mediating immune cell migration. The overexpression of active drug transporters (e.g., P-gp) in many tumors results in multiple drug-resistance phenotypes. Under hypoxia and acidosis, the activity of P-gp is increased and the P-gp-mediated efflux of cytotoxic drugs such as doxorubicin and paclitaxel is markedly increased, pumping the drugs out of cells, which explains the reduced cytotoxicity of chemotherapeutic drugs in hypoxic/acidic tumors (Lotz et al., 2007; Huang et al., 2019). Anti-glycolysis with concomitant inhibition of lactylation may enhance therapeutic outcomes, and this approach is currently being tested in clinical trials (NCT01748500, NCT01069081, and NCT01163903). Overall, targeting lactate metabolism may be a useful and promising therapeutic strategy, and research holds promise for the development of more targeted and less toxic drugs.

Clinical Significance and Future Research Directions

Microglia are important immune cells in the brain and the developing nervous system, and one of their main roles is monitoring (Zhang et al., 2014). The monitoring and clearance function of microglia decreases with age, which is related to a variety of neurodegenerative diseases, but little is known about the causes of microglial dysfunction. At present, it is believed that microglial dysfunction is related to inflammation. There is more and more evidence that lactylation is involved in the activation of inflammation, so treating lactylation in microglia appears to be a promising strategy to maintain or restore the physiological function of microglia, which may reduce neuroinflammation and slow down the progression of these neurodegenerative diseases. Targeted lactate metabolism and lactylation are emerging as effective and promising therapeutic strategies. The discovery of lactylation has brought new biological and functional considerations to the role of lactate. Therefore, the mechanism of lactylation needs further comprehensive research to identify more targets conducive to pharmaceutical research and development.

Although studies have shown that lactylation plays a role in many diseases, and in embryonic development and neuroregulation, research into the lactylation of proteins is still in the preliminary stage, and many key problems remain unsolved. First, it is still debated whether the lactylation of proteins is an inevitable result of high lactate accumulation or finely temporally and spatially controlled. Second, it is not clear whether there is a specific writer or eraser of lactylation. Third, lysine residues are currently the only known sites of lactylation, but it is unclear whether the modification occurs on amino acid residues other than lysine. Moreover, the possible competition, crosstalk, and functional interactions among diverse acylation types at the same sites also need to be further investigated.

The present review also has some limitations. Firstly, as there are fewer studies on microglia lactylation in CNS diseases, the mechanism needs to be further investigated, explored, and verified by more experiments. Moreover, the peripheral nervous system and tumor diseases may also be regulated by microglia lactylation. In conclusion, this review provides ideas for the more comprehensive study of lactylation. The study of epigenetic regulation of genes by protein lactylation is still in its infancy. In the future, more relevant and in-depth studies will lead to new perspectives on the biological and functional roles of lactate. It is likely that the development of medicines based on protein lactylation will bring hope to those suffering from a variety of diseases, including cancers.

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