

# Histone lactylation modification and its role in cerebral ischemia-reperfusion injury (Review)

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**Abstract.** Cerebral ischemia-reperfusion injury (CIRI), a major condition that poses a considerable threat to human health, has high incidence, disability and mortality rates. Mitigating brain damage during reperfusion has been the focal point of research due to the complex physiological and pathological changes that occur during this process. Histone lactylation has garnered considerable attention from researchers as a novel post-translational modification. Lactate, a metabolic byproduct, regulates gene transcription through histone lactylation, thereby linking cellular metabolism to gene expression programs and contributing to the development of diverse diseases. The present review comprehensively discusses the mechanisms underlying histone lactylation in CIRI and explores its potential clinical applications. The present review aims to offer an understanding of the role of lactylation in CIRI to facilitate the development of novel therapeutic strategies and drugs, and to offer novel insights and directions for the prevention and treatment of CIRI.

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## 1. Introduction

Ischemic stroke is a highly prevalent major health concern that considerably contributes to both mortality and disability among adults and poses substantial threats to the overall health and quality of life (1). While rapid restoration of the cerebral blood flow is paramount in saving lives and minimizing the associated complications, the process of re-establishing blood supply to the ischemic brain tissue can paradoxically exacerbate functional impairments, giving rise to cerebral ischemia-reperfusion injury (CIRI) (2-4). A relatively novel post-translational modification that is possibly mediated by lactate, histone lactylation, has emerged as a pivotal mechanism directly impacting gene transcription within the chromatin (5). Recent investigations have underscored that an elevation in the levels of histone lactylation stems from both exogenous and endogenous lactate synthesis pathways. Specifically, the inhibition of mitochondrial oxidative phosphorylation and the upregulation of glycolysis during hypoxic conditions elevate the intracellular lactate and histone lactylation levels, which in turn lead to a plethora of effects in various disorders as a result of metabolic reorganization and epigenetic modifications (6-8). Furthermore, extensive research into protein lactylation has unveiled its association with the onset and progression of numerous disorders, including tumors, inflammatory disorders, infections and cognitive impairment. Particularly, emerging evidence suggests a potential association between protein lactylation and brain function (9-12). In light of these findings, the primary aim of the present study was to elucidate the intricate relationship between lactylations and CIRI. The present review first summarizes the concept, biochemical basis and detection strategies of histone lactylation. The upstream regulation and major biological functions of histone lactylation are then discussed, followed by a focused synthesis of current evidence associating histone lactylation to key pathological processes in CIRI. Finally, the present review highlights translational perspectives and future directions.

## 2. Lactylation: Concepts, regulation and methods

*Histone lactylation: Discovery and definition.* Lactylation, which is emerging as a novel histone modification, has garnered increasing attention due to its distinct role in cellular regulation. Conventionally, the post-translational modifications of histones, such as acetylation, methylation and phosphorylation, predominantly occur at the N-terminal regions, thereby impacting the chromatin structure and regulating gene expression (13). However, lactylation represents a unique addition to this repertoire, offering new insights into the complex landscape of epigenetic modifications. Lactylation was discovered by Zhang *et al.* (14) in MCF-7 cells, which showed hypoxia-induced lactate accumulation. While this groundbreaking discovery suggested the importance of lactylation in the physiological and pathological processes of the cell, subsequent studies have further elucidated the molecular mechanisms underlying lactylation.

Lactylation involves the covalent attachment of a lactate-derived lactyl group to the lysine residues of histones (15). This process is facilitated by lactyl coenzyme A (lactyl-CoA), which is obtained from lactate via enzymatic reactions. The availability of lactate and the activity of lactate dehydrogenase (LDH), which converts pyruvate to lactate, are the key determinants of the histone lactylation levels. Moreover, lysine acetyltransferases such as p300/EP300 (KAT3B) and CREB-binding protein (CBP/CREBBP; KAT3A) have been implicated as histone lactyltransferase ('writer') enzymes that catalyze histone lactylation (for example, H3K18la) in response to increased lactate availability (16,17).

The experimental validation of histone lactylation has further confirmed its existence and functional relevance. Chromatographic analyses coupled with immunoblotting have demonstrated the presence of lactylated histones in cellular lysates, providing support for histone lactylation (18). Importantly, studies have demonstrated that exogenous lactate supplementation increases histone lactylation levels in a dose-dependent manner, highlighting the dynamic nature of this modification in response to changes in cellular metabolism (19). Moreover, isotopic labeling experiments using <sup>13</sup>C3-labeled lactate support the idea that the lactyl group in histone lysine lactylation (Kla) originates specifically from lactate metabolism (14). This mechanistic insight into histone lactylation not only broadens the understanding of epigenetic regulation but also underscores the intricate interplay between metabolic processes and chromatin structure. The elucidation of the underlying mechanisms and dynamics of histone lactylation holds notable implications in various physiological and pathological conditions, including CIRI. It offers new avenues for exploring the association between cellular metabolism and epigenetic regulation and has potential therapeutic implications in diseases characterized by dysregulated metabolism and aberrant gene expression.

*The regulation of histone lactylation.* Lactylation occurs through two distinct mechanisms: Enzymatic and non-enzymatic. Enzymatic lactylation involves key enzymes such as lysine acetyltransferases, particularly, p300 and lactyl-CoA. These enzymes catalyze the transfer of a lactyl group to the lysine residues of histones (20). Additionally, studies have

shown that lactylation can also occur non-enzymatically in an indirect manner, mediated by lactoyl glutathione, which provides a lactyl group to the lysine residues (21).

Furthermore, the strength of lactylation is primarily determined by the amount of lactate produced. Lactate levels, in turn, are regulated by cellular metabolic pathways, including glycolysis and the tricarboxylic acid cycle (TCA). Glucose serves as the main source of cellular lactate and its availability directly influences lactate levels. The regulation of lactate production occurs via the direct modulation of glucose levels or the indirect regulation of glycolysis and mitochondrial metabolism. Studies have shown that the extracellular lactate levels in rat brain tissue during resting conditions range from 0.5 to 1.0 mmol/l. However, this can increase  $\geq 2$  mmol/l upon activation and can be as high as 25 mmol/l during hypoxia (22). Previous studies have also shown that hypoxia promotes lactate production and induces histone lactylation in MCF7 cells. Furthermore, prolonged exposure to hypoxic conditions leads to an elevation in the histone lactylation levels in a time-dependent manner (14). These findings underscore hypoxia as a key factor influencing cellular lactate and histone lactylation levels.

Macrophages, which are key immune cells in the body, carry out a key role in regulating immune responses and maintaining tissue homeostasis. They exhibit remarkable plasticity and can change their phenotype in response to different environmental cues, such as inflammation, autoimmunity and cancer. Activated macrophages are polarized toward two main phenotypes: M1 and M2. M1 macrophages, with pro-inflammatory properties, undergo metabolic reprogramming leading to lactate production. By contrast, M2 macrophages enhance oxidative phosphorylation and fatty acid oxidation, thereby reducing lactate production. M1 polarization results in lactate accumulation and activation of the endogenous 'lactate clock', which induces the expression of the M2-like genes involved in inflammation resolution, thereby regulating the downstream processes of homeostatic responses (23).

*Methods for detecting histone lactylation.* Histone lactylation is commonly evaluated using site-specific antibodies in immunoblotting and immunostaining, with mass spectrometry providing confirmatory identification and mapping of lactylation sites. In studies of CIRI, these assays are most informative when applied in time-course designs and in cell-type-enriched samples (for example, myeloid/glia populations) to associate lactylation dynamics with neuroinflammatory and transcriptional changes. For mechanistic interrogation, chromatin-based approaches such as chromatin immunoprecipitation (ChIP)-quantitative PCR/ChIP-sequencing can test whether lactylation marks are enriched at promoters or enhancers of candidate genes, thereby supporting direct transcriptional regulation. Given the scope of the present review, detailed laboratory protocols are not discussed further (24-26).

*Advancements in the study of histone lactylation in diseases.* Histone lactylation has been implicated in a range of diseases and provides a general mechanistic framework that is also relevant to CIRI, because it associates lactate dynamics with transcriptional regulation in immune and vascular

compartments. Lactate can shuttle between cells and the extracellular space, and its flux is largely determined by the concentration gradients of lactate and  $H^+$ . Transmembrane transport is mainly mediated by monocarboxylate transporter (MCT) 1 (lactate import) and MCT4 (lactate export), supporting both metabolic coupling and signaling. At the chromatin level, histone lactylation connects cellular metabolism to gene expression and has been reported to participate in pathophysiological regulation in cancer, pulmonary diseases, vascular disorders and immune homeostasis.

In tumors, histone lactylation is frequently dysregulated and can promote oncogenic transcriptional programs. In pancreatic cancer, lactate drives acetyltransferase ACAT2 transcription through histone H3 lysine 18 lactylation (H3K18la), establishing a feed-forward circuit that enhances lactate production and metabolic remodeling; meanwhile, ACAT2-dependent cholesterol handling and extracellular vesicle-mediated delivery to tumor-associated macrophages favors immunosuppressive M2 polarization, contributing to poor immunotherapy responses (27). Histone lactylation has also been associated with increased YTHDF2 transcription, thereby promoting degradation of tumor-suppressor transcripts such as PER1 and TP53 and facilitating tumor progression.

Beyond cancer, lactylation-associated regulation has been described in pulmonary and vascular diseases, which is conceptually relevant to ischemia-reperfusion through shared themes of glycolytic rewiring, macrophage activation and vascular dysfunction. In pulmonary fibrosis, enhanced glycolysis in lung stromal and vascular cells is accompanied by increased macrophage histone lactylation and p300-dependent lactylation has been proposed to promote expression of fibrosis-associated genes. In vascular disease models, NR4A3-driven glycolysis elevates lactate production and increases H3K18 lactylation at target promoters, promoting vascular calcification. TRAP1-mediated aerobic glycolysis can increase lactate levels and downregulate the deacetylase HDAC3, promoting histone H4 lysine 12 lactylation (H4K12la); enrichment of H4K12la at senescence-associated secretory phenotype (SASP) gene promoters activates SASP transcription, exacerbates vascular smooth muscle cell senescence, and contributes to atherosclerosis (28,29). Metabolic imbalance resembling a Warburg-like effect has also been discussed in pulmonary arterial hypertension, suggesting that lactate-lactylation-dependent gene regulation may provide mechanistic clues for vascular remodeling.

Histone lactylation further participates in immune regulation. Lactylation-related signaling in B cell receptor-associated proteins has been associated with macrophage transitions from inflammatory to reparative states, a theme that aligns with immune reprogramming during reperfusion injury. Overall, these findings support histone lactylation as a general metabolism-to-transcription mechanism that can inform the interpretation of immune and vascular responses relevant to CIRI, which is discussed in more detail in the subsequent brain/CIRI-focused sections.

*Advancements in the study of histone lactylation in brain disorders.* The burgeoning research landscape surrounding histone lactylation in neurological disorders underscores its multifaceted roles in chronic neurodegeneration, acute

neurological insults and neurodevelopmental perturbations. In previous years, burgeoning research endeavors have illuminated the pivotal role of histone lactylation in various neurological disorders, thus presenting promising avenues for therapeutic interventions. Histone lactylation, a newly identified post-translational modification, has emerged as the fundamental regulator of gene expression within the brain, exerting profound effects on neuron function and plasticity. Mounting evidence indicates aberrant histone lactylation in the pathogenesis of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease. SIRT1 inhibits the activity of pyruvate kinase M2 through its acetylation, thereby reducing lactic acid production, improving cerebral lactate homeostasis and preventing the loss of dopaminergic neurons in the substantia nigra pars compacta, thus alleviating Parkinson's disease (30). Moreover, dysregulated histone lactylation levels have been associated with the perturbed expression profiles of genes that are important for neuronal survival, synaptic plasticity and inflammatory responses, thereby revealing their role in exacerbating disease progression. Furthermore, histone lactylation-mediated epigenetic modifications have been associated with the aggregation of misfolded proteins, oxidative stress and mitochondrial dysfunction, all of which are hallmark features of neurodegenerative disorders. In addition to playing a role in chronic neurodegeneration, histone lactylation has emerged as a key player in acute neurological insults such as ischemic stroke and traumatic brain injury. Discernible alterations in lactate metabolism and histone lactylation profile have been observed in the affected regions of the brain following such insults. These alterations are considered to modulate the expression patterns of genes pivotal for neuronal injury, inflammation and regenerative processes, ultimately shaping the outcome of neurological insult. Moreover, burgeoning evidence suggests that histone lactylation contributes to neurodevelopmental disorders such as autism spectrum disorders and intellectual disabilities. Dysregulated lactylation dynamics during the key phases of brain maturation may impede synaptic connectivity, disrupt neuronal circuitry and perturb neurotransmitter signaling cascades, thereby underpinning the emergence of cognitive and behavioral aberrations. In senescent cells and skeletal muscles of aged mice, the level of histone lactylation is significantly reduced, accompanied by a decrease in lactyl-CoA content. Activating the hypoxia-induced glycolytic pathway can restore this modification level and delay the senescent phenotype. The glycolysis-lactate metabolic axis participates in the aging process by dynamically regulating histone lactylation. From the perspective of metabolism-epigenetics crosstalk, the present review provides a theoretical basis for aging intervention strategies and also brings new insights into exploring the mechanism of histone lactylation in brain aging-related diseases (31). Further elucidation of the intricate molecular mechanisms governing histone lactylation-mediated gene regulation within the brain holds immense promise for the identification of novel therapeutic targets and interventions tailored to mitigate the burden of neurological diseases. With this framework in mind, the present review next focuses on how lactate accumulation and histone lactylation may converge to shape inflammation, cell death and repair programs during CIRI.

### 3. Histone lactylation in CIRI

*Overview of CIRI pathophysiology.* The pathophysiology of CIRI is complex, involving mechanisms such as free radical damage, calcium overload, inflammatory reactions, excitotoxicity, energy metabolism disorders and apoptosis. The repair of neural tissue following CIRI is the focal point of current research (32). However, neuroinflammatory responses can exacerbate cell damage and play a key role in CIRI. Therefore, avoiding uncontrolled neuroinflammatory responses may enable the repair of damaged neurons (33,34).

Protein lactylation carries out a key role in various diseases including CIRI (35-37). Among all the organs, the brain is the most sensitive to ischemic-hypoxic damage since it primarily relies on glucose oxidation via phosphorylation for energy supply. During cerebral tissue ischemia, reduced blood flow decreases the oxygen supply to the brain tissues and cells, leading to increased levels of intracellular reactive oxygen species, activation of RhoA and Rho kinase, and an elevation in the level of hypoxia-inducible factor 1, which upregulates glycolysis and suppresses Krebs cycle, thereby stimulating lactate accumulation. In the early stages of CIRI, the cellular oxidative phosphorylation metabolism is disrupted, leading to reliance on anaerobic glycolysis to sustain basic energy needs and accompanied by the production of a substantial amount of lactate (38,39). This accumulation of lactate results in the loss of bicarbonate ions and an increase in the level of lactate anions, thus promoting acidosis and cerebral edema. Acidosis mediates the activation of G protein-coupled receptors and downstream cAMP-dependent signal transduction, as well as the expression of the late-stage M2 class genes and CREM (a transcriptional repressor; cAMP-responsive element modulator), which further inhibit the expression of the inflammatory genes such as *TNF* and *NOS2*, thereby promoting cellular homeostasis (40,41). Yao *et al.* (42) evaluated K1a in cortical proteins of a rat model of CIRI using 4D label-free quantitative proteomics and lactylation-specific proteomics. The study identified a total of 1,003 lactylation sites on 469 proteins in the cerebral cortical tissues of CIRI rats, and found several classical pathways that may be related to CIRI, including the Ca<sup>2+</sup> signaling pathway and the cGMP-PKG signaling pathway. This provides new insights into analyzing the mechanism of CIRI from the perspective of lactylation (42). Another study reported that elevated levels of brain lactate derived from astrocytes exacerbates ischemic brain injury by promoting the formation of protein K1a. The study found that inhibiting LDHA or the glycolytic pathway to reduce lactate production can alleviate post-ischemic stroke brain injury; whereas intracerebroventricular injection of L-sodium lactate and D-lactate in mice for pretreatment, which increases brain lactate levels, will further aggravate post-ischemic stroke brain injury (43).

A wide range of signaling pathways are involved in CIRI, including the NF- $\kappa$ B, MAPK, Notch and JAK/STAT pathways (44-46). These pathways interact with each other and regulate the transcription of inflammatory genes and apoptosis. As a signaling molecule, lactate stimulates gene transcription through protein lactylation. During reperfusion, lactate migrates to the macrophages, leading to increased levels of protein lactylation in the promoter region, thereby upregulating transcription and promoting the polarization of

the M1 macrophages towards an M2 phenotype to maintain cell homeostasis (47-49). This novel finding holds immense promise for the alleviation of CIRI (Table I).

Inflammatory reactions have long been considered to play a key role in reperfusion injury, inhibiting neuronal electron transfer chains and increasing the susceptibility of the brain to hypoxic injury. Ischemia-hypoxia promotes brain cell activation and peripheral leukocyte infiltration. Microglial cells represent the primary immune cells in the brain that contribute to inflammatory responses (50,51). The initial inflammatory response caused by ischemia-hypoxia leads to neuronal damage, which persists for several days until the anti-inflammatory response reaches a relative balance. Neutrophils are the major inflammatory cells in ischemic brain tissues and their presence is positively associated with infarct size and neurological damage (52,53). In the early stages of reperfusion, the neutrophils aggregate in the perivascular marrow cells, along with the T cells and natural killer cells, while in the inflammation recovery phase, they infiltrate the site of brain injury (54-56).

Lactate is commonly regarded as a metabolic byproduct of glycolysis and is particularly evident during hypoxic conditions (Fig. 1). Under normal physiological conditions, aerobic metabolism takes place primarily in the cytosol and mitochondria. Glycolysis represents the initial step of this process, leading to the generation of pyruvate along with a limited amount of adenosine triphosphate (ATP) (57,58). Pyruvate is then transported into the mitochondrial matrix, where it is converted into acetyl coenzyme A, which subsequently enters the TCA cycle (59). The final stage of aerobic respiration involves oxidative phosphorylation, which occurs in the inner mitochondrial membrane, to generate ATP with the assistance of NADH<sup>+</sup>, H<sup>+</sup> and FADH<sub>2</sub> in the oxidized state. However, during pathological hypoxic conditions, respiration proceeds without oxygen involvement, leading to the conversion of pyruvate to lactic acid in the presence of LDH as the catalyst (60). This process results in the dissociation of lactic acid into lactate and H<sup>+</sup> ions, causing lactate accumulation in the body (61). Notably, cancer cells exhibit a unique metabolic phenomenon known as the Warburg effect, which enables them to produce ATP and lactate through glycolysis even under fully aerobic conditions. Consequently, lactic acid/lactate, a byproduct of aerobic glycolysis, has been extensively studied in cancer cells. Lactate not only serves as an end product of glycolysis but also as a key energy source (carrier) for sustaining tumor metabolism *in vivo*.

In the brain, lactate exists predominantly in the form of L-lactate, and D-lactate is scarce (62). Glycolysis of glucose in the astrocytes serves as the primary source of L-lactate in the brain (63). However, under conditions of heightened neuronal activity, L-lactate serves as an alternative energy source, supplying ATP to activated neurons while simultaneously supporting the metabolic requirements of astrocytes (64). Additionally, L-lactate also acts as a signaling molecule, supporting the astrocyte-neuron lactate shuttle hypothesis, which highlights the pivotal role of lactate in brain metabolism (65-67). Studies have shown that lactate, especially L-lactate, markedly ameliorates memory deficits, increases cerebral blood flow, enhances brain energy metabolism, attenuates neurological dysfunction and facilitates neural

Table I. Summary of cerebral ischemia-reperfusion injury.

Core dimensions	Key information
Nature of the disease	A pathological state where restoring cerebral blood flow after ischemic stroke exacerbates brain tissue dysfunction, with high disability/mortality rates
Core pathological mechanisms	Energy metabolism disorders (lactate accumulation), oxidative stress, calcium overload, neuroinflammation, apoptosis and blood-brain barrier disruption
Key regulatory molecules and modifications	Lactate (dual roles), histone lactylation, monocarboxylate transporters (lactate transporters) and GPR81 (lactate receptor)
Related signaling pathways	NF- $\kappa$ B, MAPK, PI3K/Akt and Ca <sup>2+</sup> -cGMP-PKG
Role of lactylation	Promotes macrophage M2 polarization (anti-inflammatory), regulates gene transcription, and participates in inflammation and metabolic balance
Potential therapeutic directions	Inhibit lactate dehydrogenase to reduce lactate, target histone lactylation to regulate immunity, activate GPR81 to promote repair, or inhibit neuroinflammatory pathways

GPR81, G protein-coupled receptor 81; PKG, protein kinase G.

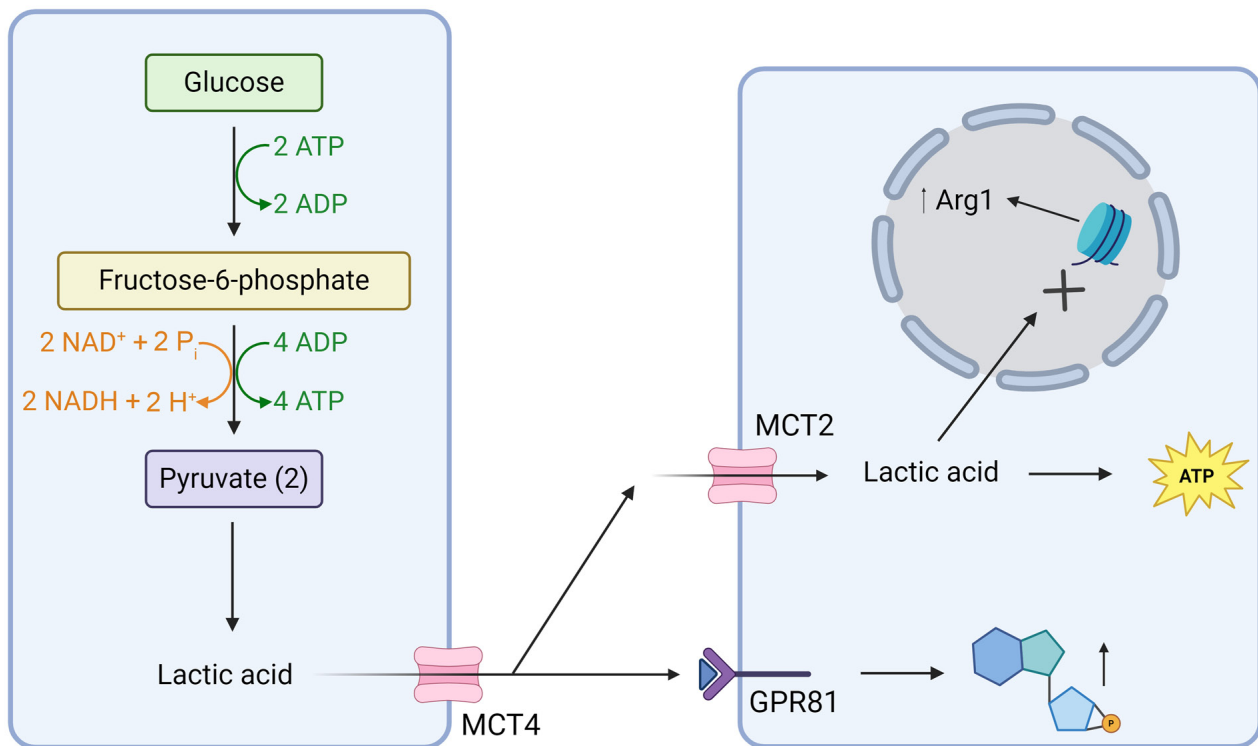


Figure 1. Schematic of lactate metabolism and signaling in brain tissue. Glucose enters glycolysis, where an initial investment of 2 ATP leads to the formation of fructose-6-phosphate. Through subsequent steps, glycolysis generates two molecules of pyruvate along with a net yield of 4 ATP and 2 NADH (plus 2 H<sup>+</sup>), using 2 NAD<sup>+</sup>, 2 Pi and 4 ADP. Pyruvate is then converted to lactate, which is exported from the cell via MCT4. Extracellular lactate can either be taken up by neighboring cells through MCT2 to support ATP production and regulate Arg1 expression, or it can bind to the receptor GPR81 to trigger signaling pathways. Together, these processes link glucose metabolism to lactylation-dependent cellular regulation. Arg1, arginase 1; GPR81, G protein-coupled receptor 81; MCT, monocarboxylate transporter; P, phosphoryl group; Pi, inorganic phosphate.

regeneration (68-73). Moreover, elevated levels of l-lactate have been observed in conditions such as diabetes and Alzheimer's disease, suggesting that lactate may play a role in cognitive impairment. Additionally, although lactate exhibits a neuro-protective effect after stroke, high concentrations of lactate may exacerbate neurological damage. Previous studies have explored the potential therapeutic effects of lactate in mitigating the progression of Alzheimer's disease and reducing

infarct volume in ischemic stroke models (74,75). While the complex mechanisms underlying the activities of lactate in the brain remain incompletely understood, its protective effects under pathological conditions, either as an energy substrate or signaling molecule, warrant further investigation (76,77).

*Lactate transporters in the brain.* The movement of lactate within and between cells for both metabolic and signaling

purposes is governed by concentration gradients, pH differences and cellular redox states. Intercellular lactate shuttling involves its transfer between white (glycolytic) and red (oxidative) muscle fibers, as well as between skeletal muscle and metabolically active organs such as the brain and heart. At the intracellular level, lactate transport mainly occurs through cytoplasmic-mitochondrial and cytoplasmic-peroxisomal shuttle systems. Moreover, lactate uptake across the plasma membrane is mediated by multiple MCTs, a process that is modulated by intracellular lactate levels and the transmembrane pH gradient (78).

According to the Human Genome Organization gene nomenclature, MCTs are classified within the solute carrier (SLC) 16 gene family, which consists of 14 members. Among them, SLC16A1, SLC16A3 and SLC16A7 encode the MCT isoforms MCT1, MCT4 and MCT2, respectively, all of which are broadly expressed in the brain. L-lactate, the predominant MCT substrate in neural tissue, is transported by MCT1, MCT4 and MCT2. Functionally, MCT4 mainly mediates lactate export from cells, whereas MCT1 and MCT2 are primarily responsible for lactate uptake, with transport direction largely determined by the prevailing lactate concentration gradient (78,79). The central involvement of MCTs in lactate trafficking, both within cells and across different cell types and organs, highlights their key role in metabolic coupling and communication in the nervous system. Notably, although MCT-dependent lactate transport is generally driven by concentration gradients, intracellular lactate levels are often higher than extracellular concentrations. This phenomenon may be explained by the ability of high-affinity transporters to efficiently capture low levels of extracellular substrates, even under near-saturating conditions, indicating that lactate transport is not exclusively governed by substrate concentration alone (79,80).

Mächler *et al.* (81) reported that circulating lactate is preferentially absorbed by astrocytes and neurons, with astrocytes exhibiting higher intracellular lactate levels. This observation supports the existence of an astrocyte-to-neuron lactate transfer mechanism mediated by MCTs. The functional significance of MCT-dependent transport in the peripheral nervous system was further demonstrated by selective deletion of MCT1 and MCT4 in Schwann cells, which led to impaired motor endplate innervation in experimental mice. Within the central nervous system (CNS), MCT4 is predominantly expressed in astrocytes, MCT1 is found in oligodendrocytes, microvascular endothelial cells, ventricular canal cells and astrocytes, while MCT2 is mainly localized to neurons (82). These neuroglial cell types are metabolically coupled to neurons across multiple CNS regions, including the spinal cord, cerebral cortex and hippocampus, supplying lactate that is efficiently taken up by neurons expressing the high-affinity transporter MCT2 (83). Supporting this concept, Suzuki *et al.* (84) demonstrated a strong association between hippocampal lactate release and memory formation in rats; suppression of astrocytic MCT1 expression disrupted long-term memory consolidation. This effect is likely attributable to reduced astrocyte-derived lactate, generated through glycolysis and delivered to neurons via MCT1 and MCT4, where it functions both as an energy source and a signaling molecule essential for memory processes. The

astrocyte-neuron metabolic coupling hypothesis therefore provides an important framework for understanding the pathogenesis of cognitive disorders characterized by memory deficits, including Alzheimer's disease (85). In line with this, another study showed that inhibition of MCT4 altered feeding behavior in rats by inducing aberrant expression of anorexigenic neuropeptides. The authors concluded that MCT4 knockdown disrupted lactate exchange between glial cells (tanycytes) and neurons (anorexigenic neurons), ultimately leading to anorexia (86). Collectively, these findings highlight the key role of MCT-mediated lactate transport in neural metabolism and signaling.

*Lactate receptor in the brain.* GPR81, also known as hydroxycarboxylic acid receptor 1 (HCAR1), has emerged as a pivotal lactate receptor, shedding light on the multifaceted roles of lactate beyond its traditional perception solely as a metabolite and energy substrate (65). Recent studies have demonstrated the role of lactate as a signaling molecule by elucidating its ability to activate GPR81 and subsequently inhibit lipolysis in adipocytes by modulating cAMP levels. Besides the adipose tissue, GPR81 is also expressed in diverse organs such as skeletal muscles, liver, kidneys and notably, the CNS, suggesting a broad spectrum of functions for GPR81-mediated lactate signaling (87-91). In the CNS, GPR81 is prominently expressed in the major neurons of the cerebral cortex and hippocampus, predominantly localized to the synaptic membrane of excitatory synapses, and enriched in the blood-brain barrier (73). This widespread distribution hints at the diverse roles of lactate-GPR81 signaling in neuronal function and metabolism. Indeed, recent investigations have unveiled connections between lactate-GPR81 signaling and various physiological and pathological processes in the CNS.

For instance, studies have demonstrated that lactate stimulation via GPR81 activation promotes cerebral angiogenesis in models of perinatal hypoxic/ischemic brain injury. This effect is attributed to the upregulation of angiogenic factors such as vascular endothelial growth factor and the concurrent downregulation of thrombospondin-1, an inhibitor of microangiogenesis. Conversely, the neuroprotective effects of lactate stimulation are notably absent in GPR81-deficient models, thereby underscoring the important role of GPR81 in mediating these beneficial effects. Furthermore, in neurological conditions such as traumatic brain injury and Alzheimer's disease, the exogenous supplementation of l-lactate has been shown to upregulate GPR81 expression, facilitating neurological recovery and ameliorating cognitive impairment (92). Additionally, emerging evidence suggests that lactate-GPR81 signaling plays a vital role in maintaining the integrity of the retinal thalamic pathway and in the development of the retinal ganglion cells, highlighting its relevance beyond the traditional boundaries of the brain (72,93).

Collectively, these findings underscore the intricate interplay between lactate and GPR81 in orchestrating various physiological processes, ranging from synaptic function and energy metabolism to cerebral angiogenesis and neuroprotection, within the CNS. Further elucidation of the molecular mechanisms underlying lactate-GPR81 signaling holds

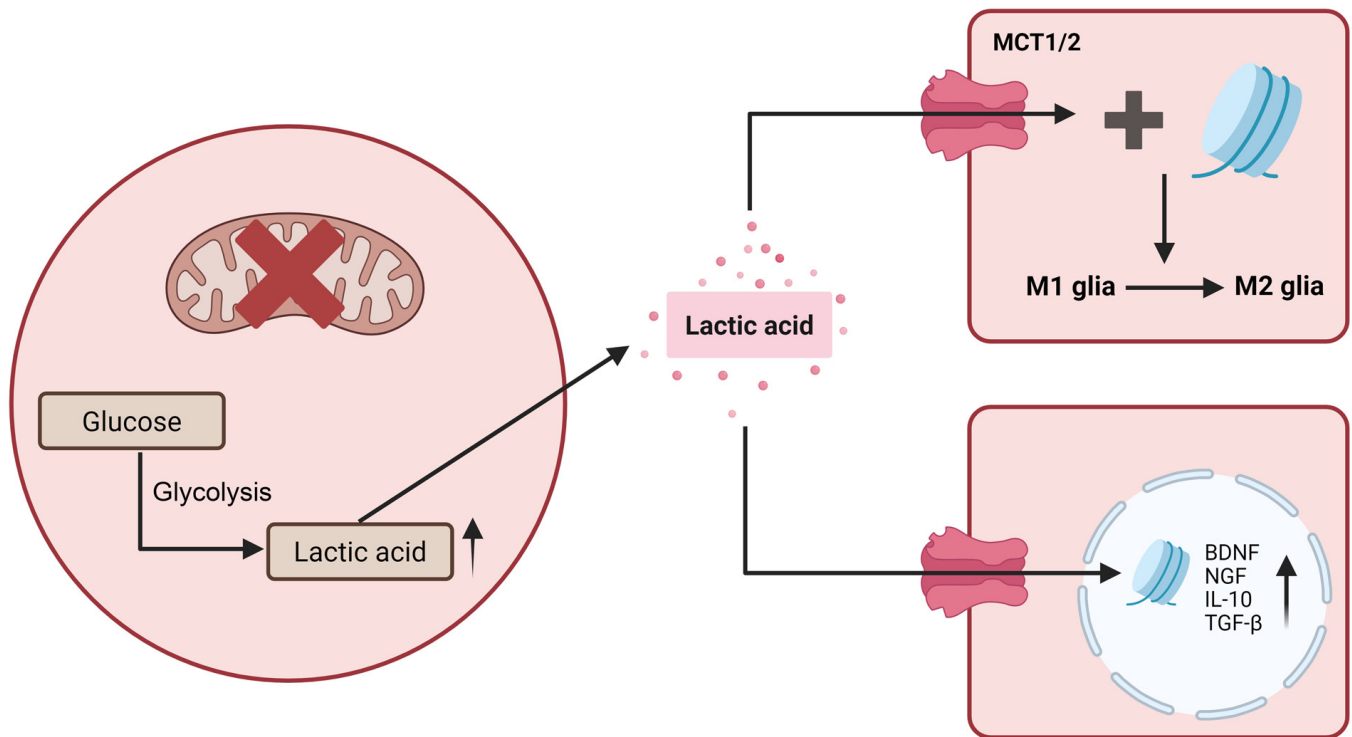


Figure 2. Mechanism of lactylation in microglial cells during cerebral ischemia-reperfusion injury. Glucose undergoes glycolysis in damaged cells, producing excess lactic acid. Lactic acid acts via two paths: Through MCT1/2, it shifts M1 glia to M2 glia; it also enters cells to upregulate neurotrophic factors (BDNF and NGF) and anti-inflammatory cytokines (IL-10 and TGF- $\beta$ ), exerting protective effects. BDNF, brain-derived neurotrophic factor; MCT, monocarboxylate transporter; NGF, nerve growth factor.

promising implications for understanding CNS pathophysiology and exploring novel therapeutic avenues for neurological disorders.

*Lactylation and neuroinflammation following CIRI.* Beyond direct effects on neuronal survival, ischemia-reperfusion injury is also driven by a robust neuroinflammatory response, making immune and glial transcriptional programs a key context in which histone lactylation may exert regulatory functions. Arg1, an enzyme involved in tissue repair and wound healing, is upregulated in response to increased lactate levels (94). This observation is mechanistically meaningful because macrophages are key initiators and regulators of post-ischemic inflammation: Upon sensing tissue damage, they activate toll-like receptors (TLRs) and drive a pro-inflammatory transcriptional program characterized by cytokines such as TNF- $\alpha$ , IL-6, IL-12 and NF- $\kappa$ B, thereby promoting a classically activated (pro-inflammatory) phenotype (14). Effective resolution of neuroinflammation after ischemia-reperfusion requires a coordinated transition toward a reparative state, and accumulating evidence suggests that lactate serves as a metabolic cue that helps shape this immune trajectory.

Importantly, histone lactylation provides direct molecular evidence associating lactate to transcriptional control of selected immune genes. Exogenous lactate can elevate intracellular lactate and lactylation levels and selectively induce Arg1 expression without markedly increasing early pro-inflammatory genes, implying a stage-dependent regulatory pattern (95). Mechanistically, this selectivity is consistent with a promoter-level epigenetic effect: p300-mediated

lactylation on histone lysine residues (classically exemplified by H3K181a in the lactylation literature) can be enriched at specific genomic loci and facilitate transcription of late-phase, homeostatic/reparative genes such as Arg1 (14). In support of this causal chain, disrupting lactate production by targeting LDHA decreases lactate availability and attenuates lactylation-associated Arg1 induction, while having limited effects on the expression of early inflammatory cytokines (14). Together, these findings strengthen a 'lactate to histone lactylation at target promoters to selective gene activation framework, providing a clearer mechanistic association between metabolism and inflammatory gene regulation that is highly relevant to the reperfusion stage. In parallel, lactate can also engage lactate-sensing GPCR pathways (for example GPR132) to influence macrophage polarization, suggesting that receptor-mediated signaling and histone lactylation may cooperate in shaping immune outcomes after ischemia-reperfusion (96).

Within the brain microenvironment, microglia are the resident immune cells that importantly influence the progression and resolution of CIRI (Fig. 2). In later phases, an M2-like microglial phenotype supports tissue remodeling and repair by producing neurotrophic factors and anti-inflammatory cytokines (such as IL-4, IL-10, IL-13 or TGF- $\beta$ ), inhibiting apoptosis and promoting neurogenesis and angiogenesis (97). In addition, K1a signals have been detected in neural cells and can be enhanced by neuronal excitation, indicating that lactylation is broadly engaged in CNS cell states under stress conditions (98). Collectively, these observations support the concept that lactylation-associated

programs may contribute to a shift from inflammation amplification toward repair-oriented gene expression in the subacute or later stages of CIRI (99).

Finally, upstream innate immune signaling can determine whether this lactate-lactylation axis is effectively engaged. The PI3K/Akt signaling pathway downstream of TLR activation can counterbalance excessive inflammation by suppressing pro-inflammatory transcriptional outputs. B-cell adaptor protein (BCAP) bridges TLR signaling to PI3K/Akt; in the absence of BCAP, PI3K/Akt activation is impaired, accompanied by reduced aerobic glycolysis, decreased lactate production and compromised histone lactylation, which in turn hinders the inflammatory-to-reparatory transition (100,101). Thus, BCAP-PI3K/Akt-glycolysis constitutes an upstream regulatory module that sustains lactate availability for histone lactylation and facilitates the activation of reparative gene programs, ultimately promoting inflammation resolution and tissue repair after CIRI.

*Clinical translation and Biomarker development and therapeutic opportunities.* Having summarized the mechanistic associations between lactate, histone lactylation and key pathological processes in CIRI, the present review next discusses how these insights may inform biomarker development and therapeutic exploration. Histone lactylation provides a mechanistically grounded bridge between lactate accumulation and gene regulation, and therefore has potential translational value in CIRI as both a biomarker axis and a therapeutic entry point (102). Because this modification is enzymatically regulated and reversible, delactylase activity of class I HDACs offers a conceptual handle for target engagement and pharmacologic modulation, while also highlighting the need to disentangle lactylation from other lysine acylations during clinical translation (103). In parallel, lactate is increasingly recognized as a signaling molecule in immune and inflammatory contexts, suggesting that lactate-linked pathways may provide clinically informative readouts when interpreted in a time-window-aware manner (104). Lactate sensing in the CNS is also supported by evidence on the lactate receptor HCAR1/GPR81 in brain, which strengthens the plausibility that lactate signals may influence post-stroke responses beyond energy metabolism (105). Additional lactate-sensing receptors such as GPR132 have been mechanistically characterized in macrophage biology, providing a framework for considering how lactate signaling could shape immune phenotypes relevant to reperfusion injury and repair (106).

From a drug-development perspective, actionable nodes exist along lactate handling and signaling. Clinical experience with lactate transport modulation is emerging; for example, the oral MCT1 inhibitor AZD3965 has been tested in a first-in-human phase I study in oncology, supporting feasibility of pharmacologic targeting of lactate transport while underscoring potential safety and tissue-specific considerations (107). For biomarker development, a practical direction is to evaluate lactylation-related signals in patient-accessible samples, and to explore non-invasive brain-periphery surrogates such as extracellular vesicles as candidate carriers of stroke-related molecular information, with careful attention to standardization and longitudinal sampling (108).

#### 4. Conclusions

In summary, the emerging concept of lactylation presents a multifaceted interplay between lactate metabolism, immune responses and tissue repair processes, holding considerable implications for CIRI and beyond. First, lactate, traditionally viewed as just a metabolic byproduct, has now been recognized as a signaling molecule capable of modulating immune responses and cellular functions. Through protein lactylation, lactate exerts regulatory effects on macrophage phenotypes, promoting their transition from a pro-inflammatory state to a reparative state. This phenomenon, observed during reperfusion following cerebral ischemia, may be a potential mechanism for mitigating inflammation and facilitating tissue repair. Furthermore, the involvement of lactylation in macrophage-mediated inflammation attenuation aligns with recent findings indicating its association with enhanced tissue repair and wound healing processes. Notably, the PI3K/Akt pathway, mediated by the BCAP, is a key regulator associating lactate metabolism to histone lactylations. This pathway not only influences macrophage polarization but also features the intricate relationship between lactate production, lactylation and immune regulation.

Despite these advancements, several key questions remain unanswered. To bridge the gap in the literature, future research endeavors should focus on elucidating the precise mechanisms by which lactylation influences the progression of CIRI. Specifically, investigations into the temporal dynamics of lactylation-mediated immune modulation, the identification of specific molecular targets and the development of targeted therapeutic interventions hold promise for furthering the understanding and management of CIRI. The evolving landscape of lactylation research offers a comprehensive framework for exploring novel therapeutic avenues for CIRI and other associated neurological disorders. By unraveling the intricate interplay between lactate metabolism, immune regulation and tissue repair mechanisms, more effective strategies can be found to mitigate the consequences of CIRI and improve patient outcomes.

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#### Authors' contributions

JT and LZ conceived and supervised the study. JT and LZ performed investigation, methodology development, formal analysis, validation and visualization, and wrote the original draft. JX contributed to investigation, software support, data curation, validation and manuscript revision. JT and LZ

administered the project and revised the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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