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REVIEW

Histone Lactylation as an Epigenetic Regulator in Alzheimer's Disease Pathophysiology: A Narrative Review

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Abstract: Alzheimer's disease (AD) represents a progressive neurodegenerative disorder clinically defined by insidious multidomain cognitive deterioration and neuropathologically characterized by extracellular amyloid-β plaques and intraneuronal neurofibrillary tangles. Its pathological core includes β-amyloid protein (Aβ) deposition, neurofibrillary tangles (NFT) and neuroinflammation, seriously threatening the health of the elderly population worldwide. With the intensification of population aging, the socio-economic burden brought by AD is increasingly heavy. However, its complex pathogenesis has not been fully clarified, and there is an urgent need to explore new molecular markers and therapeutic targets. Lactylation, a novel metabolite-derived post-translational modification (PTM) where lactate groups are covalently conjugated to lysine residues, has recently been implicated in the pathological process of AD. For example, lactylation at histone H4 lysine 12 (H4K12la) has been reported to promote neuroinflammation via a "glycolysis/H4K12la/PKM2" positive feedback loop and activate the NLRP3 inflammasome-mediated pyroptosis. Similarly, lactylation at histone H3 lysine 18 (H3K18la) may enhance microglial activation through the NF-κB pathway. However, the role of lactylation in AD appears to be complex and context-dependent, as evidenced by seemingly contradictory findings regarding its impact on Aβ pathology. Therefore, this article reviews the relevant literature on lactylation and AD, summarizes the possible mechanisms by which lactylation regulates AD, and provides theoretical basis and reference for the related research on molecular markers and therapeutic targets of AD.

Keywords: lactylation, Alzheimer's disease, post-translational modification

Introduction

Dementia, a progressive neurodegenerative disorder prevalent among older adults, most commonly manifests as Alzheimer's disease (AD). The clinical manifestations of AD are gradual decline in cognitive ability and behavioral disorders. The neuropathological hallmarks of AD encompass extracellular amyloid-β (Aβ) plaque accumulation in the parenchyma, intraneuronal formation of hyperphosphorylated tau-based neurofibrillary tangles, and progressive synaptic failure with neuronal degeneration in vulnerable brain regions.[1] AD induces progressive deterioration of memory functions and multidomain cognitive impairments. In 2018, the International Association of AD Organizations analyzed that approximately 50 million people worldwide suffer from AD, and it is projected that this number will triple by 2050, with two-thirds of them living in low - and middle-income regions.[2] The etiology of AD is very complex and is caused by multiple risk factors, including age, family history, smoking, educational level, hypertension and brain injury, etc.[3] Contemporary clinical management of AD encompasses two principal therapeutic modalities: pharmacologic interventions targeting neurochemical pathways and non-pharmacologic strategies focused on functional preservation. However,

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these drugs have certain side effects, such as increase the secretion of gastric acid and aggravate the risk of gastric ulcers, etc.[3] Current research has found that targeted therapy may be a better option. However, more experiments are still needed to prove this view.[4] Given its multifactorial pathogenesis and the absence of viable treatments, Alzheimer's disease (AD) is projected to pose a significant global public health burden.[5] The above problems pose significant challenges to the diagnosis and treatment of AD. Thus, there exists a critical and immediate requirement to delineate novel molecular markers and discover new therapeutic targets.

Histone post-translational modifications (PTMs) constitute fundamental epigenetic regulatory mechanisms that orchestrate chromatin architecture and transcriptional programs, critically underpinning diverse physiological processes —including cellular differentiation and development—while also driving pathophysiological alterations in disease states.[6–8] Comprising acetylation, succinylation, crotonylation, malonylation, 2-hydroxyisobutylation, and phosphorylation, these post-translational modifications modulate protein activity, stability, interaction networks, and subcellular localization. PTMs expand the proteoform repertoire, augmenting the structural and functional heterogeneity of the proteome.[9,10] Physiologically regulated PTMs maintain protein homeostasis, whereas dysregulated PTMs induce pathological conformational rearrangements that drive multifactorial diseases—including metabolic syndromes, oncogenesis, cardiovascular disorders, and notably neurodegenerative pathologies.[11–13] Recent research has characterized lactylation as a metabolite-mediated PTM that catalyzes the covalent attachment of lactylation moieties to lysine residues via lactate substrate utilization, consequently modulating protein architecture and biological activity.[14] Unlike classical PTMs such as acetylation or methylation, which are catalyzed by specific enzymes, lactylation is directly driven by cellular lactate levels, making it a unique metabolite-sensitive modification that dynamically reflects shifts in glycolytic flux and energy metabolism. This intrinsic link to metabolic status renders lactylation particularly significant in neurodegenerative contexts like AD, where mitochondrial dysfunction, metabolic reprogramming, and neuroinflammation converge to alter lactate homeostasis, suggesting that lactylation may serve as a critical mechanistic bridge between metabolic imbalance and transcriptional dysregulation. In 2019, Zhang's group[15] revealed lactate-derived histone lactylation (Kla) as a metabolite-sensitive epigenetic mechanism in mouse model, wherein metabolic flux-generated lactate covalently modifies histones to orchestrate transcriptional activation for physiological homeostasis. Subsequent research has shown that the histone lactylation also has unique functions in regulating brain function and brain diseases.[16–18] Furthermore, the research in APP/PS1 mice by Pan et al[19] demonstrated that the level of histone lactylation in brain tissue was positively correlated with Aβ deposition in their model system. Elevated lactylation levels, particularly at the histone H4 lysine 12 (H4K12) site, were associated with enhanced formation of Aβ and accelerated disease progression in AD mouse models.[20] These findings suggest that histone lactylation may be a contributing factor to the pathological process of AD. Furthermore, AN et al[21] demonstrated that inhibiting the non-histone lactylation can improve the cognitive function of AD. However, paradoxically, Tian et al[22] found in a lactyl-mimicking mutant that increasing the lactylation of targeted APP histones could reduce the burden of Aβ.

To sum up, some in vitro experiments have shown that the elevating lactylation at specific sites in AD can alleviate the formation of Aβ.[22] In contrast, elevated lactylation at other sites in vivo models is positively correlated with Aβ load[19–21] Part of the reason for the above contradiction may be that in vitro experiments have certain limitations and cannot completely replace in vivo experiments, in vitro studies often use simplified systems that lack the complex microenvironment of the brain (eg, intercellular crosstalk between neurons, astrocytes, and microglia), and different histones may also have certain expression differences. For example, H4K12la primarily regulates microglial inflammation via glycolytic pathways, promoting Aβ deposition,[19] while the lactylation at lysine 612 on the amyloid precursor protein (APP-K612la) enhances endosome-lysosomal degradation of APP, reducing Aβ.[22] This site-specificity highlights that lactylation's role is not universal but depends on the target protein and its cellular function. However, all the above-mentioned conjectures require further research to be confirmed. Although the specific regulatory role of lactylation in AD is controversial, lactylation plays an important role in the development of AD and may be a new molecular biomarker and therapeutic target. The ATN(I) (Amyloid-Tau-Neurodegeneration-Inflammation) framework is a cornerstone of contemporary AD research, providing a clear structure to dissect pathological domains.[23]

Therefore, this review will synthesize recent advances on lactylation in AD through the organizing lens of the ATN(I) framework and identifying the corresponding targets, such as H4K12la, K677, K331, etc. Explore how lactylation

functions as a critical metabolic-epigenetic signal within each pathological domain—Amyloidosis, Tauopathy, Neurodegeneration/Neuroinflammation—and discuss its emerging role as a central node integrating these processes into a unified pathophysiological narrative.

Overview of Lactylation

Once regarded merely as an end-product of anaerobic glycolysis, lactate is now recognized to fuel up to 10% of neuronal bioenergetics through astrocyte-neuron shuttle mechanisms.[24] Monocarboxylate transporters (MCTs) mediate lactate shuttling through the BBB, enabling its delivery to cognition-associated structures such as the hippocampal formation.[25] Emerging evidence reveals lactate functions as an endogenous signaling molecule via a novel post-translational modification mechanism—termed protein lactylation—that directly modulates protein functionality beyond its metabolic roles.[15,19,26,27] Lactylation entails the enzymatic conjugation of lactyl (La) groups to ε-amino groups of lysine residues within histone tails and non-histone proteins, with preferential enrichment at transcriptional regulatory zones such as gene promoters.[15] The incorporation of a hydroxyl moiety confers enhanced capacity for hydrogen bonding, which subsequently drives the recruitment and assembly of chromatin remodeling complexes, transcription factors, and histone-modifying enzymes, thereby orchestrating functional modulation of gene transcription.[28,29] Intracellular lactate concentration serves as the principal determinant governing the magnitude of lysine lactylation (Kla). Pharmacological inhibition of glycolytic flux attenuates lactate biosynthesis, consequently suppressing Kla modification levels. Conversely, impairment of mitochondrial function or induction of cellular hypoxia elicits lactate accumulation, which elevates Kla stoichiometry and ultimately orchestrates transcriptional reprogramming.[30] Consequently, lactylation functions as an epigenetic regulatory modality that establishes a molecular conduit between cellular metabolic flux and transcriptional output.[15] Lactylation, as a PTM, is dynamically regulated by enzymes responsible for its installation ("writers"), removal ("erasers"), and recognition ("readers").[31] The "writers" directly initiated the lactylation process by transferring the lactate group to the lysine residues of the target protein, thereby altering the structure and function of the protein. The "erasers" maintain the dynamic balance of intracellular lactylation levels by reversing lactylation, thereby preventing protein dysfunction caused by excessive or abnormal accumulation of modifications. The "reader" proteins functionally decode lactylation signatures through adduct-specific recognition, thereby transducing metabolic information into downstream effector cascades that execute discrete cellular phenotypes.[32] Consequently, lactylation constitutes a dynamically regulated epigenetic mechanism necessitating the concerted action of writers and erasers to orchestrate transcription remodeling within physiological contexts.[33] Histones are core components of chromatin and regulate processes such as gene expression, DNA replication, and repair. Previous studies have found that 28 lactylation sites have been identified on core histones. Moreover, histone lactylation exhibits a pan-cerebral distribution profile and undergoes spatiotemporally regulated reorganization across neural developmental trajectories.[15] As a metabolite-sensitive histone mark, lactylation embodies an emergent epigenetic mechanism transducing intracellular metabolic states into heritable chromatin configurations. This mechanism delineates the molecular etiology linking metabolic dysregulation to transcriptional reprogramming in pathogenic contexts.[15,34] Accumulating evidence positions histone lactylation as a pathogenic modulator critically involved in neurodegenerative pathophysiology and ischemic cerebral injury cascades.[19,35,36] In the context of AD, lactylation has been implicated in regulating key pathological processes, such as the production and clearance of amyloid-β (Aβ). Aβ is generated through the amyloidogenic processing of APP, whereby it is sequentially cleaved by β- and γ-secretases. These Aβ species progressively undergo fibrillation and cerebral deposition, priming a neuroinflammatory cascade characterized by microgliosis and astrogliosis, ultimately culminating in mature senile plaque formation that constitutes the cardinal neuropathological feature of AD. In recent years, the literature on the regulation of AD by lactylation has attracted much attention.[29,30] Studies have shown that inhibiting H4K12la can suppress NLRP3 inflammasome-mediated pyroptosis of microglia in AD model mice, thereby alleviating neuroinflammation and enhancing learning and memory abilities. Pyroptosis, a highly inflammatory form of programmed cell death, is characterized by gasdermin D (GSDMD) pore formation and the release of pro-inflammatory cytokines (eg, IL-1β, IL-18), which exacerbates neuronal damage in AD. The inhibition of H4K12la attenuates the transcriptional activation of NEK7, a critical regulator of NLRP3 inflammasome assembly, thereby disrupting this pyroptotic cascade. This mechanistic link between histone lactylation and microglial inflammatory death underscores the potential of targeting H4K12la

to modulate neuroimmune responses in AD.[37] In addition, lactylation also plays an important role in regulating neurodegeneration and cognitive impairment in AD through the IDH3β-lactate-PAx6-IDH3β positive feedback pathway. This pathway is initiated by a deficit in mitochondrial function, leading to a reduction in the activity of isocitrate dehydrogenase 3β (IDH3β), a key enzyme in the tricarboxylic acid (TCA) cycle. The consequent metabolic reprogramming towards glycolysis results in lactate accumulation. Lactate, in turn, drives the lactylation of histones (eg, at H3K18), which transcriptionally upregulates the expression of the paired-box gene 6 (PAX6). Paradoxically, increased PAX6 expression further suppresses IDH3β activity, creating a self-reinforcing positive feedback cycle that exacerbates mitochondrial dysfunction, neurodegeneration, and cognitive decline.[38] Therefore, lactylation can be used as an important molecular marker and therapeutic target in AD.

Lactylation Regulates Neuroinflammation and Apoptosis to Improve AD

As resident immunocompetent sentinels of the central nervous system (CNS), microglia critically mediate homeostatic surveillance, orchestrate neuroinflammatory responses to tissue damage, and execute frontline immunoprotective functions. During the progression of AD, they are activated in the response to β-peptides, neurotoxins and proinfammatory mediators.[39–41] Activated microglia display aberrant cytological features with hyperproliferation, releasing bioactive factors and pro-inflammatory cytokines that drive synaptic impairment and exacerbate amyloid-tau pathology progression in AD.[42] While historically described as polarizing into two distinct states—classical pro-inflammatory (M1) and alternative neuroprotective (M2) activation—this dichotomy is now recognized as an oversimplification of the continuum of microglial activation states in vivo.[43] Modern transcriptomic studies have revealed a more complex spectrum of phenotypes, including disease-associated microglia (DAM).[44–46] For the purpose of this review, we will refer to "pro-inflammatory" and "anti-inflammatory" phenotypes as functional descriptors, acknowledging that these represent ends of a spectrum rather than discrete entities. Classical activation denotes the PRR-mediated recognition of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), initiating MyD88/TRIF-dependent signaling cascades that drive pro-inflammatory responses. Myeloid differentiation primary response 88 (MyD88) is utilized by almost all TLRs (except TLR3) and initiates a signaling cascade leading to the rapid activation of nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, driving the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. Conversely, TIR-domain-containing adapter-inducing interferon-β (TRIF) is primarily engaged by TLR3 and TLR4, culminating in the activation of interferon regulatory factors and the delayed activation of NF-κB, which coordinately induce type I interferons (IFNs) and additional pro-inflammatory mediators. This ligand-receptor engagement triggers canonical signaling cascades that transcriptionally upregulate pro-inflammatory cytokine biosynthesis and stimulate mitochondrial/NOX-derived reactive oxygen species (ROS) generation. The synergistic overproduction of these ROS not only induces oxidative damage to cellular macromolecules but also functions as critical signaling molecules that amplify the NF-κB and NLRP3 inflammasome pathways, thereby establishing a self-sustaining, prototypical inflammatory microenvironment; Alternative activation refers to an activation mode that shifts from classical activation to participating in the state of cell repair and reconstruction. Within this paradigm, microglia adopt an M2-like anti-inflammatory polarization state characterized.[47] In AD pathogenesis, microglial transition toward an alternative activation state (M2-like phenotype) is pathologically suppressed.[48] Furthermore, there are still few studies on the mechanism by which lactylation regulates microglial inflammation. Pan et al[19] first discovered in the AD mouse model that the histone lactylation level of microglia was significantly increased, especially at the H4K12la site. They also found that inhibiting lactylation could effectively suppress the neuroinflammation caused by excessive activation of microglia by blocking the "glycolysis/H4K12la/PKM2 positive feedback pathway", providing early target clues for the treatment of AD. This foundational discovery was subsequently further confirmed by Wang et al.[20] This experiment found through artificially increasing the lactate level in brain tissue that the elevated lactate level in brain tissue could specifically enhance H4K12la, drive microglia to transform into A pro-inflammatory phenotype, and intensify the deposition of Aβ protein. The above results show that artificially increasing lactate levels in a dose-dependent manner led to a corresponding increase in H4K12la and exacerbated AD pathology. Meanwhile, Cheng et al[37] approached from the mechanism aspect and verified through both in vivo (APP/PS1 mice) and in vitro (Aβ treated BV-2 cells) dual models. They found that H4K12la could activate the pyroptosis pathway mediated by the NLRP3

inflammasome by up-regulating the transcriptional activity of NEK7, while inhibiting H4K12la can significantly reduce the expression of NEK7, thereby enhancing learning and memory abilities. It is worth noting that another study based on the FAD4T and APP/PS1 dual transgenic model further expanded the inflammatory regulatory mechanism of histone lactylation and found that elevated levels of H3K18la can enhance the inflammatory response of microglia through the NF—κBpathway.[35] The above research results suggest that lactylation at different histone sites may have synergistic pathogenic effects. However, the above conclusion of "lactylation promoting inflammation" forms an interesting contrast with the research of Han et al.[49] The team found that the physiological increase in lactate induced by exercise could drive microglia to transform into anti-inflammatory types by regulating epigenetic modifications, thereby alleviating neuroinflammation in the AD model. The reasons for the above different results may be that microglia are stimulated by lactate in different environments. Long-term high lactate stimulation under pathological conditions is prone to induce a pro-inflammatory phenotype, while exercise-mediated intermittent lactate fluctuations may promote an anti-inflammatory phenotype. Future research can combine single-cell sequencing and spatial metabolomics techniques to further clarify the mechanism of its transformation.

To sum up, there is a regulatory relationship between lactylation and microglial inflammation. The elevated levels of lactylation through the positive feedback pathway can promote the inflammatory response of microglia and affect the pathological manifestations of AD. However, it cannot be ignored that microglia may have an anti-inflammatory phenotype. Therefore, inhibiting the inflammatory phenotype of microglia and promoting the anti-inflammatory phenotype may be the further goals of lactylation. It is worth noting that lactylation and the progression of AD are dynamically interrelated. The early increase in H4K12la triggers the "glycolysis/H4K12la/PKM2 positive feedback pathway" in microglia, causing the cells to shift towards an inflammatory phenotype.[19] This process occurs earlier than the obvious deposition of Aβ. As AD progresses, H4K12la, through the activation of NEK7, enhances the NLRP3-mediated pyroptosis pathway, exacerbating microglial inflammation and hindering the clearance of Aβ. Overall, these findings indicate that lactylation is dynamically interwoven in the progression of AD. This dynamic interweaving highlights the necessity of conducting longitudinal studies to clarify the treatment at different stages. More studies are needed in the future to further verify the relationship between lactylation and microglial inflammation, in order to effectively promote the research on the pathological mechanism of AD.

In addition, there are also corresponding research findings on lactylation in improving neural apoptosis. Catalpol, an iridoid glycoside compound, constitutes a bioactive constituent isolated from *Rehmannia glutinosa*—a canonical herbal medicine employed extensively in traditional pharmacopeia. This molecule demonstrates pluripotent pharmacological properties relevant to therapeutic applications,[50] such as anti-inflammatory,[51] anti-tumor,[52] anti-oxidation,[49,53] anti-apoptosis,[54] and liver protection effects.[55] Furthermore, catalpol exhibits multifaceted neuroprotective efficacy, as substantiated by experimental evidence.[56] This compound attenuates amyloid-β-induced neuronal degeneration while enhancing cognitive performance in senescent rodent models.[57] Mechanistically, catalpol confers cytoprotection against oxidative insult in retinal pigment epithelium (ARPE-19) cells through potentiation of the Keap1/Nrf2/ARE signaling axis.[58] Du et al[59] study demonstrated that catalpol improved neural injury and cognitive dysfunction in N2a/APP695swe cells and APP/PS1 mice by reducing apoptosis, alleviating mitochondrial injury, relieving Aβgeneration and regulating PTMs. Meanwhile, in this study, it was also found that slight lactylation, 2-hydroxyl isobutyl and phosphorylation alterations were observed in Catalpol-treated N2a/APP695swe cells.[59] Therefore, the above experiments indicate that under catalpol treatment, slight alterations in lactylation were observed alongside inhibited apoptosis and improved cognitive function in AD models. However, given the pluripotent nature of catalpol, these changes in lactylation may be one of many contributing mechanisms rather than the sole causative factor. The specific mechanistic link between catalpol and lactylation remains to be elucidated. Nevertheless, the mechanistic basis underlying lactylation-mediated apoptotic suppression remains to be elucidated. While lactylation-driven neuroinflammation contributes significantly to neuronal damage, it does not occur in isolation. Importantly, this inflammatory milieu, fueled by glycolytic reprogramming and lactylation, can directly influence the core amyloid pathology of AD, as discussed in the next section.

Lactylation Regulates the Deposition of Aβ Protein to Improve AD

Aβ peptides are proteolytically derived from amyloid precursor protein (APP) through sequential cleavage by β-site APP-cleaving enzyme (BACE) and γ-secretase complex,[60] with subsequent clearance mediated via neuroglial phagocytic-lysosomal degradation pathways.[61] A large amount of evidence indicates that the oligomerization or fbrillization of Aβ1-42 is crucial for neurodegeneration. The pathological deposition of Aβ aggregates into senile plaques constitutes a cardinal neuropathological hallmark of AD. It may impair the potential for learning and memory and accelerate the occurrence and development of AD.[62] Accumulating preclinical and clinical evidence substantiates that therapeutic strategies targeting Aβ plaque reduction constitute a mechanistically rational and clinically viable approach for AD modification and pre-symptomatic intervention.[63] Autophagy is the basic process by which cells removing damaged in order to maintain their own stability.[64] Recent studies have shown that dysfunctional autophagy is closely related to AD.[65] EPB41L4A-AS1 represents a recently characterized long non-coding RNA (lncRNA), first identified in 2019. Since its discovery, this transcript has been functionally implicated in multiple tumorigenic pathways.[66–68] It demonstrates malignancy-specific dysregulation across diverse neoplasms: exhibiting downregulation in non-small cell lung carcinoma and bone marrow-derived mesenchymal stem cells,[69] while showing upregulated expression patterns in colorectal adenocarcinoma,[70] osteosarcoma[68] and neuroblastoma specimens.[71] Research by Wang et al[72] suggests a mechanism whereby lactylation could act as a mediator to promote Aβ clearance, possibly through regulating the transcription of autophagy-related genes via EPB41L4A-AS1. Furthermore, studies have shown that lysosomal degradation can clear Aβ deposits through autophagy.[73,74] The accumulation of Aβ in the brain of AD may be related to the dysfunction of the lysosomal pathway.[75,76] Subsequently, Tian et al[22] conducted further research on the lysosomal pathway. Through proteomic mass spectrometry analysis in this experiment, it was found that lysine 612 (APP-K612LA) is a key site for the lactylation of APP protein and affects the amyloidosis process of APP. Meanwhile, this experiment indicates that APP-K612la promotes the interaction between APP and CD2-related proteins, thereby accelerating the endosome-lysosomal degradation pathway of APP and resulting in a reduction in Aβ deposition. Secondly, this experiment constructed a lactyl-mimicking mutant (APPK612T) and a double transgenic AD mouse model of APP23/PS45. In the lactyl-mimicking mutant model, it was found that the mutant reduced Aβ protein production and slowed down cognitive deficits in vivo. Ultimately, the experiment concluded that in the double transgenic AD mouse model, App-Kla was easily regulated by L-lactate regulation, the expression of APP-Kla increased, and the production of Aβ was inhibited. Thereby reducing the pathology of Aβ and repairing the defect of spatial learning and memory. These findings suggest that lactylation of APP protein (APP-KLA) may be a new strategy for the treatment of AD.

Furthermore, studies have shown that AD is closely related to NLRP3. NLRP3 functions as a canonical pattern recognition receptor (PRR) that mediates pyroptotic cell death pathways and represents the most comprehensively characterized inflammasome complex to date.[77] The NLRP3 inflammasome constitutes a cytosolic multiprotein complex that senses pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs), initiating inflammasome oligomerization. This assembly activates caspase-1, which catalyzes proteolytic maturation and secretion of pro-inflammatory cytokines.[78] Concurrently, mTOR functions as a master regulator orchestrating cellular metabolism, growth, proliferation, survival, and autophagic pathways.[79] Accumulating evidence establishes a bidirectional regulatory axis between inflammasome complexes and autophagic machinery. Autophagy suppression potentiates NLRP3 inflammasome activation through impaired clearance of inflammasome components, whereas autophagic induction promotes lysosomal degradation of inflammasome constituents, thereby attenuating inflammatory responses.[80] Conversely, NLRP3 inflammasome activation exerts suppressive effects on autophagic flux, a regulatory mechanism pathologically substantiated in infectious pathologies, prionopathies, and ischemia-reperfusion-induced renal injury.[81,82] A study by Wang et al[20] indicated a potential pathway in which lactate-induced H4K12la drives NLRP3 inflammasome transcription, potentially resulting in autophagic dysfunction and Aβ accumulation. Subsequently, Cheng et al[37] further developed downstream molecules based on NLRP3. NEK7 functions as an essential structural component of the NLRP3 inflammasome complex, critically mediating its activation through coordination of potassium efflux-dependent oligomerization. It has been discovered by multiple research groups through various methods. This experiment established an AD model by constructing APP/PS1 double transgenic mice and Aβ-treated BV-2 cells, and detected the expression of NEK7 in vivo

and in vitro, respectively. The experimental data demonstrate that NEK7 upregulation enhances histone lactylation levels in BV-2 microglial cells, thereby promoting pyroptosis of the cells. Reducing lactylation expression can inhibit the transcriptional activity of NEK7 and thereby reduce the generation of Aβ.

In conclusion, the lysosomal pathway is the entire process by which autophagy completes degradation. Autophagy achieves substance degradation through the fusion of autophagosomes and lysosomes to form autophagolysosomes. The two jointly maintain cellular homeostasis. Dysfunction of autophagolysosomes can lead to the accumulation of abnormal substances such as Aβ, thereby exacerbating the pathological manifestations of AD. Lactylation can bidirectionally regulate the autophagy-lysosomal pathway and thereby affect the progression of AD by regulating the transcription of autophagy-related genes (such as EPB41L4A-AS1), promoting the degradation of APP lysosomes (such as APP-K612LA), and inhibiting H4K12LA-mediated autophagy disorder and inflammation. However, different lactylation sites seemed to exhibit different effects. The experimental results indicated that the expression of APP-Kla increased and the pathological manifestations of Aβ decreased. However, the elevated expression of H4K12la activated NLRP3 transcription, resulting in an increase in the pathological manifestations of Aβ as well. We believe that this contradiction might stem from the fact that lactylation is environment-specific, meaning it has a dual effect. The effect of this mechanism mainly depends on four key factors: the type of target protein (non-histone or histone), specific sites, cell type, and degree of modification. Therefore, this duality requires precise regulation. For instance, it is necessary to inhibit H4K12la and promote APPK612la. It may be a viable therapeutic strategy. Therefore, future research should focus on the role of lactylation at different sites to further verify its specific regulatory effect on AD. Beyond its intricate role in amyloid-beta pathology, lactylation's regulatory influence extends to another cornerstone of AD, tau protein. The interplay between Aβ and tau is a defining feature of AD progression, and lactylation emerges as a novel modifier of tau pathogenesis as well.

Lactylation Regulates Tau Protein to Improve AD

Tau is a protein related to microtubules and plays an important role in the structure and function of neurons. In physiological steady-state, tau protein is mainly distributed in the axons of neurons. Its main function is to bind to tubulin, increase the stability of microtubules, and ensure the normal transport of substances within neurons.[83] Pathological hyperphosphorylation of tau protein is an established molecular trigger for its conformational transition into paired helical filaments (PHFs), which serve as the structural scaffold for neurofibrillary tangle formation—a cardinal neuropathological hallmark driving neurodegeneration in tauopathies. Thereby affecting the occurrence and development of AD.[84] Many studies have shown that tau protein undergoes various PTMs, such as phosphorylation, acetylation and ubiquitination.[85,86] The latest research has found that lactylation as a new type of PTMs has been detected on the lysine residues of proteins, and it has been proved that it plays a crucial role in regulating biological functions.[87] An et al[21] found that the decreased expression of tau lactylation at the K677 site could inhibit ferritin autophagy and iron apoptosis, thereby improving the pathological progression of AD. Subsequently, gene set enrichment analysis(GSEA) revealed that lactylation of tauK677 regulates ferroptosis through the MARK pathway. In addition, an increase in lactylation was found at 34 non-histone lysine sites in this study. Further experiments indicated that replacing lysine with arginine could reduce the lactylation expression at the tauK677 site, thereby inhibiting the activation of microglia and the release of pro-inflammatory factors. Similarly, inhibiting the lactylation of tauK677 can reduce apoptosis and promote neuroprotection, and this behavior does not affect tau phosphorylation. These findings suggest that targeting tauK677 lactylation may be a new strategy for the treatment of AD. Meanwhile, Zhang et al[88] further explored the relationship between tau lactylation and tau hyperphosphorylation on the basis of previous studies. Quantitative proteomics revealed that the lysine 331 site (K331) in tau protein is a prominent site. This in vitro experiment observed that the upregulation of lactate signature genes was associated with increased tau lactylation, tau phosphorylation and lysis. Based on cell detection, it was found that the elevated lactylation of K331 exacerbated the misfolding and aggregation of tau protein, forming insoluble tau protein and further promoting the formation of NFTS in AD. Furthermore, it was found through in vitro experiments that p300 can catalyze the lactylation of tau. However, its intracellular mechanism remains incompletely understood. The above experimental results fully prove that the lactylation

of lysine in tau protein can improve the pathological manifestations of AD by regulating the excessive phosphorylation of tau protein, and the lactylation of tau can be used as a new diagnostic and therapeutic target.

To sum up, tau lysine lactylation can target and regulate the excessive phosphorylation of tau protein through the K677 and K331 sites. By inhibiting the lactylation expression of lysine, the excessive phosphorylation of tau protein can be reduced, the occurrence of NFTS can be decreased, and the effect of improving AD can be achieved. Future research can explore the physiological and pathological correlations of tau lactylation, as well as evaluate the therapeutic potential of targeting lactate metabolism or tau lactylation modification in vivo. The modifications of tau by lactylation represent a downstream consequence of a broader metabolic disturbance. To fully appreciate the origin of these epigenetic changes, it is essential to investigate the upstream metabolic alterations that drive aberrant lactylation in the first place.

Lactylation Regulates Energy Metabolism and Improves AD

The mammalian brain relies predominantly on glucose as its obligate metabolic substrate, a dependency necessitated by the exceptionally high energy demands of neuronal signaling and synaptic maintenance.[89,90] Metabolic dysregulation constitutes a cardinal pathophysiological trait in AD pathogenesis, characterized by impaired cerebral glucose utilization and mitochondrial bioenergetic failure.[91] During the onset of AD, brain glucose metabolism decreases, followed by cognitive impairment and corresponding changes related to AD.[90,92–94] The reduction of glucose metabolism leads to the decrease of ATP biosynthesis, which in turn reduces the ability of neurons to maintain the ionic gradient, and eventually results in mitochondrial dysfunction, neuronal apoptosis and AD pathology.[95–97] Pro-inflammatory polarization of microglia represents a pathognomonic feature in AD, concomitant with a metabolic reprogramming from oxidative phosphorylation to aerobic glycolysis.[19] Regarding the metabolic reprogramming of microglia, studies have shown that this transformation can enable microglia to rapidly produce ATP and promote immune function.[98,99] However, some studies have also shown that continuous glycolysis can reduce the phagocytic and migratory activities of microglia for Aβ.[100,101] Pan et al[19] found that the glycolysis/H4K12la/PKM2 positive feedback pathway promotes microglial inflammation. Meanwhile, this experiment indicates that inhibiting the expression of lactylation (H4K12la) can suppress this pathway, inhibit the pro-inflammatory expression of microglia, and improve the pathological manifestations of AD. Subsequently, Wang et al[20] found through immunoprecipitation-mass spectrometry and chromatin immunoprecipitation assay that the expression of H4K12la increased, the expression of glycolysis increased, promoting the metabolic reprogramming of microglia, triggering the transcriptional activation of NLRP3, and thereby leading to the accumulation of Aβ plaques. Furthermore, other experiments have demonstrated that microglia undergo metabolic reprogramming, with elevated glycolytic expression, which generates a large amount of lactate. This lactate promotes the release of pro-inflammatory cytokines, such as tumor necrosis TNF-α, IL-6, and IL-1β.[102,103] The above experiments indicate that lactylation can promote the metabolic reprogramming of microglia, reshape glycolytic metabolism, enhance the transcriptional activity of glycolytic genes, and thereby promote the pathological progression of AD. Another study on periodontitis shows that in macrophages, enhancing glycolytic expression, promoting histone lactylation expression, and inducing Aβ generation.[104] This indicates that lactylation can regulate glycolytic expression in multiple ways, which provides an important direction for the treatment of AD. Mitochondria serve as the central bioenergetic organelles orchestrating aerobic glucose catabolism, encompassing the tricarboxylic acid (TCA) cycle for reducing equivalent generation and the electron transport chain (ETC) for oxidative phosphorylation-driven ATP synthesis. The TCA segment mainly affects the disorder of glucose metabolism in patients with AD.[105] A recent study has discovered the relationship between mitochondrial metabolic disorders and lactylation. By knocking out IDH3β (the rate-limiting enzyme in the TCA cycle), it was found that intracellular lactate accumulation decreased, histone lactylation levels dropped, and the rate of the TCA cycle declined.[38] Meanwhile, this study found that the lactylation level of histones increased, the expression of transcription factors (such as PAX6) increased, and the expression of IDH3β was inhibited, revealing the positive feedback mechanism of IDH3β- lactate-PAx6-IDH3β behind metabolic disorders and emphasizing the regulatory potential of IDH3β as a new molecular target for the treatment of AD. The above experimental results show that lactylation can regulate mitochondrial metabolism and thereby improve AD.

To sum up, lactylation may regulate energy metabolism in different ways. In microglia, inhibiting lactylation can reduce the glycolytic expression of microglia, thereby reducing the generation of Aβ. In addition, inhibiting the

expression of lactylation can suppress the glycolytic expression of macrophages and mitochondrial metabolic disorders, thereby improving AD. This provides new molecular targets and theoretical basis for the treatment of AD.

The Multifaceted Role of Lactylation in Integrating AD Pathophysiology

Emerging evidence positions protein lactylation is a pivotal mechanistic link that interconnects the core pathological domains of AD—amyloidogenesis, tauopathy, neuroinflammation, synaptic dysfunction, and metabolic failure. The interplay between lactylation and amyloid-β pathology is bidirectional and site-specific. While H4K12la in microglia promotes a pro-inflammatory and glycolytic phenotype that impedes Aβ clearance,[19,20] lactylation of the amyloid precursor protein (APP) itself at lysine 612 (APP-K612la) enhances its endolysosomal degradation, thereby reducing amyloidogenic processing and Aβ generation.[22] Similarly, lactylation intricately modulates tau pathogenesis. Lactylation at tau K331 exacerbates its aggregation and promotes the formation of neurofibrillary tangles,[88] whereas modification at K677 facilitates ferroptosis, a novel cell death pathway linked to neurodegeneration.[21] This site-specific regulation suggests that lactylation can directly influence tau toxicity independent of its phosphorylation status, adding another layer of complexity to tau PTM cross-talk.

Critically, lactylation serves as a functional bridge between metabolic dysregulation and synaptic integrity. Sustained lactylation, driven by glycolytic reprogramming in activated glia, can disrupt neuronal mitochondrial function and redox balance, leading to oxidative stress and synaptic damage. Furthermore, lactate itself, the substrate for lactylation, can function as a gliotransmitter. Aberrant lactylation in astrocytes may impair their supportive functions, compromising synaptic plasticity and contributing to the failure of neuronal circuits that underpin cognitive decline.[106–108] The IDH3β-lactate-PAX6 feedback loop[38] exemplifies how a primary mitochondrial defect can be amplified through lactylation to create a self-reinforcing cycle of metabolic stress and neuronal dysfunction.

In conclusion, lactylation is far more than an inflammatory modifier; it is a metabolic-epigenetic bridge that weaves together the disparate pathological threads of AD. It directly influences Aβ production and clearance, modulates tau aggregation and toxicity, disrupts metabolic and synaptic homeostasis, and sustains neuroinflammation. This integrated perspective positions lactylation as a promising unifying therapeutic target whose modulation could simultaneously ameliorate multiple aspects of AD pathophysiology.

Conclusions and Perspectives

This review has synthesized the emerging role of histone and non-histone lactylation across various pathological hallmarks of AD, as conceptualized within the ATN(I) framework (Figure 1). Accumulating evidence suggests a compelling correlation between specific lactylation sites (eg, H4K12la, H3K18la, APP-K612, Tau-K677) and key disease processes, including neuroinflammation, Aβ metabolism, tauopathy, and metabolic dysfunction (Table 1). The prevailing hypothesis, derived from both in vitro and in vivo models, is that lactylation may act as a metabolic sensor that amplifies or ameliorates disease pathways in a context-dependent manner. H4K12la hinders the clearance of Aβ and promotes apoptosis by inhibiting autophagy and activating NEK7 (Figure 2). Similarly, lactylation also shows corresponding functions in regulating tau protein and energy metabolism. For example, the decreased lactylation level at the K677 site of Tau protein can inhibit ferritin autophagy and iron apoptosis, and improve cognitive function. Inhibiting lactylation can reduce the glycolytic expression of microglia, thereby reducing Aβ production. As summarized in Table 1, lactylation target a diverse array of proteins across different neural cells, orchestrating a wide spectrum of functional outcomes. In microglia, histone lactylation (eg, H4K12la, H3K18la) predominately drives pro-inflammatory responses and metabolic reprogramming via pathways such as NF-κB and NLRP3. In contrast, in neurons, non-histone lactylation of pathological proteins like APP K612, Tau K331and Tau K677 directly modulates core disease processes, including Aβ generation, tau aggregation, and ferroptosis. This cell-type-specific patterning suggests that lactylation acts as a versatile metabolic sensor, translating shifts in glycolytic flux into tailored transcriptional and functional responses. It is crucial to note that while these associations are robust, the necessity of lactylation in driving AD pathology is not yet fully established. The field would greatly benefit from more genetic loss-of-function studies (eg, conditional knockout of lactyltransferases in specific brain cells) to move beyond correlation and definitively prove causation. Notwithstanding this limitation, the modulation of lactylation presents a promising therapeutic avenue. Future research must prioritize elucidating the precise

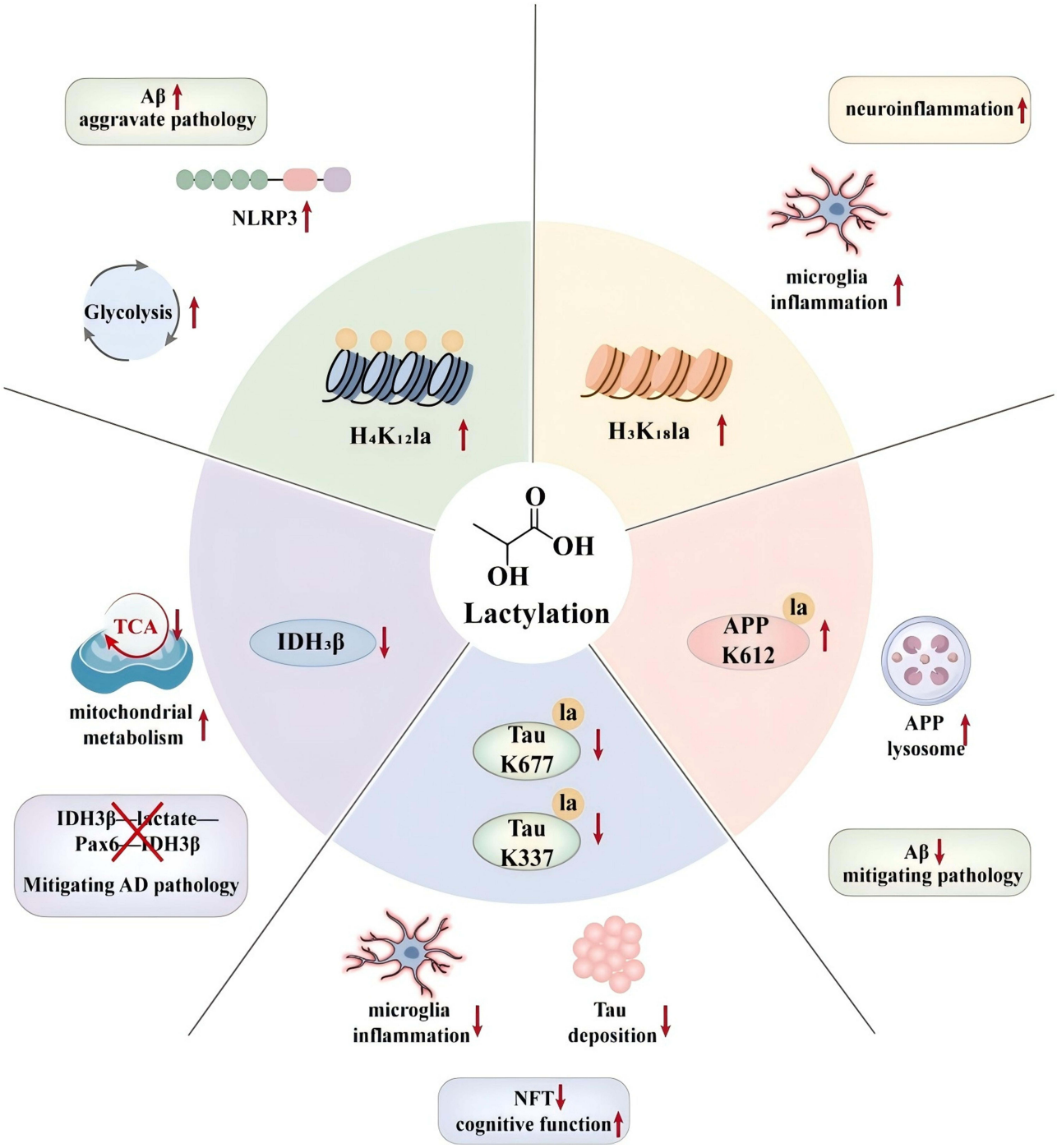

Figure 1 The schematic diagram of lactylation regulating AD.(upward arrows: expression of elevation; downward arrows: expression of reduction; false symbol: block the passage).

mechanisms, using more complex humanized models of sporadic AD, and exploring the crosstalk between lactylation and other PTMs. In conclusion, lactylation represents a fascinating and novel layer of epigenetic regulation in AD, but its translation into biomarkers and therapies necessitates a deeper mechanistic understanding and stronger causal evidence.

Notwithstanding significant advances, lactylation research confronts persistent knowledge gaps and technical challenges that necessitate resolution. A primary obstacle lies in the methodological limitations of lactylation detection and quantification. Current proteomics approaches, particularly mass spectrometry-based methods, struggle to distinguish lactylation from other homologous lysine acylations (eg, crotonylation or 2-hydroxyisobutyrylation) due to their identical

Table 1 Lactation Modification Regulates the Pathological Characteristics of AD

Author (Year)	Protein	Site	Functional Role & Effect	Observed Phenotype/Pathological Change	Experimental Model
Pan et al (2022)[19]	Histone H4	H4K12la	Promotes neuroinflammation and Aβ deposition	Microglial hyperactivation; increased Aβ accumulation	APP/PS1 AD mouse model
Wang et al (2025)[20]	Histone H4	H4K12la	Drives pro-inflammatory microglial polarization	Elevated lactate → increased H4K12la → enhanced Aβ deposition	Lactate-infused AD mice
Cheng et al (2024)[37]	Histone H4	H4K12la	Induces NLRP3-mediated pyroptosis	Impaired learning and memory; microglial pyroptosis	APP/PS1 mice; Aβ-treated BV-2 microglia
Wei et al (2023)[35]	Histone H3	H3K18la	Enhances NF-κB-mediated inflammation	Aggravated neuroinflammatory response	Senescent microglia models
Tian et al (2025)[22]	APP	K612la	Promotes endolysosomal degradation of APP → reduces Aβ	Decreased amyloid plaque formation; improved cognitive performance	APP/PS45 double-transgenic mice
An et al (2024)[21]	Tau	K677la	Facilitates ferroptosis and neuroinflammation	Impaired iron homeostasis; microglial activation; cognitive decline	Tau-transfected cells; AD mouse models
Zhang et al (2025)[88]	Tau	K331la	Promotes tau aggregation and NFT formation	Increased insoluble tau; exacerbated tangle pathology	Human AD brain samples; cell models
Wang et al (2024)[38]	IDH3β/PAX6	N/A	Disrupts TCA cycle → lactate accumulation → lactylation	Impaired mitochondrial metabolism; cognitive deficits	IDH3β-knockout models

Notes: The arrow symbol (→) used here denotes a sequential causal relationship between biological events.

mass shifts, necessitating the development of more specific enrichment tools and refined analytical pipelines.[-109] Furthermore, a critical shortage of highly validated pan-specific and site-specific anti-lactylation antibodies impedes the validation, cellular imaging, and biochemical analysis of lactylation events across different biological contexts. Wang et al[110] engineered a histone-mimetic photoaffinity probe enabling covalent capture of proteins interacting with specific histone post-translational modifications (PTMs). This methodology, when integrated with quantitative proteomics, facilitates systematic elucidation of PTM-associated interactomes and their regulatory circuitry. Second, beyond detection issues, the intricate crosstalk among heterogeneous PTM networks presents significant challenges in delineating lactylation-specific regulatory mechanisms. The integration of multidimensional metabolomic profiling has established a robust paradigm for delineating lactylation crosstalk dynamics and its mechanistic coupling to signal transduction cascades and cellular phenotypic outcomes.[111,112] Finally, the causal mechanistic framework linking lactylation to spatiotemporal control of cellular phenotypes and its pathogenic contributions remains unresolved. Moreover, extant lactylation research predominantly relies on murine model systems, introducing translational uncertainties regarding human pathophysiological relevance. Most murine models are engineered to overexpress mutant proteins to accelerate Aβ plaque formation and neurofibrillary tangle (NFT) accumulation. This design recapitulates familial AD (a rare subtype, ~5% of cases) but not sporadic AD (the dominant form, ~95%), which arises from age-related metabolic decline, vascular dysfunction, and multifactorial genetic susceptibility.[113] Therefore, the conclusion cannot be directly applied. Future research will need to further clarify the functional differences at different sites as well as the specificity of the regulation, and using mice with natural aging rather than relying solely on young transgenic models to simulate the chronic progression characteristics of human AD. In addition, dead human brain tissue can be used. However, this method also has limitations, such as tissue ischemia and temperature sensitivity, etc.

Therapeutic targeting of lactylation in AD should adopt a precise, site-specific strategy due to its dualistic nature. Based on the evidence synthesized in this review, several lactylation sites emerge as promising but distinct therapeutic targets.[19,21,38] Detrimental lactylation sites that promote disease pathogenesis, such as microglial H4K12la and H3K18la as well as neuronal Tau-K331la, represent targets for inhibition. Strategies could include developing site-specific lactyltransferase inhibitors or molecules that disrupt the interaction between the lactylated mark and its downstream effectors. Conversely, beneficial or protective lactylation sites, such as APP-K612la which enhances non-amyloidogenic

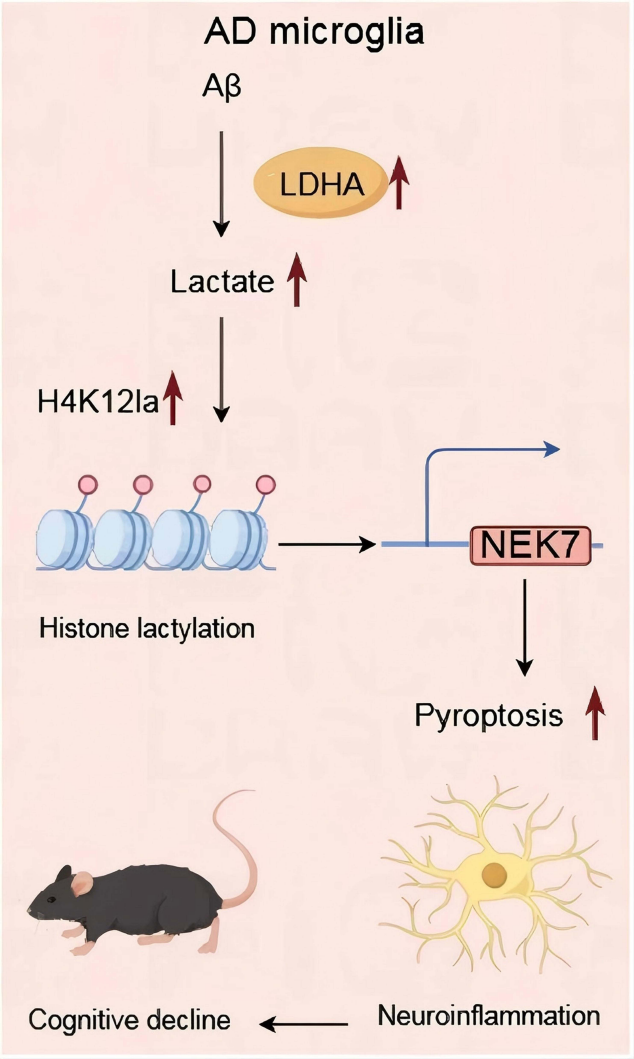

Figure 2 H4K12la improves AD by regulating Aβ through NEK7. Reprinted from Cheng, J et al.[36] Copyright 2024, Molecular Brain. (upward arrows: expression of elevation).

processing, represent targets for enhancement or mimicry.[22] This could be achieved through lactyl-mimetic compounds or by modulating upstream regulators to selectively boost this modification. Furthermore, broader approaches like modulating brain lactate levels through metabolic interventions or targeting key enzymes in the lactylation cycle (eg, p300) present additional avenues, albeit with greater challenges in achieving cellular and site-specificity. The future of lactylation-based therapeutics lies in moving beyond blanket inhibition or activation towards a sophisticated, precision medicine approach that considers the specific target protein, cell type, and disease stage.

PTMs crosstalk refers to a regulatory mechanism in which one PTM affects the occurrence of other PTMS. It is a subtle and complex mechanism.[14,114] Previous studies have found that there are more than 30 types of PTM on lysine residues, and more than 300,000 modification sites have been identified. It is worth noting that among these modified lysine residues, more than 150,000 lysine residues can have two or more types of PTM.[115] PTM crosstalk includes histone PTM crosstalk and non-histone PTM crosstalk. More and more studies have shown that PTM crosstalk is a specific grammar of histone PTM specific grammar. Used for modulating the chromatin state and transcriptional activity.[116–118] For tau protein— a critical substrate with extensive multi-site modifications—lactylation likely engages in dynamic interactions with phosphorylation, acetylation, and ubiquitination. For example, An et al[21] found that inhibiting tau K677 lactylation reduces ferroptosis without affecting tau phosphorylation, suggesting independent pathways at distinct sites, while Zhang et al[88] noted that tau K331 lactylation

exacerbates misfolding and aggregation—phenotypes classically linked to hyperphosphorylation, implying potential synergy. Future studies can further explore the mechanism of lactylation and other PTM crosstalk on AD, and focus on discussing the mechanism of non-histone lactylation.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Conception, J.T., L.W. and X.Z.; writing—original draft prepartion, J.T., Y.Z. and Y.W.; drawing pictures, G.T.; writing—review and editing, X.Z., Y.F., A.X., J.Q., R.Z. and H.D. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Disclosure

The authors declare no conflict of interest.

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