Neuropsychiatric Disease and Treatment

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REVIEW

# Epigenetic Changes in Alzheimer's Disease and Interventions for Therapy

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**Abstract:** With the ageing of society, the number of Alzheimer's disease (AD) patients has increased rapidly, imposing a heavy burden on families and society. This article reviews the causes of AD, particularly the epigenetic changes associated with AD, including DNA methylation, histone modifications, and noncoding RNA changes. The development of diagnostic reagents based on biomarkers specific to epigenetic changes and attempts to intervene in adverse epigenetic factor changes in AD for the treatment of AD are discussed. This review contributes to a better understanding of the relationship between epigenetics and AD and provides guidance for exploring diagnostic and therapeutic strategies.

**Keywords:** Alzheimer's disease, epigenetics, DNA methylation, histone modification, noncoding RNA

## Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by memory decline, language confusion and personality variation. In the AD brain, neurofibrillary tangles and pathological amyloid deposition occur. According to the World Health Organization, the number of people worldwide suffering from AD exceeds 50 million and is expected to exceed 131 million by 2050. AD patients are unable to take care of themselves, which imposes a significant burden on society and families.[1]

The causes of AD are still not clear. As shown in Figure 1, the academic community generally considers AD a multifactorial pathology involving genetic, environmental, metabolic, and neuroinflammatory factors.[2] The abnormal cleavage of amyloid precursor protein (APP), which leads to the aggregation of Aβ42 plaques in the brain, is the most widely recognized pathological mechanism of AD, triggering inflammatory responses, synaptic dysfunction, and neuronal damage.[2] The tau protein hypothesis suggests that excessive phosphorylation of tau protein, which results in the formation of neurofibrillary tangles (NFTs), disruption of the cytoskeleton, and disruption of neuronal transport disorders and cell death in the brain, is also an important cause of AD.[2] The choline theory holds that, in the brain, a reduction in synaptic acetylcholine (Ach) can lead to the degeneration of cholinergic neurons and the loss of neural transmission function, resulting in cognitive decline and AD.[2] The neuroinflammatory theory suggests that Aβ deposition activates microglia in the brain, releasing proinflammatory factors such as IL-1βand TNF-α and causing inflammatory reactions and oxidative stress, leading to mitochondrial dysfunction, DNA damage, and neuronal necrosis.[2] The genetic theory holds that familial AD is associated with mutations in the APP, PSEN1, and PSEN2 genes (encoding presenilin protein), which can lead to excessive production or inhibition of Aβ clearance, resulting in the formation of toxic plaques.[2] The theory of metal ions and free radicals suggests that with ageing, the accumulation of metal ions in the brain

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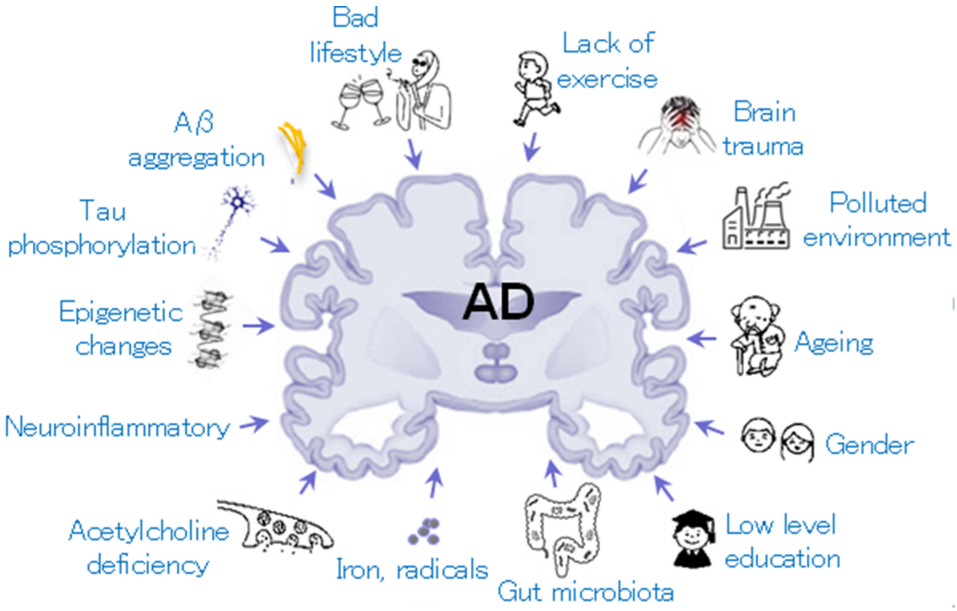


**Figure 1** Factors contributing to Alzheimer's disease. Aβ aggregation, abnormal tau phosphorylation, acetylcholine deficiency, genetic mutation, neuroinflammation, gut microbiota, iron and radicals, bad lifestyle, environment pollution, brain injury, low level of education, age and sex, and epigenetic changes are involved in the aetiology of Alzheimer's disease.

leads to the catalysis of free radical activity, damage to neurons, and the development of AD.[3] In addition, the environment, lifestyle, education level, age, and sex are related to the occurrence of AD:[4] severe traumatic brain injury may damage the blood–brain barrier, induce Aβ deposition, and increase the risk of AD; a lack of exercise, smoking, obesity, and sleep disorders may cause AD because of metabolic disorders or a decrease in Aβ clearance efficiency. The risk of disease for people over 65 years old doubles every five years. The incidence rate is higher in women than in men, which may be related to the decline in oestrogen levels.[5] Individuals with low educational levels or who lack cognitive stimulation are more prone to developing AD, which may be related to reduced synaptic plasticity in the brain.[6,7] The gut microbiota has also been reported to be associated with AD through the brain-gut axis.[8]

Recently, studies have focused on epigenetic changes associated with the occurrence of AD.[9,10] Epigenetics refers to heritable changes in gene expression or cell phenotype during mitosis or meiosis where the base remains unchanged,[11] including DNA methylation, histone methylation, histone acetylation, lactylation, RNA modification, and noncoding RNA. These modifications can regulate gene expression, thereby affecting synaptic plasticity, memory acquisition and consolidation, and neural connectivity and neural signal transmission. Research has shown that epigenetic changes play important roles in the occurrence and development of AD.[12] These include the regulation of Aβ cleavage or aggregation, tau phosphorylation, neuroinflammation, and proteins related to AD.[12]

## Epigenetic Activity and AD

Studies have demonstrated that DNA methylation and histone proteins undergo epigenetic modifications, such as deacetylation, methylation, lactylation, ubiquitination, and SUMOylation, as well as protein glycosylation and phosphorylation, all of which are involved in AD pathology. In addition, specific noncoding RNAs such as microRNAs, circular RNAs, long noncoding RNAs, and other epigenetic changes have been detected in individuals with AD.[13–16] They can not only regulate the occurrence and development of AD but also provide clues for the development of diagnostic reagents,[17] and clinical attempts have been made to prevent and treat AD by intervening in or reversing adverse epigenetic changes.[18,19]

Proteins involved in DNA and protein methylation and acetylation processes, including DNMTs, HMTs, lysine demethylases (KDMs), HATs, HDACs, methylated histone binding proteins, and acetylated histone binding proteins, can not only be used to detect the occurrence and development of AD but also provide new targets for AD treatment and drug

development. Their inhibitors, such as certain DNMTis and HDACis, have been used to intervene in or reverse epigenetic changes and have been approved for clinical use in AD treatment.[18,20,21]

# DNA Methylation and AD

## Overview of DNA Methylation

DNA methylation refers to the addition of methyl groups to DNA molecules, typically occurring at the 5' carbon of cytosine, especially on CpG islands, where cytosine and guanine are connected by phosphodiester bonds.[22,23] It is primarily catalysed by DNMTs, including DNMT1, DNMT3A, and DNMT3B, which add methyl groups to cytosine in DNA molecules to form 5-methylcytosine (5-mC).[22,23] In this process, homocysteine is a key intermediate that can affect neurodegenerative and cerebrovascular diseases, leading to changes in DNA methylation levels and, in turn, affecting gene expression regulation and the occurrence and development of diseases.[24]

## DNA Methylation and AD

Studies have shown that in AD mouse models, the DNA methylation and demethylation status of neurons in specific brain regions changes; in particular, the level of 5-hydroxymethylcytosine (5hmC) decreases in the frontal cortex and hippocampus, and age-related 5hmC enrichment is associated with AD processes.[13] Furthermore, changes in TET family proteins (key enzymes involved in DNA demethylation) and DNA methylation status have been observed in AD mouse models.[13] In addition, DNMT1 activity is dysregulated in AD.[24–26] It decreases in the hippocampus and temporal lobe but increases in the frontal lobe, temporal lobe cortex, and cerebellum.[18]

In addition, in AD patients, the promoter regions of genes related to Aβ production, such as APP, BACE1, and PSEN1, are hypomethylated, leading to increased expression of Aβ and promoting its production, and genes related to Aβ degradation, such as NEP, are highly methylated and downregulated, leading to a decrease in Aβ degradation.[27] On the other hand, Aβ deposition can induce DNA methylation abnormalities, interfere with normal DNA demethylation processes, and affect gene expression regulation,[28] driving the pathological process of AD and affecting neuronal function and survival. Additionally, environmental factors may indirectly affect Aβ metabolism and the occurrence and development of AD by influencing DNA methylation status.[18] These results indicate that the dynamic balance between DNA methylation and demethylation plays an important role in the pathogenesis of AD, providing a new perspective for understanding the epigenetic regulation of AD.

Nevertheless, the exact mechanism by which DNMT1 participates in AD is still under investigation, and its relationship with AD may be multifaceted.[29] Future studies are needed to clarify the genes and pathways regulated by DNMT1 in AD and to evaluate the potential of targeting DNMT1 as a therapeutic strategy.

## Therapeutic Strategies for AD Caused by DNA Methylation

With respect to DNA methylation related to AD, some measures have been taken to develop interventions.

As shown in Table 1, methylation inhibitors such as decitabine can regulate DNA methylation and alleviate AD-related neurodegenerative changes and neurological function.[18,20] The SIRT1 activity-targeted drug resveratrol can relieve AD pathology by regulating DNA methylation to reduce the accumulation of Aβ and tau proteins.[18,20] Gene

**Table 1** Alzheimer's Disease-Related DNA Methylation and Interventions

| Action | Targets or Agents | Effects | |
|---|---|---|---|
| DNA methylation | SORL1 DNA, SIRT1 DNA, NEP DNA | Aβ and tau aggregation, neuronal dysfunction, neuron necrosis | Induce or aggravate AD |
| DNA demethylation | APP promoter, BACE1 promoter, PSEN1 promoter | | |
| Prevent adverse DNA methylation, Induce favourable DNA methylation | Good environment, appropriate exercise, healthy diet, stress management, CRISPR/Cas9 gene editing | Reduce Aβ and tau aggregation | Prevent or ameliorate AD |
| Inhibit DNA methylation | RPEL, resveratrol | Activate SIRT1, Inhibit DNMTs, Inhibit TET | |

therapy, such as CRISPR/Cas9, can correct DNA methylation abnormalities associated with AD through gene editing, thus improving neurological function.[18,20]

Nanomaterials combined with methylation inhibitors or other drugs can be delivered to the central nervous system through nanocarriers to alleviate AD pathology.[30,31] By targeting and regulating the DNA methylation levels of AD-related genes, such as SORL1, SIRT1, and HTERT, these genes may be restored to normal expression, and the progression of AD may be delayed.[27,32,33]

Lifestyle adjustments, such as adopting a Mediterranean or MIND diet, engaging in regular exercise, and managing stress, can also influence DNA methylation and help ameliorate AD pathology.[20]

## Histone Modification and AD

Histone modification refers to the process by which histones change their structure and function by covalent addition of various chemical groups (such as acetyl, methyl, and phosphate). These modifications dynamically regulate chromatin structure and gene expression, thereby affecting cellular function.[34,35] The main types of histone modifications include acetylation, methylation, phosphorylation, ubiquitination, and ADP glycosylation.[35] By altering the interactions between histones and DNA and other chromatin proteins, these modifications affect processes such as gene transcription, DNA repair, and chromatin assembly.[34] Methylation is usually associated with gene silencing, whereas acetylation is associated with gene activation.[36] Metabolites such as acetate and butyrate can also regulate gene expression by affecting histone modifications.[37,38] Histone modifications also interact with other metabolic processes. For example, acetylation and methylation can compete for the same lysine residue, resulting in different gene expression regulatory effects. As illustrated in Figure 2, histone modifications play important roles in AD pathogenesis.

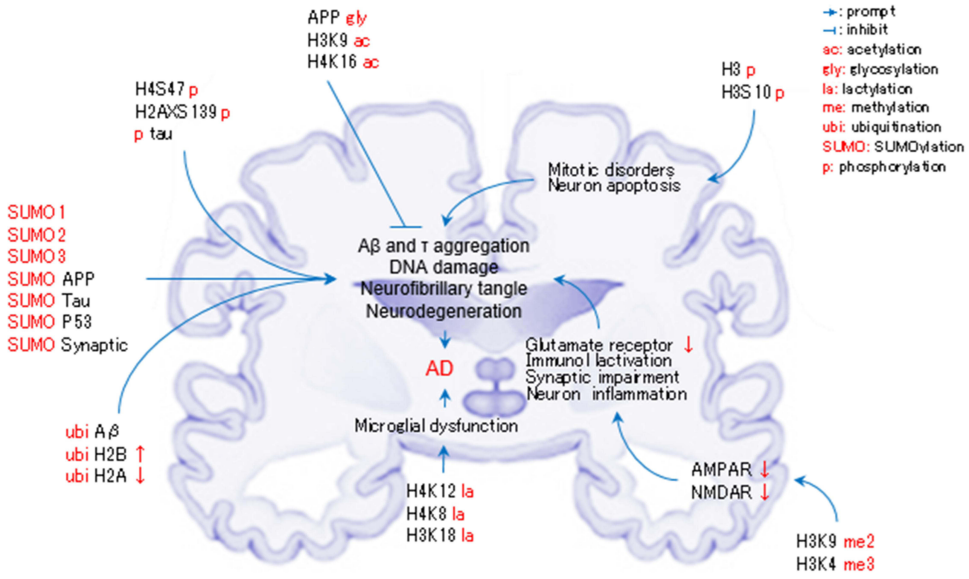


**Figure 2** Epigenetic changes in histones associated with Alzheimer's disease. In the AD brain, H3K9me2 and H3K4me3 decrease AMPA and NMDA receptors; an increase in H3K9me2 is associated with downregulation of glutamate receptor expression, whereas changes in H3K4me3 are associated with activation of immune response pathways and impairment of synaptic function. Decreased acetylation levels of H3K9ac and H4K16ac are associated with the pathology of Aβ and tau proteins, as well as the formation of neurofibrillary tangles; increasing the lactate levels of H4K12la and H4K8la, as well as H3K18la, can exacerbate AD pathology; H4K12la promotes the glycolytic activity of microglia, leading to microglial dysfunction; APP GlcNAcylation inhibits APP endocytosis, reduces Aβ production, and delays AD progression. An increase in H4S47p is associated with abnormal accumulation of Aβ and tau proteins, DNA damage in the astrocytes of AD patients, and the initiation of H2AXS139 phosphorylation to generate γH2AX, promotes the development of AD; and an abnormal increase in H3S10p in the hippocampus of AD patients is associated with neuronal apoptosis. Increased levels of phosphorylated H3 in the hippocampal neurons of AD patients can lead to neuronal mitotic disorders and neurodegeneration. The ubiquitination of Aβ and hyperphosphorylated tau protein affects its clearance efficiency and exacerbates the pathological progression of AD; increased ubiquitination of histone H2B and decreased ubiquitination of H2A lead to Aβ deposition, excessive phosphorylation of tau protein, and neurodegenerative changes. APP SUMOylation and SUMO2/3 expression can promote the generation of Aβ and tau, exacerbating the development of AD; increased SUMO1 expression can promote BACE1 cleavage of APP and the secretion of Aβ. Tau and P53 SUMOylation exacerbate tau phosphorylation and aggregation, and synaptic SUMOylation exacerbates AD; APP glycosylation promotes Aβgeneration.
**Notes**: ↑: increase, ↓: decrease.


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## Histone Methylation and AD

Histone methylation refers to the addition of methyl groups to specific amino acid residues of histones. Lysine can be monomethylated, dimethylated, or trimethylated, whereas arginine can be monomethylated or dimethylated.[39] Histone methylation is catalysed by the histone methyltransferase (HMT) enzyme, which can add the methyl group of the S-adenosylmethionine donor to its target residue.[39]

Research has shown that histone methylation affects key pathological features of AD by regulating gene expression, including deposition of Aβ, abnormal phosphorylation of tau protein, and neuroinflammation.[19] Certain histone methylation markers (such as H3K9me2 and H3K4me3) are significantly increased or decreased in the brains of AD patients and are associated with pathological Aβ accumulation, tau protein hyperphosphorylation, neuroinflammation, synaptic dysfunction, and memory and cognitive dysfunction.[14,39,40]

An increase in H3K9me2 levels is associated with a decrease in the expression levels of the glutamate receptor subunits AMPAR and NMDAR, which are crucial for the normal function of neurons.[14] An increase in H3K9me2 is also related to the downregulation of glutamate receptor expression, whereas changes in H3K4me3 are related to the activation of immune response pathways and damage to synaptic function.[41] Moreover, an increase in H3K4me3 is associated with increased gene expression in immune response-related pathways.[42,43] These changes in histone methylation may participate in the pathological process of AD by affecting gene expression and neuronal function.[44]

Energy metabolism disorders such as mitochondrial dysfunction and abnormal glucose metabolism can exacerbate the pathological process of AD through the regulation of histone methylation status through effects on the activity of histone methyltransferase and the levels of metabolic intermediates.[19]

Histone methyltransferases (KMTs) and histone demethylases (KDMs) regulate the expression of AD-related genes by modifying different histone sites. For example, G9a/GLP affects synaptic plasticity and cognitive function by inhibiting the expression of BDNF and glutamate receptors, whereas EZH2 inhibits the expression of BDNF promoter regions by increasing H3K27me3 levels.[19]

Drugs that regulate histone methylation, such as KMT and KDM inhibitors, may become potential strategies for AD treatment. By inhibiting histone methyltransferases (such as EHMT1/2 and H3K4me3-related enzymes), cognitive function and pathological features can be improved, indicating that histone methyltransferase is a potential therapeutic target.[45] Although current research is still in its early stages, these findings provide important evidence for understanding the role of histone methylation in AD and provide direction for the development of novel therapeutic approaches.[19]

## Histone Acetylation and AD

Histone acetylation is the addition of acetyl groups to the ε-amino group of histone lysine residues under the catalytic action of histone acetyltransferase (HAT), neutralizing the positive charge of lysine and changing the charge state of histones. The opposite process is that of histone deacetylase (HDAC), which is responsible for removing acetyl groups from lysine residues. Histone acetylation may regulate gene expression by changing chromatin openness, rapid turnover of histone markers, and dynamic recruitment of DNA factors, which can affect the function of transcription mechanisms.[46]

Metabolites of acetyl-CoA and NAD+ play key roles in histone acetylation and deacetylation processes.[19] Changes in the concentration of acetyl-CoA indirectly affect the activity of histone acetyltransferases (HATs), whereas changes in NAD+ levels affect the function of histone deacetylases (HDACs).[19]

Research has shown that histone acetylation is associated with learning, memory, and synaptic plasticity.[14,47] AD patients typically have a reduced availability of acetyl-CoA in the brain, resulting in lower levels of histone acetylation. HDAC2 is overexpressed, exacerbating cognitive impairment by inhibiting neuronal gene expression and synaptic function.[19] In the brains of AD patients, changes in histone acetylation levels (such as abnormalities in H3K9ac and H4K16ac) are associated with the pathology of Aβ and tau proteins, as well as the formation of neurofibrillary tangles,[47] and may exacerbate neurodegenerative processes through adverse epigenetic mechanisms.[48]

Histone deacetylase (HDAC) inhibitors such as SAHA, VPA, and TSA can increase histone acetylation levels, increase the expression of memory-related genes, improve cognitive function, reduce Aβ accumulation, affect abnormal tau phosphorylation, reduce NFT formation, and delay the progression of AD, whereas deacetylase activity has the opposite effect,[49] suggesting that

histone acetyltransferase may be a potential target for the treatment of AD.[50] However, the therapeutic effect of HDAC inhibitors still needs to overcome side effects and toxicity issues, and relevant clinical trials are currently underway.[44]

## Histone Lactation and AD

Histone lactylation is a protein modification in which lactate groups are covalently attached to lysine residues of histones through catalytic reactions in which lactate is used as a precursor substance.[51] Recently, lactic acid has received increasing attention because of its biological functions in metabolism, neurotransmitter transmission, and neurovascular coupling.[52]

AD patients often experience abnormal metabolism.[53] Disruption of metabolism leads to increased lactate levels, which in turn increase histone lactate levels, affect gene expression and exacerbate the development of AD.[53,54]

Research has confirmed that increased histone lactate levels promote the expression of the transcription factor PAX6, which further inhibits the expression of the tricarboxylic acid cycle rate-limiting enzyme IDH3β through a negative feedback mechanism, leading to energy metabolism disorders, increased lactate levels, and increased histone H4 lactate levels at Lys12 and Lys8, as well as H3 lactate levels at Lys18,[54] forming a vicious cycle that exacerbates AD.[55–57] Increased H4K12la is observed in microglia near Aβ plaques[58] is highly enriched in the promoter region of glycolysis-related genes in microglia, which activates the transcription of these genes, thereby promoting glycolytic activity in microglia and leading to positive feedback regulation and microglial dysfunction.[57,58] The positive feedback loop composed of active glycolysis, H4K12la, and pyruvate kinase M2 (PKM2) exacerbates metabolic disorders and functional impairments in microglia in AD. By inhibiting PKM2 and blocking this vicious cycle, the activation of microglia and neuroinflammation can be alleviated.[58] Therefore, blocking this positive feedback loop may be a potential strategy for treating AD.

## Histone Glycosylation and AD

Histone glycosylation is a protein modification in which sugar chains or glycosides are added to specific amino acid residues of histones under the action of glycosyltransferases, resulting in the formation of glycosidic bonds. It occurs mainly through O-linkages, such as O-GlcNAc glycosylation, where N-acetylglucosamine is covalently linked to serine or threonine residues of histones. O-glycosylation includes mucin-type O-GalNAcylation and O-GlcNAcylation. The level of O-GlcNAcylation is jointly regulated by O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA), which participate in the regulation of various cellular processes. N-glycosylation occurs in the endoplasmic reticulum and Golgi apparatus and affects mainly protein folding, stability, and subcellular transport.[59–61]

Histone glycosylation is cell- and tissue-specific. It plays a crucial role in the development and function of the nervous system, with characteristic polysaccharide structures regulating axonal pathfinding, neurite outgrowth, synapsis, neurotransmission, and other neuronal processes.[62] Neurospecific polysaccharides are necessary for performing advanced brain functions, including learning/memory and the formation of neural networks.[62] In Alzheimer's disease, histone glycosylation may be involved in the occurrence and development of the disease by affecting chromatin structure and gene expression.[44] Research has shown that histone glycosylation is associated with neuroinflammation, neurodegeneration, and cognitive dysfunction.[44] In an AD model, a decrease in O-GlcNAcylation was associated with mitochondrial network damage, energy metabolism disorders, and reduced cellular activity.[63,64]

The abnormal aggregation of Aβ is among the core pathological features of AD.[65] Glycosylation (especially O-GlcNAc modification) regulates the cleavage pathway of APP, thereby affecting the generation of Aβ and the pathological process of AD.[65] On the one hand, it can regulate the intracellular transport and cleavage pathway selection of APP, such as by inhibiting APP endocytosis, promoting nonamyloid metabolic pathway cleavage, and increasing the glycosylation levels at the Asn467 and Asn496 sites of APP to reduce Aβ production.[59,60,66–68] On the other hand, changes in the levels of APP O-GlcNAcylation may affect its interactions with other proteins and its intracellular localization, thereby indirectly affecting Aβ production.[69]

Regulating the glycosylation level of APP is a potential strategy for AD treatment. Elevated N-glycosylation levels at specific sites of APP can reduce Aβ production.[66,70] RCAN1 can increase APP N-glycosylation levels by stabilizing the glycosyltransferase complex OST, but overactivation of RCAN1 actually increases Aβ production.[63] Regulating blood glucose metabolism through drugs, such as OGT/OGA or GalNAc Ts, is expected to improve APP cleavage metabolism,

reduce Aβ production, and thus delay AD progression.[64,68] The OGA inhibitor PugNAc can increase the level of APP O-GlcNAcylation, increase the production of sAPP α, a nonamyloid metabolic pathway cleavage product, and reduce Aβ production.[68] Mucin-type O-glycosylation is catalysed by GalNAc-T family enzymes, and overexpression of GalNAc-T6 can significantly reduce Aβ production, indicating that mucin-type O-glycosylation can inhibit Aβ production by changing the conformation or transport mode of APP, reducing its sensitivity to β-secretases.[70–72] However, the application of glycosylation in the treatment of AD is still in the research stage, and further exploration is needed to determine its specific mechanism, effectiveness, and safety.

## Histone Phosphorylation and AD

Histone phosphorylation occurs at the tail of histones, regulating the structure and function of chromatin through the addition of phosphate groups to serine, threonine, or tyrosine residues.[73] It is associated with changes in chromatin. During cell division, the phosphorylation of histone H3 occurs in specific spatial and temporal patterns during mitosis and meiosis and may participate in chromatin condensation and looseness, thereby affecting gene expression, DNA repair, chromosome separation, and other functions.[73]

Histone phosphorylation plays important roles in the pathology of AD. Research has shown that there are significant changes in histone phosphorylation levels in the brain tissue of AD patients, such as an increase in the phosphorylation level of the serine 47 site of histone H4 (H4S47p), which may be associated with abnormal accumulation of Aβ and tau proteins.[44]

Histone phosphorylation is also associated with the DNA damage repair mechanism in AD patients. Research has shown that the level of gamma H2AX (a DNA damage marker) is significantly increased in the hippocampus and cortex of AD patients, indicating its important role in DNA damage and repair mechanisms in AD.[74,75] When DNA damage occurs in the astrocytes of AD patients, the serine 139 (S139) site of H2AX (a member of the H2A histone family) is rapidly phosphorylated to form gamma H2AX.[74] In astrocytes in susceptible areas of the AD brain, such as the hippocampus and cerebral cortex, the level of γH2AX, which is an indicator of H2AX phosphorylation in AD, significantly increases.

H3 is distributed mainly in the CA-1 region of the hippocampus and hypothalamus.[76] Research has shown that in the hippocampal neurons of AD patients, the level of phosphorylated H3 increases, and activated phosphorylated H3 is located mainly in the cytoplasm of neurons, which may lead to mitotic disorders, neurodegeneration, and disuse of neurons.[76]

In APP-overexpressing neuroblastoma, the phosphorylation level of serine 47 (S47) in H4 was 1.89 times greater than that in the control group.[77] Phosphorylation of H4 was also detected in the brains of patients with mild cognitive impairment, suggesting that histone phosphorylation plays a role in the development of AD.[77]

By regulating histone phosphorylation, new strategies may be developed for the treatment of AD. Using the spleen tyrosine kinase (Syk) inhibitors BAY 61–3606 and R406, Yamaguchi decreased several tau phosphoepitopes, including PHF-1, CP13, AT180, and AT270, by inactivating tau kinases and activating tau phosphatases and decreasing the levels of caspase-cleaved tau (TauC3), a pathological tau form. In vivo, the Syk inhibitor R406 decreased phosphorylated tau levels in wild-type mice. These findings suggest that Syk inhibitors offer novel therapeutic strategies for tauopathies, including AD.[78]

## Histone Ubiquitination and AD

Histone ubiquitination is a modification in which ubiquitin molecules attach to lysine residues in histones. It includes monoubiquitination and polyubiquitination.[79] Monoubiquitination is the most common form of histone modification, whereas polyubiquitination is typically associated with proteasome-mediated degradation.[79]

Histone ubiquitination may indirectly contribute to AD pathology by affecting chromatin status and gene expression, which influence memory formation and synaptic plasticity.[79] Ubiquitination is also involved in regulating the DNA damage response and protein homeostasis, which are often dysregulated in AD patients.[80] The ubiquitination of neurotoxins such as Aβ and hyperphosphorylated tau protein can affect their clearance efficiency and exacerbate AD progression.[80–83]

In the AD brain, ubiquitination at the H2BK120 site is significantly increased, whereas ubiquitination at the H2AK119 site is decreased.[52] The Bmi1/Ring1 complex, as part of the PRC1 complex, maintains gene transcription inhibition by regulating the ubiquitination of H2AK119. However, in the AD brain, silencing Bmi1 leads to a decrease in H2A ubiquitination levels, resulting in Aβ deposition, tau protein hyperphosphorylation, and neurodegenerative

changes.[82,83] The monoubiquitination of histone H2B (H2BubiK120) plays a key role in memory formation by regulating changes in H3K4me3 and affecting gene expression. Learning-induced H2B monoubiquitination (H2Bubi) is associated with enhanced transcriptional activity of memory-related genes, and the absence of H2Bubi hinders learning-induced gene transcription, synaptic plasticity, and memory formation.[84]

In addition, histone ubiquitination is associated with AD-related synaptic dysfunction and memory impairment, particularly in the regulation of gene expression related to synaptic plasticity.[85,86] These findings suggest that histone ubiquitination may play an important role in the pathological mechanism of AD and provide new directions for potential therapeutic strategies.

## Histone SUMOylation and AD

Histone SUMOylation involves covalent attachment of small ubiquitin-like modified proteins (SUMOs) to the lysine residues of histones. This modification is similar to ubiquitination and requires the coordinated action of various ubiquitin ligases that are SUMO-specific and independent of ubiquitin proteasome signalling. SUMO modification usually does not lead to protein degradation but rather regulates protein function by altering protein localization, activity, or interactions.[87] Histones can also be modified by the addition of small ubiquitin-like modifier SUMO. Only one single SUMO modification occurs on a histone or any other protein, targeting various cellular fates independent of protein degradation.

SUMO modification is related to the stability, activity, and pathological function of various key proteins in AD. Research has shown that SUMOylation of p53 is significantly increased in the brains of AD patients, leading to the dissociation of the SET/p53 complex, and the released SET interacts with PP2A in the cytoplasm and inhibits its activity, resulting in excessive phosphorylation of tau in neurons.[15] In addition, SUMOylation of p53 promotes neuronal ageing and leads to synaptic damage and cognitive impairment.[15] Their inhibitors, such as ginkgolic acid, can restore the ageing phenotype driven by p53 SUMOylation.[15]

The role of SUMOylation in AD is complex and may involve the coordinated regulation of multiple proteins. In some cases, SUMOylation may have a protective effect, whereas in other cases, SUMOylation may exacerbate pathological processes.[88] APP is a substrate for SUMOylation. The formation of Aβ plaques increases when SUMO1 is modified. The overexpression of SUMO1 also increases the production of Aβ, possibly by interfering with the cleavage site of BACE (β-secretase).[89] SUMOylation of the BACE1 K501 site can significantly increase the stability and enzyme activity of BACE1, leading to an increase in Aβ production and exacerbating the pathological features of AD, such as senile plaque formation and cognitive dysfunction.[90] However, SUMO2/3 modification may increase or decrease Aβ levels.[91,92] The overexpression of SUMO3 can increase the number of Aβ plaques, but this effect depends on its ability to form chains.[91]

HDAC1 SUMOylation can activate CREB and reduce Aβ plaques and neuronal death.[88] However, the specific role of histone SUMOylation in AD has not been determined.[93]

## Therapeutic Strategies Based on Histone Modification

In accordance with the aforementioned unfavourable histone modifications associated with AD, researchers have developed treatment strategies.

### Therapeutic Strategies Based on Histone Methylation

EHMT1/2 inhibitors have been developed that improve memory and cognitive function in AD mouse models, reduce the pathological features of Aβ and tau proteins,[39] and restore the expression level of glutamate receptors by inhibiting H3K9me2.[39] In addition, by inhibiting G9a (an H3K9me2 methyltransferase), the generation and deposition of Aβ are reduced.[94]

### Therapeutic Strategies Based on Histone Deacetylase (HDAC) Inhibitors

Research has indicated that HDAC inhibitors (such as SAHA, VPA, TSA, and 4-PBA) can improve memory and cognitive function by increasing histone acetylation levels and reducing the pathological features of Aβ and tau proteins.[42] HDAC3 inhibitors reduced Aβ accumulation and tau protein phosphorylation in AD mouse models while improving learning and memory function.[42] Valproic acid (VPA) has been shown to reduce Aβ production and age plaque formation in transgenic AD mouse models and alleviate memory impairment.[95] 4-PBA improved memory

function in AD mouse models by increasing histone acetylation levels and reducing tau protein phosphorylation.[96] TSA reduced the number of age spots and improved memory and learning behaviour in an APP/PS1 mouse model.[97]

### Treatment Strategies for Other Histone Modifications

SIRT6 (class III HDAC) has neuroprotective effects in AD through the regulation of histone deacetylation. The overexpression of SIRT6 reduced DNA damage induced by Aβ and improved cognitive function in AD mouse models.[48] The decreased expression level of SIRT6 in AD patients and AD mouse models indicates its important role in AD pathology.[50]

### Combination Therapy Strategy

SAHA, when used in combination with other drugs such as rosiglitazone, has a synergistic neuroprotective effect.[98] The combination of SAHA and rosiglitazone reduced the pathological features of Aβ and tau proteins in AD mouse models and improved cognitive function.[99]

## Noncoding RNA and AD

Noncoding RNA (ncRNA) is a type of RNA that is not translated into proteins. Although they do not directly participate in protein synthesis, they play multiple important biological functions in cells.[100] Noncoding RNAs can be classified into various types, including snoRNAs, microRNAs (miRNAs), small interfering RNAs (siRNAs), and long noncoding RNAs (lncRNAs). Among them, small nucleolar RNAs (snoRNAs) mainly participate in rRNA modification, including 2'-O-methylation and pseudouridylation; microRNAs (miRNAs) inhibit translation through incomplete complementary pairing with target mRNAs or lead to mRNA degradation through RNA interference (RNAi) mechanisms; small interfering RNAs (siRNAs) lead to the degradation of target mRNAs through RNAi mechanisms; and long noncoding RNAs (lncRNAs) regulate gene expression at multiple levels, including chromatin structure, transcription, RNA splicing, editing, translation, and degradation.[101] These RNAs may form RNA–RNA or RNA–DNA complexes through base pairing with complementary sequences, which can be recognized and acted upon by universal regulatory infrastructure, such as the RNA-induced silencing complex (RISC).[102] As shown in Table 2, in the AD process, noncoding RNAs play various roles.

**Table 2** Effects of Noncoding RNAs on AD

| RNA Type | Target(s) | Effect(s) |
|---|---|---|
| miR-16 ↓<br>miR-195 ↓<br>miR-188-3p ↓ | APP, BACE1,<br>APP, PIP2, Synj1<br>APP, BACE1 | Aβ ↑ |
| miR-132 ↓<br>miR-219 ↓<br>miR-146a ↑ | | Tau expression, phosphorylation and aggregation |
| miR-206 ↑<br>miR-133b ↓<br>miR-222 ↓ | BDNF<br>Aβ<br>G1 arrest | Neuronal apoptosis |
| miR-155 ↑<br>miR-132 ↑<br>miR-212 ↑ | SIRT1 | Inhibit neuroinflammation |
| lncRNA ANRIL ↑<br>lncRNA HOTAIR<br>lncRNA MEG3 ↓ | miR-125a<br>PI3K/AKT | Inhibit neuroinflammation<br>Inhibit neuroinflammation<br>Inhibit neuron apoptosis |

(*Continued*)


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**Table 2** (Continued).

| RNA Type | Target(s) | Effect(s) |
|---|---|---|
| lncRNA BACE1-AS<br>lncRNA NEAT1 | BACE1<br>miR-124/BACE1 | Aβ ↓ |
| ciRS-7 ↓ | miR-7<br>UBE2A<br>EGFR)<br>APP, BACE1 | Aβ ↑ |

**Notes**: ↑: increase; ↓: decrease.

## MicroRNAs and AD

MicroRNAs (abbreviated miRNAs) are small single-stranded noncoding RNA molecules (containing approximately 22 nucleotides) that function in RNA silencing and posttranscriptional regulation of gene expression.[103] miRNAs function via base-pairing with complementary sequences within mRNA molecules,[104] which results in the silencing of these mRNA molecules through cleavage of the mRNA strand into pieces, destabilization of the mRNA through shortening of its poly(A) tail, and less efficient translation of the mRNA into proteins by ribosomes.[104,105]

As shown in Table 2, the role of miRNAs in the generation and clearance of Aβ is reflected mainly in the expression of miR-16, miR-29a/b-1, and miR-195, whose expression is downregulated in AD patients and AD mouse models.[16] miR-16 has been shown to regulate the expression of APP and BACE1, thereby reducing the production of Aβ. It can also reduce the total phosphorylation level of tau protein.[106] In the brains of AD patients, the expression of miR-29a and miR-29b-1 is significantly reduced in the population with elevated BACE1 expression.[107] miR-195 expression is reduced in mild cognitive impairment (MCI) and early AD patients carrying a single ApoE ε 4 allele.[108] It can also reduce the production of Aβ by regulating the expression of PIP2 and synaptophanin1 (synj1).[108]

The overexpression of miR-188-3p can inhibit the transcription and expression of the BACE1 gene, thereby reducing the generation of Aβ and its neurotoxicity.[109]

The role of miRNAs in tau protein expression and phosphorylation is reflected mainly in the role of miR-132, miR-219, and miR-146a. Deficiency of miR-132 can lead to increased expression, phosphorylation, and aggregation of tau protein, which can have adverse effects on long-term memory.[110] By binding to the 3′-UTR of tau mRNA, miR-219 alters the expression of tau mRNA.[111] The overexpression of miR-146a enhances the abnormal phosphorylation of tau, leading to memory impairment.[112]

miRNAs also play multiple roles in neuronal proliferation and loss. In the serum of AD patients, the expression of miR-206 is elevated, which reduces BDNF expression through binding to the 3′-UTR of BDNF mRNA, thereby increasing neuronal vulnerability.[113] The expression of miR-133b is significantly reduced in AD patients, and it exerts neuroprotective effects by inhibiting Aβ-induced neuronal apoptosis.[114] Decreased expression of miR-222 is associated with the arrest of neuronal proliferation in the G1 phase and may serve as an early biomarker for AD.[115,116]

The role of miRNAs in neuroinflammation involves the upregulation of miR-155 expression in the hippocampus of AD patients, which is associated with the expression and functional enhancement of proinflammatory cytokines. The inhibition of miR-155 can significantly improve learning and memory abilities.[117] The expression of miR-132 and miR-212 is elevated in the lymphoid cells of AD patients, resulting in a decrease in the expression of SIRT1 (an anti-inflammatory effector of neuroinflammation).[118]

## Long Chain Noncoding RNAs and AD

The role of long noncoding RNAs (lncRNAs) in AD is an emerging research field. LncRNAs play important roles in neuroinflammation. For example, the lncRNA ANRIL is upregulated in PC12 cells under Aβ oligomer stimulation, and its knockdown can reduce the expression of inflammatory cytokines, inhibit Aβ-induced apoptosis and autophagy, and promote the progression of neural processes. In the course, it may bind and downregulate miR-125A to act.[119] By

increasing the stability of BACE1 mRNA and preventing binding to miR-485-5p, the lncRNA BACE1-AS can increase BACE1 levels and Aβ production.[120] It not only promotes autophagy-mediated neuronal damage but also serves as a biomarker for disease diagnosis[17] because of its upregulation in serum samples from AD patients and brain tissues from transgenic AD mice.

LncRNAs can regulate inflammatory factors. The lncRNA HOTAIR is highly expressed under inflammatory conditions, such as in tumours, traumatic brain injury mouse models, and LPS-treated microglia. Silencing HOTAIR can inhibit the activation of microglia and the release of inflammatory factors.[121]

Furthermore, lncRNAs also have neuroprotective effects. Some lncRNAs, such as MEG3, are downregulated in AD models, and their overexpression can inhibit the activation of astrocytes, reducing neuronal damage through the PI3K/AKT pathway.[122]

## Circular RNAs and Alzheimer's Disease

Circular RNA (circRNA) is a type of covalently closed transcript. It plays important roles in various cellular processes, including gene expression regulation, protein translation, and cellular signalling, and abnormalities in circular RNA may affect these processes.[123–125] Research has shown that the expression of certain circular RNAs significantly changes in AD patients. Circular RNA ciRS-7, as a sponge of miR-7, is downregulated in sporadic AD, which may lead to increased miR-7 activity, thereby reducing the expression of miR-7-targeted mRNAs, including the ubiquitin conjugating enzyme UBE2A and epidermal growth factor receptor (EGFR), associated with AD.[126] In addition, ciRS-7 promoted the degradation of APP and BACE1 in SH-SY5Y cells, indicating that ciRS-7 may play a protective role in AD and that a decrease in its level may exacerbate the pathological process.[127] Circular RNAs can also regulate the inhibitory effect of miRNAs on target mRNAs by binding to them. For example, ciRS-7 can bind to miR-7, thereby affecting the regulation of target genes by miR-7[128] and play a role in the pathogenesis of AD, as changes in miR-7 activity may affect the expression of proteins associated with AD.

Treating neuronal cells with oligomeric tau protein can reproduce some changes in circular RNA, indicating that tau protein may participate in AD development by affecting the expression or function of circular RNA.[129]

Although the potential role of circular RNAs in AD is gradually being recognized, their function in the central nervous system is still not fully understood.[130] This is due mainly to the challenges associated with the molecular tools required for detecting, quantifying, and evaluating the functions of circular RNAs in physiological processes and diseases.[130] More roles of circular RNAs in AD pathology remain to be revealed.

## Therapeutic Strategies for Noncoding RNA

miRNAs play a role in AD by regulating key pathological processes, such as Aβ production, tau protein phosphorylation, and neuroinflammation.[108,131] miRNA mimics or inhibitors can be employed to modulate miRNA expression. Research has shown that miR-195 significantly reduces the Aβ burden and cognitive impairment by targeting the BACE1 and tau proteins.[108] In addition, overexpression of miR-188-3p can reduce Aβ production and improve cognitive function.[109] By designing miRNA mimetics or inhibitors, miRNA expression can be precisely regulated to intervene in the pathological process of AD. This method has high targeting ability and specificity and may become an important direction for future AD treatment.

siRNA is also used to target key proteins for AD treatment. Research has shown that siRNAs targeting BACE1 can significantly reduce Aβ levels.[132] In addition, siRNAs can target APP and tau protein, inhibiting Aβ production and abnormal phosphorylation of tau protein.[133] By delivering siRNA to the central nervous system through delivery systems such as lipid nanoparticles, precise treatment can be achieved.[133] This method has shown significant effects in animal models and is expected to be applied in clinical practice in the future.

CircRNAs act as sponges by binding to miRNAs and regulating their activity. For example, ciRS-7 reduces Aβ production and improves cognitive function through sponging of miR-7.[127] Furthermore, circRNAs can reduce the accumulation of Aβ by regulating protein degradation pathways. By designing circRNA analogues or regulating their expression, their sponge-like effects on miRNAs can be enhanced, thereby inhibiting Aβ production and neuroinflammation, providing new ideas for AD treatment.

By designing lncRNA-targeted drugs or regulating their expression, key pathological pathways in AD can be precisely altered. For example, knocking down the lncRNA BACE1-AS or NEAT1 can reduce Aβ production and improve cognitive function.[134] The lncRNA BACE1-AS can also be used to stabilize BACE1 mRNA and reduce Aβ production, and NEAT1 can be used to regulate the miR-124/BACE1 axis to intervene in AD progression.[135,136]

## Future Directions and Challenges

Investigating epigenetic mechanisms not only deepens our understanding of AD aetiology but also guides the development of diagnostic tools and therapeutic strategies that intervene in or reverse pathogenic epigenetic alterations.

First, systematic profiling of epigenetic alterations during AD progression will expand our understanding of its aetiology. For example, as the body ages, organelles in cells are degraded, leading to the disruption of nutrient utilization and metabolic pathways. Reduced ATP and the resulting activation of histone methyltransferases such as EZH2 leads to dephosphorylation, thus inactivating the kinase AKT1 and the transcription factors JUN, JNK1/3, ERK1, etc., resulting in a decrease in the expression of the histone demethylase KDM6b and the histone acetyltransferase P300, a decrease in histone methylation (H3K27me), hypoacetylated or lactated (H4K18la), and a subsequent decrease in the transcription of the SLC40A1 gene as well as ferroportin. Iron accumulates in neurons and then is converted to free radicals that damage the neurons, triggering AD.[3] In addition, the methylation of histones (such as H3K9me2 and H3K4me3) and SUMOylation of p53 can also cause pathological accumulation of Aβ, excessive phosphorylation of tau protein, neuroinflammation, synaptic dysfunction, and a decline in memory and cognitive function.[14,15,39,40] miR-16 can regulate the expression of APP and BACE1, thereby reducing the production of Aβ and the phosphorylation level of tau protein.[16] These findings have enriched our understanding of AD pathology.

Second, the AD-specific epigenetic changes discovered in research studies can also guide the development of AD diagnostic reagents. The traditional diagnosis of AD is based mainly on consultation, supplemented by medical imaging and chemical testing;[137] these methods need to be considered comprehensively, and are insufficient for a definitive diagnosis of AD.

On the basis of the specific epigenetic changes in AD patients, new kits can be developed to provide more powerful information for AD diagnosis. For example, Fotuhi reported that the long RNA BACE1-AS was specifically upregulated in serum samples from AD patients and was developed as an AD diagnostic reagent.[17] Ashish Kumar reported prediction of AD via testing serum levels of miR-132-5p and miR-125b-5p.[138]

Although histone modifications differ widely between AD patients and normal individuals, they are not specific. Further research is needed on suitable methylation markers for AD diagnosis.

Third, identifying epigenetic changes in the process of AD is helpful for the development of targeted drugs to suppress, intervene, or reverse the adverse factors that may lead to AD.

We have summarised several epigenetic interventions; however, their clinical value remains to be validated. For example, decitabine can regulate DNA methylation and promote neurodegeneration.[18,20] Resveratrol (a SIRT1 activator) can alleviate AD pathology by regulating DNA methylation to reduce the accumulation of Aβ and tau proteins.[18,20] The HDAC (histone deacetylase) inhibitors SAHA, VPA, and TSA, which can increase histone acetylation levels, increase the expression of memory-related genes, improve cognitive function, reduce Aβ accumulation, affect abnormal tau phosphorylation, and reduce NFT formation, and have the potential to delay the progression of AD. In 2025, a peptide (bs-5YP) was developed; by reducing the methylation level of the H3 of the Slc40a1 gene, it inhibited AD development in a mouse model.[3] The SUMOylation inhibitor ginkgolic acid has been developed to alleviate the ageing phenotype driven by p53 SUMOylation.[15] By designing and utilizing miRNA mimetics,[139,140] siRNAs targeting the degradation of BACE1, APP, and tau mRNA can significantly reduce Aβ levels.[135,136] Although they have shown significant effects in animal models and may become important for future AD treatment, more clinical trials are needed to verify the safety and efficacy of these drugs before application.

## Abbreviations

AD, Alzheimer's disease; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; APP, amyloid precursor protein; BACE, β-secretase; BMI1, B-cell-specific Moloney murine leukaemia virus integration site 1; CREB,

cAMP-response element binding protein; DNMT1, DNA methyltransferase 1; EZH2, enhancer of zeste homologue 2; HAT, histone acetyltransferase; EHMT1, euchromatin histone lysine methyltransferase 1; HDAC, histone deacetylase; HMT, histone methyltransferase; IDH3, isocitrate dehydrogenase 3; KDM, histone demethylase; NAD+, nicotinamide adenine dinucleotide; NEP, neprilysin; TET, ten-eleven translocation; NFTs, neurofibrillary tangles; NMDAR, N-methyl-D-aspartate receptor; OGT, O-GlcNAc transferase; OGA, O-GlcNAcase; PAX6, paired-box 6; PKM2, pyruvate kinase M2; PSEN, presenilin; RCAN1, regulator of calcineurin 1; RING1, ring finger protein 1; RPEL (PHACTR1), phosphatase and actin regulator 1; SIRT1, silent mating type information regulation 2 homolog-1; SUMOs, small ubiquitin-like modified proteins; SORL1, sortilin-related receptor; Syk, spleen tyrosine kinase.

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## Disclosure

There is no conflict of interest among the authors.

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