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# Research Progress on Alzheimer's Disease and m⁶A Modification

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**Abstract:** As a complex neurodegenerative disease, the pathogenesis of Alzheimer's disease (AD) has not been fully elucidated. This article reviews the role and regulatory mechanism of m⁶A modification in AD, with the aim of exploring how m⁶A modification participates in the pathological process of AD by regulating the "writer", "eraser", and "reader" proteins, and evaluating its potential in diagnosis, treatment, and prognosis. This article systematically summarizes the regulatory mechanisms of m⁶A modification on amyloid metabolism, Tau protein phosphorylation, neuronal apoptosis, synaptic function, and neuroinflammation, and reviews the research progress on m⁶A-related biomarkers and targeted therapy strategies. The results indicate that abnormal levels of m⁶A modification and related enzyme expression in brain tissue and peripheral blood of AD patients lead to metabolic disorders of key genes such as APP, BACE1, and MAPT mRNA, which promote A β deposition and Tau pathology, while exacerbating neuronal damage and neuroinflammation. In addition, peripheral blood m⁶A regulatory factors and modification sites can serve as potential biomarkers for early diagnosis and prognostic evaluation of Alzheimer's disease, and targeted therapy strategies targeting METTL3, FTO, and non-coding RNA have shown promising application prospects. The conclusion is that in-depth analysis of the dynamic regulatory network modified by m⁶A is expected to provide new ideas and targets for early diagnosis, precise treatment, and prognosis improvement of AD.

**Keywords:** Alzheimer disease; m⁶A modification; RNA methylation; Amyloid protein; Tau protein

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## 1. Introduction

N6-methyladenosine (m⁶A) is one of the most common internal modifications in eukaryotic mRNA modifications, accounting for more than 80% of all RNA methylation modifications, and is widely present in mRNA, tRNA, rRNA, and non-coding RNA (ncRNA). Its chemical structure is that the N6 nitrogen atom of adenine is methylated, which usually occurs in the conserved RRACH sequence motif (R=G/A, H=A/C/U). This motif is highly conserved among different species, suggesting that m⁶A modification has important biological functions. m⁶A modifications are mainly distributed in the 3'untranslated region (3'UTR), near the stop codon, and in the

exon regions of mRNA. They are catalyzed by methyltransferase complexes ("Writers") in the nucleus, can be removed by demethylases ("Erasers") in the cytoplasm, and are recognized by methylation reader proteins ("Readers") to regulate the fate of RNA [7–9].

Compared with other neurodegenerative diseases, the abnormal pattern of m⁶A modification in AD is more complex and closely related to core pathological features. Firstly, m⁶A levels in the cerebral cortex and hippocampus of AD patients show region-specific changes. For example, m⁶A levels are increased in the cortex and hippocampus of APP/PS1 transgenic mice, and are also significantly elevated in PS19 Tau transgenic mice. Moreover, in APPNL-G-F/MAPTP301S double transgenic mice, m⁶A accumulation has a stronger correlation with Tau pathology than with Aβ pathology. Secondly, abnormal m⁶A levels and expression of related enzymes exist in the peripheral blood of AD patients [4].

## 2. Molecular mechanism of m⁶A modification and its regulatory network

### 2.1. Functions and regulation of m⁶A writers (methyltransferases)

N6-methyladenosine (m⁶A) modification, as one of the most abundant internal modifications in eukaryotic RNA, is dynamically maintained by methyltransferase complexes (Writers), demethylases (Erasers), and reader proteins (Readers). Among them, m⁶A Writers are mainly responsible for catalyzing the methylation of the N6 position of adenosine on RNA, and their core complex consists of subunits such as METTL3, METTL14, WTAP, VIRMA, and ZC3H13. Each subunit achieves precise modification of target RNA through synergistic effects. As the core catalytic subunit, the N-terminal MTase domain of METTL3 has methyltransferase activity, while METTL14 enhances the substrate specificity of the complex by providing RNA-binding sites. The two form a heterodimer to constitute the catalytic core.

Under normal physiological conditions, m⁶A Writers exhibit region-specific expression patterns in brain tissues. For instance, METTL3, METTL14, and WTAP are highly expressed in brain regions associated with learning and memory, such as the hippocampus and cerebral cortex, suggesting their important roles in maintaining neural functions. However, under the pathological state of Alzheimer's disease (AD), the expression and function of m⁶A Writers undergo significant abnormalities. Multiple studies have shown that the expression level of METTL3 in the brain tissues of AD patients is significantly reduced, and this reduction is closely related to the pathological progression of AD.

### 2.2. Functions and regulation of m⁶A erasers (demethylases)

m⁶A Erasers are primarily responsible for removing m⁶A modifications from RNA, thereby enabling the dynamic reversibility of m⁶A modifications. Currently identified m⁶A Erasers mainly include FTO and ALKBH5, both of which belong to the $Fe^{2+}$ and α-ketoglutarate-dependent dioxygenase family, but they differ significantly in substrate preference and subcellular localization. FTO is mainly localized in the nucleus and cytoplasm, and its substrates include not only mRNA but also non-coding RNAs such as tRNA and rRNA, while ALKBH5 is mainly localized in the nucleus, with its substrates primarily being mRNA and lncRNA.

Under normal physiological conditions, m⁶A Erasers play important regulatory roles in brain tissues. For example, the deletion of ALKBH5 impairs the learning and memory abilities of mice, indicating its crucial role in maintaining neural functions. However, under the pathological state of Alzheimer's disease (AD), the expression and functions of m⁶A Erasers also undergo significant changes. Multiple studies have shown that the expression

level of FTO in the brain tissues of AD patients is significantly reduced, while the expression of ALKBH5 shows region-specific changes [5].

### 2.3. Functions and regulation of m⁶A readers

m⁶A Readers are a class of proteins that can specifically recognize and bind to m⁶A modification sites. By binding to m⁶A-modified RNAs, they regulate various biological processes such as RNA splicing, transport, stability, and translation efficiency. Based on differences in their structure and function, m⁶A Readers are mainly divided into YTH domain family proteins (e.g., YTHDF1/2/3, YTHDC1/2), IGF2BP family proteins (e.g., IGF2BP1/2/3), and HNRNP family proteins (e.g., HNRNPA2B1), etc. Among them, YTHDF family proteins are mainly localized in the cytoplasm and participate in regulating mRNA translation and stability; YTHDC family proteins are mainly localized in the nucleus and participate in regulating mRNA splicing and nuclear export; IGF2BP family proteins enhance mRNA stability by binding to it; HNRNP family proteins participate in regulating RNA splicing and processing.

Under the pathological state of Alzheimer's disease (AD), the expression and function of m⁶A Readers are significantly abnormal, and such abnormalities are closely related to the pathological progression of AD. For example, the expression level of YTHDF2 is significantly increased in the brain tissues of AD patients, while the expression of YTHDC1 is significantly decreased. These changes may participate in the pathological process of AD by regulating the metabolism of target mRNAs [5].

## 3. Regulatory mechanisms of m⁶A modification in Alzheimer's disease

### 3.1. Regulation of m⁶A modification and amyloid metabolism

Dysregulation of amyloid metabolism is one of the core pathological processes of Alzheimer's disease (AD), and m⁶A modification, as a key mechanism of post-transcriptional regulation of RNA, plays multi-dimensional roles in this process. By affecting the mRNA stability, translation efficiency, or splicing process of amyloid precursor protein (APP), β-site amyloid precursor protein-cleaving enzyme 1 (BACE1), and their related non-coding RNAs, as well as Aβ-degrading enzymes, m⁶A modification directly or indirectly regulates the balance between Aβ production and clearance.

As the precursor protein of Aβ, the m⁶A modification status of APP mRNA directly affects the production of Aβ. Studies have found that there are m⁶A modification sites in the 3'UTR region of APP mRNA, and the methylation status of these sites is regulated by the m⁶A methyltransferase METTL3. When the expression of METTL3 is down-regulated, the m⁶A modification level of APP mRNA decreases, leading to an abnormal increase in its translation efficiency, which in turn increases the production of Aβ. In addition, the m⁶A reader protein YTHDF1 can recognize the m⁶A sites of APP mRNA and promote its translation process. This mechanism has been verified in an Aβ-induced cell model: after Aβ treatment, the expression of METTL3 is inhibited, and YTHDF1-mediated APP translation is enhanced, further exacerbating Aβ deposition.

### 3.2. The relationship between m⁶A modification and Tau protein phosphorylation

Hyperphosphorylation and aggregation of the Tau protein are another core pathological feature of AD. m⁶A modification directly or indirectly affects the phosphorylation state of the Tau protein by regulating the mRNA metabolism of MAPT, the gene encoding the Tau protein, and the expression of related kinases.

The m⁶A modification of MAPT mRNA is mainly concentrated in the 3'UTR region, and the methylation

status of these sites is regulated by the METTL3-METTL14-WTAP complex. Studies have found that the level of m⁶A modification of MAPT mRNA is significantly increased in the brain tissues of AD patients and the APP/PS1 mouse model, which is closely related to the up-regulated expression of METTL3 and the down-regulated expression of the demethylase ALKBH5. The reading protein YTHDF3 can recognize the m⁶A sites of MAPT mRNA, promote its translation process, leading to increased expression of the Tau protein, which in turn exacerbates its phosphorylation and aggregation.

### 3.3. The effects of m⁶A modification on neuronal apoptosis and synaptic function

The maintenance of synaptic function depends on the normal expression and function of synapse-related proteins, and the mRNAs of most of these proteins are regulated by m⁶A modification. Activity-regulated cytoskeleton-associated protein (ARC) is a key molecule in synaptic plasticity. The m⁶A modification of its mRNA is mediated by METTL3, which is recognized by the reader protein YTHDF1 to promote its translation. In AD models, Aβ treatment leads to downregulated METTL3 expression, reduced m⁶A modification level of ARC mRNA, inhibited YTHDF1-mediated translation process, decreased ARC expression, and subsequent impairment of synaptic plasticity. In addition, the mRNAs of postsynaptic density protein 95 (PSD95) and Synapsin also have m⁶A modification sites, and the methylation status of these sites is altered in AD models: the m⁶A modification level of PSD95 mRNA is reduced, leading to decreased stability and expression; while the m⁶A modification level of Synapsin mRNA is increased, enhancing translation efficiency, but the abnormally translated products may have functional defects. Electrophysiological studies have further confirmed the impact of m⁶A modification on synaptic function: METTL3 knockout mice exhibit long-term potentiation (LTP) deficits, whereas METTL3 overexpression can reverse Aβ-induced LTP impairment.

### 3.4. The role of m⁶A modification in neuroinflammation

The mRNA m⁶A modification status of pro-inflammatory and anti-inflammatory cytokines shows significant differences in AD models. The mRNA m⁶A modification levels of pro-inflammatory cytokines such as IL-1β and TNFα are increased in AD models. This modification is mediated by METTL3, and after recognition by the reader protein YTHDF1, it promotes their translation, leading to massive release of pro-inflammatory cytokines. In contrast, the mRNA m⁶A modification levels of anti-inflammatory cytokines such as IL-10 and TGFβ are decreased, resulting in reduced stability and expression, which further exacerbates the inflammatory response.

## 4. Application of m⁶A modification in clinical research of Alzheimer's disease

### 4.1. The potential of m⁶A modification as a biomarker

Early diagnosis and monitoring of disease progression in Alzheimer's disease (AD) are among the core challenges in clinical diagnosis and treatment. Although traditional biomarkers such as Aβ42, total tau (T-tau), and phosphorylated tau (P-tau) in cerebrospinal fluid (CSF) have high specificity, their application in large-scale screening is limited due to invasive sampling; while blood biomarkers such as the plasma Aβ42/Aβ40 ratio are convenient, they suffer from insufficient sensitivity. In recent years, m⁶A modification, as a core regulatory mechanism in epitranscriptomics, has provided an important direction for the development of novel biomarkers through its abnormal expression patterns in AD patients. At present, research on m⁶A-related biomarkers mainly focuses on three types of samples: peripheral blood (plasma and peripheral blood mononuclear cells), CSF exosomes, and nasal epithelial cells, each with its own advantages and disadvantages in terms of detection rate,

specificity, and clinical practicality.

As the most easily accessible biological sample, the association between m$^6$A modification levels in peripheral blood and Alzheimer's disease (AD) has been confirmed by multiple clinical studies. A case-control study involving 40 AD patients and 40 healthy controls showed that the plasma concentration of METTL3 (an m$^6$A methyltransferase) protein in AD patients was significantly lower than that in the control group [(22.33±3.01) ng/mL vs. (25.63±1.70) ng/mL, $P$<0.01]. Meanwhile, the plasma concentration of the demethylase FTO also showed a similar downward trend [(63.51±4.95) pg/mL vs. (69.60±4.60) pg/mL, $P$<0.01]. Further analysis of peripheral blood mononuclear cells (PBMCs) revealed that the mRNA and protein expression levels of METTL3 and FTO in PBMCs of AD patients were significantly down-regulated, and the total m$^6$A methylation level was reduced by approximately 77% compared with the control group [(0.000571±0.000167)% vs. (0.002514±0.001284)%, $P$<0.01]. This result suggests that the expression of m$^6$A regulatory factors and the total m$^6$A level in peripheral blood can serve as potential screening indicators for AD, but their specificity still needs to be verified by comparison with other neurodegenerative diseases (such as Parkinson's disease and vascular dementia).

## 4.2. Research on therapeutic strategies targeting m$^6$A modifications

### 4.2.1. Research and application of small molecule inhibitors

As the core catalytic subunit of the m$^6$A methyltransferase complex, hyperactivation of METTL3 can lead to abnormally elevated m$^6$A modification in the brain, thereby promoting Aβ deposition and tau pathology. STM2457 is the first highly selective METTL3 inhibitor, with an IC50 value of approximately 10 nM, and has shown significant anti-tumor activity in various tumor models. In AD research, breakthrough progress has been made in the application of STM2457 in humanized P301S tau transgenic mice (PS19): intraperitoneal injection of STM2457 (10 mg/kg/day for 4 consecutive weeks) can significantly reduce the total m$^6$A level in the mouse brain, reduce excessive phosphorylation of tau protein (Ser396/Ser404 sites) and the formation of neurofibrillary tangles (NFTs), while improving the spatial learning and memory ability of mice (the escape latency was shortened by about 30% in the Morris water maze test). Mechanistic studies have shown that STM2457 reduces the m$^6$A modification level of MAPT mRNA, the gene encoding tau protein, by inhibiting METTL3 activity, thereby inhibiting its translation process. However, the BBB permeability of STM2457 still needs to be optimized.

### 4.2.2. Non-coding RNA targeting strategy

ASO/siRNA strategies targeting m$^6$A regulators have been validated in various disease models. For instance, in hepatocellular carcinoma (HCC) models, METTL3 siRNA can reduce m$^6$A levels by inhibiting METTL3 expression, thereby suppressing tumor cell proliferation; in Alzheimer's disease (AD) models, intracerebroventricular injection of METTL3 siRNA can significantly decrease METTL3 expression in the mouse brain, reducing m$^6$A modification of MAPT mRNA and tau protein translation. However, the CNS delivery efficiency of siRNA is extremely low, with the brain uptake rate of traditional liposome carriers being less than 1%. In recent years, novel nanocarriers such as lipid nanoparticles (LNPs) and AAV9 vectors have shown promising application prospects: LNPs can enhance BBB penetration through surface modification with targeting peptides (e.g., transferrin receptor peptides), and their brain delivery efficiency is more than 10 times higher than that of traditional liposomes; AAV9 vectors have a natural tropism for the CNS, can cross the BBB via intravenous injection, and efficiently express siRNA in neurons and glial cells. Nevertheless, these carriers still have off-target effects. For example, AAV9 may accumulate in large quantities in the liver, leading to hepatotoxicity. In the

future, tissue-specific promoters (e.g., neuron-specific Synapsin promoter) need to be used to improve targeting specificity.

The ncRNA strategies targeting m⁶A modification mainly focus on lncRNAs, among which BACE1-AS is the most extensively studied target. BACE1-AS is an antisense lncRNA of the BACE1 gene, and its m⁶A modification can enhance its own stability, thereby promoting the translation of BACE1 mRNA through base pairing and increasing the production of Aβ. In AD mouse models, injection of ASOs targeting BACE1-AS can significantly reduce its expression level, decrease BACE1 protein and Aβ deposition, and improve cognitive function.

### 4.3. A Study on the correlation between m⁶A modification and the prognosis of Alzheimer's disease

Regarding cognitive decline, a study based on the ADNI (Alzheimer's Disease Neuroimaging Initiative) cohort found that the expression level of METTL3 in PBMCs of MCI patients was significantly correlated with the annual decline rate of MMSE scores: the lower the METTL3 expression, the faster the MMSE score decline (HR=1.87, 95%CI: 1.12–3.12). Another study targeting the ROSMAP (Religious Orders Study and Memory and Aging Project) cohort showed that the expression level of YTHDF1 (an m⁶A reader protein) in the brain was negatively correlated with cognitive function in AD patients, and the rate of cognitive decline in individuals with high YTHDF1 expression was 2.1 times that of those with low expression ($P$<0.05). Mechanistic studies have demonstrated that YTHDF1 can promote the translation of APP mRNA by recognizing its m⁶A modification sites, thereby accelerating Aβ deposition, which provides a biological basis for its use as a prognostic biomarker.

In terms of survival prediction, a nomogram model based on 16 m⁶A regulators showed a C-index of 0.78 for predicting 3-year survival in AD patients, which was significantly higher than the 0.65 of traditional clinical indicators (such as age, gender, and ApoEε4 genotype). Among them, high expression of regulators such as METTL14 and WTAP is associated with poor prognosis, and the mechanism may be related to the promotion of tau pathology and neuroinflammation.

Brain atrophy is an important pathological feature of AD and is closely associated with cognitive decline. A study based on MRI data found that the annual atrophy rate of the hippocampus in AD patients is significantly correlated with the level of m⁶A in the brain: the higher the m⁶A level, the faster the hippocampal atrophy (r=0.42, $P$<0.01). Further analysis showed that the expression level of METTL3 was positively correlated with the hippocampal atrophy rate (r=0.38, $P$<0.01), and its mechanism may be related to METTL3 promoting excessive phosphorylation of tau protein, leading to neuronal death.

## 5. Summary and outlook

In summary, although significant progress has been made in understanding the mechanism of m⁶A modification in Alzheimer's disease (AD), many challenges and unsolved mysteries remain. There are still controversies regarding the consistency of results among different research models, and these differences may be related to research models, brain region selection, time points, and detection methods. Future studies need to further optimize experimental designs and unify detection standards to obtain more consistent and reliable results. m⁶A modification biomarkers also need to be combined with other biomarkers (such as Aβ, Tau protein, and neuroimaging biomarkers) to construct a multi-dimensional AD diagnostic model, improving the accuracy and specificity of diagnosis. In terms of therapeutic strategies, although the development of drugs targeting m⁶A

modification has broad prospects, it still faces problems such as off-target effects, blood-brain barrier penetration, and long-term safety. Future studies need to develop highly selective and specific m⁶A modification-targeting drugs, optimize their pharmacokinetic and pharmacodynamic properties, and ensure their safety and efficacy in AD treatment. Looking forward, by integrating genomics, transcriptomics, epitranscriptomics, and proteomics data, the regulatory network and key nodes of m⁶A modification in AD can be fully revealed, providing new targets for the precise treatment of AD. In conclusion, as a dynamic and reversible epigenetic mechanism, m⁶A modification plays an important role in the pathogenesis and therapeutic strategies of AD, providing new ideas and targets for the prevention and treatment of AD. With the continuous deepening of research, m⁶A modification is expected to become an important breakthrough in the diagnosis and treatment of AD, bringing new hope to AD patients [1–10].

## Disclosure statement

The authors declare no conflict of interest.

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