Proceedings of Anticancer Research, 2026, Volume 10, Issue 4
http://ojs.bbwpublisher.com/index.php/PAR
Online ISSN: 2208-3553
Print ISSN: 2208-3545

Research Progress on the Mechanisms of m6A Methylation in Neurodegenerative Cognitive Disorders

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Abstract: *Objective*: To explore the core role of N6-methyladenosine (m6A) methylation in neurodegenerative cognitive disorders, with a particular focus on its contribution to disease progression through the regulation of common mechanisms such as neuroimmune inflammation, and to discuss its clinical translational prospects. *Methods*: A systematic review of recent research literature on m6A methylation in neurodegenerative diseases, including Alzheimer›s disease and Parkinson›s disease, was conducted, integrating analyses from molecular mechanisms, cellular phenotypes, to systemic pathology. *Results and Conclusions*: As a key epitranscriptomic regulatory mechanism, m6A methylation precisely regulates neural synaptic plasticity, autophagic clearance, and neuroimmune homeostasis through a dynamic network comprising "writer", "eraser", and "reader" proteins. Its homeostatic imbalance represents a core pathological hub leading to cognitive dysfunction: on one hand, m6A dysregulation directly mediates the polarization of microglia towards a pro-inflammatory M1 phenotype, amplifying neuroinflammatory responses; on the other hand, it exacerbates neuronal injury by affecting the metabolism of pathological proteins such as Tau and α-synuclein. Targeting m6A regulatory enzymes (e.g., FTO inhibitors, METTL3 activators) has shown potential for improving cognitive function in preclinical models. Additionally, biomarkers like m6A in peripheral blood exosomes hold value for non-invasive diagnosis. In summary, m6A methylation serves as a critical link connecting common pathological mechanisms across various neurodegenerative diseases, offering broad translational application prospects in disease diagnosis and targeted therapy.

Keywords: m6A methylation; Neurodegenerative diseases; Cognitive impairment; Neuroimmune inflammation; Epitranscriptomics; Biomarkers; Targeted therapy

Online publication: August 12, 2026

1. Introduction

Neurodegenerative cognitive disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD),

represent major global public health challenges. Their core pathological features include pathological protein aggregation, progressive neuronal loss, and the increasingly recognized neuroimmune inflammatory response [1,2]. Despite ongoing research, their pathogenesis remains incompletely elucidated, and effective disease-modifying therapies are lacking. Therefore, identifying common, modifiable early pathological nodes in these diseases is an urgent research priority.

Among numerous potential mechanisms, RNA epigenetics, particularly N6-methyladenosine (m6A) methylation, has rapidly emerged as a frontier topic in neuroscience [4]. As the most prevalent and abundant internal chemical modification in eukaryotic mRNAs, m6A is not a static mark but a dynamic, reversible process co-regulated by methyltransferases (e.g., the METTL3/METTL14 complex, "writers"), demethylases (e.g., FTO, ALKBH5, "erasers"), and binding proteins (e.g., the YTHDF family, "readers") [14]. This "chemical modification–functional decoding" rapid regulatory mode endows m6A with unique spatiotemporal advantages in mediating neurobiological processes such as rapid synaptic remodeling, neurogenesis, and stress responses [16,17].

Crucially, mounting evidence indicates that homeostatic imbalance of m6A methylation serves as a common key node driving neurodegenerative pathology. Studies have found characteristic alterations in m6A modification levels in disease models such as AD and PD, which directly participate in the onset and progression of cognitive dysfunction through multiple mechanisms, including regulating neuroimmune inflammatory pathways, affecting pathological protein metabolism, and impairing synaptic plasticity [11,19]. For instance, m6A modification can specifically regulate the activation phenotype of microglia, driving their polarization towards a neurotoxic M1 state, thereby amplifying inflammatory cascades and accelerating disease progression [25].

This review aims to systematically synthesize the latest research advances, providing an in-depth exposition, from the perspective of an "epitranscriptomic hub," of the common pathological mechanisms of m6A methylation across various neurodegenerative cognitive disorders, with a particular focus on its core regulatory role in neuroimmune inflammation. Furthermore, we will discuss the development of diagnostic biomarkers and targeted therapeutic strategies centered on m6A, offering new insights and theoretical bases for early intervention in these diseases [3].

2. Molecular mechanisms of m6A methylation and its neuroregulatory functions

2.1. Molecular regulatory network of m6A methylation

2.1.1. Enzymatic regulatory system of m6A modification

The formation of m6A modification is mediated by "writers", such as the METTL3-METTL14 complex, where methyltransferase-like protein 3 (METTL3) and methyltransferase-like protein 14 (METTL14) form a heterodimer with catalytic function, specifically recognizing the RRACH sequence (a purine-rich conserved sequence) to catalyze methylation at the N6 position of adenosine [7,8]. Demethylases ("erasers"), such as fat mass and obesity-associated protein (FTO) and AlkB homolog 5 (ALKBH5), maintain dynamic modification balance through oxidative demethylation. Notably, FTO exhibits an aberrant expression pattern in the brain tissue of AD patients, and changes in its activity significantly correlate with the efficiency of m6A demethylation and the degree of cognitive impairment [9,10]. Animal model studies have found that in diabetes-related cognitive impairment, downregulation of ALKBH5 expression leads to abnormal Tau phosphorylation, suggesting that m6A homeostasis imbalance may be a significant mechanism through

which metabolic abnormalities trigger neurodegeneration [11]. Additionally, environmental stressors such as hypoxia and neuroinflammation can reshape the m6A epitranscriptomic features of neurons by regulating the expression profiles of writers and erasers [12,13].

The regulation of m6A modification is not limited to mRNA but also includes non-coding RNAs (e.g., lncRNA, circRNA) and pri-miRNA. m6A modifications on these non-coding RNAs also possess important regulatory functions in the nervous system, such as influencing miRNA maturation or circRNA stability, further expanding the breadth and depth of m6A regulation in epitranscriptomics.

2.1.2. Functional diversity of m6A reader proteins

YTH domain-containing family proteins (YTHDF proteins), as classical reader molecules, specifically recognize m6A modifications and regulate target RNAs. Among them, YTHDF1 promotes the translation efficiency of modified mRNAs, while YTHDF2 accelerates their degradation. This selective regulation exhibits spatiotemporal specificity in the nervous system [14]. Particularly, YTHDF1 and YTHDF2 participate in the molecular regulatory network of synaptic plasticity and memory consolidation by regulating the expression programs of synapse-related genes. In AD models, dysfunction of the m6A-reader system has been observed, potentially affecting β-amyloid metabolic pathways and offering new intervention targets for therapy [15]. Furthermore, studies have found that m6A-dependent translational regulation directly participates in the synthesis of memory-related proteins (e.g., ARC), solidifying its central role in higher cognitive functions [16].

2.1.3. Precise regulation of gene expression mediated by m6A

m6A regulates gene expression through three primary mechanisms: (1) Structure-dependent degradation, altering RNA secondary structure to enhance nuclease sensitivity, e.g., YTHDF2-targeted degradation [14]; (2) Translation activation, recruiting YTHDF1 to promote ribosome binding [16]; and (3) Splicing regulation, affecting the binding sites of splicing factors, e.g., via hnRNP-dependent pathways [16]. In cognitive function studies, overexpression of METTL3 upregulates the expression of neuroplasticity-related genes (such as BDNF and PSD95) and significantly improves cognitive behavioral performance in model animals. This epigenetic regulatory mechanism is also involved in neurogenesis, influencing the construction of neuronal networks by affecting the proliferation and differentiation of neural precursor cells.

2.2. Functions of m6A in the nervous system

2.2.1. Epigenetic regulatory programs in neural development

m6A modification participates in the regulation of neurogenesis in a spatiotemporally specific manner, dynamically and coordinately regulated by writers, erasers, and readers. In neural stem cells, METTL3-mediated m6A modification has been confirmed as a key determinant of the balance between proliferation and differentiation. Gene knockout experiments demonstrate that m6A deficiency leads to neural developmental arrest and cortical abnormalities [17]. Mechanistically, METTL3-mediated m6A modification regulates histone methyltransferase Ezh2, influencing the eventual fate decision of neural stem cells towards neuronal or glial differentiation [17]. Studies on environmental stimulation confirm that housing in an enriched environment promotes the proliferation of neural precursor cells by upregulating m6A modification levels (e.g., Sox2 mRNA methylation) [18]. At the synaptic development level, the abundance of m6A modification in hippocampal neurons positively correlates with the expression of synaptic marker proteins like synapsin,

indicating its involvement in the molecular regulation of synaptic maturation. Notably, activity-dependent m6A modification rapidly responds to neuronal electrical activity, regulating the translation of immediate early genes (e.g., ARC), thereby providing an instantaneous regulatory mechanism for synaptic plasticity [18]. Experiments confirm that housing in an enriched environment significantly elevates m6A modification levels in neural stem cells, and this epigenetic reprogramming may be the molecular basis for environment-enhanced cognitive function.

2.2.2. Epigenetic regulatory mechanisms of synaptic plasticity

Synaptic plasticity, the molecular foundation of learning and memory, is exquisitely and precisely regulated by the m6A network. Electrophysiological studies confirm a correlation between the level of m6A modification and the strength of long-term potentiation (LTP) in the hippocampus [18]. Mechanistically, activation of N-methyl-D-aspartate receptors (NMDARs) induces remodeling of synaptic local m6A modifications, affecting synaptic strength by regulating the translational efficiency of key signaling molecules like calcium/calmodulin-dependent protein kinase II (CaMKII). Activity-dependent m6A modification, via YTHDF1-mediated translation activation, rapidly upregulates the expression of synaptic proteins (such as ARC, BDNF, PSD95), directly enhancing synaptic transmission efficacy [16,18]. In AD models, overexpression of METTL3 improves synaptic plasticity by restoring m6A-dependent translation of PSD95 [26]. Further studies indicate that METTL3 overexpression not only enhances PSD95 translation efficiency but also increases the density and maturity of dendritic spines, as validated by electron microscopy and confocal imaging. Additionally, METTL3-mediated m6A modification influences the expression of AMPA receptor subunits like GluA1, affecting excitatory synaptic transmission efficiency, thereby promoting synaptic functional recovery at both molecular and structural levels. In pathological states, brain tissue from AD patients exhibits global m6A modification dysregulation, and this abnormality significantly correlates with synaptic protein synthesis deficits and the extent of memory impairment [19].

3. Mechanisms of m6A methylation in cognitive dysfunction

3.1. Pathological features of m6A methylation in cognitive dysfunction

Within the molecular regulatory network, m6A dysregulation disrupts neural homeostasis, driving cognitive impairment, and its pathological features exhibit commonalities across related diseases.

Table 1. Pathological features of m6A in common cognitive disorders

Type	Core Pathology	m6A-Related Dysregulation Features
AD	Aβ Deposition & Tau Phosphorylation	Downregulated METTL3, Upregulated FTO [24]
Parkinson's Disease Dementia	α-synuclein Aggregation	Downregulated ALKBH5 leading to autophagy flux impairment [31]
Postoperative Cognitive Dysfunction (POCD)	Neuroinflammation	Decreased global transcriptomic m6A levels [5]
Diabetes-Related Cognitive Impairment	Tau Hyperphosphorylation	ALKBH5-DGKH pathway dysregulation [11]

3.2. Molecular mechanisms of m6A methylation mediating cognitive dysfunction

m6A dysregulation mediates cognitive impairment primarily through the following pathways:

(1) Synaptic protein synthesis impairment, where YTHDF1 dysfunction hinders the translation of ARC and BDNF, leading to decreased synaptic plasticity [16,21];
(2) Amplified neuroinflammation, as microglial m6A modification promotes M1 polarization, exacerbating Aβ-induced neurotoxicity [25];
(3) Pathological protein accumulation, involving downregulated ALKBH5 leading to Tau hyperphosphorylation and METTL3 deficiency impairing α-synuclein clearance [11,31];
(4) Metabolic-epigenetic interactions, e.g., hyperglycemia inhibits ALKBH5, blocking DGKH demethylation and ultimately leading to Tau pathology [11]. Additionally, dynamic changes in hippocampal m6A in aged animal models further confirm its role in cognitive decline [22].
(5) Mitochondrial dysfunction and energy metabolism impairment: m6A modification affects mitochondrial dynamics and energy supply by regulating the expression of mitochondrial-related genes (e.g., Mfn2, OPA1). In AD models, METTL3 deficiency leads to reduced m6A modification and stability of Mfn2 mRNA, inducing mitochondrial fragmentation and decreased ATP synthesis, exacerbating neuronal energy crises and apoptosis.

4. Pathological roles of m6A methylation in major neurodegenerative cognitive disorders

4.1. Association of m6A methylation with Alzheimer's disease

In AD patients and transgenic animal models, m6A modification levels show significant changes in brain regions (e.g., hippocampus and cortex). Studies in amyloid precursor protein (APP)/presenilin 1 (PS1) transgenic mice confirm that global m6A methylation levels are significantly elevated in AD-related brain regions and positively correlate with pathological features such as Aβ deposition and neuronal loss [23]. Multiple core pathways are involved:

(1) Synaptic dysfunction pathway: Reduced YTHDF1 expression in the hippocampus leads to dendritic spine loss [21];
(2) Inflammation amplification pathway: Microglial m6A modification promotes IL-1β release via Notch1 signaling, accelerating Aβ deposition [25];
(3) Tau pathology pathway: FTO-mediated impairment of Tau mRNA demethylation exacerbates neurofibrillary tangle formation [9], collectively leading to cognitive decline [24]. Aberrant m6A modification also impairs neuronal survival by regulating the expression of synaptic plasticity-related genes (e.g., BDNF, SYP) and increases neuronal sensitivity to oxidative stress and inflammation. Recent studies also indicate that m6A modification affects Aβ-induced mitochondrial damage clearance by regulating the expression of mitophagy-related genes (e.g., PINK1, Parkin). METTL3 deficiency reduces m6A modification of PINK1 mRNA, decreasing its stability, thereby weakening mitophagy and accelerating neuronal senescence and death. The dynamic balance of m6A modification is co-regulated by writers (METTL3, METTL14) and erasers (FTO, ALKBH5). In AD, METTL3 expression is significantly downregulated, while FTO expression is upregulated [24]. Studies have found that altered m6A modifications can drive microglial polarization towards a pro-inflammatory phenotype (M1), exacerbating Aβ-induced neurotoxicity and worsening AD pathology [25].

Consequently, intervention strategies targeting m6A modification have shown promising therapeutic

prospects. For example, in AD mouse models, modulating METTL3 expression via pharmacological or genetic means has been shown to restore m6A homeostasis and improve synaptic plasticity and cognitive function based on the mechanisms described above (e.g., enhancing PSD95 translation, increasing dendritic spine maturity) [26].

4.2. Role of m6A methylation in other neurodegenerative diseases

Beyond AD, aberrant m6A modification is also associated with the pathogenesis of PD, amyotrophic lateral sclerosis (ALS), and other neurodegenerative diseases.

In PD, m6A dysregulation is closely linked to the apoptosis and dysfunction of dopaminergic neurons. Autophagy regulatory mechanism: METTL3 deficiency reduces m6A modification of LC3-II and Beclin-1, impairing α-synuclein clearance [31]. Oxidative stress pathway: FTO overexpression activates antioxidant pathways by demethylating Nrf2 mRNA, alleviating neuronal damage [10]. Additionally, m6A modification participates in regulating the expression of dopaminergic neuron-specific genes (e.g., TH, DAT). In PD models, METTL3-mediated m6A modification of TH mRNA enhances its translation efficiency, while aberrant FTO overexpression reduces TH protein synthesis, further exacerbating dopamine synthesis deficits and motor symptoms. Studies show elevated m6A methylation levels in the substantia nigra of PD patients, correlating with abnormal α-synuclein aggregation. METTL3 deficiency increases neuronal sensitivity to oxidative stress, while FTO overexpression can alleviate neuronal damage by reducing m6A levels.

In ALS, aberrant m6A modification is closely related to motor neuron degeneration. Studies confirm significantly elevated m6A methylation levels in the spinal cord and motor cortex of ALS patients, correlating with TDP-43 protein aggregation [27]. m6A modification influences neuronal survival through regulating autophagy and RNA metabolism. For example, increased m6A methylation inhibits the expression of autophagy-related genes, leading to abnormal protein accumulation and accelerated motor neuron death.

Furthermore, m6A modification plays a significant role in psychiatric disorders like depression. Altered m6A modification in the prefrontal cortex of depression patients may affect the expression of synaptic plasticity and neurotransmitter-related genes, contributing to cognitive dysfunction.

In summary, m6A methylation plays a crucial role in various neurodegenerative diseases, participating in disease initiation and progression through regulation of RNA metabolism, neuronal function, autophagy, and neuroinflammatory pathways.

5. Future research directions and clinical applications

5.1Clinical application prospects of m6A methylation

5.1.1 Diagnostic and predictive value as biomarkers

Recent studies reveal characteristic changes in m6A-related molecules in neurodegenerative diseases, showing significant clinical translational potential. Non-invasive diagnosis: Serum exosomal m6A modification levels in AD patients are highly consistent with cerebrospinal fluid (CSF) findings ($r = 0.81$, $p < 0.001$), with exosomal YTHDF2 protein effectively distinguishing mild cognitive impairment (MCI) from AD stages (AUC = 0.83) [28,31]. Disease progression prediction: The co-expression pattern of m6A regulatory factors SNRPG/SNRPD2 can predict the risk of MCI-to-AD conversion (HR = 3.21) [4], while CSF m6A-modified circular RNAs (circRNAs) show 92% sensitivity for early AD detection [24], significantly outperforming the traditional Aβ42/Tau ratio.

Technological innovations enabling precise subtyping: Single-cell nanopore sequencing technologies can now resolve m6A site maps of neuronal subpopulations, e.g., specific modifications of ARC mRNA in the hippocampal CA1 region [6,30]; microfluidic chips combined with electrochemical sensor platforms allow dynamic monitoring of m6A fluctuations in living CSF with a detection limit of 0.1 fM [32]. These advances lay the groundwork for establishing a "plasma exosome m6A profile - Aβ - PET - cognitive scale" multimodal diagnostic model, potentially enabling precise staging of AD.

In addition to peripheral blood and CSF, m6A markers in saliva and urine also show preliminary diagnostic potential. For example, m6A-modified circRNAs in salivary exosomes are significantly elevated in AD patients, offering convenient, non-invasive detection suitable for elderly population screening. Moreover, combining artificial intelligence-assisted imaging with m6A models could enable higher precision prediction of disease progression, providing a time window for individualized intervention.

5.2. Progress in targeted therapeutic strategies

Breakthroughs in targeting modification enzymes: The FTO inhibitor FB23-2 blocks pathological demethylation, improving spatial memory in manganese exposure models (35% increase in Y-maze correct rate) [10]; liposome-delivered METTL3 activators (SAM-Liposomes) can restore synaptic protein PSD95 translation (2.1-fold increase in expression) [26]; AAV-mediated ALKBH5 overexpression reverses high glucose-induced Tau hyperphosphorylation (60% reduction in p-Tau Ser396) [11].

Indirect regulatory strategies also show potential: The antioxidant N-acetylcysteine (NAC) can regulate the m6A-ATF4 axis, improving cognitive deficits in PTSD models (42% reduction in Morris water maze escape latency) [29]; multi-target synergistic interventions, e.g., combining an FTO inhibitor with a METTL3 activator, can both suppress Aβ production and enhance synaptic plasticity, increasing the novel object recognition index by 50% in APP/PS1 mice [26]. Recently, gene editing and epigenetic editing technologies (e.g., the dCas13b-m6A editing system) have been used to regulate the m6A modification level of specific mRNAs precisely. In PD models, the AAV-delivered dCas13b-ALKBH5 system successfully reduced m6A levels on α-synuclein mRNA, significantly alleviating its abnormal aggregation and neurotoxicity.

5.3. Challenges and strategies for clinical translation

Current translational research faces three core challenges:

(1) Lack of detection standardization: Coefficient of variation (CV) >30% for m6A sequencing data across different platforms may lead to increased misdiagnosis rates.

(2) Low blood-brain barrier (BBB) penetration: Small molecule inhibitor concentrations in the brain are typically less than 5% of peripheral doses, potentially causing peripheral toxicity.

(3) Cell-specific effect conflicts: METTL3 activation protects synapses in neurons but promotes inflammation in astrocytes, potentially offsetting efficacy [26].

Furthermore, individual differences and disease heterogeneity represent significant issues in clinical translation. Genetic backgrounds, epigenetic states, and environmental exposures related to the m6A regulatory network vary considerably among patients, potentially leading to markedly different responses to the same intervention. Future efforts should integrate multi-omics data and real-world studies to establish personalized efficacy prediction models.

Counter-strategies focus on technological innovation and system optimization:

(1) Establishing cross-center calibration protocols (e.g., using synthetic m6A-RNA standards) to promote detection standardization.
(2) Developing exosome-encapsulated brain-targeted delivery systems (e.g., 8-fold increase in brain delivery efficiency for ALKBH5 inhibitors) [32].
(3) Integrating multi-omics data (epitranscriptomics, proteomics, radiomics) to construct disease subtyping models, coupled with long-term safety assessments in non-human primates.
(4) Utilizing artificial intelligence (e.g., AlphaFold-Epigen module) to predict associations between m6A modifications and phenotypes, ultimately achieving an individualized treatment model of "precise diagnosis – stage-based intervention."

6. Conclusions and perspectives

m6A methylation serves as a key node in epitranscriptional regulation, participating in neural development, synaptic remodeling, and neuroinflammatory processes through dynamic regulation of RNA metabolism. Its homeostatic imbalance has been confirmed as a core pathological mechanism in neurodegenerative cognitive disorders. This review systematically integrates recent groundbreaking findings, for the first time revealing the common pathological hub of m6A dysregulation across AD, PD, POCD, and metabolic disease-related cognitive deficits. These discoveries deepen our understanding of the essence of cognitive impairment and also generate new strategies with translational potential.

In the diagnostic domain, non-invasive detection systems utilizing exosomal m6A profiles and CSF circRNA-m6A, combined with single-cell nanopore sequencing to resolve specific modification sites in hippocampal neurons, may achieve "pre-symptomatic staging". Therapeutically, strategies targeting the m6A regulatory network, such as cross-target synergistic therapy, have shown groundbreaking advances. Clinical translation still faces challenges regarding molecular detection standardization, BBB penetration, and cell-specific effects, as discussed.

It is important to note that current m6A-targeted therapy research is primarily confined to animal models, and its safety and efficacy in humans require clinical validation. Future research should focus on constructing spatial epitranscriptomic maps, developing exosome-based drug delivery technologies, and AI-assisted design. Multi-center collaboration, integration of multi-omics data (epitranscriptomics, proteomics, radiomics), and long-term safety evaluations in primates are needed to advance m6A-targeted therapy from concept to clinical application, providing new avenues for the prevention and treatment of neurodegenerative cognitive disorders.

Disclosure statement

The authors declare no conflict of interest.

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