The Role of Aberrant N6-Methyladenosine in Brain Disorders

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Abstract: N6-methyladenosine (m6A) methylation, the central eukaryotic RNA epigenetic modification, dynamically modulates RNA metabolism via the “writer-eraser-reader” network and influences neural development, synaptic plasticity, and brain disease progression. METTL3 suppresses Sox2 mRNA degradation during neural development to promote neuronal differentiation, while YTHDF2 mediates axon guidance gene degradation to modulate neural circuit assembly; YTHDF1-mediated local translation of synaptic proteins is learning and memory dependent. In illness, m6A imbalance is the basis of pathogenic mechanisms in Alzheimer's disease, glioblastoma, and traumatic brain injury. m6A regulatory components are potential prospects in preclinical models, but more investigations are desirable into multi-modification interaction machinery and tool development.

1 INTRODUCTION

One of the major processes that control brain function is RNA epigenetic modification. N6-methyladenosine (m6A) modification is the most prevalent epitranscriptomic marker, representing 80% of all RNA base methylation. In mammals, mA methylates 0.1%-0.4% of all the adenine in the transcriptome at any time (Wiener & Schwartz 2021). The "writing" methyltransferase (METTL3/METTL14) complex, comprising the METTL3 adaptor protein, WTAP, and other linked proteins KIAA1429 and RBM15/15B, is deposited onto mRNA in this dynamic modification. The "reader" proteins (e.g., YTHDF 1, 2, 3) are proteins that bind specifically to the "eraser" enzyme (FTO, ALKBH5), which is responsible for removing the modification. M6A is also involved in mRNA stability, translation, splicing, and miRNA processing. Based on the context, certain reader proteins will detect the m6A marker and advance its function. Furthermore, as m6A is a reversible modification, it is possible that both labeled and unlabeled mRNA can be washed away quickly so that stringent and quick regulation of mRNA is accessible. Recent research has revealed that dynamic m6A imbalance is closely correlated with the occurrence and development of a range of brain diseases, and its mechanism is multi-level regulation including pathological protein aggregation, metabolic disorder, inflammatory activation, and epitranscriptome reprogramming, which opens a new idea for the molecular mechanism of brain diseases.

m6A modification is involved in neurodegenerative diseases with pathological protein expression spatially and temporally regulated. For instance, in the AD brain tissue, decreased m6A demethylase FTO expression increases the stability of the mRNA for the tau protein and worsens the neurofibrillary tangle. Concurrently, deletion of YTHDF1 suppresses the translational efficiency of synaptic-related genes such as BDNF and impairs cognitive ability. In PD models, METTL3-catalyzed α-synuclein mRNA methylation significantly increases translation level and fosters Lewy body formation. In psychiatric and neurodevelopmental disorders, brain function is modulated by m6A by controlling the differentiation of neural stem cells and synaptic maturation. In the model of ASD, METTL3 knockout results in abnormal Notch pathway activation, suppresses neuronal migration and synaptic plasticity, and leads to social behavior abnormality. Aberrant m6A modification in hippocampus of depression patients suppresses neurogenesis through disruption of the serotonin signaling pathway, and FTO gene polymorphisms can worsen mood disorders through disruption of m6A homeostasis. Besides, m6A interaction with

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other RNA modifications (e.g., A-to-I editing) can influence neurological function through competitive regulation of RNA structure, but its synergistic mechanism in brain disorders remains to be explored.

In brain injury repair and tumor, the bidirectional regulatory role of m6A reveals its complexity. METTL3 is involved in glioblastoma (GBM) tumor progression through increased oncogene translation, including EGFR, and the overexpression of FTO facilitates immune evasion by suppressing immune checkpoint molecules like PD-L1. In ischemic stroke models, YTHDF1 inhibits neuronal apoptosis by enhancing survival protein translation (e.g., Hsp70), and m6A dynamics imbalance could strengthen the release of inflammatory mediators (e.g., IL-6), inducing secondary injury.

2 THE MECHANISM OF M6A METHYLATION

N6-methyladenosine (m6A) is the most prevalent epigenetic mark in eukaryotic RNA, whose dynamic regulation relies on the synergistic actions of "writers," "erasers," "readers," and the "anti-readers" suggested in recent years. These regulatory elements are crucial to nervous system development, synaptic plasticity, and brain disease through the precise modulation of the level and activity of RNA methylation modification.

2.1 Writer Complex

As an m6A-modified methyltransferase complex, Writer catalyzes site-specific methylation of RNA adenine N6 by multi-subunit synergy. With METTL3 as the catalytic core, the reaction of this complex is SAM-dependent as the methyl group donor and is specifically recognized by RRACH motifs (e.g., GGACU) (Shi et al. 2019). While catalytically inactive, the METTL14 positively charged RNA-binding surface significantly increases substrate binding and optimizes methyl transfer efficiency by supporting the stability of METTL3's conformation. WTAP functions as a scaffold protein in addition to positioning the complex in the nucleus, bringing in cofactors like VIRMA to facilitate preferential 3'UTR methylation (Zhao et al. 2020). As specifically noted, the RBM15/15B subunit controls neural stem cell differentiation fate by binding to U-rich sequences for targeting non-coding RNAs (e.g., XIST), which signifies the multi-dimensional role of Writer in epigenetic programming (Zhu et al. 2020). In the pathological condition, Writer's dynamic dysregulation was highly heterogeneous: glioblastoma overexpression of METTL3 enhanced ribosomal loading efficiency by increasing the m6A modification of EGFR mRNA and promoted tumor invasion; Downregulation of METTL14 in Alzheimer's disease reduces m6A levels of synapse-related genes (e.g., Shank3), suppresses YTHDF1-mediated translation, and promotes cognitive decline (Zhao et al. 2020). Moreover, METTL3 and METTL14 enrichment within neurons illustrates dynamic methylation reactions in extrasynaptic areas, outlining new knowledge of the hypothesized regulation of synaptic plasticity (Zhu et al. 2020).

2.2 Erasers

m6A modification reversal is sustained by demethylases FTO and ALKBH5, which control RNA methylation homeostasis via different mechanisms. FTO oxidatively degrades methyl groups gradually and its function is regulated very precisely by oxidative stress (i.e., inhibition of ROS) and metabolic microenvironment (i.e., competitive binding of α-ketoglutarate by succinic acid) (Shi et al. 2019). FTO not only localizes in the nucleus but also in axons and dendrites, participates in dopaminergic neurotransmission and axonal growth, and its genetic defects can cause postnatal growth retardation and neurological dysfunction in mice (Zhu et al. 2020). Reduced FTO activity in Alzheimer's disease can directly connect the disease's pathological process by increasing BACE1 mRNA stability and promoting β-amyloid production (Zhao et al. 2020). Conversely, ALKBH5 utilizes a one-step direct demethylation reaction that is catalytically inefficient and exclusively nuclear plaque localized and unable to target cytosolic mRNA. During hypoxia, HIF-1α induces ALKBH5 and exacerbates cerebral ischemic neuron apoptosis through stabilizing HIF-1α mRNA. In glioma, PD-L1 mRNA demethylation by ALKBH5 facilitates immune checkpoint molecular expression and induces tumor immune escape (Zhao et al. 2020). Substrate specificity of FTO and ALKBH5 has been demonstrated to be strongly dependent on RNA sequence context and the recruitment of accessory proteins (e.g., proline/glutamine-rich splicing factors) and thus embodies the complexity of the functional network of Eraser (Shi et al. 2019).

2.3 Readers and Anti-Readers

The biological m6A modification process was ultimately accomplished through methylation signal recognition by the reader and anti-reader antagonistic regulation. The traditional reader protein YTHDC1 controls Mecp2 mRNA processing via RNA splicing regulation, and its mutation results in a Rett syndrome-like phenotype. Cytosolic YTHDF1 promotes translation of synaptic protein (e.g., PSD95) by binding eIF3 translation factors, whereas YTHDF2 shields neurons from cerebral ischemia via degradation of pro-apoptotic genes (e.g., Bim) mRNAs with the CCR4-NOT complex (Shi et al. 2019, Zhao et al. 2020). Non-YTH domain readers, e.g., IGF2BP family, are currently tumor targets of treatment interacting with m6A-modified mRNAs (MYC, SOX2) via the KH domain to suppress miRNA-mediated decay and preserve glioma stem cell stemness (Zhu et al. 2020). Anti-reader reverses m6A activity by competitive binding or structural interference: HNRNPC binds to the flanking U-rich motif of m6A, blocks YTH protein recognition by steric hindrance, and controls dendritic delivery of Grin2b mRNA, the NMDA receptor subunit; Fragile X mental retardation protein (FMRP) represses translational activation of YTHDF1 by binding to m6A-modified Shank1 mRNA, and loss causes synaptic plasticity damage, indicating the crucial role of anti-reader in neurodegenerative diseases (Zhao et al. 2020). Furthermore, G3BP1/2 stabilizes the transcript by being bound to un-methylated CAACUC motif and creating an antagonistic dynamic network with YTH protein and expanding the coverage of m6A regulation (Shi et al. 2019).

3 THE NORMAL ROLE OF M6A IN THE BRAIN

3.1 Neural Development and Differentiation: Dynamic Regulatory Network of m6A

m6A dynamically regulates the fate determination, neuron differentiation, and region-specific development of neural stem cells (NSCs) through epitranscriptional regulation of RNA molecules (e.g., mRNA, lncRNA, miRNA). It is dependent on the synergistic action of methyltransferase complexes (METTL3/METTL14/WTAP), demethylases (FTO/ALKBH5), and reading proteins (YTHDF/YTHDC). FTO controls the lipid metabolism microenvironment of NSCs in mouse models by modulating the m6A levels of fat generation-related genes (e.g., PPARγ). FTO knockdown causes dyslipidemia production, represses proliferation of NSCs, and initiates astrocyte differentiation, eventually decreasing the formation of neurons (Chen et al. 2019, Cao et al. 2020). METTL3 mediated m6A modification can improve mRNA stability of key genes during neurodifferentiation (e.g., NeuroD1 and Sox2), and thus initiate the differentiation of NSCs into the neural lineage. METTL3 inhibition initiates abnormal over-piling of undifferentiated NSCs, and results in abnormalities in cortical development (Livneh et al. 2020, Wei & He 2021, Yang et al. 2019). During cerebellar development, METTL3 controls cell migration and differentiation by interfering with the Shh pathway-associated genes (like Gli1) of the granule neuron precursors. METTL3 loss leads to a reduction in the thickness of the cerebellar granule layer, thereby affecting motor coordination (Livneh et al. 2020, Zhang & Wang 2023). METTL14 deficiency impairs the spatiotemporal control of radial neuron migration in the cerebral cortex, causing impaired cortical stratification (e.g., lower number of upper neurons), which is associated with the dysregulation of m6A-dependent cell adhesion molecules (e.g., Reelin) (Livneh et al. 2020, Zhang & Wang 2023). Moreover, YTHDF2 controls the accuracy of axon growth cone guidance by degrading m6A-modified axon guidance mRNA (e.g., Ephrin receptor). This failure of the mechanism could initiate aberrant associations in the neuronal network (Zhang & Wang 2023).

3.2 Synaptic Plasticity and Learning Memory: Rapid Response and Long-Term Regulation of m6A

m6A directly contributes to synaptic reorganization, memory consolidation, and maintenance of cognitive processes by dynamic control of the translational efficacy and local stability of synaptic-related mRNAs, in temporal and spatial and stimulus responsiveness. In hippocampal neurons, YTHDF1 selectively recognizes m6A-tagged mRNA unique to synaptic plasticity (e.g., PSD95, GluA1) to induce local translation. YTHDF1 knockdown is highly effective at reducing the stability of long-term potentiation (LTP) and disrupting spatial memory formation (Livneh et al. 2020, Zhang & Wang 2023). m6A modification should also be of highly specific

regulation of local protein synthesis within synapses by recruiting RNA-binding proteins (e.g., HNRNP family) or synthesizing synaptic-related mRNA (e.g., Arc, Camk2α) into dendritic or axonal terminals (Wei & He 2021, Zhang & Wang 2023). During fear conditioning experiments, the degree of hippocampal neuronal m6A develops very quickly following memory acquisition to facilitate memory consolidation by stabilizing immediate-early gene transcripts like c-Fos. Blocking methylation of m6A will prevent memory from being consolidated in the long term (Livneh et al. 2020, Zhang & Wang 2023). Environmental factors (e.g., enriched environment) can stimulate the increase in modification level of m6A on synaptic proteins by activating the mTOR signaling pathway for overexpression of METTL3. Such dynamic regulation enables the neuron to accommodate changes in requirements of synaptic strengths in a versatile way (Wei & He 2021, Zhang & Wang 2023). Downregulation of YTHDF1 expression in the hippocampus of cognitive deficit and m6A dysregulation mice models of Alzheimer's disease causes a decrease in the translation of synaptic proteins (e.g., synaptotagmin) and is implicated in synaptic and memory loss. Restoration of m6A levels can restore synaptic function to a certain extent (Livneh et al. 2020, Zhang & Wang 2023). Decreased activity of FTO in an aging brain may lead to hyper-accumulation of m6A, silencing neuroplasticity genes like BDNF. Activation of FTO may be a novel approach toward the remediation of age-associated memory disorders (Cao et al. 2020).

4 THE ROLE OF ABERRANT M6A IN BRAIN DISEASES

4.1 Alzheimer's Disease

m6A methylation is implicated in the pathological process of AD (Alzheimer's disease) through modulation of RNA metabolism and protein homeostasis. The pathological process of AD includes accumulation of beta-amyloid protein (Aβ), Tau protein abnormal phosphorylation, oxidative stress, and damage to the cholinergic system (Shafik et al. 2021, Yang et al. 2020, Xu et al. 2020). Abnormal m6A modification was found to be highly associated with neurodegenerative alterations in AD. For instance, overexpression of METTL3 can result in improper methylation of critical mRNAs and influence synaptic plasticity and Aβ removal (Han et al. 2020, Huang et al. 2020). Furthermore, dynamic disequilibrium of m6A can induce mitochondrial damage and oxidative stress and thus advance neuronal apoptosis. Recent studies have also indicated that Tau protein plays a protective function by stabilizing microtubules in normal physiological states but is controlled by m6A modification enzymes under pathological phosphorylation, resulting in neurofibrillary tangles (NFT), eventually causing cognitive impairment (Huang et al. 2020). Therapeutic strategies against m6A (e.g., inhibiting METTL3 or activating demethylases) could become potential therapeutic agents by controlling Aβ metabolism and dynamic equilibrium of Tau protein.

4.2 Parkinson's Disease

The pathological characteristics of PD (Parkinson's disease) include substantia nigra dopaminergic neuron loss that is correlated with α-synuclein accumulation and oxidative damage. m6A modification plays a part in neuronal survival through the regulation of antioxidant gene mRNA stability (e.g., SOD2, GPX4) (Qin et al. 2020, Qiu et al. 2020). Genome-wide association study identified that single nucleotide polymorphisms of m6A-related genes (like FTO, ALKBH5) are significantly related to the risk of PD, and it indicated that m6A dysregulation would enhance the progression of the disease via mitochondrial dysfunction and neuroinflammation (Qin et al. 2020, Qiu et al. 2020). Moreover, m6A modification may also impact post-translational modification of α-synuclein, but its exact mechanism is to be investigated.

4.3 Other Brain Diseases

4.3.1 Brain Injury

Following brain injury, dynamic m6A regulation plays a bivalent function in repair and neuroinflammation. ALKBH5 and FTO play a role in facilitated inflammatory responses by demethylating pro-inflammatory mediators (e.g., TNF-α, IL-6) mRNA, whereas METTL3 promotes neuronal survival by triggering anti-apoptotic genes (e.g., Bcl-2) (Xu et al. 2020). The process of oligodendrocyte development and myelination depends on m6A methylation, and METTL14 loss may lead to myelin repair disease and exacerbate white matter injury (Xu et al. 2020). Prior preclinical research has shown that blocking the m6A modification enzymes (e.g., blocking ALKBH5 or activating METTL3) can

improve the integrity of the blood-brain barrier and promote neural regeneration, which provides new ideas for the treatment of brain injury (Xu et al. 2020).

4.3.2 Brain Tumors

m6A methylation stimulates brain tumor growth through the control of oncogene expression and metabolic reprogramming. METTL3 and HNRNPC are control proteins that facilitate the translation of proto-oncogenes (e.g., MYC, EGFR) by m6A modification and suppress the expression of tumor suppressor genes (e.g., PTEN), increasing the invasiveness of gliomas (Wang et al. 2020). The most recent research discovery is that malignant gliomas are capable of hijacking energy from neurons through access to neural circuits, and m6A facilitates tumor neuroinvasion through regulation of synaptic-related genes (e.g., MMP-9). m6A reading protein IGF2BP2 also increases cancer cell chemoresistance by mRNA stabilization of glutamine metabolism-related genes (Wang et al. 2020). Small molecule m6A inhibitors (e.g., FTO inhibitors) have been reported to be able to inhibit tumor growth in preclinical models.

5 CONCLUSION

m6A methylation, the most common eukaryotic RNA epimodification, is a master regulator of brain disorders, neural development, and synaptic plasticity by a dynamic regulatory network of "writers" (e.g., METTL3/METTL14 complex-catalyzed methylation), "erasers" (e.g., FTO/ALKBH5-mediated demethylation), "readers" (e.g., YTHDF1-enhanced translation), and "anti-readers" (e.g., HNRNPC opposing recognition). In physiological regulation, m6A facilitates neural formation by stabilizing genes for neural differentiation (e.g., NeuroD1) and local synaptic translation control of mRNA (e.g., PSD95) for secure learning and memory; in pathology, m6A dysregulation creates onset of disease: in Alzheimer's disease, m6A hyperexpression or inhibition of FTO activity leads to translational efficiency suppression in synaptic proteins and deranged Aβ metabolism, in Parkinson's disease, m6A gene polymorphism decides antioxidant gene stability, in brain trauma, ALKBH5 promotes inflammation whereas METTL3 is conducive to neuronal viability, and in gliomas, METTL3/HNRNPC promotes invasiveness via oncogenes (e.g., MYC). Interference with the m6A regulatory pathway (for example, inhibition of METTL3, activation of FTO, or blocking of IGF2BP2) may well open up new avenues for therapeutic intervention in neurodegenerative disorders, brain injury, and cancer.

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