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Research Article

RNA m^{6}A Methylation in Psychiatric Disorders

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Abstract

This comprehensive review introduces the features of m^{6}A modification and its role in neuropsychiatric disorders. The research findings suggest that m^{6}A modifications and their regulators play a critical role in the occurrence and development of major psychiatric disorders, especially Alzheimer's disease, affecting synaptic protein synthesis, subtype classification, immune infiltration, pathogenesis, and inflammatory infiltration. These findings highlight m^{6}A regulators as potential new diagnostic and therapeutic targets, with m^{6}A methyltransferase METTL3 being the best-characterized regulator in these diseases. The review concludes that m^{6}A modification is a promising target for the prevention and treatment of major psychiatric disorders.

Keywords: *m^{6}A Modification; Neuropsychiatric Disorders; Alzheimer's Disease; m^{6}A Regulator; METTL3*

Introduction

RNA modifications involve covalent changes to RNA molecules, such as the addition, deletion, or chemical alteration of nucleotides at various sites within the RNA. These changes, known as epitranscriptomics, regulate RNA metabolism and the function of almost all RNA species, including mRNA, tRNA, rRNA and ncRNA [1]. Like epigenetic modifications in DNA and histone tails, RNA modifications regulate gene expression and play a role in forming synaptic connections in response to external stimuli [2]. Among the hundreds of known RNA modifications, the most prevalent post-transcriptional mRNA modification in eukaryotes is N^6-methyladenosine (m^{6}A) [2], which is highly enriched in the brain [3]. This well-understood internal RNA modification involves adding a methyl group to the nitrogen atom at position 6 of the adenosine base on RNA (Figure 1). In this study, we comprehensively introduce the features of m^{6}A and review its role in psychiatric disorders.

Biogenesis of m^{6}A modification: The methyl group at adenosine (A) on RNA molecules is modified by the m^{6}A methyltransferases (writers) and removed by the demethylases (erasers). It is recognized and bound by m^{6}A-binding proteins (readers). The writer enzymes

include METTL3/14/16, WTAP, ZCCHC4, RBM15/15B, KIAA1429, ZC3H3/13, ZC3CH3, HAKA1, CBLL1 and VIRMA; the eraser enzymes include FTO and ALKBH5; while the key reader proteins include eIF3, YTHDC1/2, YTHDF1/2/3, IGF2BP1/2/3, FMRP, PRRC2A, hnRNPC, hnRNPG, hnRNPA2B1 and METTL3 (Figure 1).

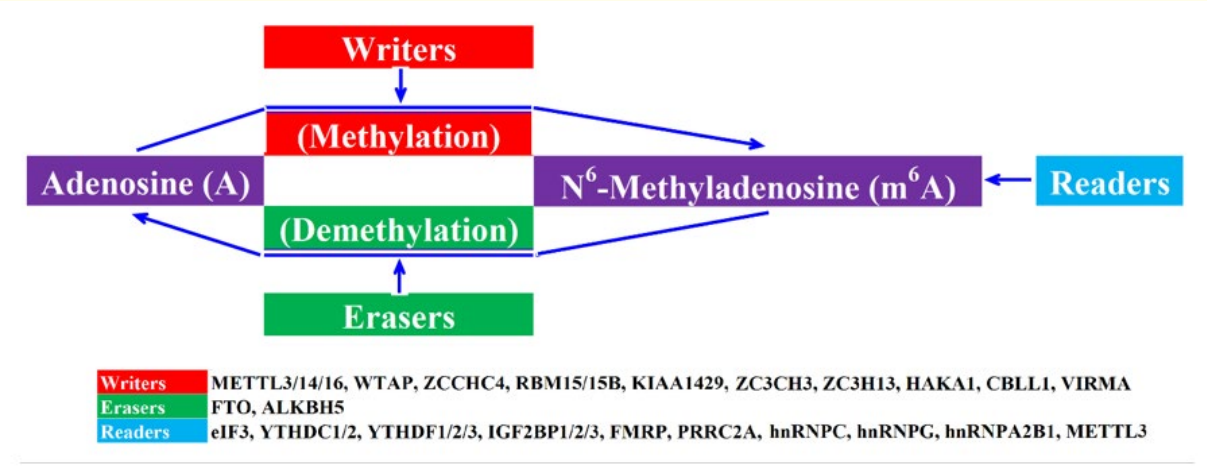

***Figure 1**: Warts in the back.*

Biological functions of m^{6}A modification: m^{6}A is an RNA modification that regulates mRNA stability, processing, splicing, nuclear export, translation, and degradation in mRNAs related to neurogenesis, cell cycle, and neuron differentiation [4-6]; additionally, it has an important biological function in enrichment and regulation of lncRNAs [7]. Enriched in synapses, m^{6}A is essential for maintaining higher brain functions including learning and memory, and the development of mammalian brain and cognition [1,2,8,9]. It also plays a crucial role in responding to environmental stimuli, potentially linking molecular and behavioral stress [2]. Dysregulation of m^{6}A is associated with various human diseases related to neurodevelopment and neurodegeneration [10].

Implication of m^{6}A modification in neuropsychiatric disorders: The m^{6}A modification is highly enriched in the brain, and its higher-order brain functions may potentially implicate it in the pathophysiology of neuropsychiatric disorders. For instance, circular RNA (circRNA), a new type of evolutionarily conserved ncRNA lacking a 5'-cap and 3'-polyadenylic acid tail, may undergo m^{6}A RNA methylation, and circRNA has been reported to contribute to the pathogenesis of Alzheimer's disease (AD) and cognitive impairment [10]. Modification of m^{6}A at the gene level is closely related to immune regulation, and depression is characterized by neuroinflammatory symptoms [11]. Additionally, modification of m^{6}A by METTL3 has been found to have potential in neuron apoptosis, which is known to contribute to autism [12]. Furthermore, chronic alcohol consumption may alter m^{6}A modification in the NAc and then lead to gene expression changes, potentially underlying behavioral neuroadaptation to alcohol in alcoholics [13]. Finally, m^{6}A modification genes such as FTO and ALKBH5 have been associated with depression in recent genetic studies [3]. All these clues suggest a crucial role of m^{6}A modification in the pathophysiology of neuropsychiatric disorders. Elucidating the link between m^{6}A and neuropsychiatric disorders presents a novel molecular mechanism underlying their pathogenesis and facilitates the development of potential therapeutic drugs for these disorders.

Methodology

A systematic literature search was conducted using the PubMed database to identify papers published up to May 2023, with the search terms "m^{6}A" and "psychiatric disorders". The study examined the top 20 common psychiatric disorders, including Major depressive

disorder (MDD), Bipolar disorder, Anxiety disorders (such as generalized anxiety disorder, panic disorder, and phobias), Schizophrenia, Obsessive-compulsive disorder (OCD), Post-traumatic stress disorder (PTSD), Attention-deficit/hyperactivity disorder (ADHD), Borderline personality disorder, Eating disorders (such as anorexia nervosa and bulimia nervosa), Autism spectrum disorder (ASD), Substance use disorders (including alcohol and drug abuse/dependence), Insomnia and other sleep disorders, Dissociative disorders (including dissociative identity disorder), Alzheimer's disease, Personality disorders (such as antisocial personality disorder and narcissistic personality disorder), Schizoaffective disorder, Adjustment disorder, Delusional disorder, Conduct disorder, and Depersonalization/derealization disorder. The present study reviewed, extracted, summarized, illustrated, and discussed the positive findings between m^{6}A modifications and psychiatric disorders.

Results

m^{6}A modifications are significantly associated with five major psychiatric disorders, namely AD, MDD, SZ, ASD, and SUD. Out of these, more than half of the studies (12) reported a positive association between m^{6}A modifications and AD. For MDD, SZ, ASD, and SUD, five, two, two, and one studies respectively reported associations.

Alzheimer's disease (AD): Some studies have reported m^{6}A modification plays critical roles in AD-related biomarkers. A genome-wide association study revealed 1458 m^{6}A-associated SNPs (m^{6}A-SNPs) in AD, with 258 found in six known AD-risk genes [5]. There was a marked alteration in circRNA m^{6}A modification in AD [10]. In AD patients, m^{6}A modifications were found in genes linked to synaptic function, including CAMKII and GLUA1 [9]. Reduced m^{6}A levels in AD patients resulted in decreased synaptic protein synthesis in genes such as CAMKII and GLUA1. Genes such as NOTCH2 and NME1 may be targeted by m^{6}A modification to regulate AD [14].

Numerous studies demonstrated associations of m^{6}A regulators with AD or AD endophenotypes. The best-characterized m^{6}A regulator is m^{6}A methyltransferase METTL3. Reduced expression of METTL3 in AD brains leads to synaptic loss, neuronal death, oxidative stress, memory deficits, and aberrant cell cycle events due to decreased m^{6}A modification in the hippocampus [15]. However, overexpression of METTL3 or STUB1 enhances autophagy and reduces p-Tau levels in Aβ1-42-treated cells [16]. KDM1A-mediated upregulation of METTL3 promotes autophagic clearance of p-Tau through m^{6}A-dependent regulation of STUB1, ameliorating AD both *in vitro* and *in vivo*. Soluble Aβ oligomers cause reduced METTL3 expression, while METTL3 overexpression rescues Aβ-induced synaptic PSD95 loss both *in vitro* and *in vivo* [15]. Furthermore, METTL3 expression positively correlates with the levels of insoluble Tau protein in postmortem human AD brains [8]. Inhibition of oxidative stress or cell cycle alleviates shMettl3-induced apoptotic activation and neuronal damage in primary neurons, and restored m^{6}A modification rescues abnormal cell cycle events, neuronal deficits, and death induced by METTL3 knockdown [15].

Furthermore, associations of other m^{6}A regulators with AD have also been reported. A study reported 19 AD-risk genes that are highly associated with key m^{6}A regulators [14]. The expression of m^{6}A regulators varies across tissues and correlates with neurodegenerative pathways [17]. Co-expression of the m^{6}A regulators SNRPG and SNRPD2 has been identified as potential biomarkers predicting transformation from MCI to AD [17]. In the mouse AD brain, the expression of the m^{6}A eraser protein FTO decreased, while the hippocampus of the human AD brain showed an upregulation of another m^{6}A eraser protein, RBM15B [8]. Additionally, the m^{6}A reader protein IGF2BP2 was abnormally highly expressed in AD patients and could bind to mRNAs in a m^{6}A-dependent manner [18]. These pieces of evidence suggest critical roles of m^{6}A modification in AD pathogenesis.

There are also several studies directly supporting the roles of m^{6}A modification in AD or AD endophenotypes. In an *in vitro* model of AD and aged animals, m^{6}A levels were shown to decrease [9]. Cingulate cortex brain tissue from AD patients, as well as neurons in AD brains, also exhibited decreased m^{6}A levels [9]. In contrast, m^{6}A methylation was elevated in the cortex and hippocampus of APP/PS1 transgenic mice [19].

Major depressive disorder (MDD): Transcriptome-wide m^{6}A profiling has revealed multiple brain m^{6}A QTLs underlying depression, with studies also demonstrating associations of m^{6}A regulators with depression, including one study identifying seven significantly upregulated m^{6}A regulators in depressed rats [11]. Constant light exposure can increase tissue-specific mRNA expression of m^{6}A regulators, thereby enriching differentially expressed genes in biological processes such as mRNA metabolic regulation [20]. METTL3-mediated m^{6}A modification facilitates the processing and maturation of pri-miR-221, resulting in upregulation of miR-221-3p and inhibition of GRB2-associated binding protein 1 (Gab1), worsening cognitive deficits in CUMS-treated rats [21]. The regulation of m^{6}A modification by FTO could also affect dopaminergic neurotransmission relevant to depression [22]. Additionally, a study has directly associated depression with m^{6}A modification [21].

Schizophrenia (SZ): The transcriptome-wide m^{6}A profiles reveal multiple brain m^{6}A QTLs underlying schizophrenia [23]. The m^{6}A modification plays an important role in cortical neurogenesis [24]. Depletion of m^{6}A occurs in Mettl14 knockout and Mettl3 knockdown embryonic mouse brains, which leads to the prolongation of the cell cycle of radial glia cells and their maintenance [24]. Moreover, m^{6}A sequencing of embryonic mouse cortex has shown that mRNAs related to transcription factors, neurogenesis, the cell cycle, and neuronal differentiation are enriched in m^{6}A tagging, promoting their decay [24]. These findings are all consistent with a potential role of m^{6}A modification in the pathogenesis of schizophrenia. Finally, a recent study has directly linked changes in m^{6}A with schizophrenia [21].

Autism spectrum disorder (ASD): Recent studies have shed light on the relationship between m^{6}A regulators, particularly METTL3, and autism. In a mouse model of autism, hippocampal tissues exhibited downregulation of METTL3, MALAT1, and Wnt/β-catenin signaling, while SFRP2 was upregulated [12]. METTL3 facilitated m^{6}A modification of MALAT1, thereby stabilizing its expression and promoting SFRP2 methylation [12]. By recruiting DNMT1, DNMT3A, and DNMT3B to the SFRP2 promoter region, METTL3 reduced SFRP2 expression and facilitated the activation of the Wnt/β-catenin signaling pathway, leading to a reduction in autism-like symptoms and hippocampal neuron apoptosis [12]. Thus, the regulation of the MALAT1/SFRP2/Wnt/β-catenin axis by METTL3 holds promise as a potential therapeutic target for reducing autism-like symptoms and hippocampal neuron apoptosis [12]. Furthermore, recent research has demonstrated a direct link between m^{6}A modification and autism spectrum disorder [4].

Substance use disorders (SUD): In the NAc of AUD subjects, 26 mRNAs were hypermethylated, three mRNAs were hypomethylated, four lncRNAs were hypermethylated, one lncRNA was hypomethylated, while three miRNAs were hypermethylated, suggesting an important role of m^{6}A modification in AUD [13].

Discussion

In this comprehensive review, we introduce the features of m^{6}A modification, including its biogenesis, biological functions, and implications in neuropsychiatric disorders. We then systematically review the roles of m^{6}A in psychiatric disorders, summarizing and discussing the positive findings between m^{6}A modifications and psychiatric disorders. Finally, we highlight the significance of epitranscriptomic studies in neuropsychiatric disorders.

The research findings indicate that m^{6}A modifications and their regulators in the brain are critical in the occurrence and development of psychiatric disorders, including AD, MDD, SZ, ASD, AUD, and cognitive decline in aging and AD. In particular, more than half of the studies focus on AD. This modification affects synaptic protein synthesis, synaptic connectivity changes, and neurodegeneration in psychiatric disorders and relevant biomarkers or endophenotypes of these diseases [2,5,8-10,14-16]. Additionally, it affects subtype classification, immune infiltration, pathogenesis, and inflammatory infiltration [8,11,14], making it a potential target for therapeutic interventions. The findings also highlight m^{6}A regulators (e.g. METTL3, FTO, and IGF2BP2) as potential new diagnostic and therapeutic targets, with m^{6}A methyltransferase METTL3 being the best-characterized regulator in these diseases. Furthermore, these findings provide insights into understanding epitranscriptomic modifications and their interindividual variation, as well as a mechanism in heightened transcriptional coordination during mammalian cortical neurogenesis.

Conclusion

In conclusion, m^{6}A modifications and its regulators play a key role in the development of major psychiatric disorders, making them promising targets for their prevention and treatment.

Authors Contribution

#Qiao Mao and Jessica Luo authors contributed equally.

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