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N6-methyladenosine: a novel therapeutic lever in Alzheimer's pathogenesis

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Abstract. In the context of continuous social development and overnutrition, Alzheimer's disease, as a neurodegenerative disease, is becoming more and more common in the elderly and gradually younger, and there is currently no effective treatment. This article reviews the role of m6A as a target site for the treatment of Alzheimer's Disease（AD）, discusses the main case characteristics of AD, including tau hyperphosphorylation, neuroinflammation, etc., and discusses the combination of m6A regulation and anti-Aβ/antitau drugs, m6A and anti-inflammatory treatment, etc., and reveals the new mechanism of AD pathogenesis after combining recent related research cases, and proposes that m6A can be used as a new target for AD, providing a new epitranscriptional perspective for the treatment of AD. In addition, it will promote the development of m6A-targeted drugs and provide relevant suggestions to solve the current treatment bottleneck.

Keywords: Alzheimer's disease, N6-methyladenosine, Aβ deposition, Tau pathology

1. Introduction

Alzheimer's Disease (AD) is a disease that is known worldwide for its progressive cognitive dysfunction and neuronal degeneration. The pathogenesis is very complex, including β-amyloid, Tau protein, neuroinflammatory response, etc., and in terms of clinical manifestations, patients with AD often have behavioral symptoms, such as cognitive impairment and psychiatric abnormalities. At present, the treatment strategy of AD can only delay part of the symptoms to a certain extent, but cannot solve the root cause of the related problems, so people need to find new targeted treatment options. As a kind of RNA epigenetic modification, N6-methyladenosine (m6A) is the most common chemical modification in eukaryotic mRNA, and the dynamic regulation of methyltransferases (such as METTL3/METTL14), demethylases, such as fat mass and obesity-associated protein (FTO), ALKBH5, and reader proteins (such as YTHDF1-3) can affect the splicing, stability and translation efficiency of RNA, and then affect the pathogenesis of AD. By studying the pathogenesis of AD, it is not difficult to find that m6A modification may be used as a new therapeutic target site, including targeting m6A-related enzymes (such as inhibiting FTO or activating METTL3), which may play an important role in intervening in Aβ deposition, Tau pathology, and synaptic dysfunction. However, some human model applications and the safety of m6A regulation are still worth further study. This article reviews the pathogenesis of AD, discusses the role of m6A as a target site in therapy, and analyzes the challenges of current research and the discovery of future development, and because this new target has the uniqueness of regulating multiple disease progression links, it will help break through the limitations of traditional therapies and open up a new avenue for the development of new AD cures.

2. AD patient's symptoms

There are several degenerative diseases of the nervous system, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, spinocerebellar ataxia. Of these neurodegenerative diseases, AD is the most common and has the largest number of patients. The main clinical manifestations of AD include memory impairment, aphasia, apraxia, agnosia, impairment of visuospatial skills, executive dysfunction, and personality and behavior changes [1].

2.1. Cognitive impairment

Among them, the main cognitive impairment of AD is chronic progressive cognitive impairment, which focuses on memory loss and impairs function in other cognitive domains, and its severity can reach dementia, which in turn affects the ability of human beings to live in daily life.

2.2. Mentally abnormal behavior

Another type of AD symptom is mental and behavioral symptoms, which include a variety of symptoms, including emotional problems (depression and anxiety), psychotic symptoms (hallucinations, delusions, etc.) as well as some agitation, impulsive behavior, etc.

3. The current treatment of AD

Alzheimer's disease is a degenerative disease of the central nervous system, and the peculiarity of this disease lies in the fact that it is closely related to age. The condition is rapidly escalating into a major public-health crisis, with cases expected to triple within the coming half-century [2]. At the pathophysiological level, Alzheimer’s disease is characterized by the buildup of extracellular senile plaques rich in β-amyloid (Aβ) peptides alongside the formation of intracellular neurofibrillary tangles [3]. At the same time, there are currently very limited means available to treat AD worldwide, and there are neither disease-modifying drugs nor curative treatments for AD, which makes treating AD patients very difficult and very challenging. At present, there are two main treatments for AD: one is lecanemab, an Aβ monoclonal antibody, and the other is tau-targeted therapy.

3.1. Aβ monoclonal antibody lecanemab

For nearly two decades, there has been a claim that amyloid elimination is used to treat AD. The results of several studies suggest that when Aβ peptides accumulate abnormally in the brain, they can become pathogenic triggers for downstream events, ultimately leading to progressive cognitive impairment [4]. Lecanemab, also known as BAN2401, is a drug that targets the basic pathophysiology of AD and has been reported to have been approved in the past 2 years, becoming the first AD treatment of its kind to achieve this transition. Lecanemab is a form of mouse antibody. Lecanemab selectively binds soluble Aβ fibrils—the soluble, neurotoxic aggregates that disrupt electrophysiological memory circuits—while also acting on insoluble fibrils (Figure 1). In preclinical models of Alzheimer’s disease, the antibody lowers overall pathogenic Aβ, curbs further deposition, and specifically diminishes fibrillar Aβ levels in both brain tissue and cerebrospinal fluid. This fibril-focused selectivity sets lecanemab apart from other anti-amyloid monoclonal antibodies [5, 6]. Therefore, it also means that the use of lecanemab will represent a significant advance in the treatment of AD.

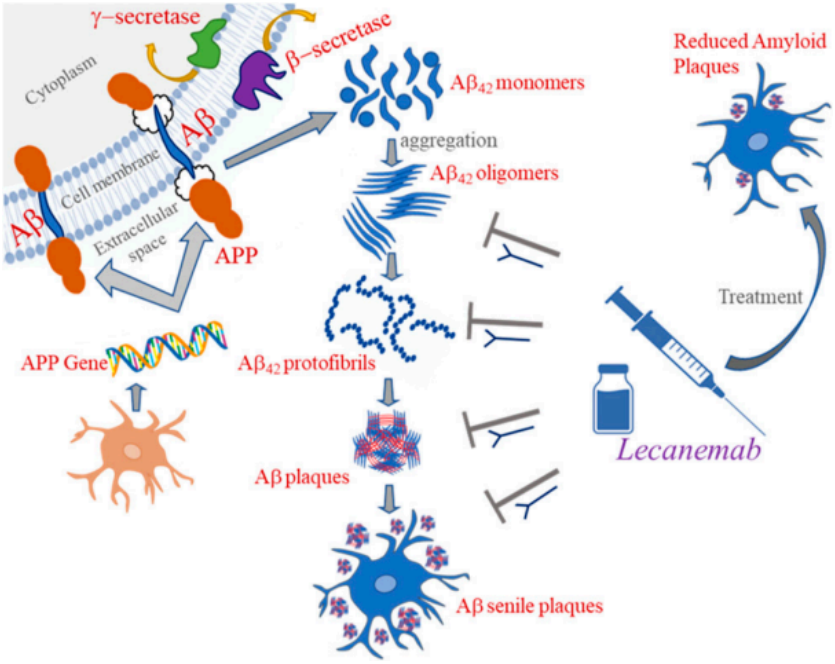

Figure 1. Mechanism of action of lecanemab [7]

3.2. Tau-targeted therapy

Tau protein is a relatively low molecular weight vascular-associated protein, and the pathological problems of tau deposition are mainly caused by neurofibrillary tangles and neuronal loss. For patients, current drug development strategies focus on inhibiting hyperphosphorylation of tau and controlling the aggregation and spread of pathological tau. In 2021, relevant studies and personnel pointed out that tau targeted therapy has great potential for the treatment of AD. They designed a tau-targeted multifunctional nanoinhibitor based on self-assembled polymer micelles modified with tau-binding peptides for AD treatment [8]. Its mechanism of action is through multivalent binding to aggregates, and this nanoinhibitor is able to effectively inhibit tau protein aggregation, recognize tau aggregates, and block their seeding in neuronal cells, thereby significantly attenuating tau-mediated cytotoxicity (Figure 2). As research continues to advance, on January 8 this year, Johnson & Johnson announced that its investigational tau monoclonal antibody Posdinemab has been granted fast-track designation by the US FDA for the treatment of early Alzheimer's disease (AD), which also shows the importance and significance of Tau-targeted therapy, which continues to provide a beneficial way to treat AD patients.

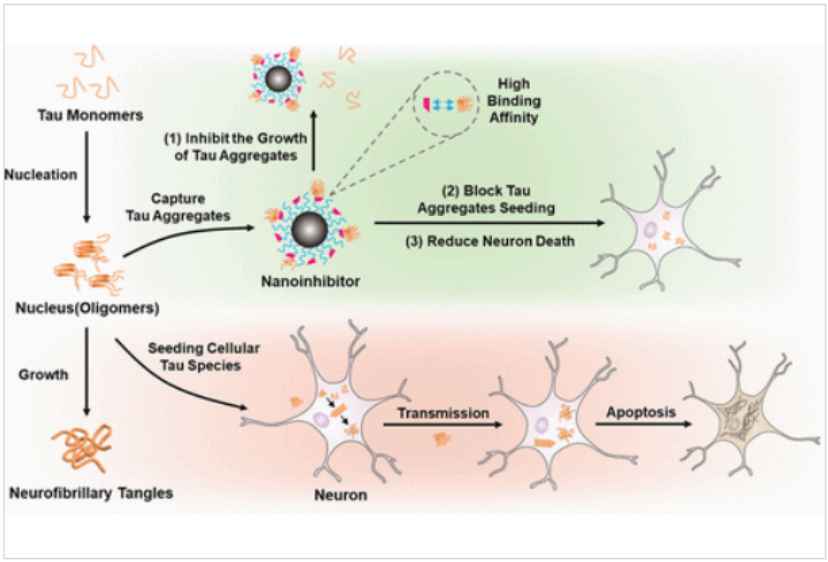

Figure 2. Illustration of the regulation mechanism of the nanoinhibitor on tau protein [8]

4. Pathogenesis of AD

As a very complex degenerative neurological disease, the pathogenesis of AD involves many aspects, such as β-amyloid, tau protein, neuroinflammation, and so on. In 2024, Xin Wang and Qiuyang Zheng from the Institute of Neuroscience, Xiamen University School of Medicine and the State Key Laboratory of Cellular Stress Biology published a review article in the journal Protein & Cell: Alzheimer's Disease: Insights into Pathology, Molecular Mechanisms, and Therapy. This article systematically summarizes the latest advances in the pathological mechanisms and disease risk factors of AD [9].

4.1. β-amyloid

Aβ has long been recognized as the main causative agent in amyloid plaques. It works in a similar way to prions to initiate fibrosis by generating misfolded β-lamellar Aβ seeds that serve as templates for larger amyloid aggregates. In addition, the latest study has also found that B2M-Aβ copolymers formed by the copolymerization of B2M and Aβ have stronger neurotoxicity and have an impact on cognitive function in AD patients.

4.2. Tau protein

Tau protein, a major component of NFT, plays a key role in regulating microtubule stability and axonal trafficking under normal conditions as a microtubule-associated protein. However, when the aberrant modification of Tau protein becomes one of the important mechanisms of AD pathogenesis, hyperphosphorylation of Tau protein leads to the formation of neurofibrillary tangles (NFTs), and because of its cell-to-cell transmissibility and self-replication, this will allow Tau protein to spread in the brain in a manner similar to prions. The pathology of NFT can start from the entorhinal cortex and olfactory endothelial and spread in a predictable pattern all the way to the hippocampus and neocortex, which will lead to the occurrence of AD and make people suffer from AD.

4.3. Neuroinflammation

Neuroinflammation is an indispensable key link in the upstream pathogenesis of AD, and was confirmed by a research team led by Tharick A. Pascoal from the University of Pittsburgh School of Medicine and Pedro Rosa-Neto from McGill University in Canada in 2021. On this basis, they suggested that Aβ, Tau and microglial activation jointly contributed to the development of AD. In recent years, neuroinflammation due to microglial activation has been identified as a key factor in the progression of AD [10, 11]. Microglia have also been found to coexist with Aβ plaques and tau fibrillary tangles in the brain [12]. Studies based on animal models have even found that activation of microglia drives tau lesions [10, 13]. Therefore, microglial activation is not only closely related to Aβ pathology and tau pathology, but also has a feature of inflammation, which plays a key role in promoting the progression of AD.

5. Therapeutic strategies targeting m6A-modifying enzymes

m6A, also known as N6-methyladenosine, is the most abundant post-transcriptional modification in eukaryotic RNA. It is abundant in the brain, and there is a lot of research evidence that m6A and its regulatory proteins are closely linked to a variety of neurological diseases, including AD. The therapeutic strategy of targeting m6A-modifying enzymes aims to intervene in Alzheimer's disease (AD) by regulating the dynamic balance of N6-methyladenosine (m6A) modifications in mRNA. This approach includes inhibition of demethylases, activation of methyltransferases, and regulation of the activity of reader proteins, thereby influencing the plasticity of gene expression.

5.1. Inhibition of demethylases (e.g., FTO)

FTO, an m6A demethylase, has been shown in studies to exacerbate the progression of Alzheimer's disease (AD) when it is present in high concentrations. And FTO mainly regulates phosphorylation of tau protein, rather than amyloid-β (Aβ) content. Therefore, there are two ways to control FTO; one is to selectively inhibit FTO with small molecule inhibitors, thereby reducing Aβ production. The other can down-regulate the expression of FTO through gene silencing techniques such as siRNA or CRISPR, which plays an important role in controlling the progression of AD.

5.2. Activation of methyltransferases (e.g., METTL3/METTL14)

m6A, a common methylation modification of RNA, is catalyzed by the METTL3/METTL14 complex, and some studies have shown that abnormal levels of m6A in the brains of AD patients may lead to synaptic damage and cognitive decline. The neuroprotective mechanism of METTL3/METTL14 can also play a role here, not only by restoring m6A homeostasis, and regulating synaptic plasticity but also by alleviating neuroinflammation, and possibly by downregulating the translation of APP (amyloid precursor protein) through m6A-dependent mechanisms, reducing Aβ production, thereby controlling the development of AD. In a 2021 Nature Neuroscience study, METTL3 overexpression in AD mice improved cognitive function and reduced Aβ deposition, an animal model that indirectly demonstrated the potential of this approach.

5.3. Regulation of reader proteins (e.g., YTHDF1/YTHDF2)

In addition, the regulation of reader proteins also plays a great role in the targeted treatment of Alzheimer's disease by m6A, including the modulation of YTHDF1/YTHDF2. YTHDF1 promotes the translation of Aβ-related proteins in AD, thereby exacerbating Aβ deposition. YTHDF2, on the other hand, accelerates the degradation of tau protein, and its dysregulation leads to neurofibrillary tangles (NFTs). Therefore, its therapeutic strategy, on the one hand, is to inhibit YTHDF1 to reduce Aβ production, and related animal models have also shown that YTHDF1 knockout reduce Aβ40/42 levels by about 30%-50%, and on the other hand, to enhance YTHDF2 to reduce tau pathology, up-regulate its amplitude and accelerate tau mRNA degradation, and finally reduce NFTs. Therefore, YTHDF1/2 modulation can theoretically be well studied when applied to AD therapy as a new target, but if it is tested in humans, it is worth further study

6. Combination therapy strategies

AD is very complex, it involves a variety of pathological mechanisms, such as Aβ deposition, tau protein abnormalities, and neuroinflammation, so the effect of a single targeted therapy regimen is very limited. Therefore, m6A modulation can be combined with other therapies to enhance therapeutic efficacy, including m6A modulation in combination with anti-Aβ/antitau drugs, and m6A with anti-inflammatory therapy.

6.1. m6A regulation in combination with anti-Aβ/anti-tau drugs

In m6A in combination with anti-Aβ drugs, YTHDF1 inhibitors reduce Aβ production, while Aβ antibodies promote the removal of deposited plaques. Based on the mechanism of YTHDF1 regulation of APP/BACE1 and the clearance of Aβ antibody, it is speculated that the combination of YTHDF1 siRNA Aβ antibody may significantly reduce amyloid plaques and thus control AD than monotherapy [14]. Of course, combination therapy may have a synergistic effect, which requires a lot of experimental validation. In combination with anti-tau drugs, YTHDF2 activator accelerates the degradation of tau mRNA, and tau ASO can directly block its transcription. At present, both YTHDF2 overexpression and tau ASO monotherapy have been shown to reduce tau pathology independently, and theoretically, YTHDF2 overexpression tau ASO may reduce pathological tau aggregation by about 70%, but its combination intervention strategy has not yet been carried out in AD, which is also worthy of experimental exploration.

6.2. m6A with anti-inflammatory therapy

On the one hand, the combination strategy of m6A and anti-inflammatory therapy in AD is to reduce neuroinflammation by targeting YTHDF2 or METTL3, thereby inhibiting pro-inflammatory pathways. On the other hand, by activating the YTHDF1-TREM2 axis or overexpressing IGF2BP1, it promotes Aβ clearance, thereby achieving the goal of enhancing the anti-inflammatory mechanism. Compared with other drugs, the targeting of m6A will be more specific and precise, showing its potential for synergistic reduction of pathology.

7. Limitations of m6A

However, m6A is not only beneficial in targeted therapy for AD, but also has limitations, such as pathological differences between animals and humans, insufficient targeting accuracy, and technical bottlenecks in delivery.

7.1. Differences in the application of animal models and human models

Currently, many studies on m6A in the direction of AD are stuck in animal models, and there will be many problems when these strategies are translated into human studies. First, Aβ deposition is rapid and dense in mouse AD models, while in humans there will be more complex tau pathology and chronic inflammation, and this mechanism will affect the progression of Aβ deposition in human patients. In addition, in animal models, YTHDF1 knockout can reduce Aβ, but the difference is that humans will be more sensitive to m6A regulation because their own neurons will trigger its inhibition to trigger other related reactions and toxicity.

7.2. Precise targeting challenges

There are also challenges to precise targeting, including functional redundancy and tissue specificity of reader proteins. Among the reader proteins, the YTHDF family and IGF2BP1 partially overlap in mRNA regulation and are prone to redundancy. In addition, due to the different m6A modification profiles of microglia, neurons, and astrocytes, they require cell-specific delivery that would otherwise compromise their normal function.

7.3. Delivery system bottlenecks

Finally, the delivery system is prone to bottlenecks, on the one hand, due to the penetration of the blood-brain barrier, the nanocarrier materials are relatively inefficient in the brain and are easy to be intercepted by other organs. On the other hand, the system requires long-term external intervention to maintain its effectiveness. Currently, only siRNA/m6A inhibitors can be maintained by repeated supplementation of AD medications, and there is also a lack of other intelligent control systems

8. Conclusion

Compared with traditional therapies, the study of m6A has brought a new direction to Alzheimer's disease, and can simultaneously intervene in Aβ deposition, tau pathology and synaptic dysfunction by regulating methyltransferase METTL3 or inhibiting demethylase FTO so as to achieve multi-target synergistic therapy. However, there are still many challenges to this approach, such as the fact that most of the current research is limited to animal models, but the complexity of the human brain and the long-term nature of the course of AD may affect efficacy. In addition, the m6A's precise control and conveyor system presented a number of safety challenges. Of course, this also brings a clear direction for future research, which can start with the development of brain-targeted delivery systems, the establishment of humanized animal models and patient iPSC-derived neuron platforms, the exploration of personalized m6A regulatory protocols, and the combination of biomarker-layered therapies. As a modification approach, m6A is expected to be a milestone in the field of AD therapeutics, but it also requires a lot of time, manpower, and money to develop and apply, such as the safety trial of FTO inhibitors and the specificity of METTL3 modulators, etc., but it is also because of this active research investment that it will eventually lay a solid foundation for human and clinical translation.

References

[1] Mirinisa Kaizeer, Y.C., Guo, H.F. (2021) Pathogenesis and research progress of Alzheimer's disease. *Anatomy Research*, 43(3): 6.
[2] Vitek, G.E., Decourt, B., Sabbagh, M.N. (2023) Lecanemab (BAN2401): an anti-beta-amyloid monoclonal antibody for the treatment of Alzheimer disease. Expert Opinion on Investigational Drugs.
[3] Chowdhury, S., Chowdhury, N.S. (2023) Novel anti-amyloid-beta (Aβ) monoclonal antibody lecanemab for Alzheimer's disease: A systematic review. *Int J Immunopathol Pharmacol*, 37: 3946320231209839. DOI: 10.1177/03946320231209839.
[4] Lord, A., Gumucio, A., Englund, H. (2009) An amyloid-β protofibril-selective antibody prevents amyloid formation in a mouse model of Alzheimer's disease. *Neurobiology of Disease*, 36(3): 425-434.
[5] Söllvander, S., Ekholm-Pettersson, F., Brundin, R.M. (2015) Increased number of plasma B cells producing autoantibodies against Aβ42 protofibrils in Alzheimer's disease. *Journal of Alzheimer's Disease*, 48: 63–72. DOI: 10.3233/JAD-150236.
[6] Chowdhury, S. (2023) Monoclonal antibody treatments for Alzheimer's disease: Aducanumab and lecanemab. *Discoveries*, 11(3).
[7] Chowdhury, S., Chowdhury, N.S. (2023) Novel anti-amyloid-beta (Aβ) monoclonal antibody lecanemab for Alzheimer's disease: A systematic review. *International Journal of Immunopathology and Pharmacology*, 37: 1–9. DOI: 10.1177/03946320231209839.
[8] Zhu, L., Xu, L., Wu, X., Deng, F., Ma, R., Liu, Y., Huang, F., Shi, L. (2021) Tau-targeted multifunctional nanoinhibitor for Alzheimer's disease. *ACS Applied Materials & Interfaces*, 13(20): 23328–23338. DOI: 10.1021/acsami.1c00257.
[9] Zheng, Q., & Wang, X. (2024) Alzheimer's disease: insights into pathology, molecular mechanisms, and therapy. Protein Cell. https: //doi.org/10.1093/procel/pwae026
[10] Salter, M.W., Stevens, B. (2017) Microglia emerge as central players in brain disease. *Nature Medicine*, 23(9): 1018-1027.

[11] Ising, C., Venegas, C., Zhang, S. (2019) NLRP3 inflammasome activation drives tau pathology. *Nature*, 575(7784): 669-673. DOI: 10.1038/s41586-019-1769-z

[12] Sheffield, L.G., Marquis, J.G., Berman, N.E. (2000) Regional distribution of cortical microglia parallels that of neurofibrillary tangles in Alzheimer's disease. *Neuroscience Letters*, 285(3): 165-168.

[13] Hopp, S.C., Lin, Y., Oakley, D. (2018) The role of microglia in processing and spreading of bioactive tau seeds in Alzheimer's disease. *Journal of Neuroinflammation*, 15(1): 269.

[14] Sevigny, J., Chiao, P., Bussière, T. (2016) The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature*, 537(7618): 50-56. DOI: 10.1038/nature19323

[15] Li, M., Wang, X., Lu, S. (2021) YTHDF2 mediates neuronal mRNA degradation and its deficiency protects against neurodegeneration. *Nature Communications*, 12: 3155.