# Molecular Mechanism of Alzheimer's Disease: Aβ -amyloid protein deposition, abnormal phosphorylation of tau protein and neurofibrillary tangles

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**Abstract.** Alzheimer's disease (AD) is a prevalent neurodegenerative disorder that seriously endangers the physical and mental health of the elderly population. Currently, the molecular pathogenic mechanism of this disease has not been fully elucidated, and there are limitations in clinical treatment methods, making it difficult to curb the progression of the disease at its root. This article systematically analyzed the interactive effects of the three core pathological mechanisms in AD, namely Aβ deposition, excessive phosphorylation of Tau protein, and neuroinflammation, and reviewed the advantages and disadvantages of traditional interventions, nano-delivery carriers, and nasal administration as new treatment technologies. The results show that the pathological process of AD is dominated by a multi-dimensional interactive network, and the APOE4 gene and chronic neuroinflammation play a key role in upstream regulation. Simply removing pathological proteins cannot stop disease progression, while targeted precise intervention such as p-tau217 and ceRNA regulatory networks show significant potential. This study clarified the multi-factor interwoven pathological regulatory mechanism of AD, complemented the cognitive limitations of single pathological research, and provided theoretical support for the development of early screening markers and precise targeted treatment. The causal relationship between neuroinflammation and pathological protein lesions is still unclear at present. Future research can focus on the pathological dynamic changes during the disease latency period, optimize multi-target combined treatment plans, improve nano-nasal administration technology, and promote the clinical translation and application of new treatment strategies.

**Keywords:** Pathological mechanisms, Neuroinflammation, Nano-delivery, Nasal administration, Targeted therapy.

## 1. Introduction

Alzheimer's disease (AD) is the main cause of cognitive impairment and decline in living ability among the elderly. Lack of social interaction and insufficient communication between parents and children are important risk factors. The risk of developing AD is closely related to lifestyle, social status and physical health. AD has become a global epidemic health problem, with the mortality rate increasing year by year. The number of patients in China ranks first globally, and it is predicted that the number of patients will significantly increase by 2050. Mild cognitive impairment (MCI), as the pre-stage of AD, affects 15% - 20% of people over 65 years old. 10% - 20% of MCI patients will progress to AD each year [1]. Active social interaction, regular exercise and a healthy lifestyle can effectively delay cognitive decline. Early screening and intervention of MCI can reduce the risk of AD and alleviate the disease burden on families and society [2].

The traditional pathological mechanism suggests that the deposition of Aβ amyloid protein in the brain and the excessive phosphorylation of tau protein jointly damage neurons, leading to a continuous decline in cognitive function. AD is a multifactorial disease. Recent studies shown that neuroinflammation is involved in its pathogenesis [3]. Inflammatory mediators can induce neuronal degeneration, which can both synergize with Aβ and tau lesions to aggravate the condition and may also be the initiating factor of AD, prompting the academic community to re-examine whether the abnormality of these two proteins is a pathogenic trigger or a secondary result of the disease. Currently, clinical drugs can only alleviate symptoms but cannot reverse the disease course. Soft nanoparticles, especially nano-liposomes and exosomes, can effectively bypass the blood-brain

barrier and target brain tissues, and are new delivery strategies for improving the utilization of drugs in the brain and preventing AD. Among them, nasal administration has great potential in preclinical and clinical research of neurodegenerative diseases [4]. At present, there is no cure for AD. Conventionally, symptoms are improved through nursing and rehabilitation training. New therapies targeting the lymphatic system and mitochondrial damage are still in the basic research stage and have significant limitations in clinical translation.

Given the severe prevalence of AD, the unclear molecular pathogenesis and the limitations of clinical treatment, this article focuses on the three core mechanisms of β-amyloid (Aβ) protein deposition, abnormal phosphorylation of tau protein, and neurofibrillary tangles. It systematically reviews the epidemiological characteristics of AD, analyzes the interaction between the two key protein lesions and neuroinflammation, summarizes the advantages and disadvantages of traditional interventions, Nanodelivery carriers, and nasal administration as new treatment technologies [4], and clarifies the delaying effect of a healthy lifestyle on cognitive decline. This study aims to clarify the intrinsic correlations of the core molecular pathologies of AD, provide a theoretical basis for the early screening, individualized prevention and control, and the development of targeted drug delivery systems of AD, and promote the clinical translation of targeted treatment for AD.

## 2. Aβ

### 2.1. Mechanism

Aβ protein is a peptide fragment produced by the cleavage of amyloid precursor protein (APP) by β- and γ-secretases [5]. In the brains of AD patients, specific subtypes such as Aβ-42 accumulate abnormally to form extracellular plaques, blocking synaptic signal transmission. This deposition not only directly interferes with the communication between neurons but also triggers a neuroinflammatory response by activating microglia, further exacerbating neuronal damage. The deposition of these extracellular plaques has extremely strong neurotoxicity. Firstly, soluble Aβ oligomers are considered the main toxic form, as they can directly bind to the postsynaptic membrane, interfere with the normal distribution of neurotransmitter receptors such as glutamate, and block long-term potentiation (LTP) of synapses, thereby severely damaging the communication and information transmission between neurons. Secondly, Aβ deposition not only creates a physical barrier but also acts as a pathological stimulus, overactivating the innate immune cells in the brain - microglia and astrocytes. Activated microglia release large amounts of pro-inflammatory cytokines (such as IL-1β, TNF-α) and reactive oxygen species (ROS), triggering a strong neuroinflammatory response [6]. This chronic inflammatory microenvironment not only fails to clear the plaques but instead exacerbates oxidative stress, causing healthy surrounding neurons to be "misattacked", forming a vicious cycle.

### 2.2. Treatment

In recent years, several clinical trials of Aβ immunotherapy have clearly demonstrated for the first time that removing the aggregated Aβ in the brains of patients with AD can delay the progression of the disease. However, the clinical improvement effects brought by these therapies are limited. This situation indicates that the academic community needs to not only deeply explore the pathogenesis of AD but also carry out intervention at an early stage of the disease's pathological process. Monoclonal antibody drugs such as Lecanemab, Donanemab, and Aducanemab can remove abnormal Aβ in the brain and delay the development of early AD, providing clinical evidence for the participation of Aβ accumulation in the pathogenesis of AD, and further supporting the Aβ cascade hypothesis, which states that the misfolding and aggregation of Aβ is the key initiating event in the onset of AD [7]. This will subsequently trigger a series of chain pathological reactions, ultimately forming the complete clinical and pathological characteristics of the disease. A set of AD immunoprevention programs is also needed, combined with clinical trial data and mechanism studies of preclinical disease models, to screen high-quality antibodies, optimize intervention timing, discover early biomarkers, and reduce potential side effects of the drugs.

## 3. Tau

### 3.1. Mechanism

Under normal conditions, Tau protein acts as a microtubule-binding protein and is selectively spliced by the MAPT gene to produce various subtypes, including four structural domains: N-terminal, proline-rich, microtubule-binding, and C-terminal. It can bind and stabilize microtubules, maintaining the stability of the cytoskeleton and ensuring the material transportation and structural integrity of neurons. Tau protein can be regarded as the "framework" and "transport track" within nerve cells, supporting the morphology of nerve cells and responsible for transporting nutrients and neural signals. Under physiological conditions, tau is naturally disordered and highly soluble, and does not spontaneously aggregate; however, in more than twenty neurodegenerative diseases, tau undergoes incorrect folding to form fibrillar aggregates [8]. When Tau protein undergoes excessive phosphorylation, it dissociates from microtubules, and the originally stable microtubules lose support and rapidly disintegrate, causing the microtubule network structure within neurons to completely collapse. This change directly blocks the axonal transportation function, interrupts the transmission of neurotransmitters, collapses the track, and prevents the delivery of nutrients and the transmission of signals. As a result, nerve cells will gradually die, and eventually, progressive loss of neurons will occur, leading to continuous decline in various functions of the patient, such as cognition and behavior.

### 3.2. Treatment

The massive loss of neurons is the core pathological feature of AD. Currently, there are still no effective intervention methods that can effectively block the neurodegenerative process of AD. Many studies have begun to develop targeted intervention strategies based on Tau protein. Some researchers have developed monoclonal antibodies (mAb2A7) that can specifically recognize phosphorylated Tau protein at position 217 (p-tau217). The analysis of clinical samples shows that the expression abundance of p-tau217 in the brain tissue of AD patients is significantly positively correlated with the degree of brain atrophy and the severity of cognitive impairment. The experimental data at the animal level confirmed that the nasal administration route can help mAb2A7 cross the blood-brain barrier and accumulate in the lesion brain regions of AD model mice. This antibody can specifically bind to the pathogenic p-tau217 and significantly inhibit the pathological aggregation process of Tau protein, while not interfering with the normal soluble Tau protein in the body. This antibody can significantly inhibit the apoptosis process of neurons in the lesion area, alleviate brain tissue atrophy problems, and improve the cognitive impairment and abnormal movement ability of model mice. The proteinomics detection results further confirmed that mAb2A7 can repair the dysregulated synaptic-related proteins in the AD lesion brain regions and restore the normal physiological function of synapses. In contrast, the 13G4 antibody targeting all Tau protein can, to a certain extent, reduce the pathological damage of brain tissue, but it will interfere with the normal physiological function of Tau and cause movement function impairment in mice. Based on the current research conclusions, p-tau217 can be used as an ideal specific therapeutic target for the neurodegenerative lesions of AD, and also opens up a new idea for the development of precise targeted drugs for AD [9].

## 4. Neuroinflammation

The classic pathological features of AD mainly consist of the deposition of Aβ amyloid plaques in the brain and the formation of neurofibrillary tangles due to excessive phosphorylation of Tau protein. These two types of abnormal proteins have long been regarded as the core biological markers and pathogenic core for AD diagnosis. However, numerous recent studies have confirmed that simple protein deposition cannot fully explain the long course of AD and the progressive loss of neurons. Neuroinflammation, as the core driving mechanism throughout the latent period, progression stage and terminal stage of the disease, plays a key role in upstream regulation, amplification of damage, and promotion of disease progression in the AD pathological network [10].The onset of AD is the

result of the combined effects of genetics, aging, systemic chronic inflammation, metabolic disorders, brain infections, cranial trauma, and environmental risk factors. Among them, the chronic neuroinflammation mediated by the inherent immune disorder of the brain is an important intermediate link connecting various risk factors with protein pathology and neuronal damage. Microglia and astrocytes in the brain are the main functional cells that maintain the immune homeostasis of the central nervous system.

Under normal physiological conditions, they are responsible for clearing cellular metabolic waste, identifying abnormal lesions, maintaining synaptic stability and normal neuronal functions, and play a role in protecting and repairing the brain. However, under the pathological conditions of AD, the high-risk genetic factor APOE4 significantly disrupts the immune balance in the brain. As the strongest genetic risk factor for late-onset AD, APOE4 not only accelerates the early deposition of Aβ plaques, aggravates the pathological aggregation of Tau protein and diffusion, and increases the degree of brain atrophy, but also directly leads to abnormal activation of microglia and astrocytes, defective phagocytic function, and disordered metabolic pathways, causing the brain immune cells to shift from "protective homeostasis" to "persistent pro-inflammatory state". Long-term activation of glial cells will release a large amount of inflammatory factors and complement components, inducing chronic, low-grade, and persistent neuroinflammation. This inflammation has a clear bidirectional nature: in the early stage of the disease, it is a protective response of the body to clear abnormal proteins and repair brain tissue, while the long-term persistent inflammatory response will transform into a pathogenic damage mechanism, further exacerbating the accumulation of Aβ and Tau pathology, inducing synaptic damage, neuronal apoptosis, and disruption of neural circuits, ultimately causing irreversible cognitive decline and motor function impairment in patients.

Currently, there are still key scientific issues that have not been clarified in the field of research: the causal sequence relationship between neuroinflammation and Aβ and Tau protein deposition is not clear. Whether inflammation is a secondary reaction after protein deposition or an upstream initiating factor that triggers abnormal protein aggregation still lacks complete mechanism evidence. At the same time, traditional AD treatment is still limited to a single targeted approach of "clearing pathological proteins", which can only alleviate clinical symptoms and improve the quality of life of patients, but cannot block the upstream inflammatory disorder and neurodegenerative process, and is difficult to curb the development of the disease from its root. Therefore, future research and clinical diagnosis of AD need to break away from a single pathological perspective. In mechanism research, it is necessary to focus on analyzing the dynamic changes of neuroinflammation during the 15 to 20-year latent period of the disease, clarifying the interaction network of upstream multiple factors such as APOE4-mediated immune disorder, systemic inflammation, and metabolic abnormalities; in diagnosis, develop early visualizable and highly specific neuroinflammation detection technologies to achieve early warning of the disease; in treatment, break away from the limitation of targeting Aβ and Tau alone, incorporate anti-inflammatory immune regulation, homeostasis repair, and upstream multi-factor intervention into the treatment system, providing new theories and treatment directions for the precise prevention and treatment of AD [11].

## 5. Regulate the Network

The pathological process of AD is driven by a multi-dimensional and interactive pathological regulatory network, rather than being solely dominated by a single Aβ deposition or Tau protein lesion. This regulatory network integrates multiple mechanisms such as genetic susceptibility factors, brain innate immune status, protein metabolic abnormalities, neuroinflammatory responses, and systemic environmental stimuli. Each link is interconnected and mutually amplified, forming a continuously deteriorating pathological cycle. Among them, the APOE4 gene, as the core regulatory node, can disrupt lipid metabolism in the brain, damage the homeostasis of glial cells, and amplify chronic inflammatory responses, thereby exacerbating Aβ plaque deposition and abnormal Tau protein phosphorylation from the upstream; and the accumulated pathological proteins will

continuously activate microglia and astrocytes, further releasing inflammatory factors, and continuously damaging synaptic structures and neuronal functions [11].

Meanwhile, external risk factors such as aging, systemic inflammation, and metabolic disorders will continuously stimulate the entire pathological network, promoting the slow progression of the disease over a latency period of more than ten years. It is precisely because of the complex regulatory network of AD, which is intertwined with multiple factors and mutually causal, that a single treatment method for removing pathological proteins alone cannot block the upstream pathogenic pathways. Only by comprehensively analyzing the interaction mechanisms of the network and targeting the upstream inflammation and immune disorders can break through the current treatment bottleneck and achieve early prevention and precise treatment of AD. Based on the above complex network interaction mechanisms, systematically analyzing the multi-dimensional regulatory network of AD at the post-transcriptional level is particularly crucial. For this reason, some studies aim to construct the lncRNA-miRNA-m mRNA ceRNA (competitive endogenous RNA) regulatory network of AD and screen key biomarkers related to AD [10]. The RNA-mediated lncRNA-miRNA-mRNA ceRNA regulatory network is an important research direction for analyzing the multi-dimensional pathogenesis of AD and exploring new disease markers [12].

Previous studies have reported that by using public gene expression databases, RNA molecules that are differentially expressed in Alzheimer's disease can be screened.he differentially expressed mRNAs obtained through this screening are mainly concentrated in immune-related pathways such as antigen processing and presentation. This once again confirms the central role of the imbalance of central immune homeostasis in the pathological progression of AD. Based on the differentially expressed RNAs obtained through this screening, a ceRNA regulatory network for AD can be established, and key upregulated lncRNAs such as LINC01094 and LINC00092, as well as various downregulated key lncRNAs, can be selected from it. This ceRNA regulatory network improves the multi-factor interaction pathogenic system of AD at the epigenetic level. The key RNA molecules obtained from this network are expected to become early diagnostic markers for AD and also provide potential molecular targets for developing new drugs targeting upstream central inflammation and immune disorders, compensating for the limitations of the current treatment strategies that solely target Aβ and Tau pathological proteins [12].

## 6. Conclusion

This article systematically reviews the core pathological mechanisms of AD, focusing on the independent pathogenic roles of Aβ amyloid protein deposition and abnormal phosphorylation of tau protein, clarifying the driving value of neuroinflammation throughout the entire course of AD, and revealing the pathological interaction relationship of these three elements in a mutually connected and vicious cycle. At the same time, the article summarizes the advantages and disadvantages of existing immunotherapies targeting Aβ and tau proteins, confirming that p-tau217 can serve as a highly specific target for precise treatment of AD, and that the nasal nano-delivery carrier can effectively bypass the blood-brain barrier, compensating for the deficiency of traditional treatments that cannot reverse the disease course. It also supplements the multi-dimensional pathogenic mechanism of AD through the construction of a ceRNA regulatory network. The research results of this article explore core issues of unclear pathogenesis of AD and limited clinical treatment methods, clarify the bidirectional regulatory effect of neuroinflammation on the two types of pathological proteins, mitigate existing constraints of single pathological mechanism research, and provide solid theoretical support for the exploration of early screening markers for AD and the development of individualized targeted treatments. The current limitations lie in that the causal relationship between neuroinflammation and Aβ and Tau deposition has not been fully clarified, and the existing protein-targeted therapies can only delay rather than reverse the disease course. Clinical translation still faces bottlenecks. Future research should focus on the dynamic mechanism analysis of the long latent period of AD, develop highly specific early warning technologies, and explore multi-target combined intervention strategies, in order to curb the progression of the disease from its root.

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