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# Alzheimer's Disease: The Pathogenic Mechanism of β-amyloid Protein Deposition and Plaque Formation

**Zhitong Xia***

College of Life Sciences and Technology, China Pharmaceutical University, Nanjing 210000, Jiangsu, China

***Author to whom correspondence should be addressed.***



**Abstract:** Alzheimer's disease (AD) is a common chronic neurodegenerative disorder with a complex pathogenesis. The progression of AD is closely related to the dysregulation of gene expressions such as β-amyloid precursor protein, presenilin 1, and presenilin 2. The core pathogenic mechanisms mainly involve two key pathways: abnormal deposition of β-amyloid protein (Aβ) in the brain, forming senile plaques, and excessive phosphorylation of Tau protein, inducing neurofibrillary tangles. Together, these two factors lead to neuronal damage and necrosis, as well as atrophy of brain tissue structure, ultimately resulting in cognitive decline in patients. This article focuses on the core dimension of β-amyloid deposition and plaque formation in the core pathogenic mechanism of AD and systematically elaborates on it, while also considering the pathogenic role of abnormal Tau protein. Firstly, Aβ is a peptide fragment composed of 39 to 43 amino acid residues produced by the hydrolysis of amyloid precursor protein by β-secretase, which is the main component of senile plaques in AD. Aβ42 is prone to form neuronal plaques, while Aβ40 tends to deposit in the cerebral vessels. Abnormal accumulation can cause significant neurotoxicity. Secondly, the pathogenic mechanism is analyzed. Due to the imbalance between Aβ production and its clearance, it accumulates abnormally in brain regions related to memory and cognition, such as the cerebral cortex and hippocampus, forming plaques. This disrupts neuronal signal transmission, damages synaptic functions, and triggers inflammatory responses, accelerating nerve damage. Moreover, insufficient sleep reduces the efficiency of Aβ clearance and increases the risk of deposition. Additionally, treatment directions such as inhibiting ubiquitin-binding enzyme UBE2N and applying Aβ-targeted clearance drugs, as well as the application value of serum Aβ as an early peripheral biomarker, are discussed. The principles, classifications, and application scenarios of two core detection techniques, namely enzyme-linked immunosorbent assay and APOE genotyping, are elaborated. At the same time, the pathogenic mechanism of Tau protein over-phosphorylation, losing normal function, aggregating to form neurofibrillary tangles, and subsequently destroying the neuronal transport system, leading to cell death, is also explained. This provides theoretical support and practical references for the early risk assessment of AD, deepening exploration of its pathological mechanism, and the development of targeted treatment plans.

**Keywords:** Alzheimer's disease; β-amyloid protein pathogenic mechanism; Tau protein

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# 1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder. Its onset may be related to dysregulation of genes such as β-amyloid precursor protein (β-APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2). The core mechanism of this disease involves abnormal deposition of β-amyloid protein in the brain, forming plaques, excessive phosphorylation of Tau protein leading to neurofibrillary tangles, and ultimately causing neuronal death and brain atrophy. In summary, the basic approach to treating AD is to activate certain purine receptors to improve AD cognitive impairment by protecting neurons, clearing Aβ plaques, and participating in inflammatory responses; inhibiting certain purine receptors can reverse AD memory deficits by reducing neuronal synaptic plasticity damage, Aβ deposition, accelerating amyloid precursor protein hydrolysis, and participating in inflammatory responses [1]. This article mainly discusses the pathogenic mechanism of Alzheimer's disease caused by the deposition of β-amyloid protein and the formation of plaques. The deposition of β-amyloid protein is a key step and early change in the onset of Alzheimer's disease. Active and passive immunization to remove Aβ is an important strategy for preventing and treating AD [2]. Multiple genetic studies, biochemical data, and animal models have shown that the aggregation of β-amyloid protein (Aβ) forms oligomers, protofilaments (PFs), and mature fibers. Due to the instability, structural heterogeneity of the fibers, and the misfolding and aggregation of Aβ, various structures and morphologically diverse aggregates are formed. These aggregates are associated with neurodegenerative diseases [3].

# 2. Deposition and plaque formation of β-amyloid protein

## 2.1. Basic introduction of the protein

β-amyloid protein (Aβ) is a peptide fragment produced by the hydrolysis of the amyloid precursor protein (APP). It consists of 39 to 43 amino acid residues and is the main component of senile plaques in patients with Alzheimer's disease. The β-secretase plays a crucial role in the formation of Aβ, and its level or activity directly affects the synthesis of Aβ. Abnormal deposition of Aβ leads to neuronal damage and cognitive decline. When it accumulates both within and outside neurons, it causes toxic effects. Specifically, Aβ42 is more likely to form neuronal plaques, while Aβ40 tends to deposit in cerebral blood vessels. Exploring the pathogenic mechanism of β-amyloid protein deposition and plaque formation is to clarify the molecular mechanism of the core pathological process of Alzheimer's disease, fill the key gap in the research on the pathogenesis of AD, and provide a scientific basis for the development of early screening and targeted treatment. At the same time, clarifying the pathogenic pathway of β-amyloid protein deposition can not only improve the pathological theoretical system of Alzheimer's disease, but also provide core experimental and theoretical support for developing Aβ-targeted clearance drugs and formulating sleep intervention and other prevention strategies.

## 2.2. Pathogenesis

β-amyloid protein (Aβ) is formed through the cleavage of amyloid precursor protein (APP) and is cleared

through metabolic pathways. In patients with Alzheimer's disease (AD), the imbalance between Aβ production and clearance leads to its abnormal accumulation in regions of the brain related to memory and cognition (such as the cerebral cortex and hippocampus), forming "senile plaques." These plaques disrupt the signal transmission between neurons, damage synaptic function, trigger inflammation, and further accelerate neuronal damage. Lack of sleep reduces the efficiency of clearing Aβ and increases the risk of its deposition in the brain.

## 2.3. Treatment principles

Inhibiting the ubiquitin-binding enzyme UBE2N can reduce Aβ accumulation and improve the pathological features of Alzheimer's disease. The level of UBE2N in the hippocampus of Alzheimer's disease patients is significantly elevated (If using lenvatinib monoclonal antibody) [4]. The progression of the disease can be slowed down by specifically removing the plaques in the brain. For instance, there are cases where the use of Denamarin has shown that after 6 Denamarin treatments, the load of Aβ protein in the brain decreased to 7.02 CL, reaching the withdrawal criteria. Denamarin can achieve deep Aβ clearance in real-world conditions and maintain good safety [5].

The concentration of Aβ in the serum of healthy individuals varies by age group: the serum Aβ concentration in the elderly is significantly higher, while in patients with pre-dementia Alzheimer's disease, the serum Aβ is significantly lower, showing a strong negative correlation with the brain Aβ load and the severity of overall cognitive impairment. Moreover, the circadian rhythm fluctuation of serum Aβ is extremely small, making it a non-daily rhythm-dependent early peripheral biomarker and a practical tool for early detection of Alzheimer's disease [6].

## 2.4. Detection methods

There are mainly two methods for detecting the markers related to Aβ: enzyme-linked immunosorbent assay (ELISA) and APOE genotyping.

### 2.4.1. Enzyme-linked immunosorbent assay (ELISA)

ELISA immunoassay technology relies on the specific binding of antigens and antibodies, and is mainly used for detecting biomolecules (such as proteins, hormones, and antibodies) in biological fluids. Its core principle is to fix the antigen or antibody on a solid-phase support (such as a microplate), while maintaining its immunological activity. The antibody/antigen is labeled with an enzyme (such as peroxidase), and then a substrate (such as TMB) is used to induce a color reaction. The detectable color change (or optical density) produced by the enzymatic catalytic reaction of the substrate allows for quantitative or qualitative analysis of the target substance.

ELISA is mainly divided into four types: The direct method involves allowing the enzyme-labeled primary antibody to directly bind to the antigen, which is simple but has lower sensitivity. For example, ELISA versus PCR for the diagnosis of chronic Chagas disease: systematic review and meta-analysis [7]. The indirect method involves first allowing the primary antibody to bind to the solid-phase carrier, and then amplifying the signal through the enzyme-labeled secondary antibody. This method is suitable for antibody detection. For example, the preliminary establishment of the prokaryotic expression method of the A4L protein of bovine nodular dermatitis virus and the indirect ELISA antibody detection method [8]. This experiment successfully expressed and obtained high-purity recombinant A4L protein using Escherichia coli; the rabbit-derived A4L protein

polyclonal antibody prepared can specifically bind to the eukaryotic-expressed A4L protein, and an LSDV ELISA antibody detection method based on the A4L protein was established. The sandwich method involves using double antibodies to capture the antigen, which has strong specificity and is often used for hormone or tumor marker detection. For example, the double antigen sandwich ELISA antibody detection method for swine fever virus [9]. This experiment utilized the BioEdit software to compare the complete sequences of the E2 proteins of swine fever virus and bovine viral diarrhea virus, screened the specific sequences of the E2 protein of swine fever virus, constructed the pCDNA3.1-2×rE2-His recombinant expression vector, and established a double-antigen sandwich ELISA method to evaluate its specificity, sensitivity, and repeatability. All showed good results. The competitive method can be used for determining antigens and also for determining antibodies. This method is commonly used for detection when interfering substances in the antigen are difficult to remove or when sufficiently purified antigens are not easily obtainable.

### 2.4.2. APOE genotyping

The APOE genotyping test examines the polymorphism of the apolipoprotein E gene located in the q13.32 region of chromosome 19. This gene has three alleles (ε2, ε3, ε4), resulting in six genotypes, encoding three protein subtypes (e2, e3, e4). The genotyping results are closely related to lipid metabolism, the risk of cardiovascular and cerebrovascular diseases, as well as neurodegenerative diseases such as Alzheimer's disease (AD). The ε4 type is a protein associated with an increased risk of Alzheimer's disease (especially homozygous ε4/ε4), and may also increase the risk of atherosclerosis and hyperlipidemia; the ε2 type is a protein that may reduce the risk of Alzheimer's disease, but is also associated with type III hyperlipoproteinemia risk; the ε3 type is the most common, belonging to the "neutral" allele, with relatively lower disease risk.

In AD (Alzheimer's disease) detection, the ε4 allele is a significant genetic risk factor for sporadic AD: one ε4 allele will increase the risk of disease by 3 to 4 times. Two ε4 alleles will increase the risk by 10 to 12 times. Combined with family history, imaging examinations, and biomarkers (such as Aβ), the genotyping results can be used as an early screening tool for a comprehensive risk assessment. Polymerase chain reaction (PCR) is the standard technique for APOE genotyping.

## 3. Tau protein abnormality and neurofibrillary tangles

The accumulation of tau protein is the most common pathological phenomenon in degenerative brain diseases, including Alzheimer's disease (AD), progressive supranuclear palsy (PSP), traumatic brain injury (TBI), and over twenty other diseases. The accumulation of neurofibrillary tangles (NFT) containing tau protein is most closely related to cognitive decline and cell loss [10]. Pathological tau is closely related to the progression of neurodegenerative diseases, and the spread of tau aggregates is associated with the severity of the disease [11].

The tau protein is crucial for maintaining the structural stability of neurons. Under normal circumstances, it promotes the polymerization of microtubule proteins, maintains the stability of microtubules, and reduces their dissociation. In a healthy and mature brain, each tau molecule contains 2 to 3 phosphate groups. However, in the brains of Alzheimer's disease patients, the tau protein undergoes abnormal, excessive phosphorylation (each molecule contains 5 to 9 phosphate groups), loses its normal biological function,

reduces its affinity for microtubules, and aggregates to form neurofibrillary tangles (NFTs). These tangles disrupt the transport system of neurons, cut off the supply of nutrients, and accumulate metabolic waste, ultimately leading to cell death. The severity of tau protein lesions is usually directly related to the decline in cognitive ability.

## 4. Conclusion

This article conducts a systematic analysis of the core pathogenic mechanism of Alzheimer's disease (AD), clearly identifying that the deposition of β-amyloid protein (Aβ) forms senile plaques and the excessive phosphorylation of Tau protein leads to neurofibrillary tangles, which are two key pathological pathways jointly driving the progression of AD. Aβ is generated by the hydrolysis of amyloid precursor protein by β-secretase, with Aβ42 being more prone to form neuronal plaques, while Aβ40 tends to deposit in the cerebral vessels. When the balance between Aβ production and clearance is disrupted, abnormal aggregation occurs in brain regions related to cognition, such as the cerebral cortex and hippocampus, thereby disrupting neuronal signal transmission, damaging synaptic functions, and triggering inflammatory responses. Concurrently, there are pathological changes in the Tau protein. Under normal conditions, Tau protein is responsible for maintaining the stability of neuronal microtubules, but in the brains of AD patients, Tau protein undergoes excessive phosphorylation, loses its affinity for microtubules, and aggregates to form neurofibrillary tangles. These tangles will disrupt the material transportation system of neurons, block nutrient supply, and accumulate metabolic waste, ultimately causing neuronal death. At the same time, therapeutic strategies such as inhibiting ubiquitin-binding enzyme UBE2N, applying Aβ-targeted clearance drugs, and detection techniques such as enzyme-linked immunosorbent assay and APOE genotyping also provide an important practical basis for the early screening, risk assessment, and clinical intervention of AD. By analyzing the molecular mechanisms of Aβ deposition and abnormal Tau protein, this article not only improves the theoretical framework of the pathological process of AD but also builds a key bridge for the transformation from basic research to clinical practice, and is of great significance for promoting research and development in the field of neurodegenerative diseases.

In the future, researchers can delve deeper into the synergistic pathogenic mechanism between Aβ deposition and abnormal Tau protein, clarify the specific molecular pathways of their interaction, and provide new ideas for the development of dual-targeting therapeutic drugs. At the same time, researchers can combine cutting-edge technologies such as gene editing and artificial intelligence to optimize the detection methods of serum Aβ and other biomarkers, improve the sensitivity and specificity of early diagnosis of AD, and help achieve early detection and intervention of the disease. Additionally, researchers can conduct more large-sample, long-term follow-up clinical studies to verify the efficacy and safety of Aβ-targeted drugs in the real world, promote the popularization and application of related treatment plans, and contribute to the solution of this major public health problem of Alzheimer's disease.

## Disclosure statement

The author declares no conflict of interest.

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