Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/33/20240896

# Research progress and future development direction of Alzheimer's therapy

**Dingjiayi Zhai**

College of Pharmacy, Changzhou University, Changzhou, Jiangsu, 213164, China

2100390115@smail.cczu.edu.cn

**Abstract.** Dementia has become a global crisis, numbering over 50 million people in the world, more than half of whom are Alzheimer's disease (AD)'s patients. AD is a heterogeneous disease that has complex pathobiologic properties. The exact AD mechanism is unclear at this point, but the pathological hallmarks constitute amyloid-β (Aβ) plaques and tau neurofibrillary tangles and most treatments are based on this. AD has a serious impact on society and on humanity, but drugs approved to treat AD are few and ineffective. The article analyzes the possible causes of pathological hallmarks and describes existing treatment options, as well as their shortcomings and potential future treatments. It also speculates on the direction of possible future therapeutic options providing reference for more new technologies and methods of treating AD in the future. However, there are still many unclear pathogenic mechanisms and more effective treatments are needed for further research on AD in the future.

**Keywords:** AD, pathological hallmarks, therapy.

## 1. Introduction

Alzheimer's disease (AD), one of the main causes of dementia in older individuals, is widely recognized that the main pathological features are amyloid-β (Aβ) plaques and tau neurofibrillary tangles in the brain. Alzheimer's patients lose synapses and neurons as the disease progresses, eventually manifesting dementia symptoms such as memory loss. Memory loss is a central symptom. The symptoms of mild dementia are mainly reduced memory, and they are prone to negative emotions and personality disorders when dealing with unfamiliar and complicated things. Moderate dementia patients will also have seizures, mental abnormalities and other phenomena. People with severe dementia may also have stiff limbs or paralysis, along with symptoms of systemic disease [1].

The incidence of AD will increase as the percentage of older people increases. The increasing incidence of AD is gradually becoming an important problem faced by the world. China has become the world's largest number of people with AD, with nearly 10 million people affected. The data shows that someone in the world gets dementia every 3.2 seconds. The World Health Organization reports that at the end of 2022, there were 55 million cases of dementia worldwide. It is estimated that the number of patients will skyrocket, reaching 78 million in 2030 and 139 million in 2050. Of those patients, about 70 percent were Alzheimer's patients [2]. It will put a huge burden and pressure on both families and society. This phenomenon requires people to pay attention to and take measures.

Although a large number of studies have focused on the cause of AD, research on its pathogenesis is still immature at this stage. Many related drugs and vaccines have been also developed, but the treatment

DOI: 10.54254/2753-8818/33/20240896

of AD is still a major problem in today's aging society. AD is characterized pathologically by "senile plaques", primarily composed of Aβ polypeptides, and intra-neuronal neurofibrillary tangles (NFT) and astrocyte hypertrophy. Many of the early AD treatments developed focused on Aβ, but were not as effective in mitigating the disease process, so gradually, treatment strategies changed in different directions. These drugs can only alleviate symptoms in the early stages, but not a complete cure, and for severe patients, symptom relief and disease improvement are less effective. More effective treatments are needed at this stage. So there's a lot of room for improvement in the treatment of AD.

This article analyzes the possible pathological hallmarks, compares the existing therapeutic methods and has the implications for the possible directions for the future. It is of vital essential to fight against the growing threat of this deteriorating disease.

## 2. Pathological hallmarks

Most scholars believe that the main pathological hallmarks of AD are amyloid-β (Aβ) plaques and tau neurofibrillary tangles. Moreover, there are some new pathological findings on AD.

### *2.1. Amyloid-β (Aβ) plaques*

Aβ peptide which are 38–42 amino acids in length was first recognized as the main component of meningovascular amyloid. Aβ aggregates which are detectable in AD brain are major neuropathologic criteria for the diagnosis of AD. The current accepted wisdom is that Aβ deposition is the earliest evidence of neuropathological changes in AD that can now be detected. From some animal models, it is proved that Aβ injections in mice can cause memory loss, which is a main symptom of AD. An extended extension on the amyloid hypothesis has a high degree of recognition. The hypothesis is that this amyloid deposition does not exist independently, which is associated with other hallmarks of AD. The accumulation process of cerebral amyloid and tau pathology is slow, and Aβ deposition is positively correlated with tauopathy, and Aβ deposition is associated with loss of synaptic function, inflammation, neuronal loss, and ultimately dementia [3]. Though with the deepening of research, the clear relationship between Aβ and AD, the study of the disruption of Aβ aggregation is a possible way to help cure AD.

The effects of Aβ on Alzheimer's are multifaceted, and in addition to those mentioned above, Abeta can act in conjunction with metal ions. Numerous studies in the last decade have demonstrated that One of the reasons for the precipitation of the Aβ protein is the interaction of Aβ with a number of neocortical metal ions, of which the common ones are zinc (Zn), iron (Fe), and copper (Cu) [4]. The causes of Aβ deposition "senile plaques" are complex, and although the mechanism of its impact on Alzheimer's disease is not clear. So far, most scholars still regard Aβ as a breakthrough in treatment.

### *2.2. Tau neurofibrillary tangles*

Tau protein is primarily expressed by neurons in the brain, and is encoded by MAPT gene on chromosome 17. Under pathological circumstances, hyperphosphorylated tau proteins which is transferred from neural axons to dendrites and it can inhibite glutamate receptor-specific transport or synaptic anchoring increasing in quantity, resulting in impairing synaptic function there [5].

The hyperphosphorylated tau proteins which can mediate by many tau kinases are polymerized into neurofibrillary tangles. Neurofibrillary tangles (NT) are microtubule-associated proteins, which are a highly phosphorylated pathologically insoluble aggregate of tau found in neurons of patients. Under some conditions, tau proteins will polymerize into oligomers and Fibrils which means hyperphosphorylated tau proteins may be one of key element of neurodegeneration in AD. A great deal of evidence confirms that human tau fiber aggregates have prion-like self-replicating ability. Tau pathology can subsequently spread through the synapse to more distant neurons. In the Braak stages I and II of the disease, Tau inclusions first observed to appear in the hippocampus and medial cortex. In Braak stages III and IV, it then spreads to insular cortices and occipitotemporal, people have the potential for subclinical manifestations. Finally, doctors can observe tau pathology throughout most of the cortex coupled and patients meeting the clinical criteria for AD dementia.These findings demonstrate a link

DOI: 10.54254/2753-8818/33/20240896

between cognitive decline and neurodegeneration and the onset and spread of tau pathology. Nowadays tau pathology is also one of the main directions for scholars to study AD treatment.

### *2.3. Astrocyte hypertrophy*

Astrocyte hypertrophy, adjacent to "senile plaques", is now identified as a major marker of most forms of chronic neurodegeneration and brain damage including AD. Though the role of astroglia in this disease has been understudied, there are some evidences which suggest that astrocyte is related to several major AD pathophysiological processes including Sleep disorder, neuroinflammation, impaired cerebrovascular function, synapse degeneration and low metabolic level[6]. Although there are still many details to refine, what is clear is that astrocyte modulation could provide a new drug targets for AD.

### *2.4. ApoE4*

Apolipoprotein E (ApoE) is a kind of apolipoproteins found in chyme and intermediate density lipoproteins and is important for the normal metabolism of triglyceride-rich lipoprotein components. ApoE is expressed in many organs, most in liver and brain, and mediates isomer-dependent cholesterol metabolism in peripheral tissues. While in the central nervous system, ApoE is produced primarily by astrocytes and can transport cholesterol to neurons via the ApoE receptor. This is something new to the research of AD. APOE ε2 protects against AD and APOE ε4 raises risk of AD. The carriers of the APOEε4 allele have accelerated amyloid deposition in the brain as they age. That means the older they are, the more amyloid deposits they have in the brain compared to non-carriers. ApoE ε4 competitively bind to Ab receptors on glial cells to impede Aβ clearance. ApoE promotes seeding and fibrillization of Aβ, resulting in increased amyloid deposition amyloid deposition[7].Some of ApoE enhances tau pathogenicity by increasing microgliosis and neuroinflammatory cytokine release[8]. Therefore, ApoE is an important risk factor for AD, especially in the elderly. Lower ApoE levels may reduce the pathology associated with amyloidosis and pathological changes.

### *2.5. Microbiome*

More and more research is now showing that gut flora is linked to many diseases in the human body. The gut-brain axis connects the gut and the brain through extensive interconnections, which has an effect on maintaining homeostasis. Multiple studies have shown the patients of AD have a different gut microbial composition than normal individuals, and there is a link between the gut microbiota and AD [9]. Differences in composition of gut microbial have also been observed in mouse models of AD, and studies have confirmed that changes in the gut microbiota are associated with cerebral β-amyloidosis [10]. Proper diet and exercise contribute to the balance of gut microbes and have great potential to alleviate disease.

## 3. Therapeutic methods

Globally, there are only four drugs currently approved by the FDA for the treatment of cognitive impairment and dysfunction in AD. Three of them are cholinesterase inhibitors (ChEIs) including donepezil, rivastigmine, and galantamine. Another type of drug is memantine which is an uncompetitive NMDA receptor modulator. This class of Alzheimer's drugs designed to slow cognitive decline can cause brain shrinkage. Although there is no complete cure or very effective treatment of the disease, many treatment options like diets, drugs, vaccines, are tested currently in different stages of Alzheimer's clinical.

### *3.1. Cholinesterase inhibitors*

Acetylcholine neurons can innervate most of the brain regions responsible for activities such as learning memory stress response and cognition, which are closely associated with the symptoms of Alzheimer's patients. Moreover, the degeneration of these neurons is regarded as a main factor in process of AD. The cholinergic theory of Alzheimer's disease focuses on the gradual loss of cholinergic innervation and it

DOI: 10.54254/2753-8818/33/20240896

is thought to be an important cause of early attention deficit and memory problems in AD patients. ChEIs work by enhancing synaptic levels of acetylcholine to change the situation. It has a certain effect on improving memory, but it cannot prevent the development of the disease. Even a class of drugs designed to slow the rate of cognitive decline may cause the brain to shrink, which is not beneficial for long-term disease treatment. The available findings do not favor the use of the drug in patients with mild AD, and ChEI may exacerbate cognitive decline in the early clinical stages [11].

### *3.2. Anti-NMDA*

It interferes with the specific binding of NMDA receptors thereby inhibiting glutamate-mediated neurotoxicity. This toxicity occurs with neuronal death in the progression of AD and is thought to influence the course of AD, but the exact mechanism is unknown. The drug has also been shown to provide some clinical relief in AD.

### *3.3. Healthy Diet*

For the prevention and treatment of diseases, the most often proposed by doctors is to develop healthy habits, which is also widely regarded as an effective way. Recent studies have focus on the use of specific combinations of nutrients to protect synapses and mitigate cognitive deterioration, as it is widely recognized that holistic dietary adjustments are more effective than single-nutrient supplementation strategies. Relevant studies have mainly focused on the impact of protein, lipids, dietary fiber (DF), vitamin D, on the gut microbiota, and the gut microbiota is closely related to AD. Neurodegenerative Delay (MIND) diet and the Ketogenic diet (KD) are recognized for healthy diet structure, which facilitates the slowing of Aβ protein deposition and mitigates the effects of glucose metabolic damage and inflammation [11,12].

These drugs are early research results and have been clinically tested and observed over a long period of time. The effect of diet modification is slower, and the detailed mechanism is still to be studied. However, there are still some new technologies also have potential for treating Alzheimer's disease.

## 4. Future

### *4.1. Vaccine*

The decrease in tau pathology mentioned above is an effective way to reduce the symptoms of dementia. Therefore, many vaccines are being developed to target tau pathology. AADvac-1 is a vaccine made to facilitate tau pathology clearance from the brain. It is the first tau antibody vaccine to enter into instrumented clinical human trials. Vaccinated participants who developed tau antibodies specific for the peptide antigen are more than 95 percent. Antibody detected in CSF was average concentration 0.3 percent of serum. In this trial, it was reported that AADvac-1 slowed down the rate of increase of Neurofilamentlightchain (NfL) in the blood [13].

However, more evidences suggests that development of AD and associated neurodegeneration is associated with dysfunction of amyloid precursor protein. Additionally, APP fragments have been proved to destroy synaptic plasticity and accumulate dystrophic neural protrusions in patients with AD [14]. Moreover, APP malfunction has been associated with tau phosphorylation, accumulation and aggregation. Scholars speculate that it is main driving factor of AD. Therefore, APP has great potential as a future therapeutic target for diseases.

### *4.2. Gene therapy*

Gene therapy is defined as the introduction of exogenous normal cellular genes into target cells to correct abnormal genes or compensate for missing genes (missing proteins) in order to treat certain genetic disorders. This technology arose very early, and in 2017, the United States government approved a therapy that modifies patients' autoimmune cells (yescarta gene therapy) to help treat patients with specific lymphoma. At present, many animal models have been established to verify the therapeutic effect of different gene therapy on Alzheimer's disease. As mentioned above, APOE ε2 protects against

DOI: 10.54254/2753-8818/33/20240896

AD. Therefore, one of the therapeutic methods is to use gene therapy methods to overexpress ApoE2 as an effective means to overcome loss of function correlated to ApoE4 [15]. Other evidence shows that the damage or loss of membrane/lipid rafts (MLR)-related signaling protein leads to the loss of synaptic and cognitive dysfunction. It is a potential alternative to treat AD using gene therapies that target neuroprotective mechanisms in an attempt to restore neurotrophic receptors (NTRs) with MLR-localized functions [16].

### *4.3. Regenerate mitochondria*

Numerous studies have shown that autophagy can clear misfolded proteins(such as Aβ) from the brains of Alzheimer's patients and compromised autophagy is associated with increasing age [17].From the above pathological hallmarks, it can be inferred that up-regulation of autophagy may improve clinical features such as memory decline. This has been tested in many animal models.

It is worth noting that autophagy can be a double-edged sword. Normal levels of autophagy help maintain tissue homeostasis and cell survival, but excessive levels may stimulate tumor growth.

### *4.4. Gene-editing technology*

Genome editing refers to the introduction of specific sequence changes in cellular DNA. CRISPR/Cas is the adaptive immune system of bacteria and archaea, which can detect specific sequences and silence foreign nucleic acids by cutting foreign DNA and integrating it into the host chromosome of proximal CRISPR to protect itself from viruses and plasmids. There has now been some research into AD treatments regarding gene therapy. By delivering CRISPR-Cas9 to the brain of 5XFAD and APP/PS1 transgenic mice after intravenous injection, the human APPswe allele was selectively and effectively edited in vivo, which not only alleviated Aβ-related pathology, microglial proliferation and neurite dystrophy in transgenic mice, but also improved the cognitive function of mice [18]. Using amphiphilic R7L10 nanoparticles as vectors, direct injection into the hippocampal CA3 region of APPNL-G-F/NL-G-F and 5XFAD transgenic mice delivered the CRISPR-Cas9 system to target Bace1, which reduced the expression of Bace1 and ameliorated cognitive deficits to a certain extent in AD mouse models [19]. The APP gene in HEK293T cells and SH-SY5Y neuroblastoma was modified by CRISPR/Cas9, which achieved the A673T mutation and resulted in decreased expression of Aβ40 and Aβ42 peptides [20].

## 5. Conclusion

A large number of studies have shown that drugs targeting AB are almost ineffective in patients with mild cognitive impairment and early AD. Nowadays because scientists continue to make great progress on the understanding of AD pathobiology, the research progress of treatment methods is also advancing continuously. While a large number of studies support that A β protein deposition can significantly promote the pathogenesis of AD, therapeutic regimens targeting it have not been successful in clinical trials. Because all current therapies have some drawbacks, combination therapies may be a key research direction in the future. In view of the available treatment methods for AD are still limited, the treatment methods are few, and the effect is not ideal, it is necessary to use new research methods and techniques. Although there have been a number of monotherapies in clinical period. Combination therapy can include immunotherapy for multiple proteins and different pathological forms for the same protein. Alzheimer's disease should be detected early and treated as soon as possible. And now the hot technology AI is very likely to help with AD assisted diagnosis and treatment. Identify therapeutic regimen targets based on DNA, RNA and amino acid databases and design target proteins using AI. Certainly, the use of new technologies and methods should be based on scholars' research on the mechanisms of AD. The core of this article is also to explore the treatment trends of AD based on the pathogenesis of AD, and to provide constructive reference for better combination of AD treatment and advanced technology in the future

DOI: 10.54254/2753-8818/33/20240896

## References


[1] Wei Wenjing et al 2019 Assessment and application of dementia symptom management :a literature review J Nurs Sci 2019 34(3) 100-103

[2] Alzheimer's Association 2022 Alzheimer's disease facts and figures Alzheimers Dement J Alzheimers Assoc 18 700-789

[3] De Strooper B and Karran E 2016 The Cellular Phase of Alzheimer's Disease Cell 164 603–615

[4] Armstrong RA 2011 The pathogenesis of Alzheimer's disease: a reevaluation of the "amyloid cascade hypothesis" Int J Alzheimer's Dis

[5] Hoover BR Reed MN Su J et al 2010 Tau mislocalization to dendritic spines mediates synaptic dysfunction independently of neurodegeneration Neuron 68 1067–1081

[6] Price B R Johnson L A & Norris C M 2021 Reactive astrocytes: The nexus of pathological and clinical hallmarks of Alzheimer's disease Ageing Research Reviews 68 101335

[7] Huynh TV Davis AA Ulrich JD and Holtzman DM 2017 Apolipoprotein E and Alzheimer's disease: the influence of apolipoprotein E on amyloid-b and other amyloidogenic proteins J Lipid Res 58 824–836

[8] E Zhao L Ricart Arbona RJ Monette S et al 2018 AAVrh10-Mediated APOE2 Central Nervous System Gene Therapy for APOE4-Associated Alzheimer's Disease Hum Gene Ther Clin Dev 29 24–47

[9] Z Li H Zhu Y Guo et al 2020 Gut microbiota regulate cognitive deficits and amyloid deposition in a model of Alzheimer's disease J Neurochem 155 448-461

[10] Han J-Y Besser LM Xiong C Kukull WA and Morris JC 2019 Cholinesterase Inhibitors May Not Benefit Mild Cognitive Impairment and Mild Alzheimer Disease Dementia Alzheimer Dis Assoc Disord 33 87–94

[11] M Lilamand B Porte E Cognat et al 2020 Are ketogenic diets promising for Alzheimer's disease? A translational review Alzheimers Res Ther 12 42

[12] M Morris C Tangney Y Wang et al 2015 MIND diet associated with reduced incidence of Alzheimer's disease Alzheimer's Dement 11 1007-1014

[13] Novak P et al 2019 AADvac1 an Active Immunotherapy for Alzheimer's Disease and Non Alzheimer Tauopathies: An Overview of Preclinical and Clinical Development J Prev Alzheimers Dis 6 63–69

[14] Kametani F Hasegawa M 2018 Reconsideration of amyloid hypothesis and tau hypothesis in Alzheimer's disease

[15] Rosenberg JB et al 2018 AAVrh10-Mediated APOE2 Central Nervous System Gene Therapy for APOE4-Associated Alzheimer's Disease Hum Gene Ther Clin Dev 29 24–47

[16] Wang S Leem J S et al 2021 Synapsin-caveolin-1 gene therapy preserves neuronal and synaptic morphology and prevents neurodegeneration in a mouse model of AD Molecular Therapy - Methods & Clinical Development 21 434–450

[17] Fang EF et al 2019 Mitophagy inhibits amyloid-b and tau pathology and reverses cognitive deficits in models of Alzheimer's disease Nat Neurosci 22:401–12

[18] Chan KY, Jang MJ, Yoo BB, et al 2017 Engineered AAVs for efficient noninvasive gene delivery to the central and peripheral nervous systems Nat Neurosci 20 (8) 1172-1179

[19] Park H Oh J Shim G et al 2019 In vivo neuronal gene editing via CRISPR-Cas9 amphiphilic nanocomplexes alleviates deficits in mouse models of Alzheimer's disease Nat Neurosci 22(4) 524-528

[20] Guyon A Rousseau J Bégin FG et al 2021 Base editing strategy for insertion of the A673T mutation in the APP gene to prevent the development of AD in vitro Mol Ther Nucleic Acids 24 253-263