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Alzheimer's Disease: Hypotheses and therapies

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Abstract. Alzheimer's disease (AD) is the most common neurodegenerative disease characterized by dementia and progressive cognitive decline. Despite decades of research, the fundamental causes of Alzheimer's remain unclear and expect to be multifactorial. Among numerous hypotheses, the amyloid cascade hypothesis, suggesting that the accumulation of beta-amyloid (Aβ) peptides triggers a cascade of pathological events, including tau hyperphosphorylation, synaptic dysfunction, and neuronal death, remains the core framework due to recent breakthroughs in its related drugs. At the same time, emerging evidences also promote the attention on other contributing factors such as tau pathology, neuroinflammation, mitochondrial dysfunction, and genetic predispositions, particularly involving APOE-ε4 and TREM2 variants. In addition, non-AD co-pathologies, such as Lewy body disease, cerebrovascular pathology, and TDP-43 proteinopathy, would further complicate disease progression, especially in elderly patients. This review critically examines and elaborates on most of the current human understanding of the etiology of AD, involves different AD treatment interventions designed based on different understandings, and emphasizes new strategies for personalized and combination therapy aimed at preventing or reversing disease progression.

Keywords: Alzheimer's disease, therapeutics strategies, neurodegeneration, β-amyloid peptide, tau protein.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by gradual decline in cognitive function, the formation of beta-amyloid plaque, and existence of neurofibrillary tangles in brain structure. It is the most common form of senile dementia, accounting for 60-80% of dementia cases. A typical Alzheimer's patient presents with memory decline in the early stages, gradually progressing to loss of thinking, language, judgment, and daily functioning, ultimately leading to complete dependence on care. This disease mainly affects people aged 65 and above, but in rare cases, early-onset Alzheimer's disease may occur around the age of 50 [1,2]. Nowadays, more than 50 million people are affected by dementia, and by 2050, the prevalence of dementia will double in Europe and triple worldwide, and that estimate is 3 times higher when based on a biological (rather than clinical) definition of Alzheimer's disease [3].

The study of Alzheimer's disease did not initially receive widespread attention, but in the 1960s, with the research of British psychiatrists Tomlinson and Roth, they proposed that Alzheimer's disease is associated with amyloid plaques, questioning the difference between early-onset and late-onset dementia. During this period, Alzheimer's disease gradually became recognized as the main cause of senile dementia. In the late 1970s and 1980s, AD research entered a critical stage. Robert Katzman proposed in 1976 that Alzheimer's disease not only affects younger dementia patients, but is the main

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cause of dementia in all age groups. This theory has driven extensive research on Alzheimer's disease.[4] With the increasing attention to AD, various hypotheses have sprung up like mushrooms after rain. Based on these hypotheses, researchers have made unremitting efforts in the past thirty years and have ultimately achieved breakthrough progress in recent years.

2. Hypotheses

2.1. Cholinergic Hypothesis

The Cholinergic Hypothesis was proposed in the 1970s by Peter Davies and A D. Smith et al. It is based on the discovery that acetylcholine levels would significantly decrease in the brain of Alzheimer's disease patients. Acetylcholine is an important neurotransmitter in the brain. It is responsible for signal transmission between nerve cells, particularly in areas related to memory and cognition. This hypothesis suggests that cognitive impairments in Alzheimer's disease could be closely related to functional damage of cholinergic neurons or even the whole cholinergic system in the brain. Particularly, cholinergic neurons in areas responsible for learning and memory like the hippocampus and cerebral cortex would be most affected [5].

Acetylcholine is synthesized by choline and acetyl CoA in cholinergic cells through the catalytic action of choline acetyltransferase (ChAT). ChAT shows functional decline in Alzheimer's patients, leading to a decrease in ACh levels in the brain. Research has shown that reduced ChAT expression in Alzheimer's disease patients is associated with cognitive decline. At the same time, the degradation of acetylcholine would be catalyzed by acetylcholinesterase (AChE), which rapidly decomposes ACh into choline and acetic acid. In the brains of Alzheimer's disease patients, AChE activity significantly increases, leading to a further decrease in ACh levels [6,7]

In addition, with further research on AD, the accumulation of β - amyloid protein has been found to have a direct toxic effect on the cholinergic system. Aβ can cause neuronal apoptosis and further decrease in acetylcholine levels through interactions with cholinergic neurons and their receptors, especially the α 7 nicotinic receptors in nicotinic acid receptors (nAChRs), which have been observed to have a direct binding relationship with β - amyloid proteins. Research has shown that Aβ can bind to and inhibit the function of α 7 receptors, which not only exacerbates ACh dysfunction but is also closely related to the progression of AD.[8,9] Based on this information, we can know that nowadays research on Alzheimer's disease is no longer limited to any single hypothesis. Researchers have already reached a consensus that AD is extremely complex, so they often try to cross hypotheses to obtain further experimental results. However, considering the extreme complexity of AD, which can greatly confuse readers in the event of hypothesis crossover, it is still necessary to understand each important hypothesis separately.

2.2. Amyloid Cascade Hypothesis

The amyloid cascade hypothesis is currently one of the most widely accepted theories for explaining the pathological mechanisms of Alzheimer's disease (AD). It was first proposed by John Hardy and David Allsop in 1991. This hypothesis mainly emphasizes that the main pathological changes in AD stem from abnormal metabolism and accumulation of beta-amyloid protein, which ultimately leads to a series of neurodegenerative neuropathologies. Firstly, Aβ aggregation triggers phosphorylation of Tau protein, forming neurofibrillary tangles (NFTs), which can lead to the breakdown of neuronal structure. Secondly, Aβ would also induce the activation of microglia, resulting in chronic inflammatory reactions and further deteriorated neuronal damage and death. Apart from that, the accumulation of Aβ is also related to synaptic dysfunction or even synaptic loss, which disrupts communication between neurons and affects cognitive function.[10,11]

Aβ protein is a short peptide generated by the cleavage of amyloid precursor protein (APP) by two enzymes -- β-secretase and γ-secretase. Under normal circumstances, Aβ would be cleared in time. However, in AD patients, due to excessive production of Aβ or decreased Aβ clearance ability, soluble Aβ aggregates into oligomers and eventually forms an entire extracellular plaque. These plaques are one

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of the hallmark features of AD pathology, typically appearing in the hippocampus and cerebral cortex, which are brain regions responsible for learning and memory.[12]

Although the amyloid cascade hypothesis has gained widespread support, with recent research, Tau protein tangles (neurofibrillary tangles) have been found to potentially play an important role in the progression of Alzheimer's disease. And the pathological changes of Tau are often more closely related to cognitive decline in AD patients, because researchers have found that A β plaques also appear in the brains of some elderly people who do not have AD, while neurofibrillary tangles only appear in the neurons of AD patients. In addition, some researchers have suggested that the pathological mechanism of AD may involve more factors, such as mitochondrial dysfunction, neuroinflammation, and disruption of the blood-brain barrier, and A β may be just one link rather than the root cause. This theory has received a lot of evidences in recent years, especially in experiments on drugs guided by the idea of clearing A β plaques. During those experiments, AD patients with these traits have much less reduced brain function decline after treatment compared to patients without these traits.[13-15]

2.3. Tau Protein Hypothesis

The Tau Protein Hypothesis is another important theory in Alzheimer's disease research. It is proposed by German neuropathologist Heiko Braak and his colleague Eva Braak in 1990s. This hypothesis focuses on the abnormal phosphorylation and aggregation of Tau protein, which is considered one of the most critical causes of neurodegenerative changes in Alzheimer's disease. Unlike the amyloid cascade hypothesis, the Tau hypothesis focuses on the formation of neurofibrillary tangles and their damage to neurons, rather than assuming that the aggregation of Aβ is the initial trigger for the entire pathology of AD.[16]

Tau protein itself is a microtubule associated protein, mainly distributed in the axons of neurons. Its main function is to help maintain the stability of the neuronal cytoskeleton by binding and stabilizing microtubules, thereby ensuring the normal operation of the intracellular transport system. In a healthy brain, Tau protein undergoes normal phosphorylation and dephosphorylation processes. This will help regulate its binding state with microtubules to adapt to changes in the intracellular environment. In the brains of Alzheimer's patients, Tau protein undergoes abnormal hyperphosphorylation. This will result in each unit of Tau protein carrying 5-8 phosphate groups. This process disrupts its normal function, causing Tau proteins to detach from microtubules and entangle with each other, forming neurofibrillary tangles. As a result, the microtubule structure is disrupted and intracellular transport is also hindered. This phenomenon directly leads to the instability of neurons, ultimately causing functional damage or even death of neurons. Another point worth noting is that this phenomenon is particularly significant in memory and cognition related areas of the brain, such as the hippocampus and entorhinal cortex, in AD patients.[17,18]

Tau protein neurofibrillary tangles and Aβ plaques are both highly significant pathological features of AD. In this context, the Tau protein hypothesis is closely related to the amyloid cascade hypothesis. Actually, more and more evidence suggests that Aβ and Tau proteins may exacerbate disease progression through synergistic effects. However, unlike the amyloid cascade hypothesis, in the Tau protein hypothesis, researchers generally believe that the pathology of Tau protein is the core pathology in the pathogenesis of AD, and the accumulation of Aβ only accelerates the pathology of Tau protein.[17-19]

2.4. TREM2 Immune Hypothesis

The TREM2 immune hypothesis has been one of the hot topics in Alzheimer's disease research in recent years. TREM2 is a transmembrane receptor primarily expressed on microglia in the brain, closely related to the regulation of immune responses in the brain. The immune hypothesis suggests that AD is not only caused by abnormal accumulation of Aβ or Tau protein, but also related to immune dysregulation and inflammatory response in the brain.[20]

The immune hypothesis illustrates and emphasizes the close relation between the dysfunction of the brain's immune system and the occurrence of Alzheimer's disease. As age increases, microglia gradually

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lose their ability to clear Aβ and begin to overactivate, releasing a large amount of inflammatory factors. Long term neuroinflammation leads to damage and death of neurons. Normally, TREM2 plays a regulatory role in this process by promoting the activation and proliferation of microglia, helping to clear Aβ plaques, and reducing neuroinflammation. However, in cases of TREM2 mutation or dysfunction, the immune system is unable to effectively control the accumulation of Aβ, which exacerbates the inflammatory response and forms a vicious cycle.[21,22]

3. Therapies

3.1. Therapies Based on Cholinergic Hypothesis

The treatment methods based on the cholinergic hypothesis mainly focus on improving cognitive function in Alzheimer's patients by enhancing cholinergic neurotransmission. There are currently four major categories of drugs guided by this principle, namely acetylcholinesterase inhibitors, nicotine receptor agonists, choline precursor supplements, and glutamate modulators. However, only two of them, acetylcholinesterase inhibitors and the glutamate modulators, successfully gained widespread recognition and developed into clinical drugs[23]

Firstly, acetylcholinesterase inhibitors. This type of drug partly reverses the reduced concentration of acetylcholine in the synaptic cleft, and thereby partially repairs the decreased neural transmission efficiency through the inhibition of the activity of acetylcholinesterase which reduces the degradation of acetylcholine. Common acetylcholinesterase inhibitors include Donepezil, Galantamine, and Rivastigmine.[23,24]

Then here is another successful drug type, glutamate modulators. Although glutamate modulators are mainly based on the excitotoxicity theory of glutamate, they are often combined with cholinergic therapy. In the late stage of AD, excessive glutamate may cause neuronal overactivation and death, so controlling glutamate levels also has a certain effect on neuronal protection in late AD patients. Memantine, an NMDA receptor antagonist, is the most common glutamate modulator. This medication is suitable for patients with moderate to severe AD. Its mechanism mainly lies in preventing the death of neurons in AD patients due to excessive excitation by regulating the release of glutamate. At the same time, it is often used in combination with acetylcholinesterase inhibitors to maximize efficacy.[23,24]

Although treatments based on the cholinergic hypothesis can improve symptoms of AD to some extent, their limitations are also evident. Firstly, most importantly, these drugs typically only improve symptoms and cannot alter the progression of the disease or cure AD. At the same time, long-term use of such drugs may result in side effects such as nausea, vomiting, diarrhea, and other gastrointestinal reactions. Finally, the effectiveness of this medication is limited for patients with moderate to severe AD.[23,25]

3.2. Therapies Based on Amyloid Cascade Hypothesis

The amyloid cascade hypothesis suggests that the onset of Alzheimer's disease is caused by the deposition of Aβ protein to form amyloid plaques. Therefore, many therapeutic strategies based on this hypothesis aim to block the generation of A β, clear A β deposition, or prevent its toxic effects on nerve cells.[26]

β - and γ - secretase inhibitors are AD drugs based on the theory that Aβ protein is produced by the cleavage of amyloid precursor protein through β - secretase and γ - secretase. Therefore, inhibiting the activity of these enzymes can reduce the production of Aβ. Although many of these types of drugs have emerged, they have not been allowed to enter the market due to their strong side effects such as liver dysfunction or even further cognitive decline.[25,26]

Monoclonal antibodies (mAb) against Aβ are currently the most promising clinical drugs for Alzheimer's disease. It would target and bind to Aβ plaques, promoting their clearance or preventing their accumulation thus to reduce the toxic effect of Aβ on neural cells. Just last year, a monoclonal antibody against Aβ, lecanemab, was successfully approved by FDA due to its consistent and reliable effect on reducing the cognitive decline caused by AD. At the same time, many other mAb with stronger

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drug efficacy and fewer side effects is waiting to flow from the laboratory into the world like the donanemab. We could confidently expect more groundbreaking news from this field in the near feature [26-28].

Although many drugs based on amyloid cascade reactions have shown significant reductions in Aβ levels in early trials, most of them do not consistently improve cognitive function. Meanwhile, the issue of their side effects still exists. Currently, monoclonal antibodies against Aβ such as Lecanemab represent the forefront of this field, but their long-term efficacy and safety still require further research and verification [26,28].

3.3. Therapies Based on Tau Protein Hypothesis

The treatment methods based on the Tau protein hypothesis mainly focus on three points. Firstly, try to prevent the entire process from starting at its root, that is, directly preventing the abnormal phosphorylation of Tau protein. Secondly, targeting the already hyperphosphorylated Tau protein, prevent its aggregation. Finally, for the abnormal Tau proteins that have already gathered, promote their clearance. Based on these guiding principles, several treatment strategies have been developed.[18,29]

The mechanism of Tau protein phosphorylation inhibitors is to reduce pathological changes in Tau by inhibiting protein kinases involved in Tau phosphorylation. At present, some Tau protein phosphorylation inhibitors have already emerged, such as GSK3β inhibitors and CDK5 inhibitors. However, most of them are still in the preclinical research stage [29].

Tau aggregation inhibitors, corresponding to the second Tau protein hypothesis therapeutic focus mentioned earlier, achieve therapeutic goals by preventing the aggregation of Tau to form neurofibrillary tangles. Methylene blue is a known small molecule compound that can prevent the formation of Tau nerve fiber tangles. The improved version of methylene blue has shown some effectiveness in clinical trials, but the improvement in cognitive function is not significant [29,30].

Tau remover aims to utilize the immune system to eliminate the already formed hyperphosphorylated Tau protein. Many related products such as Gantenerumab, Aducanumab, and AADvac1 have already been researched and entered the clinical trial stage.[29,31]

Although treatment methods based on the Tau protein hypothesis have some scientific basis in theory, most drugs have not shown significant cognitive improvement in clinical trials, and most others have not yet completed large-scale clinical trials. In this field, further in-depth research and more effective drug development are needed in the future [29-31].

3.4. Therapies Based on TREM2 Immune Hypothesis

The therapeutic approach based on the TREM2 immune hypothesis focuses on regulating the activity of microglia by affecting the function of TREM2. Previous studies have already shown that regulating the function of microglia can clear Aβ and Tau pathological substances and alleviate inflammation [20,22,32].

TREM2 agonist is a feasible AD drug, thanks to its ability to promote microglial activation and phagocytic function. In addition, besides directly activating TREM2, it can also affect the function of microglia by regulating its downstream signaling pathways. This makes it possible for another class of drugs to regulate the TREM2 signaling pathway to exist. The design purpose of these drugs is to promote the transmission of TREM2 signaling, thereby enhancing the phagocytic ability and anti-inflammatory function of microglia thus to attenuate the pathologies of AD [22,32].

The therapies based on TREM2 immune hypothesis has great potential in the field of AD treatment. However, compared to other therapies, most of its treatment methods are still in the research and development stage. Future research will further validate the effectiveness of TREM2 targeted therapy in AD patients [20,22,32].

4. Conclusion

Since the focus on Alzheimer's disease began, countless hypotheses have been proposed. This article only lists the four most representative ones. In addition to these four, other studies, such as those on the

relationship between genes and AD or the impact of co pathologies on AD, are also in full swing. Since the 1990s, the clinical treatment of Alzheimer's disease has been stagnant for more than 20 years. However, the efforts of researchers during these 20 years have not been in vain. With the emergence of new approved drugs for Alzheimer's disease in 2023, the entire research field is eager to prepare for a resurgence of vitality. It is believed that in the near future, more and more further experimental studies on AD will be reported, and AD, the mountain that has been weighing on humanity for over a century, will eventually be solved.

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