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The Pathogenesis of Alzheimer's Disease and Treatment

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Abstract. Alzheimer's disease is caused by intracellular tau-containing neurofibrillary tangles and extracellular plaques containing Aβ, along with some genetic risk factors like mutations in *APP*, *PSEN1*, and *PSEN2*. This disease is currently affecting tens of millions of people worldwide. At present, there are only drugs with therapeutic effects. Other non- drug and drug therapy all come out with little effect on treating Alzheimer's Disease. Recently, researchers have discovered potential progress in therapy connected with genome editing with CRISPR-associated protein 9 (Cas9), or clustered regularly interspaced short palindromic repeats. This approach has blazed a new way in AD treatment. This article will take a review of the article and propose a few discussions on this novel approach.

Keywords: AD, Pathogenesis, Treatment.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease which cannot be cured entirely. The reason AD why is developed is awfully complex and remains unclear. It is widely accepted that it is caused by the interactions of several different factors [1]. The incomprehension of how AD is developed makes it difficult to develop helpful treatment.

The current treatment of AD follows a combination of non-drug treatment and drug therapy. The non-drug treatment contains cognitive training, physical exercise, acupuncture therapy and aromatherapy [1]. When discussing useful drugs, at present, only two kinds of drugs which can treat the symptoms of AD effectively. The two categories of medications are N-methyl D-aspartate (NMDA) receptor blockers and antagonists of cholinesterase. Some therapies focused on disease-modifying, such as anti β-amyloid (Aβ) agents, γ-secretase inhibitors and β-secretase inhibitors. However, they all failed because of side effects or other reasons, including false targeting, tardy treatment and unsuitable doses [2].

The clinical features of the AD vary. AD usually presents with cognitive impairment. The impairment develops through a process: from a subjective decrease in mental abilities to impaired response on objective cognitive testing and to the occurrence of dementia, a combination of subjective cognitive impairment and mild cognitive impairment (MCI) [3].

The occurrence and prevalence of AD are included in those of dementia. Besides AD, there are many other neurodegenerative pathologies which can lead to dementia. Globally, the frequency of all forms of dementia is predicted to increase from 50 million in 2010 to 113 million by 2050 [3]. Simultaneously, there is a minor decrease in the number of patients in high-income countries. The primary risk factor for dementia and AD is age. In the global elderly population over 65, women experience dementia at a

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higher rate than males. According to some research, women are more likely than males to have dementia, or there is no gender difference in dementia frequency [3].

When diagnosing AD, the occurrence and severity of cognitive impairment should be checked in the first place. Getting information about the patient's daily activity from the cohabitants or family members and carrying out a cognitive evaluation by experienced clinic doctors play an important role in the primary diagnosis. After that, further diagnosis can be carried out through biomarkers. [4] To image biomarkers which cause cognitive impairment, CT, FDG-PET and MRI are the first choices, but they cannot detect biomarkers for AD specifically. In 2004, the appearance of Aβ-PET imagining shows that this method is a better marker for AD. At the same time, the function of MRI becomes to exclude other causes in the first place [3]. Alzheimer's disease is diagnosed using clinical biology. It is necessary to have a combination of the distinct clinical phenotype of Alzheimer's disease (phenotype positive) and biomarker evidence of the disease's pathology (tau positive and amyloid positive) [5].

2. Pathogenesis

As mentioned before, the pathogenesis of AD is the result of the mutual effect of several factors. In the late 1960s and early 1970s, overall biochemical investigation focused on the brains of the AD patients began. Up till now, there are two widely accepted and characteristic factors are Aβ-containing plaques and tau-containing neurofibrillary tangles [3]. Other factors, like Apolipoprotein E, absence of synaptic homeostasis and dysfunctional proteostasis also account for the clinical manifestation of AD.

2.1. Aβ-containing plaques

Amyloid precursor protein (APP), a single transmembrane protein that aids in the growth and differentiation of neurons, is the source of Aβ peptides. APP is mostly found in synapses. α-secretase and γ-secretase usually cut the APP protein when it becomes dysfunctional, but β-secretase and γ-secretase cut it abnormally and produce Aβ as a result. Aβ (particularly $A\beta_{42}$) is insoluble and has a high possibility to aggregate outside the neurons, forming Aβ-plaques. [6] They create pathological alterations in dendritic spines and synaptic effectiveness, as well as blocking normal neuronal signaling [3].

2.2. Tau-containing neurofibrillary tangles

Tau protein is a special protein which is found on the surface of microtubules inside the axons. The protein's purpose is to maintain the stability of the microtubules. When an enzyme called kinase is activated, resulting from Aβ plaques, it will bring a phosphate group to the tau protein, and the tau protein will change its shape. The protein will no longer support the microtubule but aggregate inside the cell. The microtubule will collapse at the same time, accounting for neuron deaths. [7]

2.3. Genetic risk factors

The genetic risk factors for AD are uncommon primarily passed down mutations in *APP*, *PSEN1*, and *PSEN2*, as well as more prevalent but less penetrant genetic variants like *APOE*. With these mutations, AD can have a quite early onset, earlier about 40 years. Dominantly inherited AD cases are almost all caused by mutations in *APP*, *PSEN1*, and *PSEN2*, among all the genetic risk factors. However, it is discovered that a specific variant of *APP* (A673T) can protect the carrier from AD and cognitive decline even if they are not AD patients [8].

2.4. The cholinergic hypothesis

Acetylcholine (ACh) is an excitatory neurotransmitter that is important for memory, attention and learning in brains. An enzyme called choline acetyltransferase (ChAT), located on the presynaptic neuron, is responsible for synthesizing ACh in the cholinergic neurons. It was discovered that memory loss and cognitive impairment were caused by cholinergic neuron degeneration in the brains of AD patients. It is thought that Aβ interferes with cholinergic neurotransmission and influences choline absorption and ACh release. [9]

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3. Treatment

Both drug therapy and non-drug therapy are used to treat AD. As mentioned earlier, currently only drugs with therapeutic effects are available.

3.1. Drug therapy

3.1.1. Cholinesterase inhibitors

Acetylcholinesterase (AChE) is a protease which is mainly found on postsynaptic neuromuscular junctions. Its function is to degrade ACh and stop neurotransmission. According to the cholinergic hypothesis, the deficit in the synthesis of ACh is account for AD. Thus, increasing the level of ACh by inhibiting AChE is feasible for becoming a therapeutic method to repair cognitive impairment. AChE inhibitors can inhibit the degradation of AChs, increasing cholinergic levels. In particular, the medication donepezil is very reversible and selective compared with other conventional AChE inhibitors, considered as a leading drug. Having the best pharmacological effect on cognitive improvement, donepezil owned a response rate of 40%-58%, and an existence of side-effects ranging from 6% to 13% in AD. Most studies state that this drug can provide a moderate benefit on various aspects connected with AD, including cognition, behavior, and activities, even if it is non-economical [10].

3.1.2. NMDA receptor antagonists

It is believed that NMDA receptors are crucial to the pathogenesis of AD. The overactivation of them leads to an abnormal level of Ca^{2+} influx, activating signal transduction, and overstimulates glutamate, one of the main amino acids in the central nervous system, having the excitatory effects. This accounts for excitotoxicity, dysfunction of synapse, neuron deaths, and cognitive decline. [11] However, most of the NMDA receptor uncompetitive antagonists that have entered the clinical trials failed because of some problems on side effects and efficiency. Only memantine is approved to treat AD in this kind of drugs [2].

3.1.3. Anti-Aβ agents

Anti-Aβ agents have long been considered as a way to treat AD because researchers think that the drugs can relief the symptoms by removing Aβ accumulation. These anti-Aβ agents target different stages of Aβ accumulation. For example, aducanumab, which is a monoclonal antibody, targets Aβ protofibrils, whereas donanemab targets Aβ plaques. [12] Compared with other anti- Aβ monoclonal antibodies, donanemab has the advantage of targeting the Aβ peptides only existing in the plaques. This reduces the chances of having side effects, in particular amyloid-related imaging abnormalities [13]. In July 2024, the U.S. Food and Drug Administration authorized donanemab for the treatment of mild form of dementia and slight cognitive decline.

3.2. Non-drug therapy

3.2.1. Cognitive training

Cognitive training is an intervention method to improve cognitive function by applying various cognitive tasks. In recent years, cognitive training has gradually changed from a strategy-focused paper-and-pencil and teaching-based training method to a difficult-adaptive and ability-enhancing computer-aided cognitive training [1].

3.2.2. Physical exercise

The cognitive function can be improved after engaging in physical exercise. It is found that resistance exercise has the most profound influence on the attention and memory of AD patients.

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3.3. Potential progress in therapy connected with CRISPR-Cas9

Genome editing with CRISPR-associated protein 9 (Cas9), or clustered regularly interspaced short palindromic repeats, is a potent technique. [14] Its function suggests that it might be able to treat particular gene mutations. As mentioned before, familial AD is mainly caused by dominant mutations in *APP*, *PSEN1*, and *PSEN2*. Thus, methods that can edit genes may have the possibility to treat familial AD, including CRISPER-Cas9. To achieve a wide spread of influence on genome editing, researchers have used modified adeno-associated virus (AAV) variants. It is a kind of variant which can also cross the blood-brain barrier (BBB) [15]. It is found that in most familial AD cases, patients own a heterozygous mutation which causes the disease. Because humans naturally possess one copy of either *PSEN1*, *PSEN2*, or *APP*, which does not result in any symptoms. Therefore, it is hypothesized that a feasible therapeutic approach for the treatment of ancestral AD is to disrupt the allele responsible for AD in grown-up patients with the condition.

The APP^{swe} allele is precisely destroyed through genome editing mediated by CRISPR-Cas9. The two sgRNAs, SW1 and SW2, are intended to specifically target the K670N/M671L double-base mutation in APP^{swe}. Due to mismatches between the sgRNAs and the wild-type (WT) sequence, which are present in the seed sequence and are poorly tolerated by Cas9, it is expected that SW1 and SW2 will be able to distinguish the mutant APP sequence from the WT sequence. The sgRNA SW1 and Cas9 are packaged into a single AAV9 vector, and the promoter that drives it is elongation factor 1-alpha short. The virus Cas9-SW1 is injected into the hippocampi of 5XFAD mice that are 3 months old. With several mutations that occur on the genes code for parts of APP, these 5XFAD animals possess human APP cDNA. The expression of full-length mutant APP is eliminated thanks to genome editing of the mutation that located on the APP^{swe} allele. The consequences of APP mutations are halted concurrently. Furthermore, the infrequency of off-target events caused by Cas9-SW1 editing is corroborated by the comparable number of mutations found by whole-genome sequencing in individual mouse brains [15].

Additionally, Cas9-SW1 editing decreases problems related with amyloid-plaques in the same kind of mice. Ninety days after gene editing, the levels of both $A\beta_{x-40}$ and $A\beta_{x-42}$ species decreased by more than 60%. After a single injection, editing has an impact on amyloid pathology that lasts for at least 180 days [15].

Furthermore, APP/PS1 mice, a transgenic mouse model of Aβ pathology with a different beginning of clinical symptoms than 5XFAD mice, had reduced Aβ pathologies due to Cas9-SW1 editing. Furthermore, Cas9-SW1 systemic administration reduces Aβ-associated diseases and enhances cognitive function in 5XFAD animals [15].

4. Conclusion

After decades, the pathogenesis of AD is still undiscovered, but the connection between several critical molecules, like Aβ plaques and tau tangles, and the development of AD is being widely accepted. Some critical genes, like mutations in *PSEN1*, *PSEN2*, and *APP*, start to attract more attention. After a long period of study on the treatments of AD, CRISPR-Cas9-mediated genome editing is becoming a therapy against AD with high potential, with its significant influence on APP^{swe} and Aβ-associated pathologies. This seems like a permanent solution towards AD. However, the natural aging of people and some ethical issues need to be considered.

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