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A review of current developments in Alzheimer's disease treatment methods

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Abstract. This article will summarize the results of recent years of exploration into deeper causes of Alzheimer's disease with possible therapeutic strategies. The most popular pathological hypothesis for the causation of Alzheimer's is the Aβ cascade hypothesis. Aβ has a dominant role in the pathophysiology of Alzheimer's disease, according to genetic and pathological data. Another significant histological characteristic of Alzheimer's disease brains is the presence of neurofibrillary tangles made of the protein tau, which is related with microtubules. In the brain, neuronal loss, neuroinflammation, and oxidative stress can result from the cascade consequences of tau toxicity. But as research has progressed, it has been found the Aβ. The accumulation of protein and neurofibrillary tangles composed of phosphorylated tau are only manifestations of AD, not the result. This is also the reason why many drugs fail the phase III clinic. So people began to look for a way out of the problem, starting in the direction of the gene. How to diagnose AD early in the MCI stage, how to find markers for early diagnosis and how to inhibit the progression from the MCI stage to the dementia stage are all questions that need to be investigated in the future.

Keywords: AD, tau Aβ, ApoE, gene, review treatment.

1. Introduction

Alzheimer's disease is a complicated neurodegenerative condition caused by a number of causes. In existing pathological studies, synaptic dysfunctions, such as synapse loss and synaptic plasticity defects, are closely associated with cognitive decline [1]. At present, at least 50 million people worldwide suffer from Alzheimer's disease. Whereas various types of neurodegenerative symptoms result from the deficiency of various neurotransmitters, such as cholinergic and glutamatergic deficits in cognitive decline, synaptic plasticity deficits and dysregulation of excitatory and inhibitory neurotransmitter homeostasis in epilepsy like symptoms, monoamine neurotransmission in neuropsychiatric symptoms. Dementia due to AD is associated with severe progressive disability throughout the course of the disease, and after 5-12 years patients usually face the outcome of death. There is a tremendous strain on caregivers and the public health system at this time. Unfortunately, there are presently no disease-modifying medicines that can stop or halt the course of the disease, despite the urgent need for such. This review is based on the facts and literature already available. To highlight the developments in Alzheimer's disease research, we will discuss Aβ, NTFs, apoE proteins, and genes created by phosphorylated tau protein. These summaries allow us to observe the research on Alzheimer's disease at a higher level and complement each other.

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2. The progress and predicament about Amyloid β protein

During the past decades, researchers always deemed that Aβ was the ultimate reason which causes the Alzheimer's disease and did tremendous amounts of efforts to find the methods to clean the Aβ. However, they are never able to reach a satisfactory conclusion. The ongoing failures in middle and late-stage clinical trials are impeding the development of a new generation Alzheimer's drug. The R&D of AD drugs targeting A has been frustrated repeatedly for a variety of reasons, including defects in target selection. Due to the formation of oligomers, the toxicity of drugs, and the complexity of Aβ plaque structure in vivo, the drug cannot pass the blood-brain barrier.

But in the research achievements which are about Aβ, the most exciting and newest conclusion was announced by BIIB. The research medicine termed Lecanemab reached the primary endpoint and all the key secondary endpoints in the Clarity AD trial phase III, with highly statistical significance [2]. About the Clarity, the AD Clarity trial is an 18-month placebo-controlled, double-blind, parallel-group, open-period continuation trial to confirm the safety and effectiveness of lecanemab in early AD subjects. The primary endpoint of the study was the change from baseline in the total clinical dementia score (CDR-SB) after 18 months of treatment. In a double-blind experiment with 854 patients, this study shows a decrease in cerebral Aβ protein and a continuous decrease in the clinical decline of several clinical and biomarker endpoints [3].

A medicine called Aducamumab was authorized by the FDA to treat Alzheimer's on July 6, 2021 (trade name: Aduhelm). Aduhelm is a therapeutic therapy for Alzheimer's disease and is based on reducing pathogenic Aβ, a surrogate endpoint in the brain. The approval of Aduhelm marks the approval of the first Alzheimer's disease medication and the first novel Alzheimer's treatment licensed since 2003 [4]. However, the researchers come from the Nathan S. Kline Institute's Center for Dementia Research in Orangeburg, NY, USA, which proposed that cells never die first and then extracellular Aβ plaques appear [5]. That is, even if every Aβ plaque is cleaned, cells that have already died cannot be rebuilt for their functions or replaced with new ones. Although there is currently a lack of data on the mediating effect of reduced Aβ load on Alzheimer's treatment and on cognitive decline in patients, a few examples from previous clinical trials of anti-Aβ therapy are strong enough to emphasize that perhaps there is no such direct mediating effect between the three. Despite the significant reduction in Aβ load in clinical trials, the associated positive and negative immunological treatment arms were not able to confirm a clinical benefit, and we were unable to observe a significant difference [6].

3. Research and progress on Tau induced neurofibrillary tangles

Tau is a scaffold protein in the microtubule binding protein family, and in normal neurons, tau is mainly enriched in the periphery of neuronal axons, where its main functions include regulation, maintenance of microtubule stability, and trafficking functions in the axons of auxiliary neurons. Studies have identified post-translational modifications (PTMs) of tau as important ways to regulate its protein structure and function. Its PTM takes several forms, and in pathological situations, tau phosphorylation is 2-3 times more than usual. As a result of this hyperphosphorylation, tau detaches from microtubules, is more abundant in the cytoplasm, clumps together to form insoluble fiber bundles, and ultimately results in NTFs, another significant pathogenic aspect of AD. Many phosphorylation sites in pathological states were identified in the brain tissue of AD patients, based on which mechanistic scientists have developed many specific antibodies. Kinases associated with phosphorylation include GSK3- β, Cdk5, CDK2, etc.

Several hypotheses exist for the pathogenesis of tauopathies. In the field of AD, the Aβ hypothesis has come as an integration with the tauopathy theory. Under pathological conditions, the normal assembled protein function of postsynaptic tau is dramatically elevated, eventually in a Aβ Signaling mediated to produce toxicity [7].

An alternative hypothesis is that tau protein aggregation prevents clearance mechanisms from the cell, and this early dynamic aggregation ultimately promotes fiber formation and growth. Drugs targeting this process include various tau polymerization inhibitors such as methylene blue and others[8].

A third hypothesis is that tauopathy impairs axonal material transport, including mitochondrial

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damage, among others. Impaired mitochondrial function, which in turn enhances oxidative stress, is more prone to phosphorylation and makes the mitophagy system disordered. Researchers at Columbia University Irving Medical Center have shown that mice with reduced levels of toxic tau protein by stimulation of its type 1 receptor (pac1r) with the pituitary adenylate cyclase activating polypeptide (PACAP) also have improved cognition in mice at early stages of tau protein accumulation. However, PACAP is rapidly degraded in vivo and is not an ideal therapeutic approach [9].

Trx0237 (rember), a small molecule drug, also known as methylene blue by rember, taurx therapeutics, is a tricyclic phenothiazine structural compound. In 1996 the compound was found to be able to block the tau protein-protein interaction and since then many studies have shown its activity in the treatment of neurodegenerative diseases. Trx0237, a second-generation inhibitor used in the treatment of AD and frontotemporal dementia, is structurally more stable and able to improve drug absorption, bioavailability and tolerability through structure-activity modification. Whether trx0237 or rember, the mechanism behind this is to affect downstream protein abnormalities such as AD and other neurodegenerative diseases, either by inhibiting tau aggregation, or by dissolving the abnormal tau protein aggregates that have formed. At present, this drug has entered phase III clinical trials [10].

4. Study on a newly discovered apolipoprotein

A class of glycoproteins known as apolipoprotein E (ApoE) is involved in the control of lipid metabolism and is widely expressed in the central nervous system (CNS) by astrocytes, microglia, vascular mural cells, and cells of the choroid plexus. ApoE has three allelic mutants: apoEε2 and apoEε3 and apoEε4. The two locations at the ApoE gene level that affect the protein level — amino acids 112 and 158 — are altered differently in each of them, depending on whether cysteines or arginines are present. If both apoE sites encoded by Cys on one chromosome, apoe2 if Cys on chromosome 112 and Arg on chromosome 158, and apoE3 if ARG on both sites, that's apoE4. This gene encodes apolipoprotein E, responsible for the transport of chylomicrons. ApoE4 is a significant genetic risk factor for AD that affects both the risk of developing AD and the age at which AD first manifests [11-12].

The main reason is that neuronal apoE4 can induce tau pathology, leading to neuroinflammation and neuronal damage and impairing learning and memory functions [13-15]. Regarding its in-depth investigation, the problem of Neural APOE upregulates MHC-I expression to promote selective neurodegeneration in Alzheimer's disease was addressed in an updated publication published in Nature Neuroscience on May 6, 2021. The Gladstone Institute for Neurological Disease's Yadong Huang team was the first to discover a connection between ApoE expression in neurons and MHC-I expression, which in turn led to tau pathology and selective neurodegeneration. Re specific knockout of the ApoE gene prevents neuronal, synaptic, and hippocampal volume loss in neurons from aged apoE knock in mice, highlighting the crucial role of apoE in neurons in general neurodegeneration [16].

It was previously proposed that once it could be demonstrated that impairing the binding capacity of apoE is essential to the treatment of Alzheimer's disease, subsequent therapeutic techniques may be employed with this objective. While this study reveals potential new targets for the creation of drugs to stop or reverse selective neurodegeneration in AD, these targets include lowering or blocking apoE expression in neurons, cutting off the apoe-MHC-i signaling pathway in neurons, obstructing the mechanism of MHC-i-induced tau pathology, or preventing the presentation of MHC-I from neurons to immune effector cells.

5. Research progress in the treatment of AD from the perspective of gene editing

The University of California, San Diego School of Medicine conducted the first human phase 1 clinical trial. The aim of this experiment is to evaluate the safety and effectiveness of gene therapy. In this therapy, brain-derived neurotrophic factor (BDNF) is delivered to the brain of patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI). The results show that mild cognitive impairment usually precedes general dementia. BDNF gene therapy has the potential to reconstruct brain circuits, slow down cell loss and stimulate cell function, which is different from other AD therapies currently under development [17].

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Research team from the Royal College London has proposed a very promising new gene therapy for the treatment of AD. In 2011 the team published that at the cellular level PGC-1 α was able to block a β Formation. In this study, the team focused on PGC-1 α Implications in neurodegenerative diseases. Western blotting of nuclear extracts from cortical brain of AD patients and controls revealed that PGC-1 α content was significantly lower than normal. Western blotting experiments showed that PGC-1 α Overexpression causes a β Reduction. It thus appears that PGC-1 α could prevent the development of early AD, we could also detect a β in the brains of AD patients at an early age β when using the therapy for it.

Researchers from the University é Laval College of medicine and the University é Laval Research Centre, Quebec, Canada have successfully edited the genomes of in vitro grown human cells, introducing a mutation that confers protection against Alzheimer's disease to the patient [18]. In the Icelandic population, this mutation was first discovered in 2012. The mutation lowers the likelihood of acquiring Alzheimer's disease and has no known negative effects for carriers. They will be able to incorporate such alterations into the human cell genome using an upgraded version of the CRISPR gene editing technique. The CRISPR journal just released information on this discovery.

Recent findings by researchers show that boosting new neuron production in AD mice rescues memory deficits in animals which were published on August 18 in the Journal of experimental medicine. In this study, the experimental staff improved the activity of neural stem cells through gene modification to promote neurogenesis function in AD mice [19]. By deleting the Bax gene, which plays an important role in the process of neural stem cell death, researchers found that more newly born mature neurons were generated in mice, and the function of mice in spatial recognition and contextual memory was restored. According to the research, the newly generated neurons will participate in the neural circuit of storing memory and restoring normal function. The above results suggest that promoting neuron production may be a feasible strategy for the treatment of Alzheimer's disease.

6. Conclusion

In the current study, Aβ accumulation, tangles of tau protein are all among the symptoms of AD, not the cause. Even more difficult to understand is the continued belief of pharmaceutical companies in this theory, even after the repeated failures of experimental drugs based on it, at a cost of billions of dollars. Still, there is increasing recognition that progress may be faster if other ideas can be supported earlier. These current ideas are beginning to be emmetropized and validated by basic research and clinical trials. Because of the multifactorial pathogenesis of AD, future pharmacotherapies may be tailored to individualized precision medicine based on the premise that each patient's genetic profile, neuroimaging, and specific biomarker levels are determined. These above characteristics, which tau protein possesses, are conducive to the development of tau protein target drugs. But it is also sobering to realize that its clinical research still faces many challenges. For example, awareness of disease development is not yet comprehensive; Alzheimer's disease cannot be effectively diagnosed until the early stages; there are insufficient sensitive biomarkers; the therapeutic window is narrower; it is not yet known how to penetrate the blood-brain barrier to deliver drugs to targets, and so on. But these issues are also common to all AD drug developments. The Aβ and tau hypotheses are analogous to two parallel roads: one has too many cars, and navigation suggests a bypass to avoid congestion, so everyone returns to the tau mechanism. At the level of gene regulation, apoE4, by what mechanism is cognition affected? What are the implications for the spread of other pathologies caused by AD, such as tau protein? Whether novactam or chance is responsible for regenerating neurons that are already dead Many questions remain to be answered. Given where the front line of AD treatment theory is, it is difficult to draw the following conclusions: The road is rambling, and in the face of failed clinical trials, we should never be pessimistic.

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