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Analysis of Immunotherapy Methods for Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) belongs to a degenerative disease caused by lesions in the central nervous system, characterized by aging and irreversibility. With the aggravation of the aging process worldwide, the proportion of AD patients has been increasing year by year. Due to its irreversibility and accompanying symptoms such as amnesia, dementia, and personality changes, AD patients greatly affect families and society. AD has become a major challenge for social security and public health systems in various countries. Scientists have been attempting to identify the pathogenesis of AD and develop treatments for over a hundred years. Regrettably, up to now, it is still not possible to fully explain the causes of AD formation through existing hypotheses and propose a radical treatment. Immunotherapy is one of the important targeted treatment methods in recent years, and it has attracted extensive attention due to its significant efficacy in cancer treatment. This research summarizes the progress of immunotherapy for AD treatment, and selects the amyloid protein cascade hypothesis and Tau protein hypothesis, two major and widely recognized explanations, as the main basis for treatment. It elaborates on the active and passive immunotherapies based on these two hypotheses and their progress, hoping to provide reference for subsequent experimental research.

Keywords: Alzheimer's disease, immunotherapy, mechanism, treatment

1. Introduction

Alzheimer's disease (AD) belongs to a neurological disorder, showing clinical symptoms such as memory impairment, cognitive decline, and intellectual regression. It predominantly affects the elderly population, and also a leading cause of dementia among them. AD poses an assignable challenge to public health and social security systems worldwide. Unfortunately, the etiology of AD is complex, what's worse, the exact pathogenesis remains unclear. Abnormal deposition of β-amyloid and hyperphosphorylation of microtubule-associated protein Tau are currently the two main pathogenic mechanisms that have been most extensively studied and serve as the basis for developing intervention drugs. As research progresses and more cases are identified, neuroinflammatory response, mitochondrial dysfunction, abnormal autophagy function, oxidative stress hypothesis [1].

Amyloid beta protein (Aβ) is regarded as a significant pathological feature in AD patient. Amyloid precursor protein (APP) is the precursor of Aβ, a 38-43 aa residue peptide. There are two ways to cleave APP: in the extracellular domain with β-secretase cleavage and the other in the transmembrane region with γ-secretase cleavage. In the non-amyloidogenic pathway, APP is first cleaved by α-secretase in the lumenal domain, causing the detachment of almost the entire extracellular domain and the production of membrane-tethered α-C terminal fragments (APPsα). Subsequently, the α-C

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terminal fragment is cleaved by γ-secretase within the transmembrane domain, releasing the p3 (43kDa) peptide into the extracellular environment, and the other fragment is an intracellular fragment called AICD (Figure 1A). The cleavage of APP in the lumenal domain is carried out by β-secretase, and similar to the non-amyloidogenic pathway, the extracellular domain is shed, producing membrane-tethered β-terminal fragments (APPsβ). Subsequently, the terminal fragment is also cleaved by γ-secretase within the transmembrane domain, producing a 4kDa Aβ peptide and AICD (Figure 1B). In a healthy brain, the p3 protein fragment is usually eliminated, while in the AD brain, the Aβ is inclined to form aggregated amyloid oligomers, leading to the development of the disease [2]. The Aβ protein hypothesis is the central hypothesis of AD etiology, and the imbalance between the production and clearance of Aβ can be used to cause AD. If there is an increase in Aβ production, and in sporadic Alzheimer's disease (sAD), a decrease in Aβ clearance will be happened.

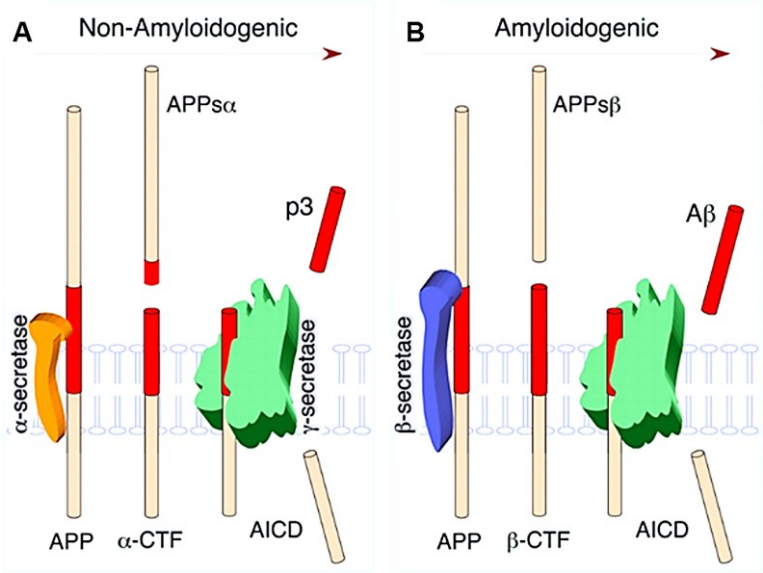

Figure 1: The formation process of amyloid protein [2]
(A) non-amyloidogenic (B) amyloidogenic

However, the hypothesis has been proposed for a long time and is widely accepted, but its mecha nism still exists some doubtful point. The main point of contention is whether this single peptide is i nvolved in the disease process, or whether Aβ is merely a secondary marker or a byproduct of the di sease process, and not a therapeutic target. Through genetic evidence and research on Aβ oligomers, researchers suggest that in the absence of toxicity, targeting Aβ does not accelerate the disease proc ess, and Aβ is a constant companion of the AD disease process, but neither drives nor alleviates the disease process, so whether Aβ has an additional etiological role remains to be determined.

Currently, there are no specific drugs for AD in clinical practice. The only AD drugs are five typ es (donepezil, galantamine, memantine, rivastigmine, and tacrine), which can only temporarily allev iate AD symptoms in clinical practice but cannot fundamentally reverse AD [3]. Elucidating the co mplete pathogenesis of AD and developing effective drugs for AD treatment remain research hotspo ts and challenges. This research systematically summarizes the current research on AD from the asp ects of pathogenesis, drug development progress, and future treatment directions, aiming to provide references for AD research and clinical treatment.

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2. Mechanism of pathological tau protein

The tau protein can be enriched in axons and regulates microtubule (MT) dynamics, participating in their stabilization and regulation. The binding of tau to EB can inhibit the complex of EB proteins-MTs, while tau phosphorylation can reverse this inhibition. Under pathological conditions, the imbalance of phosphatase and kinase activities leads to tau hyperphosphorylation, which causes tau protein to detach from microtubules, undergo conformational changes, and mislocalization. The free tau protein first forms soluble oligomers and then insoluble tau deposits in PHFs and NFTs within the cell body and dendrites, which can affect neuronal function and lead to cell death. Research shows that hyperphosphorylated tau, after being released from microtubules in dendrites, can diffuse to dendritic spines and accumulate there in a soluble form. Dendritic spines are rich in F-actin (a component of dendritic spines) [4]. Excessive phosphorylation at sites in neurons that control F-actin binding mislocalizes tau protein to the postsynaptic part of spiny mammalian neurons.

Pathological tau protein can spread from diseased cells to healthy cells and convert healthy tau into its misfolded pathological form, forming PHFs and NFTs. One of the pathways for the spread of pathological tau is related to microglia in the central nervous system. Microglia have phagocytic and secretory properties and can phagocytose neurons or synapses, and secrete tau protein via exosomes [5], promoting the diffusion of pathological tau protein. In addition, microglia and astrocytes activated by hyperphosphorylated tau protein can disrupt the secretion of chemokines and cytokines in the blood-brain barrier (BBB).

3. Advances in AD treatment mechanisms

Currently, several approved drugs on the market are mostly enzyme inhibitors based on the cholinergic theory and glutamatergic hypothesis, such as donepezil, galantamine, and memantine mentioned earlier. These drugs can effectively improve and alleviate cognitive functions in AD patients but cannot reverse the progression of AD. Presently, targeted drugs based on the amyloid cascade hypothesis and tau protein hypothesis are undergoing extensive laboratory and clinical trials, with the potential for breakthrough progress [6].

3.1. Immunotherapy based on Aβ pathology

As previously mentioned, Aβ tends to self-assemble into soluble amyloid oligomers, eventually forming mature plaques. The Aβ aggregation can trigger a pathological cascade reaction in AD, making Aβ a popular target in AD clinical research. Immunotherapy has received widespread attention, particularly in fighting tumors, especially cancer. Abnormal proteins in tumor cells often serve as important targets for immunotherapy. Immunotherapy has gradually gained attention as a novel drug development approach because abnormal protein expression and accumulation, including Aβ, in AD and similar diseases share similarities with tumor cells. Immunotherapy for AD can be mainly divided into passive immunotherapy and active immunotherapy. The former involves directly injecting antibodies to target and eliminate Aβ in the brain, while the latter requires vaccines to stimulate the immune system and induce autoantibodies production. Next, this research will discuss the treatment mechanisms of the immunotherapies and present their recent clinical progress.

Patients treated with gantenerumab exhibited a non-significant slowing of cognitive decline on the CDR-SB of -0.31 and -0.19 compared to baseline. For safety, the incidence of ARIA-E in the gantenerumab group was 25%, with the majority of patients being asymptomatic. In terms of potential pathology, another sub-study involving 383 people also showed that total tau, and neurogranin, obviously changed in the expected direction.

Active immunotherapy induces specific immune responses of immune cells and various cytokine-mediated non-specific responses by accumulating large amounts of exogenous Aβ antigens and

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adjuvants in lymph nodes. The efficacy of vaccines and off-target effects can be compromised due to the complex physiological conditions affecting antigen transport in the body, the permeability limits of cells to large molecular antigens, and the inherent susceptibility of antigens to degradation. Therefore, the development of effective vaccine delivery platforms is crucial for optimizing active immunotherapy for AD.

Notable examples of virus-like particles (VLPs) vaccines include the recombinant hepatitis B vaccine developed by Merck, approved in 1986, which expresses the hepatitis B surface antigen (HBsAg) in yeast and self-assembles into VLPs. Recombinant hepatitis B vaccine technology has been transferred to China in 1989, training engineers and helping establish production facilities, effectively protecting millions of infants from hepatitis B infection. Gardasil, targeting human papillomavirus (HPV), was the first HPV vaccine approved and was developed by Merck through the expression of the major capsid protein L1 in yeast, which self-assembles into VLPs. The widely acclaimed nine-valent vaccine Gardasil 9 was approved by the FDA in December 2014 and in China in 2018. Hecolin, a VLP vaccine for hepatitis E virus (HEV), was the world's first approved hepatitis E vaccine, approved in China in 2012, using E. coli to express the structural protein P239 of the hepatitis E virus, which self-assembles into VLPs.

Liposomes have garnered significant attention because they can encapsulate different forms of antigens. By mimicking the lipid bilayer of cell membranes, they facilitate fusion with antigen-presenting cells (APCs) for further processing. Liposomes are considered a promising delivery vector for Aβ vaccines. For cargo loading, Aβ antigen can be encapsulated within lipid membranes or anchored on the surface of liposomes. Encapsulation within liposomes can be used to prevent antigen degradation and adapt to different routes of administration, while surface anchoring helps trigger targeted antibody responses in specific conformations [7]. Liposome carriers played a significant role in COVID-19 vaccines, and further technical optimization is needed for AD treatment to enhance targeting.

3.2. Immunotherapy based on Tau protein pathology

Mechanism of Action: Similar to Aβ-based immunotherapy, tau-based immunotherapy aims to redu ce tau-induced damage by targeting pathological tau. Moreover, there is no evidence that the reducti on of pathological tau causes adverse reactions, making sustained immune responses a promising di rection. Tau protein immunotherapy can be divided into two approaches: delivering anti-tau antibod ies across the blood-brain barrier (BBB) into neuronal cells via receptor-mediated endocytosis, wher e the tau-antibody complex binds to the cytoplasmic Fc receptor E3 ubiquitin-protein ligase TRIM2 1, promoting the proteasomal degradation of complexes and avoiding tau aggregation within cells [8].

Passive immunotherapy provides another possible method to the safety issues arising from active strategies. Patients do not produce their own antibodies, and the effect of immunization may be short-lived, thereby reducing the risk of adverse immune reactions. Passive immunotherapy also provides higher specificity for the targeted epitopes. Since the epitope spectrum can change during the development of the disease, tailored treatments can be designed for individuals based on the disease stage once diagnosis is sufficiently advanced. The reduction of pathological tau has rarely been associated with adverse reactions, and the sustained immune response can be able to make active immunization a highly promising direction while the induction of antibodies against native proteins may lead to the potential adverse immune reactions. Therefore, it is emphasized that mild adjuvants should be used with tau immunogens to reduce the occurrence of toxic adverse reactions [9].

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4. Conclusion

The treatment and drug research for AD have undergone decades of development, with various drugs being developed based on different pathological mechanisms. Although many encouraging advancements have been made in understanding the complexity of the disease and drug targets through years of experimentation and clinical trials, the multifactorial nature of AD pathogenesis makes it extremely difficult to prevent the onset of the disease or halt its progression. Over the past few decades, attempts have been made to treat AD using small-molecule drugs based on the cholinergic hypothesis. However, due to the complex pathogenesis of AD, these treatments have been unable to halt the disease progression. Immunotherapy has garnered significant attention due to its strong targeting ability and high affinity for targets. Studies have shown that the lesions of a β and tau are fundamental to the disease process. Targeting both pathological forms of these proteins is considered to show good therapeutic potential. Additionally, some researches have indicated a close synergistic effect between these two proteins, suggesting that combination immunotherapy is necessary to resolve the complexity of the disease. Combination therapy can be flexibly applied to address drug targets, administration methods, or timing, allowing for the simultaneous targeting of multiple targets or addressing a single target in two different ways. Multiple administration methods can be used to develop combination therapy, thereby sequentially combining continuous action on targets, which is essential for addressing the complexity of AD and further deepening the understanding of the disease. Active and passive immunotherapies targeting Aβ and tau proteins have demonstrated considerable efficacy in clinical stages and are expected to achieve the transformation of drug development and commercialization. Combination therapies targeting these two proteins are also expected to make progress. There is no doubt that targeted immunotherapy will bring new breakthroughs in the AD treatment. However, the complex pathology of AD remains a major obstacle to its complete treatment. A clear understanding of the pathological mechanism is undoubtedly crucial for targeted medication. Further research on the pathology is urgently needed to provide more research conclusions and experimental data to support targeted therapy.

References

[1] *Zhang, J., Zhang, Y., Wang, J., et al. (2024). Recent advances in Alzheimer's disease: Mechanisms, clinical trials and new drug development strategies. Signal transduction and targeted therapy, 9(1), 211.*

[2] *Thinakaran, G., & Koo, E. H. (2008). Amyloid precursor protein trafficking, processing, and function. The Journal of biological chemistry, 283(44), 29615-29619.*

[3] *Ataei, B., Hokmabadi, M., Asadi, S., et al. (2024). A review of the advances, insights, and prospects of gene therapy for Alzheimer's disease: A novel target for therapeutic medicine. Gene, 912, 148368.*

[4] *Hering, H., & Sheng, M. (2001). Dendritic spines: structure, dynamics and regulation. Nature reviews. Neuroscience, 2(12), 880-888.*

[5] *Danzer, K. M., Kranich, L. R., Ruf, W. P., et al. (2012). Exosomal cell-to-cell transmission of alpha synuclein oligomers. Molecular neurodegeneration, 7, 42.*

[6] *Vaz, M., & Silvestre, S. (2020). Alzheimer's disease: Recent treatment strategies. European journal of pharmacology, 887, 173554.*

[7] *Congdon, E. E., & Sigurdsson, E. M. (2018). Tau-targeting therapies for Alzheimer disease. Nature reviews. Neurology, 14(7), 399-415.*

[8] *Castillo-Carranza, D. L., Sengupta, U., Guerrero-Muñoz, M. J., et al. (2014). Passive immunization with Tau oligomer monoclonal antibody reverses tauopathy phenotypes without affecting hyperphosphorylated neurofibrillary tangles. The Journal of neuroscience: the official journal of the Society for Neuroscience, 34(12), 4260-4272.*

[9] *Boimel, M., Grigoriadis, N., Lourbopoulos, A., et al. (2010). Efficacy and safety of immunization with phosphorylated tau against neurofibrillary tangles in mice. Experimental neurology, 224(2), 472-485.*