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Mechanisms and Intervention Strategies of Beta-Amyloid and Tau Proteins in Alzheimer's Disease

Kexin Liu

International Education College, Xinyang Normal University, Xinyang, China
2749895545@qq.com

Abstract. Alzheimer's disease (AD) is a progressive neurodegenerative disorder that poses a major threat to the health and quality of life of the aging population worldwide, with its complex and multifactorial pathological mechanisms remaining incompletely elucidated. Mounting evidence indicates that amyloid-beta (Aβ) deposition and tau hyperphosphorylation are not independent events but interact synergistically to drive the onset and progression of AD, creating a self-amplifying pathological cascade. This paper firstly systematically summarizes the biological properties of Aβ and tau proteins, and further explores their synergistic interaction modes and pathogenic effects in the AD pathological cascade. Furthermore, it reviews the latest advances and clinical challenges in targeted therapeutic strategies against Aβ and tau, including antibody-based therapies, small-molecule inhibitors, and gene-targeted interventions. The purpose of this study is to clarify the synergistic pathological network between Aβ and tau, summarize updated progress on targeted therapies, and offer theoretical support for accurate early diagnosis and individualized clinical treatment of AD.

Keywords: Alzheimer's disease, amyloid-bata protein, tau protein, pathological mechanisms, targeted treatments

1. Introduction

With the global aging population is increasing, Alzheimer's disease (AD) incidence rate continuously increasing and has become a common neurodegenerative disease. Its core clinical manifestations are cognitive decline and memory impairment. However, the pathological mechanism of this condition has not been fully elucidated, and there are no clinical cure methods available [1]. The abnormal aggregation of β-amyloid protein forms senile plaques [2] and the excessive phosphorylation of tau protein are the symbolic pathological causes of Alzheimer's disease and both play a crucial role in driving the occurrence of AD [3]. The abnormal aggregation of amyloid-β (Aβ) forms senile plaques, while tau hyperphosphorylation constitutes neurofibrillary tangles. Both are hallmark pathological features of AD and dominate the initiation and progression of AD lesions [2, 3]. They jointly promote the development of the disease through pathways such as neuroinflammation, oxidative stress, and neuronal apoptosis. In recent years, The core research direction of AD focuses on Aβ and tau proteins [4]. However, the interaction mechanism between these two still requires further exploration. This article focuses on Aβ and tau proteins,

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systematically reviewing their biological characteristics, pathological effects, and intervention strategies. This review aims to offer solid theoretical evidence for early clinical diagnosis and targeted drug research and development of AD.

2. Basic biological characteristics

2.1. The production, metabolism and pathological characteristics of β-amyloid protein

Aβ is a peptide fragment derived from amyloid protein (APP), formed by the cleavage of β-secretase and γ-secretase. It mainly consists of two subtypes: Aβ40 and Aβ42. Among them, Aβ42 has stronger hydrophobicity and accumulates in an oligomeric form, being the main carrier of neurotoxicity [5]. Under physiological circumstances, intracerebral Aβ maintains metabolic homeostasis through multiple clearance pathways, including enzymatic degradation, microglial phagocytosis, blood-brain barrier clearance and glymphatic system-mediated interstitial fluid drainage, thus exerting no neurotoxic effects [6]. When the APP cleavage regulation is imbalanced, excessive Aβ is produced or the clearance pathway is blocked, Aβ will gradually form oligomers and fibrils, and eventually deposit in the brain to form senile plaques [7, 8]. Specifically, Aβ oligomers are the earliest and most potent neurotoxic species. They directly impair mitochondrial axonal transport, disrupt neurotransmitter release and synaptic transmission, and further trigger irreversible cognitive impairment [5].

2.2. The structural function of tau protein and the regulatory mechanism of phosphorylation

Tau protein is a microtubule-binding protein that is mainly expressed in the central nervous system and peripheral nervous system. Its function is to bind and stabilize the microtubule cytoskeleton within neuronal cells [9]. The activity of tau protein is jointly regulated by intracellular kinases and phosphatases, which maintains its normal phosphorylation level. Among them, glycogen synthase kinase 3β (GSK-3β) is one of the important pathways for regulating phosphorylation, and when activated, it will promote the phosphorylation of the protein [10]. Under the pathological conditions of AD, excessive activation of various kinases will lead to excessive phosphorylation of tau protein, loss of its ability to bind to microtubules, and subsequently disintegration of the microtubule structure and disruption of the neuronal information transmission system [11]. The dissociative tau protein will further undergo incorrect aggregation [12], eventually forming neurofibrillary tangles, which damage the function of neurons and induce cell death [13].

3. The pathological role in AD

Alzheimer's disease is a multifactorial neurodegenerative disorder driven by multiple aberrant pathological changes in brain tissue. Among numerous pathogenic contributors, abnormal accumulation of amyloid-β (Aβ) and aberrant modification of tau protein are two most representative pathological hallmarks. This section will elaborate on their respective pathogenic mechanisms, including neuronal toxic deposition of Aβ and neurofibrillary tangle formation induced by tau hyperphosphorylation, to clarify how they collectively drive the progression of AD.

3.1. The damage mechanism of Aβ deposition on neurons

The deposition of Aβ is the primary factor in the pathological process of Alzheimer's disease. The aggregated AB can directly act on the neuronal cell membrane, causing calcium homeostasis

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imbalance, triggering mitochondrial dysfunction and intense oxidative stress, and inducing neuronal apoptosis. On the other hand, it can activate microglia and astrocytes in the brain, triggering persistent chronic neuroinflammation, which causes long-term continuous damage to surrounding healthy neurons and synaptic structures. This results in progressive atrophy of core brain regions for memory and cognition, including the hippocampus and cerebral cortex, leading directly to memory impairment and cognitive decline in patients. Moreover, accumulated Aβ can also obstruct synaptic signal transmission and disrupt intercellular communication, aggravating the progressive deterioration of neural function in AD sufferers [14].

3.2. Excessive phosphorylation of tau protein is associated with the formation of neurofibrillary tangles

The correlation between neurofibrillary tangles caused by tau hyperphosphorylation and the clinical progression and severity of cognitive impairment in Alzheimer's disease is far stronger than that associated with amyloid plaques [11]. After intracellular tangles form, they not only directly destroy the neuronal skeleton and the material transport system, but also interfere with the nuclear signal pathways, induce synaptic loss, and accelerate the degenerative death of neurons. At the same time, pathological tau proteins can spread among neurons in a "Similar to Prions" manner [9], allowing the pathological damage to gradually spread from local brain regions to the entire brain, promoting the disease to progress from mild cognitive impairment to full dementia [11]. In addition, these tangles impede nutrient transport inside neurons, gradually inducing neuronal atrophy and worsening patients' cognitive function.

3.3. The synergistic cascade reaction between AB and tau protein

AB and tau protein do not independently cause the disease. Instead, there is a clear and definite synergistic and mutually amplifying vicious cycle [5]. A large number of studies have confirmed that excessive AB can activate multiple kinase pathways in the brain, directly promoting the excessive phosphorylation and aggregation of tau protein. By contrast, pathological tau protin will exacerbate the deposition of Aβ, inhibit the normal clearance of Aβ, and further amplify the neurotoxicity of Aβ. Their synergistic effects severely damage neurons, accelerating the onset and progression of Alzheimer's disease, and constitute the core pathogenic driver of AD The interaction between Aβ and tau protein jointly continuously activates pathways such as neuroinflammation, oxidative stress, and neuronal apoptosis, further damaging and exacerbating the degree of neurodegeneration, leading to the gradual loss and death of nerve cells. Disruption of the intracellular environment may also be due to their influence on the metabolism and energy supply of cells [15].

4. The intervention policies of AD

With the growing understanding of AD pathological mechanisms centered on Aβ deposition and tau hyperphosphorylation, multiple intervention strategies targeting key pathological links have been developed. This section will systematically elaborate on three main therapeutic directions: Aβ-targeted therapy, tau-targeted therapy, and dual-target combined intervention strategies, analyzing their mechanisms, current progress and limitations in clinical application.

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4.1. Therapeutic approach targeting Aβ

At present, the intervention strategies targeting Aβ are the mainstream direction in the development of AD drugs. There are mainly three approaches: reducing Aβ production, preventing Aβ aggregation, and promoting its clearance [16].

By regulating the activities of β and γ secretases, the abnormal cleavage of APP can be inhibited at the source, and the production of toxic Aβ monomers can be reduced. Among them, APP hydrolase 1 at the β site (BACE1) can initially hydrolyze APP without causing adverse reactions. Meanwhile, inositol compounds and multivalent complexes consisting of Aβ-specific ligands and metal nanoparticles can inhibit Aβ fibril formation, reduce its neurotoxic potential, and block Aβ aggregation in vitro. This provides a new idea for the future treatment of AD. Additionally, Aβ degrading enzymes and Aβ antibodies can effectively hydrolyze and remove Aβ. Currently, the therapeutic effects of targeted Aβ immunotherapy are not satisfactory, and there are adverse reactions, which are still in the clinical trial stage. Further verification and long-term observation are still needed [16].

4.2. Therapeutic approaches targeting tau protein

Interventions targeting tau protein have also become a new research hotspot in recent years. The main directions include reducing excessive tau phosphorylation, inhibiting tau aggregation, tau-targeted immunotherapy, and artificial intelligence-based therapeutic strategies. By regulating the balance of key kinases such as GSK-3β and CDK5 with the PP2A phosphatase, correcting the abnormal phosphorylation modification of tau protein, and maintaining the normal functions of neuronal scaffolds and axons. The most direct treatment method is to inhibit tau protein aggregation through tau protein aggregation inhibitors and targeted antibodies, and at the same time inhibit its transmission like a prion virus between neurons, preventing the comprehensive spread of damage. Immunotherapy is divided into active and passive methods. Active immunization is low-cost and provides long-lasting efficacy, yet it may trigger irreversible autoimmune reactions as an adverse effect. Passive immunization is more flexible, it is also relatively reversible, but its efficacy lasts longer, increasing the possibility of side effects [11]. Compared with Aβ-targeted drug therapy, tau protein-targeted therapy has a stronger association with the improvement of clinical symptoms in Alzheimer's disease and holds greater potential for therapeutic value [17].

4.3. Dual-target combined intervention strategy

The therapeutic limitations of single-target interventions have become increasingly obvious in preclinical and clinical trials. For example, anti-Aβ therapies show limited cognitive benefits in advanced AD patients, while tau-targeted monotherapies alone cannot block the upstream toxic effects of Aβ, which continues to induce tau hyperphosphorylation and propagation. Therefore, dual-target strategies that simultaneously intervene in both Aβ and tau pathological cascades have emerged as a promising direction. By combining anti-Aβ and anti-tau therapies, they aim to interrupt the synergistic pathological cycle between the two, reducing both plaques and tangles more effectively. Preclinical studies have confirmed that they exert stronger neuroprotective and cognition-enhancing effects than monotherapies, and enable the use of lower doses to lower the risk of adverse reactions. Although clinical validation remains preliminary, this approach offers new hope for overcoming single-target therapy bottlenecks in AD treatment [5, 17]

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5. Conclusion

This article systematically reviewed the pathogenic mechanisms and intervention strategies. However, it still has obvious limitations. For instance, this study is a theoretical review, and no animal experiments were performed to validate the conclusions. Due to the complex mechanism of AD, there is a lack of sufficient research data on Aβ and tau proteins in the academic community, and the dynamic temporal changes have not been fully analyzed. Further exploration and research on more profound molecular mechanisms can still be carried out.

Given the overall shortcomings and bottlenecks in current research, future studies on Alzheimer's disease can be advanced in the following directions like further exploring the individual dynamic change patterns of Aβ and tau proteins in the early stage of Alzheimer's disease, and clarifying the process of their mutual influence and synergistic effect. Moreover, Continuing to explore the combined intervention therapy targeting both Aβ and tau proteins. This approach can compensate for the deficiencies of single-target therapies and verify the clinical value of combination interventions. Meanwhile, by integrating emerging technologies including gene editing, targeted delivery and artificial intelligence, researchers can develop novel therapeutic strategies that are safer and more effective, and capable of slowing or even reversing disease progression.

With the continuous advancement of related research and the continuous progress of various technologies, the precise diagnosis and treatment techniques for Aβ and tau proteins will also be continuously improved. In the future, it is certain to bring new breakthroughs for the early detection and intervention of Alzheimer's disease, effectively reducing the burden that aging brings to society.

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