Synergistic Effect of Aβ42 and Tau Protein in Alzheimer's Disease

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DOI: 10.32629/jcmr.v5i3.2764

Abstract: Alzheimer's disease (AD) is a neurodegenerative disease that can't be cured at present, which is different from what we call infectious diseases, and is usually related to senile dementia. Although there is no radical cure at present, early diagnosis and intervention can delay the progress of the disease and improve the quality of life of patients. The mechanism of Aβ42 and Tau protein in AD is of great significance for early diagnosis and treatment of diseases. In this paper, the interaction between these two proteins is deeply analyzed, and their role in the pathological development of AD is discussed, and how to use this knowledge to improve the accuracy of clinical diagnosis and develop new treatment strategies.
***Keywords*:** Alzheimer's disease; Aβ42; Tau protein; Synergy; clinical diagnosis introduction

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that gradually deprives people of their memory and cognitive abilities. As biomarkers of AD, Aβ42 and Tau protein, their mechanism of action and their interaction in disease development have far-reaching significance for clinical diagnosis and treatment[1]. This article will discuss the importance of these two proteins in AD, analyze their interaction, and explore their potential application in clinical diagnosis, so as to provide a new perspective for early diagnosis and intervention of AD.

2. Biological characteristics of Aβ42 protein and its role in AD

2.1 Formation and metabolism of Aβ42

Aβ42 is a polypeptide produced by the cleavage of Amyloid Precursor Protein, APP) by specific enzymes, with a length of 42 amino acids. The process involves two main secretory enzymes: β -secretase (BACE1) and γ-secretase complex. Under normal circumstances, APP is mainly cleaved by α-secretase pathway, resulting in non-amyloid peptide fragments. When the activities of β-secretase and γ-secretase increase abnormally, it will lead to the excessive production of Aβ42. The formation process of Aβ42 is a dynamic equilibrium, which has the same important metabolic function. In healthy brain, Aβ42 can be eliminated by many ways, including enzymolysis, intracellular phagocytosis, transport through the blood-brain barrier and so on. However, in patients with Alzheimer's disease, this metabolic balance is broken, and the clearance efficiency of Aβ42 is reduced, which leads to its accumulation in the brain. These factors work together, leading to the formation and deposition of Aβ42 in the brain and the formation of senile plaques[2]. The formation of senile plaque is one of the pathological features of AD, which is closely related to the occurrence and development of neurodegeneration. The breakthrough of the formation and metabolic mechanism of Aβ42 reveals the pathogenesis of AD and develops new preventive strategies.

2.2 Aβ42 plays an important role in neurodegeneration

The role of Aβ42 in neurodegeneration is various. The aggregate of Aβ42 can directly damage the neuronal membrane, lead to the increase of calcium influx, activate various intracellular signal pathways, and trigger oxidative stress and inflammatory reaction. These reactions further damage organelles, such as mitochondria and endoplasmic reticulum, resulting in energy metabolism disorder and abnormal protein folding. Aβ42 can also affect the release of neurotransmitters and signal transduction, interfere with synaptic plasticity, and lead to the impairment of learning and memory functions. Aβ42 can also activate microglia, trigger neuro inflammation, release a variety of inflammatory mediators, and aggravate nerve injury. The neurotoxic effect of Aβ42 is also related to its aggregation state. The monomer Aβ42 is relatively less toxic, but when it forms oligomer or fibrous aggregate, its toxicity is significantly increased. These aggregates can interfere with many biological processes in cells, including cell cycle, apoptosis, cell signal transduction and so on. The aggregation of Aβ42 may also affect the stability of extracellular matrix, lead to the change of extracellular environment, and further aggravate neurodegeneration. Therefore, Aβ42 plays a central role in the neurodegeneration of AD, and its toxic effect is the key link in the pathogenesis of AD[3].

2.3 Relationship between Aβ42 Aggregation and AD Pathology

The aggregation of Aβ42 is closely related to AD pathology, and the abnormal aggregation of Aβ42 is one of the early events in the development of AD pathology. In the brain of AD patients, Aβ42 first forms soluble oligomers, then gradually forms insoluble fibrous aggregates, and finally forms senile plaques. These senile plaques are mainly distributed in the cortex and hippocampus of the brain, which is closely related to the cognitive dysfunction of AD patients. The formation of Aβ42 aggregates directly damages neurons and can affect the function of nerve cells through various mechanisms. The formation and deposition of Aβ42 aggregates may also affect the stability of neural networks[4]. The formation of senile plaques leads to the loss of synaptic connections and affects the transmission of nerve signals. In addition, Aβ42 aggregates can also activate microglia, cause neuroinflammation, and release a variety of inflammatory mediators, such as tumor necrosis factor -α(TNF-α) and interleukin -1β(IL-1β), which further damage neurons and aggravate neurodegeneration. The formation of Aβ42 aggregates may also affect many biological processes in cells, including cell cycle, apoptosis, cell signal transduction and so on, leading to cell dysfunction and cell death. The relationship between Aβ42 aggregation and AD pathology is various, involving the damage of nerve cells, the destruction of neural network, the activation of neuroinflammation and so on. Understanding the mechanism of Aβ42 aggregation is of great significance for revealing the pathogenesis of AD and developing new therapeutic strategies.

3. Biological characteristics of Tau protein and its role in AD

3.1 Tau structure and function of tau protein

Tau protein is a highly conserved microtubule-associated protein, which is mainly expressed in the central nervous system. It is composed of 352 to 441 amino acids, and has multiple microtubule binding domains (MTBRs), which are rich in proline and tyrosine and can be closely combined with tubulin. The main function of Tau protein is to stabilize the microtubule structure of nerve cells and promote the assembly and dynamic stability of microtubules[5]. Microtubule is an important part of cytoskeleton, which is very important for maintaining cell morphology, axonal transport and cell division. Tau protein enhances the stability of microtubules by reducing the depolymerization rate and increasing their growth rate. Tau protein is also involved in regulating intracellular signal transduction, cell cycle and apoptosis.

3.2 Abnormal phosphorylation of tau protein and neurofibrillary tangles

Abnormal phosphorylation of Tau protein is one of the main pathological features in neurodegenerative diseases such as Alzheimer's disease. The phosphorylation of Tau protein is regulated by many kinases and phosphatases, and the imbalance of these enzymes will lead to excessive phosphorylation of Tau protein. Abnormal phosphorylated Tau protein lost its ability to bind to microtubules, dissociated from microtubules and began to form abnormal aggregates. These aggregates further form a double helix filament structure, which eventually leads to the formation of nerve fiber tangles. Neurofibrillary tangles are one of the symbolic pathological features of AD, which are mainly distributed in the cortex and hippocampus of the brain. The formation of neurofibrillary tangles has a serious impact on the structure and function of nerve cells. They interfere with the normal function of microtubules, lead to axon transport disorders, and affect the transport of neurotransmitters and other essential substances[6]. Neurofibrillary tangles may also affect intracellular signal transduction, leading to cell dysfunction and cell death. Abnormal phosphorylation of Tau protein may also activate microglia, trigger neuroinflammation, release inflammatory mediators, and further aggravate nerve injury. Abnormal phosphorylation of Tau protein and the formation of neurofibrillary tangles are the key links in the pathological development of AD.

3.3 Tau influence of tau protein in nerve conduction

Tau protein plays an important role in nerve conduction by maintaining the stability of microtubules, which are the main transport channels of axons and are responsible for transporting neurotransmitters, organelles and intracellular signal molecules from the cell body to the end of axons[7]. Tau protein ensures the efficiency and accuracy of axon transport by promoting the assembly and stability of microtubules. Axon transport is a key link in the process of nerve signal transmission, which ensures the timely replenishment of neurotransmitters and the rapid transmission of signal molecules. In neurodegenerative diseases such as AD, abnormal phosphorylation and aggregation of Tau protein will destroy the stability of microtubules, affect axon transport, and lead to obstacles in nerve signal transmission. This signal transmission obstacle not only affects the communication between nerve cells, but also may lead to the loss of nerve cell function and cell death. Abnormal phosphorylation of Tau protein may also interfere with synaptic plasticity by affecting intracellular signal transduction, leading to cognitive impairment such as learning and memory. Abnormal phosphorylation of Tau protein may also affect nerve conduction through other mechanisms. For example, it may affect the metabolism and energy supply of

nerve cells, leading to the disorder of intracellular environment. The formation of Tau protein aggregates may also interfere with the stability of extracellular matrix, lead to the change of extracellular environment, and further aggravate nerve injury.

4. Interaction mechanism between Aβ42 and Tau protein

4.1 Interaction between Aβ42 and Tau protein

The abnormal accumulation of Aβ42 is widely regarded as one of the initial events of AD, which forms senile plaques in the brain. These plaques not only physically damage nerve cells, but also may affect the homeostasis of Tau protein through various signal transduction pathways. Aβ42 can activate specific kinases, such as GSK-3β, by increasing the level of intracellular oxidative stress, resulting in hyperphosphorylation of Tau protein. This phosphorylation changes the structure of Tau protein and dissociates it from microtubules, thus promoting the aggregation of Tau protein and forming neurofibrillary tangles. The existence of Aβ42 may also affect the clearance mechanism of Tau protein, including the autophagy function and proteasome activity of cells, leading to the accumulation of abnormally phosphorylated Tau protein in cells. This interaction may also affect the signal transduction of nerve cells by changing the intracellular calcium balance, and then affect the phosphorylation state of Tau protein[8]. The interaction between Aβ42 and Tau protein constitutes a vicious circle in the pathological process of AD, in which the accumulation of Aβ42 promotes the abnormal phosphorylation and aggregation of Tau protein, which may aggravate the neurotoxicity of Aβ42.

4.2 Synergy between them in AD pathology

The synergistic effect of Aβ42 and Tau protein in the pathology of AD is a kind of interaction and mutual promotion, which plays a vital role in the progress of AD. The aggregation of Aβ42 can not only directly damage nerve cells, but also affect the homeostasis of Tau protein through various mechanisms, leading to abnormal phosphorylation and aggregation of Tau protein. Conversely, the abnormal aggregation of Tau protein can also affect the clearance of Aβ42 and aggravate the neurotoxicity of Aβ42. This synergy also involves the activation of inflammatory response. Aggregates of Aβ42 and Tau protein can activate microglia, trigger neuroinflammation and release inflammatory mediators, such as interleukin and tumor necrosis factor, which further aggravate the damage of nerve cells. The interaction between Aβ42 and Tau protein may also affect the energy metabolism of nerve cells, leading to mitochondrial dysfunction, and then affect the viability of cells. In the course of AD, the synergistic effect of Aβ42 and Tau protein leads to the gradual loss of nerve cell function and cell death, which forms the basis of the pathological characteristics of AD and plays a role in promoting the progress of the disease.

4.3 The influence of interaction on nerve cells

The interaction between Aβ42 and Tau protein has many effects on nerve cells, and this effect plays a core role in the pathological process of AD. The aggregation of Aβ42 can directly damage the nerve cell membrane, lead to the increase of calcium influx, activate a variety of intracellular signaling pathways, and trigger oxidative stress and inflammatory response. These reactions further damage organelles, such as mitochondria and endoplasmic reticulum, resulting in energy metabolism disorder and abnormal protein folding. Abnormal phosphorylation and aggregation of Tau protein destroy the stability of microtubules, affect axon transport, and hinder the transport of neurotransmitters and other essential substances. This transportation obstacle affects the communication between nerve cells, and then affects cognitive functions such as learning and memory. The abnormal aggregation of Tau protein may also interfere with synaptic plasticity by affecting intracellular signal transduction, leading to further damage of cognitive function. The interaction between Aβ42 and Tau protein may also trigger neuroinflammation by activating microglia, and release a variety of inflammatory mediators, which further damage neurons and aggravate neurodegeneration. This inflammatory reaction not only aggravates the damage of nerve cells, but also may lead to the disorder of intracellular environment by affecting the metabolism and energy supply of nerve cells. The interaction between Aβ42 and Tau protein leads to the gradual loss of nerve cell function and cell death, which forms the basis of the pathological characteristics of AD and plays a role in promoting the progress of the disease.

5. Clinical treatment strategy of AB42 and Tau protein

5.1 Progress in clinical diagnosis and treatment of Aβ42

The abnormal accumulation of Aβ42 is one of the early signs of Alzheimer's disease, and it is of great significance for the clinical diagnosis and treatment of Aβ42. In recent years, AD can be diagnosed earlier by using biomarkers, such as detection of Aβ42 level in cerebrospinal fluid and positron emission tomography (PET) technology. The development of these technologies has greatly improved the accuracy of early diagnosis. In terms of treatment, although there is no drug to cure AD at present, some drugs and vaccines are being developed to reduce the production of Aβ42 or promote its

elimination. For example, some drugs reduce the production of Aβ42 by inhibiting the activities of β-and γ-secretase, while others act by promoting the decomposition or inhibiting the aggregation of Aβ42[9]. The effectiveness and safety of these treatments still need further clinical trials to verify.

5.2 Progress in clinical diagnosis and treatment of Tau protein

Abnormal phosphorylation and aggregation of Tau protein is another key pathological feature of AD. The diagnosis of Tau protein mainly depends on the detection of Tau protein level in cerebrospinal fluid and PET imaging technology, which can detect abnormal aggregation of Tau protein. In terms of treatment, drug research and development for Tau protein mainly focuses on inhibiting the phosphorylation of Tau protein, promoting its normalization and reducing the formation of Tau protein aggregates. Some drugs reduce the phosphorylation of Tau protein by targeting specific kinases, while others reduce the dissociation of Tau protein by stabilizing microtubules. Immunotherapy is also a potential therapeutic strategy to remove abnormal Tau protein by activating the immune system. The effectiveness and safety of Tau protein therapy strategy also need to be evaluated through clinical trials.

5.3 Aβ42 and Tau protein combined diagnosis and treatment potential and challenges

The combined diagnosis of Aβ42 and Tau protein provides a new possibility for the early and accurate diagnosis of AD. By detecting the levels and morphology of these two proteins at the same time, the pathological state of AD can be understood more comprehensively. Joint diagnosis and treatment are facing challenges, including how to accurately evaluate the interaction between the two proteins and how to design drugs that can affect both Aβ42 and Tau proteins. Combination therapy may increase the side effects and complexity of drugs, which need to be carefully evaluated in clinical trials. Despite these challenges, the combined diagnosis and treatment strategy of Aβ42 and Tau protein provides a new perspective and hope for clinical intervention of AD.

6. Conclusion

To explore the interaction between Aβ42 and Tau protein in Alzheimer's disease (AD) and its effect on neurodegeneration. By analyzing the biological characteristics and pathological effects of these two proteins, we revealed their key roles in the pathogenesis of AD[10]. The potential and challenges of the combined diagnosis and treatment strategy of Aβ42 and Tau protein are emphasized, which provides a new theoretical basis and research direction for the early diagnosis and treatment of AD in the future. With the deepening of research, we expect to develop more effective diagnosis and intervention measures to slow down the progress of AD and improve the quality of life of patients.

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