Proceedings of ICBioMed 2025 Symposium: Computational Modelling and Simulation for Biology and Medicine
DOI: 10.54254/2753-8818/2025.LD24053

Mechanisms of Tau Protein in Alzheimer's Disease Pathogenesis and Potential Therapeutic Strategies: A Brief Review

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Abstract: Under normal physiological conditions, tau protein can maintain the function of microtubules, while under pathological conditions, it dissociates from microtubules and aggregates, thereby disrupting microtubule function and ultimately leading to neuronal damage and the development of neurodegenerative diseases. Under pathological conditions, tau protein undergoes modifications such as phosphorylation, acetylation, ubiquitination, and truncation. These changes lead to the formation of neurofibrillary tangles through various mechanisms and ultimately cause Alzheimer's disease. In response to these diverse pathogenic mechanisms, people have developed a variety of potential therapeutic approaches targeting the underlying causes, such as modulating autophagy, inhibiting tau protein aggregation, clearing tau protein and so on. These studies demonstrate that the progression of neurodegenerative diseases, headed by Alzheimer's disease (AD), can be inhibited. This article aims to discuss the limitations in the aforementioned mechanisms and their corresponding therapeutic approaches, and to explore whether there are methods and ideas to address these shortcomings. Regrettably, the current potential therapeutic approaches are still unable to completely cure Alzheimer's disease, and the conditions required for treatment are rather demanding. However, these therapeutic methods may potentially serve as means for the early diagnosis and prevention of Alzheimer's disease. This article may provide more ideas for new therapeutic approaches to AD and other neurodegenerative diseases.

Keywords: Tau protein, Alzheimer's disease, function, post-translational modification, treatment

1. Introduction

Alzheimer's disease is the most common neurodegenerative disease and the primary cause of dementia [1]. Tau protein is a microtubule-associated protein, mostly located in the axons of neurons. Tau protein plays an important role in maintaining the normal functions of material transport and signal transduction in nerve cells, as well as in maintaining the stability of the cytoskeleton. Research indicates that a variety of neurodegenerative diseases, including Alzheimer's disease, are associated with structural and functional abnormalities of tau protein. Therapeutic approaches targeting tau protein have naturally become a research hotspot for the treatment of AD. However, there are still some limitations in tau protein-related treatments for AD. This article will explore possible ideas and

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methods to address these limitations and provide new insights for the treatment of AD and other neurodegenerative diseases.

2. The basic functions and modifications of tau protein

2.1. The functions of tau protein

Under physiological conditions, tau protein is primarily located in the axons of neurons in the human brain. Tau protein can bind to tubulin and promote its polymerization to form microtubules. Microtubules play crucial roles in maintaining cell shape, material transport, signal transduction, cell division, and other activities. Tau protein can also maintain the stability of microtubules, reduce the dissociation of tubulin, and induce the bundling of microtubules. After microinjection of tau protein into fibroblasts that lack tau protein, an increase in the density of microtubules within the cells can be observed. Moreover, tau protein can attenuate the effect of nocodazole (a drug that blocks microtubule assembly), thereby slowing down the disappearance of microtubules in the cells [2]. The aforementioned experimental methods can corroborate the role of tau protein in promoting microtubule assembly and maintaining microtubule stability. In addition, tau protein can interact with tubulin components, and these interactions help regulate the growth processes of cells [2].

2.2. The modifications of tau protein

Tau protein undergoes various post-translational modifications, including phosphorylation, acetylation, ubiquitination, and others, among which phosphorylation is the most common form of post-translational modification of tau protein. Additionally, tau protein can also be truncated.

2.2.1. Tau protein phosphorylation

Tau protein contains 85 potential phosphorylation sites. Phosphorylation at different sites can lead to distinct functional properties of tau protein. For example, phosphorylation at Ser262, Ser293, Ser324, and Ser356 reduces the binding of tau protein to microtubules [3]. Under pathological conditions, the phosphorylation of tau protein is abnormally increased. Abnormal phosphorylation of tau protein reduces its ability to bind to microtubules, thereby decreasing the stability of microtubules, leading to damage of neuronal axonal microtubules and affecting synaptic function [4]. Normal tau protein is not prone to aggregate into filaments. However, hyperphosphorylated tau protein can undergo self-aggregation to form paired helical filament tau (PHF-tau). PHF-tau is toxic to nerve cells and is not easily cleared. Its neurotoxic effects include the activation of caspases and the initiation of apoptosis. Hyperphosphorylated tau protein is not recognized by the heat shock protein 70-interacting protein-heat shock protein 90 complex (Hsp70/90), thereby avoiding clearance [3].

2.2.2. Tau protein acetylation

Another important form of post-translational modification of tau protein is acetylation. Acetylation of tau protein at different lysine sites can lead to completely different effects. Acetylation of tau protein at certain sites can prevent its hyperphosphorylation and aggregation, such as at lysine residues 259, 290, 321, and 353. However, acetylation at lysine residues 163, 280, 281, and 369 has the opposite effect. Acetylation at these sites inhibits the degradation of tau protein, leading to the aggregation of hyperphosphorylated tau protein [5].

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2.2.3. Tau protein ubiquitination

Although ubiquitination is a very important form of post-translational modification in eukaryotic cells and plays a positive role in various normal cellular functions such as signal transduction and maintaining protein stability, the ubiquitination of tau protein can affect the normal function of nerve cells. The ubiquitination of tau protein can occur after its hyperphosphorylation and aggregation into PHF-tau. This process is induced by the interaction between the carboxyl terminus of Hsp70 interacting protein (CHIP) and the Hsp70/90 complex. Moreover, CHIP can further enhance the aggregation of tau protein, leading to the formation of neurofibrillary tangles (NFTs) and the development of neurodegenerative diseases [6].

2.2.4. Tau protein truncation

Tau protein can be truncated by Caspase 3 or 6 at specific sites such as Asp421 and Glu391. When tau protein is truncated at these sites, it can promote further aggregation of tau protein [6]. In addition, the truncated tau protein fragments can spread between neurons, triggering the formation of tangles in other neurons, thereby expanding the scope of neurodegenerative changes [6].

3. The Mechanisms by which tau protein causes neurodegenerative diseases

Hyperphosphorylation of tau protein can lead to a variety of neurodegenerative diseases, the most common of which is Alzheimer's disease. After hyperphosphorylation, tau protein aggregates to form NFTs, which alter neuronal morphology and lead to the loss of synaptic function, ultimately resulting in neuronal loss. Research indicates that there is a correlation between the occurrence and severity of dementia in patients with neurodegenerative diseases and the number of neurofibrillary tangles [7]. In addition, hyperphosphorylated tau protein can also sequester other microtubule-associated proteins, impede the assembly of microtubules, and disrupt their structure. In addition to directly causing neuronal damage, hyperphosphorylated tau protein can also accumulate in the endoplasmic reticulum as misfolded proteins, inducing endoplasmic reticulum stress and ultimately leading to neurodegenerative diseases [7]. When tau protein is truncated by caspase-3 at specific sites, it can inhibit the autophagy function of nerve cells, preventing lysosomes from degrading excessive tau protein and leading to abnormal secretion of tau protein [6]. Under normal conditions, phosphorylated tau protein can be cleared through the autophagy pathway. However, under pathological conditions, the autophagy-related signaling pathways are inhibited. Dysfunction of the autophagy-lysosome system leads to the aggregation of tau protein. Moreover, aggregated tau protein can further suppress autophagy function, creating a vicious cycle that ultimately causes neuronal pathology [8].

4. Potential therapeutic approaches for Alzheimer's disease related to tau protein

Since the loss of normal tau protein function can ultimately lead to Alzheimer's disease, potential therapeutic approaches for Alzheimer's disease can be explored by targeting the pathogenic mechanisms of tau protein. These approaches include modulating autophagy, inhibiting tau protein aggregation, enhancing tau protein clearance, and reducing the level of tau protein phosphorylation. The following are several potential therapeutic directions currently being experimentally validated, and they hold promise for becoming drugs that can delay the onset and progression of AD.

4.1. Autophagy modulators

Enhancing autophagy function can improve the clearance of phosphorylated tau protein by neurons; therefore, autophagy modulation may potentially delay the progression of Alzheimer's disease.

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Autophagy modulators, by inducing and enhancing autophagy, can to some extent clear soluble excess tau protein, reduce the aggregation of hyperphosphorylated tau protein, and thereby decrease its cytotoxicity, thus delaying the progression of AD [6]. Autophagy modulators mainly include mTORC-dependent and mTORC-independent types. mTORC-dependent autophagy inducers, such as rapamycin, can significantly reduce neurofibrillary tangles in experimental mice. mTORC-independent autophagy inducers, such as AMPK activators like metformin and trehalose, can reduce the levels of insoluble tau protein [6].

4.2. Tau protein kinase inhibitors

Tau protein kinases can phosphorylate tau protein, promoting its aggregation. Glycogen Synthase Kinase 3 beta (GSK3β), Cyclin-Dependent Kinase 5 (CDK5), and Microtubule Affinity-Regulating Kinase (MARK) are three major tau protein kinases. GSK3β is abundant in the brain. Its function is to phosphorylate tau protein, neurofilaments, and various transcription factors. Dysregulation of GSK3β can lead to diseases such as AD and bipolar disorder [9]. GSK3 inhibitors include Paullones, lithium, Thiadiazolidindiones (TDZD) and so on. However, lithium, as a therapeutic agent, has too many contraindications and limited therapeutic efficacy. In contrast, TDZD holds promise as a new treatment for AD [9]. Cdk5 also promotes the formation of NFTs. Its overexpression can induce phosphorylation of tau protein at multiple sites. Inhibitors of Cdk5 include R-roscovitine, aloisine, and indirubin-3'-oxime [9]. MARK functions to phosphorylate microtubule-associated proteins and dissociate them from microtubules. Steurosporine and hymenialdisine are inhibitors of MARK [9].

4.3. Tau protein aggregation inhibitors

Hyperphosphorylated tau protein can aggregate to form PHF-tau within cells. If the aggregation of tau protein can be inhibited, it may also delay the progression of AD. Research indicates that methylene blue (MB) can inhibit the aggregation of tau protein. Leuco-methylthioninium, which is derived from MB, has lower toxicity and may potentially serve as a new therapeutic agent for AD. Compounds such as phenothiazines, porphyrins, and polyphenols can also prevent the aggregation of tau protein [9].

4.4. Microtubule-stabilizing drugs

Hyperphosphorylation of tau protein can cause it to lose its original function of binding to and stabilizing microtubules, making microtubules more prone to dissociation and thereby disrupting neuronal function. Therefore, maintaining microtubule stability and protecting their normal function is also a direction for protecting neurons and controlling the progression of AD. Paclitaxel, epothilone D (EpoD), and the octapeptide NAPVSIPQ (NAP) have been found to bind to tubulin and improve microtubule transport functions within axons, increase microtubule density, and also reduce the levels of phosphorylated tau protein, thereby protecting neurons [9]. However, paclitaxel has difficulty crossing the blood-brain barrier, resulting in low concentrations in the brain. In contrast, NAP can cross the blood-brain barrier and effectively exert its function in promoting microtubule assembly and stabilizing microtubules.

4.5. Tau immunotherapy

Immunotherapy is a hot research topic in disease treatment in recent years, and immunotherapy targeting tau protein mainly focuses on tau protein kinases. Monoclonal antibodies targeting tau protein kinases can effectively inhibit these kinases, exerting effects similar to those of tau protein kinase inhibitors, thereby reducing the levels of phosphorylated tau protein within cells [9]. Tau

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protein fragments between cells also play an important role in the development of AD. Using immunotherapy can target and clear tau protein fragments between neurons, effectively preventing the spread of tau protein fragments and their impact on other nerve cells [9].

4.6. Targeting glycosylation and chaperone therapy

Research indicates that a specific type of glycosylation, O-linked β-N-acetylglucosamine (O-GlcNAc), can effectively reduce the phosphorylation of tau protein at pathologically relevant sites [9]. Therefore, using targeted drugs to carry O-GlcNAc to specifically bind to sites on tau protein and prevent its hyperphosphorylation is a potential therapeutic strategy. Inhibiting O-GlcNAc hydrolase can also achieve the goal of increasing O-GlcNAc levels and reducing tau protein phosphorylation [9].

The role of molecular chaperones is to regulate the conformation and function of other proteins, as well as to promote the clearance of misfolded proteins. Heat shock proteins (HSPs) are a class of chaperone proteins. Among them, HSP27 can directly bind to hyperphosphorylated tau protein and reduce its concentration. HSP70 and HSP90 can also prevent tau protein aggregation. Current research on HSPs is focused on developing HSP90 inhibitors that can bind to drugs targeting the abnormal phosphorylation sites of tau protein, in order to reduce tau protein phosphorylation levels and inhibit tau protein aggregation [9].

5. Challenges and prospects in tau-related therapeutic research

Although tau protein-related therapies are a hot research area in the treatment strategies for AD, these therapeutic approaches still have some limitations.

5.1. Blood-brain barrier permeability

One of the main reasons for the failure of many drug experiments is the presence of the blood-brain barrier. Drugs are unable to enter the central nervous system or enter in insufficient amounts. Increasing the drug dosage may, to some extent, raise the concentration of the drug in the central nervous system, but it may also increase drug toxicity and metabolic burden [10]. Therefore, finding ways to enable drugs to cross the blood-brain barrier and effectively exert their therapeutic effects in the brain is of great significance for the treatment of AD. Research has found that liposomes and exosomes are nanovesicles capable of carrying drugs across the blood-brain barrier, and they represent methods of significant research value and potential [10].

5.2. Pathological stage dependency

Another important reason for the poor therapeutic outcomes of current AD treatments may be the relatively late onset of symptoms. Typically, by the time AD patients exhibit clinical symptoms such as memory loss and dementia, significant brain atrophy and neuronal damage have already occurred [10]. Neither traditional therapeutic approaches nor future potential treatments such as tau immunotherapy can reverse the damage to or death of neurons that have already occurred. Therefore, treatment for AD may be more effective if initiated in the early stages. This requires the ability to detect early aggregation of tau protein in order to intervene promptly.

5.3. Risk of off-target effects

Although the aggregation of hyperphosphorylated tau protein is a significant cause of AD, normal tau protein maintains the physiological functions of neurons. Tau protein kinase inhibitors and tau protein immunotherapy drugs in potential AD treatments may have toxic side effects. In addition to

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targeting the inhibition of phosphorylated tau protein, kinase inhibitors and monoclonal antibodies may also inhibit normal tau protein, leading to microtubule damage and thereby affecting the normal function of nerve cells [11]. In addition to potentially affecting the central nervous system, excessive inhibition of physiological tau and disruption of microtubule function can also easily lead to peripheral neuropathy.

6. Conclusion

The aggregation of abnormal tau protein into PHF-tau is considered a significant cause of neurodegenerative diseases, such as Alzheimer's disease. It may lead to pathology through mechanisms, such as disrupting microtubule function, forming neurofibrillary tangles, inducing endoplasmic reticulum stress, and affecting autophagy function. However, to date, there is still no definitive and effective treatment for AD. Current clinical management primarily focuses on improving lifestyle habits and providing symptomatic treatments to enhance brain function. This includes non-pharmacological interventions, such as quitting smoking and alcohol, maintaining a healthy diet, and engaging in regular exercise, as well as pharmacological treatments using drugs like the cholinesterase inhibitors Donepezil, Rivastigmine, and Galantamine (GAL), and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine, which aim to improve neuronal transmission, cognitive function, and memory [12]. Therefore, the mechanisms by which tau protein leads to AD are of great significance in guiding the research of current AD therapeutic drugs. Therapeutic approaches targeting the various pathogenic mechanisms of tau protein provide some new ideas, such as modulating autophagy, inhibiting tau protein kinases, preventing tau protein aggregation, stabilizing microtubules, and using immunotherapy to clear tau protein. However, these potential therapeutic approaches still face many challenges, such as the inability of drugs to cross the blood-brain barrier, the inability to initiate intervention early, and the potential impact on normal tau protein function. Combination therapy that integrates multiple treatment methods may become a breakthrough direction for delaying the progression of AD. Neither the current clinical therapies aimed at improving function nor the potential new treatments can completely cure or reverse the neuronal damage already caused by abnormal tau protein. In future research, it may be necessary to develop more precise targeted therapeutic approaches and methods for early detection and diagnosis of AD, in order to prevent AD by targeting abnormal tau protein in a timely and accurate manner. In addition, the method of inducing the differentiation of stem cells into neurons in vitro may potentially repair the damaged central nervous system, but this requires specific experimental research.

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