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Review Article

New Treatment for Alzheimer's Disease: Tau-Targeting Drugs and Therapies

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Abstract

Alzheimer's disease is a neurodegenerative disorder, the most common form of dementia in older people, and is characterized by synaptic loss and brain atrophy. The first part to be damaged during the disease is the hippocampus, which is the memory center, and then the cerebral cortex, which controls logical and social behavior. Alzheimer's disease is pathologically characterized by the formation of tau neurofibrillary tangles and amyloid-β plaques in the brain. The formation of intracellular neurofibrillary tangles, the main cause of tauopathies, begins with the accumulation of hyperphosphorylated tau protein isoforms. These isoforms cause neuronal death and contribute to the development of complex neurodegenerative diseases such as Alzheimer's, Parkinson's, and other neurodegenerative diseases. Many of the treatments developed for Alzheimer's disease have focused on amyloid-β plaques, but since these treatments have failed to halt the progression of the disease, attention has been focused on tau pathologies. However, clinical trials of many drugs have been discontinued due to toxicity and failure to demonstrate the desired effect. Most of the tau-targeted agents currently being tested are immunotherapies. New research presents various potential approaches for preventing cellular toxicity resulting from tau aggregation. These include many methods, such as preventing toxic tau aggregation and post-translational modifications of tau protein, and developing tau-targeted immunogens. Since the accumulation of tau tangles is a major cause of Alzheimer's, it is significant to investigate therapies that restore normal tau mechanisms and prevent tau accumulation. In recent years, nanoparticle-based drug delivery technologies have offered promising opportunities for treating this disease.

Keywords: Alzheimer's disease, dementia, neurodegenerative disorder, tau protein, amyloid-β plaques, tau-targeted immunotherapy

1. Introduction

Approximately 57 million people worldwide suffer from dementia, and this number is expected to reach 139 million by 2050. 60–70% of these cases are caused by Alzheimer's disease (AD). In addition, Alzheimer's and related diseases cost the healthcare system hundreds of billions of dollars each year. Over the years, many treatments have been developed for Alzheimer's disease, with initial research focusing on amyloid-β, the main component of plaques that accumulate in the brain. However, immunotherapies have often been ineffective or have had harmful effects on the body. Therefore, the presence of tau pathology in several neurodegenerative diseases, including Pick's disease and primary age-related tauopathy (PART), has made tau an attractive therapeutic target. Tauopathies are a group of neurodegenerative diseases characterized by abnormally phosphorylated tau protein. Although significant progress has been made in the study of tau pathologies in tauopathies, how the tau protein causes neuronal death has not yet been fully elucidated. Also, the clinical efficacy of tau-targeted therapies has not yet been fully proven, and many trials are currently ongoing. One of these trials, antisense oligonucleotides, has shown promising results. The positive results of these experiments could help develop tau-targeted drugs for the treatment of Alzheimer's disease in the future and pave the way for treatments for other types of dementia [1], [2].

2. The General Overview of Tau Pathologies in Alzheimer's Disease

Alzheimer's is the most common age-related neurodegenerative disease, and extracellular plaques composed of amyloid-β and intracellular tangles composed of hyperphosphorylated tau protein are two major pathological hallmarks of this decline. Tau is a protein associated with microtubules and has many functions, including maintaining the stability of microtubules in neurites, normal microtubule structure in neurons, and establishing connections between axons. In Alzheimer's disease and many other neurodegenerative diseases called "tauopathies," tau proteins are a major component of intraneuronal and glial fibrillary changes. Tau protein has been evaluated as a promising target for the development of therapeutic pathways because it has a broad pathological role in many neurodegenerative diseases. Thus, when tau undergoes various modifications, it can lead to microtubule destabilization, neuronal dysfunction, and cell death. Although a different set of modifications is observed in each neurodegenerative disease, Alzheimer's disease is the most common of these. There are various forms of tauopathies, one of which is a disruption of the 3R:4R ratio of tau protein, which normally has a precise balance between the four-repeat (4R) and three-repeat (3R) isoforms. Several other isoforms of tau can also have a significant impact on the aggregation of Alzheimer's disease. Recently, García-Escudero and colleagues discovered a truncated tau isoform unique to humans, resulting from the retention of intron 12. This process leads to the formation of a truncated tau protein supplemented with 18 additional amino acids and a sharp decrease in the aggregation ability of that isoform. This tau isoform has a similar biochemical composition and ability to bind to microtubules as the others, but the resulting variation stabilizes the tau protein and is therefore thought to play a beneficial role [3], [4].

Tau proteins also play a role in establishing various connections between other cytoskeletal elements and proteins. Thus, although the significance of tau pathology in Alzheimer's disease was not previously fully understood, the numerous mutations identified in the tau gene that lead to pathological aggregation of tau protein, the formation of FTDP-17, and the gradual damage of neocortical areas have proven that disruption of tau function alone can initiate neurodegenerative processes. Therefore, a deeper study of the characteristics of the spread of tau-related neuroinflammation in tauopathies is crucial to clarify the role of immunotherapies as potential therapeutic targets in the treatment of Alzheimer's disease and other tauopathies. Despite previous suspicions, the fact that mutations in the tau gene lead to abnormal aggregation of tau and the development of FTDP-17 has shown that tau dysfunction is sufficient to cause neurodegenerative diseases. In Alzheimer's disease, the major pathological effects of the tau protein create major changes in the progression of the disease. Tau's role in enhancing axonal transport is undeniable, demonstrating its importance for message transmission within the brain [3], [5], [6].

3. Molecular Mechanism of Tau Pathologies

Tau is a protein associated with microtubules located in the q12 and q21 regions of human chromosome 17. This protein has six major isoforms in the human brain. The isoforms can arise in different ways, one of which is the alternative splicing of exons 2 and 3, which creates isoforms with no (0N), one (1N), or two (2N) extra segments. Also, alternative splicing of exon 10 produces isoforms with three (3R) or four (4R) repeats. In a healthy brain, a 1:1 ratio of 3R and 4R isoforms is observed. This 3R:4R ratio change is associated with abnormal splicing of exon 10. Tau is divided into four functional domains: an amino-terminal projection domain, a proline-rich region, a microtubule-binding domain, and a carboxyl-terminal domain. The microtubule binding region contains repeats that bind to heterodimers of α- and β-tubules, which form polymerized microtubules and thus facilitate axonal transport. Studies in wild-type mice have shown that 63 different posttranslational modifications of the tau gene have been identified, including truncation, glycation, and oxidation. The most common posttranslational modification of tau is phosphorylation, as the longest isoform of Tau in the human brain has 80 serine and threonine residues and 5 tyrosine residues, which have a high phosphorylation capacity. Thus, tauopathies are a group of clinically, morphologically, and biochemically heterogeneous diseases characterized by the accumulation of fibrillated tau protein. Alzheimer's disease is considered a secondary tauopathy because it causes NFTs of the tau gene, which are found in amyloid plaques, mainly in fibril forms composed of amyloid-β (Aβ) peptide. From a mechanistic perspective and with regard to potential treatment, tauopathies have been shown to be highly heterogeneous and to be associated with other pathological conditions, which may have additive or synergistic effects. From a pathogenetic perspective, tauopathies are clinically apparent in up to 80% of elderly individuals. There is also an interaction between Aβ and tau genes in Alzheimer's. Although Aβ is known to cause tau pathology, the toxicity of Aβ has been shown

to be dependent on the tau gene. In the coming years, it is expected that more information will be obtained about tauopathies and the interaction between Aβ and tau [7], [8], [9], [10].

4. Tau-Targeted Drugs and Modern Therapeutic Strategies

Although rapid technological advances have opened up new possibilities for treating neurodegenerative diseases, the number of drugs that have shown success in clinical trials for tau-related neurodegenerative disorders is still in the minority. There are also some methods known to science, including studies in cellular and animal models showing that siRNAs targeting tau significantly reduce tau pathologies in P301S tau transgenic mice. A group of drugs that inhibit tau aggregation has also been identified, the most common of which is methylene blue. A special intranasal hydrogel is used to deliver this drug to the brain. Another therapeutic strategy is to prevent tau degradation, which can be achieved through the ubiquitin-protease system, the endosome-lysosome system, and the autophagy-lysosome system. Proteolysis-targeting chimeras targeting tau have been developed that can reduce total tau and phosphorylated tau levels in mouse models of tauopathy by inducing proteasome-mediated degradation. To promote lysosomal targeting of tau, lysosome-targeted chimeras and antibody-based PROTACs have also been generated. Recent studies have generated a specific pathogenic tau-specific autophagy that enhances autophagic flux and clears pathological tau, which reduces cognitive impairment in mice with Alzheimer's disease. In addition, several drugs have been developed that target tau hyperphosphorylation, including lithium and phosphate modifiers. Long-term lithium administration reduces amyloid plaque formation and tau hyperphosphorylation in transgenic mice that overproduce Aβ and tau. Significant advances have been made in immunotherapies for the treatment of tauopathies in recent years. However, studies in mice have shown that immunizations cause various side effects, including axonal damage and encephalomyelitis.

Also, nanoparticles have a number of superior properties compared to other drugs and therapies, including increased drug efficacy, better adaptation to the biological environment, and more precise targeting of brain areas affected by Alzheimer's disease. Thus, nanoparticles successfully cross the blood-brain barrier, achieving higher drug concentrations in areas affected by Alzheimer's disease. The use of nanotechnology in targeted therapy for Alzheimer's disease has great potential and could revolutionize the search for treatment options [6], [11], [12], [13], [14].

5. Conclusion

This review provides information on the role of tau protein in Alzheimer's disease and its use as a therapeutic target. Although amyloid-β-based therapies have long been used in the treatment of Alzheimer's disease, the low clinical efficacy of these treatments has made tau pathologies a more promising target. The significant role of abnormally phosphorylated and aggregated tau protein in neuronal death has demonstrated that tauopathies play a central role in neurodegenerative processes. In recent years, the molecular mechanisms of the disease have been further investigated as a result of the information obtained about tau isoforms, posttranslational modifications, and Aβ–tau interactions. Also, new therapeutic approaches such as antisense oligonucleotides, siRNAs, PROTACs, and drugs that inhibit tau aggregation have shown promising results in the treatment of the disease. However, many of these approaches are still in the clinical trial stage, and their effectiveness has not been fully proven. Consequently, tau-targeted therapeutic approaches have enormous potential for the treatment of Alzheimer's disease and other types of dementia. Continuing clinical research in this area may lead to the development of more effective and disease-modifying treatments in the future.

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Conflict of Interest

The author declares no competing interests.

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Abbreviations

Alzheimer's disease (AD), Primary Age-Related Tauopathy (PART), Neurofibrillary Tangle (NFT), Amyloid Beta (Aβ), Ribonucleic Acid (RNA).

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