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Tau Protein Pathology and Tau-Targeted Therapeutic Strategies in Alzheimer's Disease: Mechanisms, Clinical Evidence and Future Perspectives

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Abstract:

Alzheimer's disease (AD) is the most dominant form of dementia characterized by neurodegeneration which leads to progressive cognitive decline and memory loss, the common symptoms of AD. While amyloid-β peptide accumulation has traditionally been the primary focus of AD research, there is growing evidence that tau pathology also contributes significantly in disease progression. Tau is a microtubule-associated protein that normally stabilizes microtubules and supports axonal transport within neurons. However, abnormal hyperphosphorylation causes tau to detach from microtubules, misfold and aggregate into toxic filaments which ultimately lead to neurodegeneration and eventually cell death. This paper reviews the structure of tau protein, its physiological and pathological behaviours and tau's mechanism in terms of disease progression. This paper also examines clinical and preclinical evidences and discusses the efficacy and limitations of three tau-targeted therapeutic approaches: gosuranemab, a monoclonal antibody designed to prevent the spread of extracellular tau; BIIB080, an antisense oligonucleotide that reduces tau production by targeting MAPT mRNA; and leuco-methylthioninium bis (LMTM), a tau aggregation inhibitor. Studies also suggest the potential of combination therapies targeting multiple pathological pathways to enhance efficacy. Though no tau-targeted therapy has yet to demonstrate definitive clinical benefit, continued research supports tau as an important therapeutic target and contributes to the development of more effective treatments for AD.

Keywords: Tau protein; Alzheimer's disease; Tau-targeted therapy.

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1. Introduction

Neurodegenerative diseases (NDDs) are incurable chronic progressive disorders that destroy neurons in patients' brains and nervous systems, leading to cognitive and mobility impairments. Common neurodegenerative diseases include AD, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD). The progressive decline of neuronal structure and activity that characterizes these disorders worsens over time and can have a serious negative effect on both patients and their caregivers' quality of life. Although NDDs primarily affect older adults, several risk factors including genetic mutations, lifestyle choices and medical conditions can significantly contribute to their development and progression.

Among these disorders, AD is the leading cause of dementia and the most common form of NDD worldwide. The World Alzheimer Report published in 2019 states that about 80% of the dementia that affects over 50 million individuals is caused by AD [1]. Common symptoms of the disease include the gradual decline of memory, particularly the ability to retain new information, cognition, language and problem solving abilities. Though the exact pathological trigger of AD remains unknown, the most dominant hypothesis suggests the accumulation of Aβ plaques and intracellular neurofibrillary tangles (NFTs) composed of abnormal tau are the main causes of the disease.

Despite Aβ plaques being historically considered the primary catalyst of the disease and are believed to accelerate the hyperphosphorylation of tau protein, recent studies have shifted greater attention toward tau protein because of its substantial role in neuronal dysfunction and AD progression [2]. Tau is a microtubule-associated protein largely located within neuronal axons, where it is fundamental for maintaining the stability of microtubules and promoting intracellular transport. However, abnormal hyperphosphorylation causes tau proteins to dissociate from microtubules and aggregate into tau filaments. These filaments then combine to make insoluble NFTs. The accumulation of NFTs disrupts axonal transport of nutrients and signaling molecules, impairing synaptic communication and in the long run, contributing to neurodegeneration within the central nervous system (CNS) [3]. Due to all the above factors, tau protein has arisen as a critical therapeutic target in AD research, some researchers even believe that it might have a bigger impact on AD progression than Aβ plaques. Currently, AD remains incurable, yet many tau-targeted therapeutic strategies are under investigation, aiming to reduce tau hyperphosphorylation, inhibit tau aggregation and prevent the spreading of pathogenic tau all over the brain. These treatments include small molecule inhibitors, monoclonal antibodies, vaccines and antisense oligonucleotides such as gosuranemab, BIIB080 and LMTM that target key pathways involved in tau pathology [4]. Even though many of these therapy strategies have shown promising results in their pre-clinical trials, their efficacy in human trials still remains a major challenge for researchers.

This paper examines the role of tau protein in the pathogenesis of AD and explores present and future tau-targeted treatment strategies, as well as potential AD combination therapies involving tau. Specifically, it focuses on the physiological and pathological roles of tau in AD, three therapeutic approaches that targets different stages of tau pathology and the future potential of combination therapies.

2. Tau

2.1 Protein Properties

Tau protein was originally described as an intracellular microtubule-associated protein (MAP) that supports microtubule formation and stability through mechanisms regulated by its phosphorylation state. Microtubules are one of the fibre systems making up the neuronal cytoskeleton. Tau is a heat-stable protein mostly present in neurons, especially in axons. It weighs a total of ~60 kDa molecularly and 352-441 amino acids (AA). The microtubule-associated protein tau (MAPT) gene, which has 16 exons and is found on chromosome 17q21, encodes the human tau protein. The N-terminal region, proline-rich domain (PRD), microtubule-binding domain (MBD) and C-terminal region are the four major structural components of the tau protein. Tau is bonded to MTs by the MBD [5]. In the human CNS, alternative splicing of exons 2, 3 and 10 of the 6-kb MAPT mRNA transcript produces six different protein isoforms, with sizes ranging from 37-46 [6]. Isoforms with 0, 1, or 2 N-terminal repeats (0N, 1N, 2N) are created by alternative splicing of exons 2 and 3 produces, whereas exon 10 results in tau with three or four MT-binding repeats in the MBD (3R or 4R). Only the shortest tau isoform, 0N3R, is expressed in developing human brains, but all six isoforms are present in healthy adult brains, with approximately equal levels of 3R and 4R tau isoforms [7]. These isoforms vary in their ability to bind microtubules and may impact tau function and aggregation propensity.

Under normal physiological conditions, tau binds with microtubules through its repeat domain and flanking regions. It performs its normal functions: stabilizing microtubules and promoting their assembly. It also regulates axonal

transport by influencing the activity of the motor proteins dynein and kinesin, which move payloads toward the cell body and axonal terminal (the plus and minus ends of microtubules) [8]. Through these functions, tau helps maintain neuronal polarity and the movement of nutrients, vesicles and signaling molecules across the cell.

The interaction between tau and microtubules is regulated by phosphorylation, a post-translational modification that is essential for normal tau activity. Phosphorylation modifies the tau molecule's structure, controls tau's binding affinity for microtubules and helps regulate dynamics of the microtubules. In its natural condition, tau is in a balanced phosphorylation form that supports both microtubule stability and flexibility [8,9]. However, disruption of this balance from current unknown causes can result in abnormal hyperphosphorylation of tau, a key feature in AD pathology.

2.2 Tau in AD

It has been demonstrated that various post-translational modifications of tau, such as acetylation, glycation, glycosylation, phosphorylation and ubiquitination can impact tau's ability to attach to microtubules and increase its propensity to form filaments. Specifically, abnormal hyperphosphorylation is one of the earliest and most important pathological changes of tau in AD. Excessive phosphorylation of tau decreases its affinity for microtubules, weakening its ability to bind and stabilize the neuronal cytoskeleton. In a healthy human brain, tau has about 1.9 moles of phosphate for every mole of protein. However, studies show that there are 6-8 moles of phosphate for every mole of protein in tau that was extracted from AD brains.

While the exact mechanisms that initiate tau pathology remain unknown, research suggests that abnormal regulation of kinase and phosphatase activities is responsible for the hyperphosphorylation of tau. Particularly, increased activity of protein kinases, such as glycogen synthase kinase-3β (GSK-3β) and cyclin-dependent kinase 5 (CDK5), as well as decreased activity of protein phosphatase 2 A (PP2A) contribute to the hyperphosphorylation [3]. Highly phosphorylated tau proteins are less efficient to promote microtubules polymerization and stabilization.

As tau detaches from microtubules, it undergoes conformational changes that alter its normal structure and make it more likely to misfold. The misfolded tau proteins then self-associate forming soluble tau oligomers. Recent evidence suggests that these oligomeric species may be the most neurotoxic form of tau as they damage synaptic function and disrupt cellular homeostasis [5]. As aggregation progresses, tau oligomers assemble into paired helical filaments (PHFs) and straight filaments that accumulate in neurons. These filaments are the major structural components of NFTs, one of the pathological hallmarks of AD [9]. The density and distribution of NFTs have been shown to have a strong correlation with the severity of dementia and cognitive loss in AD patients.

Growing evidence demonstrates that pathological tau spreads like a prion throughout the brain. Neighboring cells may absorb misfolded tau released from damaged neurons, where it serves as a template to encourage the misfolding and aggregation of normal tau proteins [9]. According to a distinctive pattern described by Braak staging, this propagation starts in the transentorhinal and entorhinal cortex before spreading to the hippocampus and neocortex.

Pathological tau is harmful because it loses its normal physiological roles and develops toxic properties. The detachment of tau from microtubules destabilizes the neuronal cytoskeleton and impairs axonal transport, reducing the movement of organelles, nutrients and signaling molecules throughout the neuron [8]. In addition, the abnormal tau also mislocalizes to dendrites and synapses and impairs synaptic plasticity. This leads to synapse loss and disturbed neuronal communication. Pathological tau can also enhance neuronal hyperexcitability, increase DNA damage by losing its nuclear protective functions and boost the neurotoxic effects of amyloid-β. Together, all these effects contribute to neuronal death, progressive neurodegeneration and the cognitive decline that characterizes AD.

3. Tau-Targeted Therapeutic Strategies

Given the strong association between tau pathology, neurodegeneration, and cognitive decline in AD, tau has emerged as a major therapeutic target. As a result, a variety of tau-directed therapeutic strategies have been developed, aiming to reduce tau hyperphosphorylation, inhibit aggregation, promote clearance of pathological tau and limit its propagation throughout the brains. However, despite extensive research, no tau-targeting therapy has yet been approved for clinical use.

3.1 Gosuranemab

Gosuranemab (BIIB092) is a humanized immunoglobulin G4P monoclonal antibody specifically targeting the N-terminal tau fragments that are produced from neurons and detected extracellularly in the interstitial fluid (ISF) and cerebrospinal fluid (CSF) [10]. The antibody was developed from the mouse IgG1 antibody IPN002, which was produced by immunizing mice with aggregated 2N4R human tau protein. Preclinical research showed that IPN002

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has a strong binding affinity for N-terminal tau. IPN002 was also capable of reducing abnormal electrical activities in neurons caused by extracellular tau fragments. Gosuranemab was initially designed to be a possible treatment for progressive supranuclear palsy (PSP), but because tau pathology plays a key role in both AD and PSP, it was subsequently investigated as a therapeutic candidate for AD [11].

Gosuranemab is able to bind strongly to an eight-amino-acid epitope at the N-terminus of tau, a region that is conserved across all six tau isoforms, allowing it to recognize pathological tau species from multiple tauopathies. Structural studies showed a high complementarity between gosuranemab and its N-terminal tau epitope, providing a molecular basis for its high affinity and specificity. The antibody is designed to target the extracellular tau. This allows it to prevent neuronal uptake of pathological tau and reduce free tau levels in the brain in order to limit propagation of tau and decrease the accumulation of tau in cells and neurons throughout the brain [11].

Further experimental research revealed that gosuranemab achieves significant target involvement in ISF and CSF and suppresses tau seeding activity produced from brain homogenates and ISF samples [11]. Gosuranemab in vivo treatment significantly reduced the amount of unbound tau in mouse models, indicating its successful CNS involvement. Ex vivo experiments using CSF from patients with AD demonstrated a decrease in both free and total tau, which further supports the antibody's biological activity [12].

Phase I and Phase II clinical trials of gosuranemab in AD showed that the antibody was generally well tolerated. It had an acceptable safety profile and had no significant side effects. However, gosuranemab did not show meaningful improvements in cognitive outcomes or disease progression despite substantial decreases in free extracellular tau and strong indications of target engagement [13]. As a result, its development for AD was stopped.

3.2 MAPTRx

MAPTRx (BIIB080) is an antisense oligonucleotide (ASO) designed to target and reduce the concentration of MAPT messenger RNA (mRNA). It aims to decrease the production of all tau isoforms, including post-translationally modified and toxic species of tau regardless of its location [14,15]. MAPTRx is a chemically modified synthetic oligomer that works intracellularly by attaching itself to intron 9 of the tau pre-mRNA. This causes the mRNA to be broken down by endogenous ribonuclease H1 and be prevented from creating tau protein [14]. The goal of this upstream approach is to stop tau from accumulating both intracellularly and downstream.

Preclinical studies demonstrated that MAPTRx effectively decreased tau expression and pathology without disrupting its regular functions. In mouse models, treatment dramatically reduced by about 50% of endogenous tau levels and decreased the cell-to-cell propagation of tau oligomers. Researchers also observed improvements in neuronal functions and cognitive performances with no notable negative effects reported. To note, MAPTRx did not affect microtubule assembly, axonal transport or sensory, motor and cognitive behaviors despite significantly lowering tau levels [14].

Clinically, BIIB080 was assessed in a phase 1b multiple-ascending-dose (MAD) experiment in patients with mild AD. The study evaluated the safety and tolerability of intrathecal administrated BIIB080. The majority of side effects were mild or moderate in severity and the results demonstrated that this ASO was generally well tolerated. This phase 1b trial also showed a clear dose-dependent decrease in total tau and phosphorylated tau (p-tau181) levels in CSF, suggesting successful target engagement and tau production suppression [15]. These results demonstrated that BIIB080 was effective in lowering human CNS tau levels.

Furthermore, following continued treatment with BIIB080, a 48-week ongoing long-term extension (LTE) study was conducted that demonstrated persistent reductions in tau-related biomarkers. Among the 33 participants in the LTE study, the 16 individuals who received high-dose BIIB080 showed favorable numerical trends toward slower clinical decline. Continued treatment was also associated with persistence decreases in CSF total tau and phosphorylated tau levels, which indicated long-lasting target engagement and tau production suppression [15, 16]. These findings provide additional support for the biological activity of BIIB080 and its potential as a disease-modifying therapy strategy.

Despite the strong biomarker results, the clinical benefits of BIIB080 remain uncertain, as the phase 1b study was not designed to evaluate cognitive changes [16]. Consequently, large and longer term clinical trials are required to determine whether reducing tau production can translate into meaningful clinical benefits in patients with AD.

3.3 Leuco-methylthioninium bis

Leuco-methylthioninium bis (LMTM), also known as hydromethanesulfonate, is a second-generation tau aggregation inhibitor derived from methylthioninium (methylene blue) [17]. It was developed to improve pharmacokinetic properties, particularly brain bioavailability and absorption, compared to earlier methylthioninium formulations.

LMTM has been investigated in clinical studies for AD, including phase III trials evaluating its potential as both a monotherapy and an add-on treatment strategy [18].

LMTM targets tau aggregation by interfering with tau–tau interactions that lead to the formation of PHFs and NFTs. Preclinical studies have shown that methylthioninium compounds inhibit tau aggregation in vitro. They can also decrease tau-associated behavioural impairments and disassemble PHFs isolated from AD brain tissue in genetically modified mouse models at concentrations relevant to human dosing [19].

LMTM was further assessed over a 15-month period in a large phase III randomized controlled trial with about 891 patients with mild-to-moderate AD. Overall, the treatment did not show significant differences compared with placebo. The treatment did not significantly alter the primary cognitive and functional outcomes, such as measures of cognitive decline and daily functioning. However, when the results were analyzed further, researchers suggested that individuals receiving LMTM alone had a slower rate of cognitive decline compared to those receiving typical AD medications in addition to LMTM. With gastrointestinal and urinary tract side events being the most commonly reported and the main reason for stopping high dose LMTM, the safety of LMTM as monotherapy was mostly in line with earlier methylthioninium studies [17]. These findings are still exploratory, but they suggest that background medication use may have an impact on treatment response.

Further analyses also indicated that smaller doses of LMTM (approximately 4 mg twice daily) would have produced comparable or greater effects than higher doses. However, this finding was not confirmed in main analyses and needs more clinical validation [18]. Overall, even though LMTM did not show clear clinical benefit in the main trial, it still contributed important evidence supporting tau aggregation as a therapeutic target in AD.

4. Potential Combined Therapy Strategies

Currently, most therapeutic approaches target a single pathological mechanism. That said, increasing evidence suggests that combination therapies may provide a more effective treatment for AD, especially in its mild to severe stages. Since amyloid-β and tau pathology develop at different stages of the disease, combining anti-amyloid and anti-tau therapies may allow multiple aspects of disease progression to be targeted at the same time. In addition, other pathological processes, including neuroinflammation, synaptic dysfunction, impaired protein clearance and neuronal loss, are now also recognized as important contributors to disease progression and represent possible therapeutic targets.

Combination therapies may have advantages, but they still exhibit several challenges as it is uncertain if they will produce additive or synergistic effects. Concerns have been raised that combination therapies may enhance unfavorable reactions such as neuroinflammation and amyloid-related imaging abnormalities (ARIA). Furthermore, the best time to provide medication, dosage plans and methods for evaluating its effectiveness have not yet been established. Before combination therapies can be widely utilized, extensive preclinical and clinical research is required to assess their safety, tolerability and efficacy. Despite these obstacles, combination therapies continue to be a potential direction for future research on AD and may eventually provide higher therapeutic advantages than therapies that only focus on one single part of the disease.

5. Conclusion

Tau pathology is becoming increasingly recognized as a key player in the development and progression of AD. Abnormal post-translational modifications, especially hyperphosphorylation, of tau disrupt these functions and initiate a series of pathological events. Hyperphosphorylated tau detaches from microtubules, undergoes conformational changes and forms toxic oligomers. These toxic oligomers aggregate to form PHFs and NFTs and accumulate and spread in a pathological way, leading to neuronal dysfunction, neurodegeneration and cognitive decline.

The therapies discussed in this paper demonstrate several different approaches of targeting tau pathology. Gosuranemab was developed to prevent the spread of extracellular tau between neurons. BIIB080 was designed to reduce the production of tau protein through suppression of MAPT mRNA. LMTM was intended to inhibit tau aggregation and tangle formation. These therapies have shown promising biological effects in experimental models but their clinical effects have been less consistent and efficacious. The improvements in biomarkers have not always translated into significant cognitive benefits for the patients.

These results highlight the complexity of AD and indicated that focusing on a single pathological mechanism would not be enough to limit the disease's progression. As a result, increasing attention is being directed toward combination therapies that simultaneously target tau, amyloid-β, neuroinflammation and other pathological processes. Even though there are still vital challenges, ongoing advances in the understanding of tau continue to provide valuable insight into AD pathology. Further research will

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be needed to understand how tau-targeted therapies can be best used to slow disease progression and improve patient outcomes.

This paper summarizes the current knowledge of tau pathology in AD and several tau-targeted therapies, however it does not provide a comprehensive review of all emerging treatment strategies. Due to the large number of therapies currently under development, this paper only discussed three representatives in detail. Other approaches including tau vaccines were beyond the coverage of this paper. As research continues, future reviews should include a wider range of therapeutic approaches and evidence from longer-term clinical trails to provide a more complete understanding of potential tau-targeted therapies in AD.

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