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Anti-Tau Therapy for the Treatment of Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is the most prevalent type of dementia, which is defined by cognitive decline, behavioral changes, and neurodegeneration. Surprisingly, while amyloid-β plaques had been extensively studied to develop therapies and treatment strategies for the past several decades, tau was not recognized as a pivotal and major contributor to neurodegeneration and cognitive impairment in AD until relatively recently. In this review, we will cover the tau contribution to AD pathogenesis and we will examine tau-directed therapies, including tau kinase inhibitors, tau aggregation inhibitors, immunotherapeutics, gene-silencing approaches, and ways to enhance tau clearance. We will evaluate where we are now and possible future directions with respect to advances in tau-directed therapies, as well as the challenges and considerations associated with the field.

Keywords: Alzheimer's disease, neurodegeneration, amyloid-β, amyloid-β, immunotherapeutics, Tau protein.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder and the most frequent cause of dementia worldwide. It represents 60-70% of all dementia cases [1]. In 2020, it was estimated that more than 50 million people were living with dementia. This number is expected to triple by 2050 due to increased life expectancies and aging populations [2]. Clinically, AD is characterized by progressive cognitive deficits, memory loss, executive dysfunction, behavioral changes , and, finally, loss of independence and death. Histopathologically, AD is marked by two proteinopathies that are both considered pathological hallmarks of the disease: the extracellular accumulation of amyloid-β (Aβ) peptide in senile plaques and the intracellular accumulation of neurofibrillary tangles (NFTs) made of hyperphosphorylated tau protein [3]. For several decades, the amyloid cascade hypothesis of AD, which posits that the accumulation of Aβ leads to neurodegeneration and cognitive decline through a pathogenic cascade consisting of tau pathology, has influenced therapeutic development for AD [4]. Nevertheless, emerging evidence suggests that tau pathology is more closely related to clinical symptoms and disease progression than Aβ deposition [5]. Tau is a microtubule associated protein that stabilizes the cytoskeletal architecture of neurons, particularly in axons. Under normal conditions, tau promotes microtubule assembly and regulates the transport of materials within the axon. In AD and other tauopathies, tau becomes abnormally hyperphosphorylated, dissociates from microtubules , and aggregates into insoluble paired helical filaments (PHFs) that coalesce into NFTs [6]. The microtubule -stabilizing aggregates of tau disrupt microtubule stability and function, hinder axonal transport, impair synaptic functioning, and ultimately lead to cell death. Furthermore, pathological tau has been shown to propagate in a prion-like manner trans-synthetically, spreading neurodegeneration among regions of connected brain networks [7]. While early agent development efforts primarily focused on Aβ, the disappointing outcomes of multiple amyloid-targeted agents in clinical trials have shifted attention towards tau as a more appealing therapeutic target. For instance, Aβ-targeted monoclonal antibodies, such as solanezumab and bapineuzumab, failed to produce significant cognitive improvements, despite the reduction in amyloid burden [8]. Emerging evidence supports tau-based biomarkers (phosphorylated tau in cerebrospinal fluid (CSF) or plasma and tau PET imaging) correlating most closely with neurodegeneration and cognitive decline, framing the rationale for

tau-based therapeutics [9]. Researchers have been investigating a range of tau-directed therapy approaches, including immunotherapies, antisense oligonucleotides, kinase inhibitors, tau aggregation inhibitors, and measures to enhance tau clearance. In addition to lowering tau pathology, these techniques aim to halt or reverse the course of the illness; they also explore the potential for therapeutic approaches that may influence AD.

2. Tau Protein and Its Pathological Role in AD

Tau is a microtubule associated protein (MAP) that is highly soluble and primarily expressed by neurons in axons. Tau facilitates the assembly of microtubules and stabilizes their formation in the axon, which is important for axonal transport [10]. Tau is encoded by the MAPT (microtubule associated protein tau) gene on chromosome 17q21, and through alternative mRNA splicing, the adult human brain expresses six isoforms of tau, including 3- and 4-repeat isoforms [11]. Under normal physiological conditions, tau facilitates assembly and stabilizes microtubules in the axon, thereby maintaining structural integrity and intracellular transport in neurons. The tau protein is normally regulated through phosphorylation, a common post-translational modification. Excessive phosphorylation of the tau protein, as occurs in Alzheimer's disease (AD) and other forms of tauopathy, is due to numerous kinases, such as GSK-3β, CDK5, or MAPKs, which lead to the loss of tau binding to its microtubules [12]. At this stage, tau releases from microtubules, leading to a destabilized cytoskeleton and impaired axonal transport [13]. Detachable tau may misfold and aggregate into paired helical filaments (PHFs), which then clump further to form neurofibrillary tangles (NFTs), features of the pathological process of AD [6]. NFT formation is correlated with impairment of synaptic communication, mitochondrial defects, oxidative stress, and ultimately apoptosis [14]. Tau aggregates are dense in the entorhinal cortex and hippocampus, areas essential for memory and learning, which are the first disrupted in AD. Furthermore, accumulating evidence suggests that pathological tau may spread in a prion-like manner. In essence, misfolded tau can cross synapses from one neuron to another, causing misfolding and aggregation of native tau in the second cell [7]. The mechanism of tau transmission proposed above accounts for the topographical nature of tau pathology previously characterized in Braak staging, in which tau lesions emerge from the transentorhinal cortex and systematically spread to neocortical regions [3]. Once thought to be in the background of AD pathology, the severity of tau pathology , rather than amyloid burden, is shown to correlate more closely with neuronal dysfunction and cognitive impairment in AD patients

[15]. Tau is now considered not only a feature of disease progression but also a major contributor to neurodegeneration, and as such, a robust target for therapeutic investigation.

3. Therapeutic Strategies Targeting Tau

Tau pathology is crucial for the initiation and progression of Alzheimer's disease (AD); therefore, there has been a concerted effort to develop tau-directed therapies to modify tau expression, phosphorylation, aggregation, or prion-like propagation to slow or halt neurodegeneration. There are a number of potential ways to approach tau-targeted therapies, and several strategies have been devised and are currently being evaluated in preclinical and clinical studies , targeting different aspects of tau malfunction.

3.1. Inhibition of Tau Hyperphosphorylation

Hyperphosphorylation of tau is the key step in the pathological detachment of tau from microtubules, followed by tau aggregation. As such, inhibiting tau phosphorylation through the inhibition of the various kinases that drive tau hyperphosphorylation has been a significant target for therapy. Major kinases that contribute to tau hyperphosphorylation include glycogen synthase kinase-3β (GSK-3β), cyclin-dependent kinase 5 (CDK5), and MAPKs. GSK-3β inhibitors, like tideglusib, have shown some efficacy in preclinical models by reducing tau phosphorylation and improving cognitive performance [16]. Unfortunately, the results from GSK-3β inhibitors in clinical trials have been limited, perhaps due to off-target effects and insufficient target engagement [17].

3.2. Tau Aggregation Inhibitors

Another possible avenue here is to inhibit the conversion of monomeric tau into toxic oligomers and fibrils. Tau aggregation inhibitors (TAIs) are small molecules designed to inhibit the formation of paired helical filaments. LMTX (leuco-methylthioninium bis(hydromethanesulfonate)) is an analogue of methylene blue that has promise in preclinical models, preventing tau aggregation and promoting disaggregation of existing tau fibrils [18]. However, in clinical studies, the results is controversial, with benefits seen in only a subgroup of patients with AD not taking other AD medications [19]

3.3. Immunotherapy (Active and Passive)

Immunotherapy is designed to help the immune system clear pathological tau species. There are two methods devised to achieve this: the first is through active immunization (the production of anti-tau antibodies from vaccination), and the second relies on passive immunization (dosing monoclonal antibodies). AADvac1 is an active tau vaccine that targets the pathological tau epitope and has shown overall good safety and immunogenicity in Phase I, with ongoing Phase II studies [20]. Gosuranemab (BIIB092) is a monoclonal antibody targeting extracellular tau to slow propagation , and semorinemab is another monoclonal antibody currently under trial; initial results have been mixed, but some indicate a delay in cognitive decline in early-stage AD [21].

3.4. Microtubule Stabilizers

Since tau normally stabilizes microtubules, one therapeutic avenue is to mitigate tau dysfunction by using microtubule-stabilizing agents. Epothilone D, a CNS-penetrable microtubule-stabilizing agent, demonstrated positive effects in animal models, increasing microtubule density and reducing cognitive dysfunction [22]. However, clinical development stopped, even though epothilone D showed promise, due to toxicity issues during clinical trials .

3.5. Modulation of Tau Expression

Technologies such as antisense oligonucleotides (ASOs) or RNA interference have been developed to reduce tau mRNA content, subsequently decreasing total tau protein levels. BIIB080 (IONIS-MAPTRx) is an ASO currently in Phase I/II clinical trials. BIIB080 reduced tau levels in the cerebrospinal fluid of AD patients and has a good safety profile [23].

3.6. Facilitating Tau Clearance

The development of strategies that promote tau degradation pathways, such as the ubiquitin-proteasome system and the autophagy-lysosome pathway, is being investigated. Compounds such

as rapamycin (although an mTOR inhibitor) promote autophagy and have been shown to induce clearance of aggregated tau pathology using both cellular and animal models [24].

4. Challenges and Limitations of tau-based therapies

Therapies Despite the strong potential for tau-targeted therapies to change the course of Alzheimer's disease (AD), there are substantial challenges and limitations to fully translating them into clinical care and therapeutic effect.

4.1. Blood–Brain Barrier (BBB) Penetration

One specific and significant barrier in neurotherapeutics is the delivery of biologics across the blood-brain barrier. The BBB is an endothelial interface that is tightly regulated to prevent and limit the entry of large molecules, such as monoclonal antibodies, antisense oligonucleotides, and other tau-targeting mechanisms. Most biologics have limited brain bioavailability, with a negligible portion of systemic doses being less than 0.1% [25]. Alternative delivery mechanisms for these biologics, such as receptor-mediated transcytosis or intrathecal delivery, are being researched, but using these routes often comes with additional risks and complexities [26].

4.2. Differentiating Physiological and Pathological Tau

A key obstacle for tau-centered therapies is the inability to distinguish normal (physiological) tau from pathological tau species. Tau plays an important role in neuronal function and is known for stabilizing microtubules and maintaining axonal transport during the normal, healthy function of neurons. As such, strategies that non-specifically diminish overall tau levels may interfere with normal cellular activity that could, in itself, cause neurotoxicity or promote neurodegeneration [27]. Because pathological tau is defined by specific post-translational modifications, including hyperphosphorylation, truncation, and conformational changes, these aberrant forms typically exist alongside the native, healthy tau. The question then becomes how to definitively identify a toxic form of tau. This limits applications in the development of specific immunotherapies or specific small molecules aimed only at pathological tau without interfering with normal tau [28].

4.3. Complex Systemicity of Alzheimer’s Disease

Alzheimer's disease is a multifactorial illness with overlapping physiological consequences, including amyloid-β deposition, tauopathy, neuroinflammation , oxidative stress, synaptic dysfunction, and/or vascular damage. The clear association between tau pathology and cognitive decline is likely a correlation rather than causation, and therefore targeting tau in isolation may not be effective, especially in 'end-stage disease,' where pathology likely involves the superimposed effects of multiple processes [29]. Clinical trials of tau-based therapeutics have reported variable cognitive benefits, which may be attributed, in part, to poor cognitive response because the intervention occurred too late, or the lack of appropriate engagement with the relevant tau species. Further complicating the response to treatment, many patients have co-pathologies such as TDP-43 aggregates, Lewy bodies, or cerebrovascular lesions [30].

4.4. Timing & Stage of Intervention

The efficacy of tau related therapies may be highly dependent on the timing of therapeutic intervention. Tau aggregation and propagation can begin very early in the preclinical stage of AD, often occurring many years before any clinically obvious cognitive symptoms appear [3]. When clinical symptoms such as cognitive decline are observed , there is a possibility that substantial neurodegeneration has already occurred due to tau pathology. Therefore, the timing of diagnosis and subsequent therapeutic intervention may be crucial, although it can be limited by tau biomarker availability and/or accuracy.

4.5. Variability in Clinical Endpoints

There have been multiple tau-based therapies that have progressed to clinical trials, but the results have been inconsistent. For example, although monoclonal antibodies such as gosuranemab and semorinemab have shown significant reductions in CSF tau levels, these studies failed to show a modest or even no change in cognitive endpoints in Phase II/III studies [20]. These discrepancies lead to further concern about the translatability of biomarkers into meaningful clinical endpoints, and the necessity of trial design, patient stratification and validated surrogate endpoints.

5. Future Directions

While there are currently challenges, the future of tau-targeted therapy in Alzheimer's disease (AD) is bright, particularly with innovations and advancements in diagnostics, precision medicine, and pathophysiological approaches to treatment likely to significantly improve our ability to make an early diagnosis, monitor the course of disease, and treat more effectively.

5.1. Progress in Tau Biomarker Development

The emergence of tau-specific biomarkers—perhaps the most innovative development in the past few years—has advanced the ability to track tau pathology in vivo and within biofluids (e.g., tau filtration assays). Tau-PET imaging studies may utilize radiotracers, such as [^18F]flortaucipir and [^18F]MK-6240, to visualize and quantify tau aggregates in a variety of brain regions, and offers high specificity [31, 32], which will assist in early diagnostics and in monitoring treatment effect in clinical treatment trials. Similarly, fluid-based biomarkers such as phosphorylated tau (p-tau181, p-tau217, and p-tau231) within cerebrospinal fluid (CSF) and plasma have benefits, including convenience and strong empirical diagnostic performance, which have led to increased interest [33]. p-tau cognate biomarkers have great promise, as they can assess AD-related pathology even during the preclinical phase, and their dynamic and continuous nature supports their use as surrogate endpoints in clinical studies [34].

5.2. Combination Therapies

Given the multifactorial nature of AD, it is increasingly likely that tau-directed therapies will be used in combination with other agents, including anti-amyloid agents, anti-inflammatory agents, or neuroprotective agents. There is a synergistic additive effect that can be obtained by applying distinct therapeutic agents at once to treat the multi-faceted pathological processes driving neurodegeneration. As an example, recently conducted clinical studies have paired monoclonal antibodies targeting amyloid (e.g, lecanemab, or donanemab) in combination with tau immunotherapies, with researchers suggesting that aims to reduce amyloid may prevent tau propagation, or increase the beneficial effects of the anti-tau approaches[35, 36]. Although the studies are ongoing still to be fully reported to see decisive results, the idea of targeting dual mechanisms in AD reflects an integrated approach to AD and potential therapies.

5.3. Personalized and Precision Medicine

Another promising avenue is personalized medicine, which incorporates genetic, biomarker, and clinical profiling for effective treatment for individual patients. With substantial variation in the onset of disease, tau isoform, comorbidities, and response to treatments, AD likely will continue to require more individualized treatment, rather than one sized fits all approaches. For example, we know APOE4 carriers respond differently to both amyloid and tau pathology and would benefit from more individualized dosing approaches in combining substances or using alternative drugs or medications [37]. Similarly, stratifying patients based on plasma p-tau217 levels or tau-PET burden could identify patients for clinical trials, increase statistical power and enhance outcomes in treatment [38].

5.4. New Therapeutic Platforms

Emerging therapeutic platforms, such as gene therapy, RNA interference (RNAi), antisense oligonucleotides (ASOs), and nanocarrier drug delivery systems are being actively evaluated as methods to improve the specificity and efficacy of tau-targeted therapies. In terms of gene therapy options, gene therapy techniques focused on MAPT (the tau gene) using CRISPR-Cas9 or RNAi could block tau expression from the transcription level. For drug delivery, brain-penetrant nanoparticles with tau aggregation inhibitors or kinase modulators are in development to improve drug distribution across the blood–brain barrier [39].

6. Conclusion

Tau pathology is a fundamental characteristic of Alzheimer's disease and provides a reasonable target for therapeutic intervention. The clinical advancement of tau-based therapeutics has been slower than expected, however, opportunities using immunotherapy, gene silencing, and protein clearance show potential for altering the disease course. Continued investigation of tau biology as well as better trial design and biomarker development, will be essential to the success of tau therapies in Alzheimer's disease.

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