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Review Article

Therapeutic strategies for the treatment of tauopathies: Hopes and challenges

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Abstract A group of neurodegenerative diseases referred to as tauopathies are characterized by the presence of brain cells harboring inclusions of pathological species of the tau protein. These disorders include Alzheimer's disease and frontotemporal lobar degeneration due to tau pathology, including progressive supranuclear palsy, corticobasal degeneration, and Pick's disease. Tau is normally a microtubule (MT)-associated protein that appears to play an important role in ensuring proper axonal transport, but in tauopathies tau becomes hyperphosphorylated and disengages from MTs, with consequent misfolding and deposition into inclusions that mainly affect neurons but also glia. A body of experimental evidence suggests that the development of tau inclusions leads to the neurodegeneration observed in tauopathies, and there is a growing interest in developing tau-directed therapeutic agents. The following review provides a summary of strategies under investigation for the potential treatment of tauopathies, highlighting both the promises and challenges associated with these various therapeutic approaches.

Keywords: Alzheimer's disease; Amyloid; Drugs; Fibrils; Microtubules; Neurons; Tau; Tauopathy; Therapeutics

1. Introduction

The presence of inclusions comprised of the tau protein [1,2] within brain cells is a hallmark pathological feature of a group of progressive neurodegenerative diseases referred to as tauopathies, which include Alzheimer's disease (AD) and a major class of frontotemporal degeneration (FTD), such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and Pick's disease, which are associated with underlying tau pathology [3]. Furthermore, although single or repetitive traumatic brain injury may lead to AD or other neurodegenerative diseases [4,5], recent studies suggest that a distinct tauopathy known as chronic traumatic encephalopathy may result from repetitive brain trauma, especially in contact sports such as football [4,6,7]. Moreover, there are a host of other very rare familial and sporadic neurodegenerative tauopathies that are characterized by prominent or mainly tau pathology [8]. Finally, a tauopathy now known as pathologic aging-related tau pathology, which was previously referred to as tangle predominant senile dementia, may or may not be associated with cognitive impairments or other clinical manifestations [9,10]. Although most of the non-AD tauopathies are orphan diseases, there may be compelling economic and scientific reasons for conducting clinical trials of disease-modifying therapies in these disorders, as illustrated for PSP [11].

Tau is normally a microtubule (MT)-associated protein that is thought to provide stability to axonal MTs [12,13], where it may also affect axonal transport through modulation of MT motor function [14–16]. In humans, tau exists as 6 isoforms that are generated through alternative messenger RNA splicing of three exons, one of which encodes a MT-binding sequence such that the resulting protein has either 3- or 4-MT-binding repeat domains (i.e., 3-R

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or 4-R tau), as well as 0, 1, or 2 alternatively spliced amino-terminal exon sequences. Tau becomes hyperphosphorylated in all tauopathies, which promotes its disengagement from MTs [17–20]. Hyperphosphorylated tau subsequently forms inclusions that are found predominantly within neurons, where they are referred to as neurofibrillary tangles (NFTs) when found within the neuronal soma and neuritic threads when found in dendritic processes [8,21]. There is compelling evidence that tau hyperphosphorylation and the subsequent formation of higher order multimeric structures leads to neuronal dysfunction and death. For example, there is a strong correlation between the extent of tau pathology and the degree of dementia in AD patients [22–24], and mutations within the tau gene are known to cause forms of frontotemporal lobar degeneration (FTLD) referred to as frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17) or familial FTLD-Tau [25,26]. The mechanism by which hyperphosphorylated and misfolded tau species leads to neuronal dysfunction is still uncertain, but the prevailing hypothesis is that one or more misfolded tau species causes a gain-of-function toxicity [27]. An alternative and not mutually exclusive theory is that reduced binding of hyperphosphorylated tau to axonal MTs results in an alteration of MT structure and/or function that affects axonal transport, ultimately leading to neurotoxicity. Furthermore, in different variants of FTLD-Tau disorders, as exemplified by CBD, glial tau pathology is very abundant in gray and white matter regions [3], and there is increasing recognition of other types of aging-related astroglial tau pathology [28]. However, the significance of glial tau pathology in mechanisms of neurodegenerative tauopathies and aging-related cognitive decline is still enigmatic. Nonetheless, given the high likelihood that pathologic tau species play a critical role in the onset and progression of neurodegeneration, there is great incentive to identify approaches that will mitigate gain-of-function and/or loss-of-function toxicities.

The objective of this review is to provide brief summaries of a number of tau-directed therapeutic strategies currently being pursued within academic and industry laboratories. As of this writing, most of these endeavors are still at a preclinical stage, although there are a growing number of clinical trials examining tau-directed therapeutics (see Table 1). Thus, there is a growing sense of optimism that a disease-modifying treatment will ultimately be identified for neurodegenerative tauopathies, although currently there is no known effective treatment for any neurodegenerative tauopathies, including AD or other forms of FTD.

Table 1
Current clinical programs using tau-directed therapeutic agents

Therapeutic type	Name	Company	Clinical stage
Vaccine	AADvac-1	Axon Neuroscience	Phase 1
Vaccine	ACI-35	AC Immune/Janssen	Phase 1
Antibody	BMS-986168	Bristol-Myers Squibb	Phase 1
Antibody	ABBV-8E12	AbbVie/C2N	Phase 1
Microtubule stabilizer	TPI-287	Cortice Biosciences	Phase 1
Tau aggregate inhibitor	TRx0237	TauRx	Phase 3

2. Modulating post-translational modifications of tau

Tau undergoes a number of post-translational modifications that can modulate the function, turnover, or multimeric assembly of the protein. In addition to phosphorylation, these include acetylation [29,30], glycosylation [31,32], methylation, nitration, and sumoylation [33,34], and several of these modifications are being investigated as potential targets for therapeutic intervention [35], as detailed further in the following section.

2.1. Inhibiting tau phosphorylation

Phosphorylation is by far the most well-studied post-translational modification of tau, as it has been known for some time that tau hyperphosphorylation is a feature of all tauopathies. Tau is phosphorylated even in the absence of disease, but in tauopathies, the extent of phosphorylation is increased ~four fold [36–38]. At least 40 phosphorylation sites have been described for tau, and up to 25 of these may undergo increased phosphorylation within tauopathy brains [39–41]. A number of studies have revealed that hyperphosphorylation of tau greatly reduces its ability to bind to MTs [18–20], thereby leading to the hypothesis that MT structure and/or axonal transport may be affected in tauopathies [42–44]. In addition, increased phosphorylation of some ser/thr residues of tau has also been reported to increase the propensity of the protein to assemble into the fibrils that comprise NFTs and neuropil threads [45,46]. Besides directly enhancing tau misfolding, the increased cytosolic tau concentrations that result from hyperphosphorylated tau disengaging from MTs could also promote a concentration-dependent fibrillization of tau. Thus, increased tau phosphorylation could contribute to both loss-of-function and gain-of-function toxicities.

There has been considerable interest in identifying inhibitors of the kinases that catalyze tau phosphorylation, particularly because the pharmaceutical sector has prior experience in the development of kinase inhibitors, albeit largely for the treatment of cancers. However, there is still uncertainty as to which kinase(s) are most relevant to tau phosphorylation in neurons, and several candidate ser/thr kinases have been implicated, including glycogen synthase kinase-3β (GSK-3β), cell cycle-dependent kinase 5 (CDK5), MT-affinity regulated kinases (MARKs), protein kinase A (PKA), mitogen-activated protein kinases (MAPKs), and others [47–49]. Among these, the most well-studied and arguably most validated are GSK-3β and CDK5. It is beyond the scope of this brief review to summarize all the data supporting the involvement of these kinases in tauopathies, and the reader is referred to recent reviews