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Tau-Based Therapeutic Approaches for Alzheimer's Disease – A Mini-Review

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Abstract
The accumulation of aggregated, hyperphosphorylated tau as neurofibrillary tangles and neuropil threads are cardinal features of Alzheimer's disease (AD). The other lesions found in AD include amyloid plaques and congophilic amyloid angiopathy, both associated with the extracellular accumulation of the amyloid-beta (Aβ) peptide. AD is the most common cause of dementia globally. Currently, there are no effective means to treat AD or even to slow it down. The dominant theory for the causation of AD is the amyloid cascade hypothesis, which suggests that the aggregation of Aβ as oligomers and amyloid plaques is central to the pathogenesis of AD. Numerous therapies have been developed directed to Aβ-related pathology, in particular various immunotherapeutic approaches. So far all of these have failed in clinical trials. Recently, there has been more focus on therapy directed to tau-related pathology, which correlates better with the cognitive status of patients, compared to the amyloid burden. Immunotherapeutic targeting of tau pathology has shown great potential in treating tau pathologies in mouse models of AD. A number of studies have shown the efficacy of both passive and active immunization. This review summarizes recent advances in therapy targeting pathological tau protein, in particular focusing on immunotherapeutic approaches which are showing great promise.

Introduction

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder that is characterized by extracellular amyloid-beta (Aβ) deposition in the form of amyloid plaques and congophilic amyloid angiopathy, as well as intracellular neurofibrillary tangles (NFTs), containing pathological tau aggregates [1]. The neuropathological definition of AD requires the presence of both neuritic amyloid plaques and NFTs [1]. The most toxic species of Aβ and aggregated tau are thought to be oligomeric, with both of these pathologies spreading via extracellular soluble oligomers, which under some conditions have been shown to use a 'prion-like' mechanism [2]. AD is the most common cause of dementia globally, affecting approximately 36 million people currently and around 115 million by 2050 [3]. The associated costs are enormous, being estimated in the USA alone to be about USD 200 billion in 2013. Presently, available treatments have minimal or no effect on the course of disease. Numerous therapies are

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being developed directed to Aβ-related pathology. Among the most advanced approaches for Aβ pathology are various immunotherapeutic approaches; however, two recent phase III clinical trials of passive immunization directed to Aβ failed to show any significant clinical benefit [4]. Partially as a result of these clinical failures with anti-Aβ therapies, more focus has been placed on approaches directed to tau-related pathology.

Pathogenesis of AD and Anti-Aβ-Directed Immunotherapy

The dominant theory for the causation of AD has been the amyloid cascade hypothesis [5]. This theory suggests that the accumulation of Aβ peptides, particularly in a highly toxic oligomeric form, is the primary pathogenic driver that downstream leads to tau hyperphosphorylation, NFT formation and ultimately synaptic and neuronal loss. Missense mutations in amyloid precursor protein or in the presenilin genes PRES 1 and 2 cause early-onset familial forms of AD (FAD), affecting <1% of AD patients [6]. The most common form of AD is late-onset sporadic AD (LOAD). Extensive evidence supports the amyloid cascade hypothesis in FAD patients and in models of FAD [6]. However, evidence proving that Aβ is central to the pathogenesis of the common LOAD is more limited. Recent genome-wide association studies on LOAD have implicated a number of different genes involved in innate immunity, cholesterol metabolism and endocytosis, suggesting greater etiological heterogeneity [6]. Potentially conflicting evidence to the amyloid cascade hypothesis has also come from clinical and autopsy data from the initial human active vaccination trial directed to reducing amyloid plaque pathology [7]. Postmortem analysis was available from 9 subjects, which showed a considerable degree of plaque removal and reduced Aβ load compared to comparable nonimmunized controls [8]. Despite this, there were no differences between placebo and active immunization groups in terms of long-term survival outcome, time to severe dementia and outcome measures such as Alzheimer' Disease Assessment Scale – cognitive (ADAS-Cog), MMSE or Disability Assessment for Dementia. Several passive immunization trials are underway directed to Aβ pathology; however, the two most advanced phase III trials of both bapineuzumab and solanezumab were recently reported and both failed to show overall clinical improvement or disease-modifying outcomes [4, 9]. The lack of clinical efficacy in these trials may have been related to the immunization having begun too late in the disease process, at a point when extensive tau pathology already exists and can progress independent of the initial trigger of Aβ-related pathology [4]. Alternatively, one can use this data to suggest that the amyloid cascade hypothesis is an oversimplification. A number of investigators have suggested alternative theories, whereby accumulation of aggregated, toxic forms of Aβ and tau are dual pathways both downstream from a common upstream pathogenic deficit [4]. In either of these scenarios it is essential for therapy to specifically address tau-related pathology to be highly effective in clinically symptomatic AD. This is particularly important as numerous studies have shown that the degree of tau-related pathology correlates better with the degree of dementia compared to amyloid plaque burden, making tau an attractive target in AD [1].

The Tau Protein and Tau-Directed Therapy

Tau is a microtubule-associated protein that is primarily expressed in the cell bodies and axons of neuronal cells of the central nervous system [10]. In the central nervous system, human tau is expressed in 6 isoforms arising from alternative mRNA splicing from a single gene on chromosome 17q21, containing 16 exons [10]. The size range of the 6 isoforms is between 352 and 441 amino acids, which differ by the absence or presence of 29 (exon 2) or 58 (exon 2 + 3) amino acids inserts in the amino terminal. The carboxy-terminal half of tau contains 3 or 4 semihomologous repeats of 31 or 32 amino acids, encoded by exon 10. The repeats (3R, 4R) correspond to the microtubule-binding region of protein tau. Tau has several phosphorylation sites, with phosphorylated tau binding microtubules with lesser affinity and/or having a greater propensity to aggregate into paired helical filaments, producing NFTs.

Given the importance of tau phosphorylation in AD, a number of studies have tried inhibition of kinases involved in the process or the activation of protein phosphatase to dephosphorylate tau (see table 1) [11, 12]. Kinases involved in tau phosphorylation include glycogen synthase kinase 3 (GSK-3β), cdk5, p38, JNK, CK and DYRK1A [11]. Lithium and valproate have been shown to inhibit GSK and when given to transgenic (Tg) models reduce tau-related pathology [13]; however, this effect was not corroborated in small clinical trials for both compounds [14, 15]. Several small-molecule inhibitors of GSK-3β such as SB 216763, CHIR-98014 and SRN-003–556 are in preclinical development [12]. SB 216763 was

Table 1. Preclinical approaches

Approach	Mechanism of action	Reference
GSK-3 inhibitors		
SB216763, CHIR98014	Reduces tau phosphorylation	[12]
SRN-003-556	Reduces soluble phosphorylated and aggregated tau	[12]
Lithium	Reduces tau pathology	[14]
Valproate	Reduces tau pathology	[15]
Other inhibitors		
HSP90	Inhibition of tau degradation	[12]
Active immunization		
Tau 379-408 (pSer396-404)	Reduces tau pathology and improves cognitive tasks	[21]
Tau195-231 (P202/205), Tau207-220 (P212/214), Tau224-238 (P231)	Significant decrease of tau pathology with increase of the microglia burden	[24]
Y10A peptide (Ser422)	Reduces tau pathology	[25]
pBri	Reduces tau-related pathology	[30]
Passive immunization		
PHF1 antibody	Decreases tau pathology and functional impairments	[26]
PHF1 and MC1	Decreases tau pathology with improvement of locomotor activity	[27]
DA31, MC1, PHF1	Reduction of tau pathology	[28]
Anti-tau oligomers	Reduces hyperphosphorylated tau and blocks tau aggregation	[29]

shown to reduce the amount of tau phosphorylation; however, adverse effects were detected in control animals [11]. Tideglusib is another inhibitor of GSK-3β which was in phase IIb trials for mild-to-moderate AD; these are now completed but the results have not been reported (www.clinicaltrials.gov). In a small pilot study tideglusib produced positive trends in MMSE, ADAS-cog, GDS and Global Clinical Assessment cognitive scales without statistical significance in the small sample of 30 patients (see table 2) [16].

Another tau pathology-directed approach is inhibition of tau aggregation [17]. The most advanced of such agents are methylene blue and its derivatives [17, 18]. Methylene blue has a range of effects in addition to tau aggregation inhibition [12]. The first methylene blue derivative was Rember (TauRx Therapeutics Ltd.), which showed stabilization of progression of AD over 50 weeks [12]. A next generation derivative, LMTX, is currently in a phase III clinical trial.

A further strategy to reduce NFT pathology is to increase tau degradation. Tau degradation has been shown to be inhibited by Hsp 90, a chaperone protein that is involved in folding of denatured proteins. Curcumin has a wide range of activities, among which is to inhibit Hsp 90. A trial in a tau Tg model showed reductions in pathology and cognitive benefits [19, 20]. A number of Hsp 90 inhibitors are known; however, the targeting of a chaperone protein has the potential for adverse effects [12].

Table 2. Clinical trials

Approach	Mechanism of action	Reference
Tideglusib	Inhibitor of GSK 3β (in phase IIb) – completed but results not yet reported	[16]
TauRx	Inhibits tau aggregation (in phase II)	[12]
LMTX	Reduces the level of aggregated and misfolded tau (in phase III)	[12]
AADvac1	Peptide targeting pathological tau (in phase I)	Clinical-Trials.gov

Immunotherapeutic approaches have been very successful at reducing amyloid-related pathology in AD models, although this approach has yet to be shown as successful in clinical trials. In part driven by the success of immune therapy in amyloid pathology reduction, our group tested the first active immunization against tau pathology in a P301L tau Tg mouse model in 2007 [21]. This model develops NFTs in several brain regions and the spinal cord. The immunization was performed with a tau fragment peptide (amino acids 379-408, with pSer396

and 404), using alum as an adjuvant. Two groups were immunized from 2 to 5 months and from 2 to 8 months. Immunohistochemical analysis using PHF1 and MC1 antibodies showed a significant reduction in tau-related pathology compared to controls. In addition, an improvement in the vaccinated groups was seen on a number of sensorimotor tasks. Antibodies generated by this vaccination were found to cross the blood-brain barrier, bind to phosphorylated tau and reduce pathology without significant adverse effect [21]. Subsequently, we tested the same immunogen: tau 379-408 (pSer396 and 404) in another active immunization study using a novel mouse tau Tg model (htau/PS1), developed by one of the authors of this study (A.B.) [22, 23]. The animals were immunized from 3–4 months of age for 4 months. A significant reduction of tau pathology was observed in the brains of vaccinated mice compared to controls, which correlated with a cognitive rescue, which was tested using three separate tasks [23]. A further active immunization study used a mixture of three peptides containing the phosphorylation epitopes: tau195-213 (P202/205), tau207-220 (P212/214) and tau 224-238 (P231) [24]. This immunization was performed in a double-mutant tau (K257T/P301S) Tg model that develops NFT like inclusions at 6 months of age. A significant decrease of tau pathology was observed in the hippocampus, the cortex and the brain stem at 8 months after immunization which was accompanied by an increase in the microglial burden. Recently, another tau immunogen was tested containing pSer422 in THY-Tau22 Tg mice, which develop late-stage hippocampal pathology and cognitive defects. The mice that were immunized for 18 weeks showed a reduction in tau pathology which correlated with improved performance on spatial memory [25]. Passive immunization with monoclonal antibodies to phosphorylated tau has also shown benefits in Tg models. The first study, conducted by our group, used the PHF1 antibody (recognizes pSer396-404 tau) in P301L tau Tg mice by intraperitoneal injections and showed a reduction in tau pathology both biochemically and immunohistochemically, in association with behavioral benefits [26]. These results were confirmed by another group using both the PHF1 and the MC1 antibodies (MC1 recognizes an abnormal tau conformation) in two tau Tg models (P301L and P301S Tg mice) [27]. A reduction of tau pathology was observed in both models as well as a reduction of neurofilament positive axonal spheroids in the spinal cord with an improvement in locomotor activity [27]. A further study compared DA31 (a pan-tau antibody), MC1 and PHF1 in P301L Tg tau mice [28]. MC1-injected mice from 7 to 10 months showed a reduction of tau-related pathology both immunohistochemically and biochemically [28]. Anti-tau oligomer antibodies which block tau aggregation have also been shown to be effective in P301S Tg mice; however, this study used cranial intraventricular injections, limiting its clinical translatability [29]. An additional recent novel approach is the use of active immunization that produces an immune response to both pathological Aβ and tau conformers concurrently; this has been shown to be effective in a number of different AD Tg models [30]. These various preclinical tau pathology-directed immunotherapy studies have led to the first phase I vaccine trial, AADvac1, which uses a pathology-related tau peptide conjugated to KLH for active immunization; this trial is ongoing (www.clinicaltrials.gov). At first examination it is difficult to understand how antibodies binding to a protein which is accumulating intracellularly can have beneficial effects. Recent studies have demonstrated that anti-tau antibodies can cross the blood-brain barrier, be taken up by neurons via low-affinity Fc receptors and bind to pathological tau within the endosomal/lysosomal system [31]. In addition, evidence has shown that injections of fibrillar tau brain extract into the brains of Tg mice expressing wild-type human tau can induce the formation of human tau into filaments, as well as the spread of pathology from the site of injection into neighboring brain regions in a prion-like manner [32]. Therefore, if the spread of certain pathological forms of tau that lead to PHF pathology in AD occurs via such a mechanism, antibodies to disease-associated forms of tau would not necessarily need to enter cells in order to be effective.

Conclusions

There is a critical need to develop better treatments for AD. It is clear from studies in AD animal models that tau-directed immunotherapy and related approaches can reduce pathology and produce cognitive benefits. The disappointing results with Aβ-directed therapies and the knowledge that tau-related pathology correlates more directly with the cognitive status of patients makes this area of research particularly important and exciting currently. The importance of Aβ and tau oligomers as the most toxic species and the growing realization that both pathologies can spread in a prion-like mechanism make these the most critical targets for novel therapies. Many questions remain, in particular related to the uncertainties regarding the etiology or etiologies of LOAD as well as what the best models might be for testing effective AD therapies.

We hypothesize that the best hope for effective therapies for symptomatic AD will be approaches that reduce pathological conformers of tau alone or in combination with Aβ oligomers.

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