Chapter from the book *Alzheimer’s Disease Pathogenesis-Core Concepts, Shifting Paradigms and Therapeutic Targets*

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1. Introduction

The microtubule-associated protein tau is required for microtubule assembly, axonal transport, neurite outgrowth, and stability of microtubules (Binder et al. 1985). Tau self-assembly, aggregation, and accumulation in neurofibrillary tangles (NFTs) are major pathological hallmarks of Alzheimer disease (AD) and other neurodegenerative diseases (Lee et al. 2001, Alonso et al. 2008). Although the importance of tau in AD and other tauopathies is well established (Iqbal et al. 2009, Ballatore et al. 2007, Haroutunian et al. 2007) still unanswered is whether NFTs are the primary neurotoxic factor (Brunden et al. 2008, Marx 2007, Kayed & Jackson 2009).

Despite the poor correlation between NFTs and disease progression, and evidence showing, that neuronal loss in AD actually precedes NFTs formation research until recently focused on them and other large meta-stable inclusions composed of aggregated hyperphosphorylated tau protein. Lately, the significance and toxicity of NFTs have been challenged and new aggregated tau entity has emerged as the true pathogenic species in tauopathies and a possible mediator of Aβ toxicity in AD. Tau intermediate aggregate (tau oligomers; aggregates of an intermediate that is between monomers and NFTs in size) can cause neurodegeneration and memory impairment in the absence of Aβ. This exciting body of evidence includes results from human brain samples, transgenic mouse and cell-based studies, thus tau oligomers present a new and novel drug target for AD treatment.

In this chapter, we summarize the characterization and toxicity of tau oligomers; discuss the evidence supporting their critical role in AD pathogenesis, and the potential and challenges for targeting them by immunotherapy and drug discovery as a novel approach for AD treatment.

2. Tau oligomer formation

A key early finding about tau in NFTs accumulated in AD and non-AD tauopathies was the fact that it is abnormally phosphorylated (Spires-Jones et al. 2009, Grundke-Iqbal et al. 1986). The sequence of early tau phosphorylation suggests that there are events prior to NFT formation that are specific to particular phosphorylated tau epitopes, leading to conformational changes and cytopathological alterations. Using phosphorylation dependent tau antibodies, three stages of NFT development were introduced: (1) pre-NFT, (2) intra-,
and (3) extra-neuronal NFT. The pre-NFT state, in which neurons display nonfibrillar, punctate regions in the cytoplasm, dendrites, somata, and nuclei, was observed especially with phospho-tau antibodies TG3 (pT231), pS262, and pT153. Intraneuronal NFTs were homogeneously stained with fibrillar tau structures, which were most prominently stained with pT175/181, 12E8 (pS262/pS356), pS422, pS46, pS214 antibodies. Extracellular NFTs, which contain substantial filamentous tau, are most prominently stained with AT8 (pS199/pS202/pT205), AT100 (pT212/pS214), and PHF-1 (pS396/pS404) antibodies, which also stain intracellular NFT. Moreover, the severity of AD and neuronal loss correlates with the patterns of tau phosphorylation in NFT (Augustinack et al. 2002, Trinczek et al. 1995).

Tau hyperphosphorylation is thought to be an early event in the cascade leading from soluble to insoluble tau protein, but evidence demonstrating that hyperphosphorylation is sufficient for filament formation is lacking. Why does hyperphosphorylation promote aggregation of tau proteins into abnormal filaments? One possibility is that the negative charge imparted by phosphorylation neutralizes the basic charges of tau, thus facilitating intermolecular interaction and aggregation (Alonso et al. 2001a, Alonso et al. 2001b). An alternative explanation is that hyperphosphorylation detaches tau from microtubules, thus increasing the pool of unbound tau. Unbound, hyperphosphorylated tau may compete with microtubules for binding to normal tau and other microtubule associated proteins, thereby sequestering them and enhancing disassembly of microtubules (Alonso et al. 2001a). As compared to microtubule-bound tau, this unbound tau may be more degradation-resistant and more likely to aggregate. Reduced proteolysis of hyperphosphorylated tau may also increase the pool of soluble tau available for formation of paired helical filaments (PHF). Thus, abnormal phosphorylation of tau may result in an increase in the total cellular pool of tau, and may change its solubility, thus negatively regulating stability of microtubules (Litorsky & Johnson 1992, Litersky & Johnson 1995, Litersky et al. 1993).

One important contributor to tau phosphorylation and NFT formation may be amyloid. The “amyloid cascade” hypothesis holds that the accumulation of Aβ peptides in senile plaques results in the formation of NFTs and neuronal cell death (Busciglio et al. 1995). In primary neuronal cultures, Aβ is capable of inducing tau phosphorylation (Busciglio et al. 1995). Aβ42 fibrils induced formation of neurofibrillary tangles in P301L tau transgenic mice (Gotz et al. 2001), and pre-aggregated Aβ42 induced PHF formation mediated by distinct phospho-epitopes of tau in cells overexpressing wild-type and mutant forms of human tau (Ferrari et al. 2003, Pennanen & Gotz 2005). Aβ oligomers, but not the soluble or fibrillar forms of Aβ, induced tau hyperphosphorylation in cells overexpressing human tau (De Felice et al. 2008); this phenomenon is not Aβ-specific, but rather conformation specific, as demonstrated by the ability of soluble oligomers from a non-disease related protein, hen egg white lysozyme, to mimic tau hyperphosphorylation induced by Aβ aggregates (Vieira et al. 2007).

Amyloid formation is a complex process that involves many morphologically and conformationally distinct species. The critical role of soluble amyloid oligomers in neurodegeneration has become generally accepted for multiple neurodegenerative diseases (Haass & Selkoe 2007, Brunden et al. 2008, Glabe 2006, Glabe 2008). Very little is known about tau oligomers, because reliable methods for preparing homogeneous populations of tau oligomers are lacking, which prevents researchers from studying them and testing chemical and other approaches to combating their formation and toxicity. Unlike Aβ peptide, which is highly prone to aggregation and spontaneously forms amyloid in vitro, tau is an unfolded, soluble protein. In vitro aggregation of tau into filaments can be achieved using high concentrations and via the addition of promoters (Avila et al. 2004,
Barghorn et al. 2005, Barghorn & Mandelkow 2002). Mechanistic studies of full-length tau protein aggregation and filament formation in vitro have revealed striking similarities to Aβ aggregation; tau aggregates via either a nucleation-dependent mechanism (Congdon & Duff 2008) or the formation of intermediates (Xu et al.). In vitro, amyloid fibrils can accelerate the aggregation of the same protein via a nucleation-dependent mechanism, i.e., “seeding” (Jarrett et al. 1993, Kelly 2000). Seeding refers to the addition of a substoichiometric amount of fibrils, intact or sonicated, to a monomeric solution of the same protein, thus increasing the rate of conversion to amyloid fibrils. Lately, we and others have reported methods for preparing homogeneous Aβ and α-synuclein amyloid species (e.g., oligomers and fibrils) (Kayed et al. 2003, Kayed et al. 2007). These techniques provide an opportunity to test the effectiveness of different amyloid species as seeds. We have observed that amyloid oligomers similar to fibrils, can seed and induce monomer aggregation and oligomer formation (Kayed et al. 2007, Kayed & Glabe 2006). As we mentioned above it is well established that aggregated Aβ makes an important contribution to tau phosphorylation and aggregation in animal models and cell cultures. These experiments have used aggregated Aβ, which is likely to contain different prefibrillar and fibrillar Aβ aggregates. We recently demonstrated that Aβ42 and α-synuclein oligomer seeds induce the conversion of unstructured, monomeric human recombinant tau into β-sheet rich toxic tau oligomers (Lasagna-Reeves et al. 2010). This study show the ability of oligomer to cross-seed in vitro and induce tau aggregation.

Tau oligomers prepared by this novel method were largely SDS-stable apparent trimers and display a spherical morphology similar to oligomers formed by other amyloidogenic proteins (Kayed & Glabe 2006, Kayed et al. 2004). When shaken in PBS buffer for longer periods of time, tau oligomers prepared by this method continue to aggregate and eventually form tau filaments. Biophysical characterization of tau oligomers demonstrates that tau oligomers are β-sheet rich with minimal ellipticity as compared with the natively unfolded monomeric tau, which shows a random coil with minimal ellipticity (Lasagna-Reeves et al. 2010). Dynamic oligomers represent a toxic amyloid species that is conformationally distinct from fibrils and monomers. Targeting oligomers is a challenge that requires reliable protocols and reagents. Further investigations and analysis are needed to elucidate the synergy between different oligomer species and the contribution of amyloid oligomers to the induction of tau aggregation and to understand fully the role of tau oligomers in tauopathies.

2.1 Tau oligomers toxicity in vivo

The correlation between NFT in the brains of AD patients the disease progression remains contentious. Many studies have shown corelation between NFT and disease progression (Braak & Braak 1991, Delacourte & Buee 2000, Morsch et al. 1999, Bretteville & Planel 2008, Congdon & Duff 2008, Arriagada et al. 1992, Bird et al. 1999, Hernandez & Avila 2008, Rankin & Gamblin 2008, Lasagna-Reeves 2008, Cash et al. 2003, Tabaton et al. 1989). Other stereological studies show that neuronal loss actually exceeds NFT formation (Gomez-Isla et al. 1997, Terry 2000, van de Nes et al. 2008, Vogt et al. 1998). This and the exciting data published in the last half decade, emerging from biochemical, cell-based and transgenic mouse studies suggest that pre-filament forms of tau may be the most toxic and pathologically significant form of tau aggregates (Brunden et al. 2008, Marx 2007, Kayed et al. 2009, Meraz-Rios et al. 2009). This evolutionary transition was overdue in the tau field and similar to the transition witnessed for Aβ in the last 15 years driven by the characterization of Aβ intermediate species and...
their crucial role in Aβ-mediated toxicity (Harper et al. 1997, Roher et al. 1993, Walsh & Selkoe 2004, Walsh & Selkoe 2007).

Analogous to Aβ oligomers, tau oligomers have been shown to be neurotoxic when applied extracellularly to cultured neuronal cells (Lasagna-Reeves et al. 2010) and to provoke an increase in intracellular calcium levels (Gomez-Ramos et al. 2006, Gomez-Ramos et al. 2008). Detailed characterization of newly developed tau animal models suggests that tau oligomers play a key role in eliciting neurodegeneration and behavioral impairments. These phenotypes are concurrent with accumulation of soluble aggregated tau species and dissociated from the accumulation of NFT (Brunden et al. 2008). Cell death and synaptic lesions occurred independently of NFT formation (h-tau mice) expressing non-mutant human tau (Andorfer et al. 2005, Polydoro et al. 2009); hippocampal synapse loss, impaired synaptic function and microgliosis precede the formation of NFT in the P301S mutant human tau transgenic mouse model (P301S Tg) (Yoshiyama et al. 2007), similar results were found in (Tau(RD)/deltaK280) mouse model, (Mocanu et al. 2008), fly model (Wittmann et al. 2001) and zebra fish model (Paquet et al. 2009). Tau oligomers were biochemically characterized in JNPL3 mice expressing human tau with the P301L mutation, and the conditional model (rTg4510) expressing the same P301L human tau mutant; surprisingly, the accumulation of oligomeric tau correlated best with neuronal loss and behavioral deficits in these models, whereas NFT did not. These findings suggest that the accumulation of tau oligomers, behavioral deficits and neuronal loss precede the formation NFT (Berger et al. 2007, Spires et al. 2006). Tau oligomers were biochemically characterized in post mortem human brain, and a correlation between disease progression and the accumulation of granular tau oligomers in the brains of AD patients was reported. Moreover, increased levels of tau oligomers detected in the frontal cortex at very early stage of the disease (Braak stage I), when clinical symptoms of AD and NFT are believed to be absent. This finding suggests that an increase in tau oligomer levels occurs before NFT formation and before individuals manifest clinical symptoms of AD (Maeda et al. 2007, Maeda et al. 2006). Tau-positive fine granules (TFGs) resembling tau oligomers were found in the cerebral white matter of post mortem tissue from the parkinsonism-dementia complex of guam (PDC) tauopathy (Yamazaki et al. 2005). The data discussed here support the notion that soluble oligomers of amyloid proteins including tau are the acutely toxic structures of these proteins, rather than insoluble aggregates such as plaques and tangles. This concept has become more generally accepted for multiple neurodegenerative diseases including AD and tauopathies (Haass & Selkoe 2007, Brunden et al. 2008).

Recently, we investigated the neurotoxicity of different forms of tau in vivo by injecting well characterized oligomers, fibrils, or monomers of full length recombinant h-tau-441 (2N4R) into the hippocampus of C57BL/6 wild-mice. We found that the mice injected with tau oligomers presented with memory deficits in their performance of the novel-object recognition task, (Lasagna-Reeves 2010) which is widely used for evaluating memory in AD mouse models (Huang et al., 2006; Mouri et al., 2007; Scholtzova et al., 2008; Zhang et al., 2006). These observations correlate with previous studies in humans and primates that have shown hippocampal lesions to result in impaired object recognition (Reed and Squire, 1997; Zola et al., 2000).We also showed the loss of synaptic-related proteins and mitochondrial respiratory chain components in conjunction with the activation of the mitochondrial dysfunction markers and the pro-apoptotic protein caspase-9. Our results strongly suggest
that tau oligomers result in learning impairment through the disruption of synaptic and mitochondrial functions. If we take into consideration these studies and the novel data presented above, we can postulate that tau oligomers generated intracellularly could be released either by binding and local rupture of the membrane, or after cell death. The oligomers in the extracellular space could be taken up by healthy neurons in the vicinity disrupting normal activity like lysosomal function and stimulate further aggregation of functional monomeric tau. Thus, understanding the negative impact of tau oligomers in neuronal damage, specifically in reference to important cellular mechanisms, such as mitochondrial and synaptic function, will likely be of great importance to understanding the relevant disease processes and progression in AD and other tauopathies.

2.1.1 Tau based therapies

The important role of tau in neurodegenerative diseases, supports tau as a potential target for the development of disease modifying therapeutics. Therapeutic approaches targeting tau include, (1) interference with the splicing machinery to decrease the four-repeat tau isoforms, (2) activation of proteolytic or proteasomal degradation pathways, (3) prevention/reduction of tau hyperphosphorylation using inhibitors of tau kinases, (4) pharmacological stabilization of microtubule networks, (5) inhibition of tau aggregation by small molecules, and (6) tau-directed immunotherapy (Schneider & Mandelkow 2008).

**Inhibition of tau hyperphosphorylation:** This approach to treat AD was first introduced in 1998 (Gong & Iqbal 2008). Although a kinase inhibitor was shown to reduce tau hyperphosphorylation and the formation of soluble aggregated tau and to prevent motor deficits in mice expressing mutant human tau (Iqbal & Grundke-Iqbal 1998), a major drawback to targeting kinases is that these enzymes are commonly found throughout the body playing normal physiological roles and their inhibition may have unwanted side effects.

**Activation of proteolytic or degradation pathway:** Tau was found to be sensitive to calpain proteolysis (Johnson et al. 1989). Recently, puromycin-sensitive aminopeptidase (PSA), which was identified by a genetic screen as a modifier of tau pathology (Abazov et al. 2006), was shown to be effective in degrading both recombinant and PHF tau purified from AD brain(82)

**Stabilization of microtubules:** Microtubule-binding drugs could be beneficial in treating tauopathies by functionally substituting for the MT-binding protein tau (Trojanowski et al. 2005). Paclitaxel, a drug known to bind and stabilize microtubule, was tested in transgenic mice and showed to be effective in restoring axonal transport and ameliorating motor impairments (Zhang et al. 2005)

**Inhibition of tau aggregation by small molecules:** The last decade has witnessed a renaissance of interest in inhibitors of tau aggregation as potential disease-modifying drugs. A search for non-toxic, cell penetrant inhibitors of tau aggregation capable of crossing the blood-brain barrier (BBB) was performed using a high throughput screen, which resulted in the identification of more than 139 hits (Pickhardt et al. 2005, Larbig et al. 2007). This and the recent report of a phase-II clinical trial with the tau aggregation inhibitor MTC (ma ethylene blue derivative) could hold promise for the validation of the concept. The research on tau aggregation inhibitors was recently reviewed (Bulic et al. 2009).

**Tau clearance by immunotherapy:** Tau immunotherapy is a new concept (Sigurdsson 2009). A few reports of tau immunotherapy in animal models have been published, all using active vaccination (Boimel et al., Asuni et al. 2007, Boutajangout et al. 2010). In these reports, the
authors used tau fragments phosphorylated at positions commonly associated with NFT, such as Ser396 and Ser404. Behavioral analysis showed improved performance after immunization as compared to controls, biochemical and immunohistochemical analyses showed reduction of both soluble and insoluble tau species, moreover the studies showed reduction of phosphorylated NFTs in the brains of these animals. One study clearly demonstrated that antibodies were able to cross the blood-brain barrier and bind to phosphorylated tau (Asuni et al. 2007). Although the use of phosphorylated tau antigens seems promising for vaccination studies, such an approach mainly targets NFTs, rather than pre-filament tau species (tau oligomers) which form at early stages of NFT development (Kayed & Jackson 2009, Kayed 2010).

![Diagram of tau aggregation and therapeutic approaches](image)

**Fig. 1.** Schematic presentation of tau aggregation, and the potential therapeutic approaches targeting tau oligomers.

### 3. Conclusion

Despite extensive efforts to develop anti amyloid treatments the results have been disappointing. This led to the resurgence of tau as a potential therapeutic target for the treatment of AD. The question remains, which form of tau is the best target? The elegant studies over the past decade argue that soluble tau oligomers represent the primary pathological species of tau, therefore elucidating the pathways and mechanisms triggering their formation and understanding their mechanisms of toxicity are of immense importance. Studies focused on developing anti tau therapies must dissect the targets and better illuminate mechanisms of action for such approaches on each tau entity. As a starting point, it is important to evaluate the effects of immunotherapy and other therapeutic approaches on tau oligomers, this will be helpful for optimization of these approaches and may lead to the development of disease modifying therapies for AD and other neurodegenerative diseases.
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