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# The role of wild-type tau in Alzheimer's disease and related tauopathies

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## Abstract

Tau oligomers have recently emerged as the principal toxic species in Alzheimer's disease (AD) and tauopathies. Tau oligomers are spontaneously self-assembled soluble tau proteins that are formed prior to fibrils, and they have been shown to play a central role in neuronal cell death and in the induction of neurodegeneration in animal models. As the therapeutic paradigm shifts to targeting toxic tau oligomers, this suggests the focus to study tau oligomerization in species that are less susceptible to fibrillization. While truncated and mutation containing tau as well as the isolated repeat domains are particularly prone to fibrillization, the wild-type (WT) tau proteins have been shown to be resistant to fibril formation in the absence of aggregation inducers. In this review, we will summarize and discuss the toxicity of WT tau both in vitro and in vivo, as well as its involvement in tau oligomerization and cell-to-cell propagation of pathology. Understanding the role of WT tau will enable more effective biomarker development and therapeutic discovery for treatment of AD and tauopathies.

**Keywords:** Tau accumulation and toxicity, Tau oligomers and aggregates, Conformational ensembles, Cell-to-cell propagation, Neurodegenerative diseases

## Introduction

Alzheimer's disease (AD) is the 6$^{th}$ leading cause of death in the United States, and there are more than 25 million people suffering from AD worldwide. While several hypotheses have been proposed to elucidate the disease mechanisms, the exact cause of AD pathology is still unknown and remains to be investigated. Wild-type (WT) *MAPT* gene encoding for microtubule-associated protein tau is carried by most patients with tauopathy, and aberrant accumulation of WT human tau is a hallmark of sporadic AD [1, 2]. Tau is an intrinsically disordered protein and a microtubule binding protein that plays an important role in the regulation of microtubule stability and axonal transport [3]. Under pathological conditions, tau is hyperphosphorylated and detached from microtubules, and it undergoes misfolding and conformational changes. Cytosolic accumulation of tau triggers the fibrillogenesis pathway, with monomers spontaneously forming into oligomers in the initial stage followed by subsequent fibrillization into intracellular paired helical filaments (PHFs) and neurofibrillary tangles (NFTs) (**Fig. 1A**) [4].

While the presence of the large insoluble NFTs in the brain have been previously suggested to be the main cause of cognitive impairment, recent studies suggest that the spontaneously formed soluble tau oligomers prior to fibrillization contain the principal toxic tau species [5-12]. These toxic tau oligomers induce neuronal cell death as well as neurodegeneration and AD pathology in animal models including mice, *Drosophila* and Caenorhabditis elegans (*C. elegans*). While tau proteins may contain mutations or undergo other pathogenic processes such as truncation, and specific regions of tau (e.g. repeat domains) have been identified to be more aggregation-prone [13], the focus of this review will be on WT tau proteins which are less susceptible to fibrillization and mainly involved in the early oligomerization process. We will specifically discuss the critical roles of WT tau in AD pathogenesis, including tau-induced toxicity, formation of tau oligomers as well as their involvement in cell-to-cell propagation of disease pathology (**Fig. 1B**).

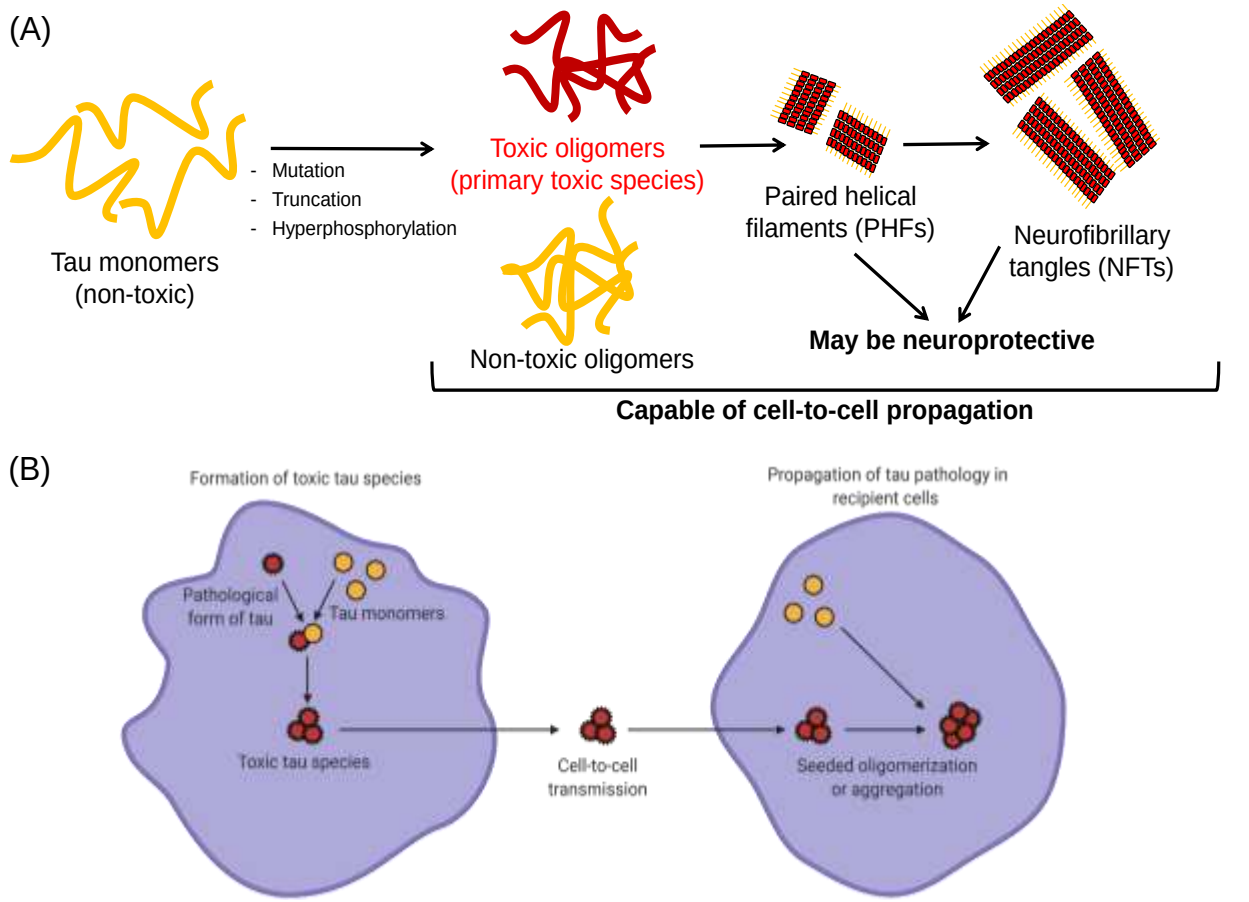


**Fig. 1. Tau oligomerization/aggregation cascade and cell-to-cell propagation.** (A) The intrinsically disordered tau monomer is capable of forming tau oligomers spontaneously and producing both toxic and non-toxic soluble tau species. Subsequently, tau oligomers are able to form large insoluble aggregates with β-sheet structures, including paired helical filaments (PHFs) and neurofibrillary tangles (NFTs). PHFs and NFTs may be neuroprotective by sequestering toxic oligomers. (B) The toxic tau species (oligomers or aggregates) can be secreted by cells and transmitted to nearby recipient cells. In recipient cells, the uptake of toxic species can further induce seeded oligomerization or aggregation, resulting in cell-to-cell propagation of disease pathology. Schematics were created with BioRender.com.

## Tau toxicity

The gain of the toxic function of tau has been primarily attributed to the formation of toxic tau oligomers [10, 14]. The toxic tau oligomers have been postulated to cause cellular dysfunctions such as mitochondrial impairments and apoptosis induced by activated caspase, both of which impede synaptic energy production and result in cell death [15, 16]. These oligomers can be either on- or off-pathway, where on-pathway corresponds to their ability to subsequently form fibrils, and off-pathway does not fibrillize. In addition, the tau oligomers are capable of inducing tau misfolding and promoting propagation of tau pathology, thereby enhancing their toxicity. In this section, we will review the toxicity of WT tau, and we will summarize the formation of oligomers and discuss the mechanism of tau spreading in the subsequent sections.

In an initial study, the formation of filamentous inclusions is not observed with an overexpression of human WT tau in the mouse brain [17]. Strikingly, it has been further reported that these aged mice expressing WT human tau exhibit synaptic dysfunction [18] as well as learning and memory impairments [19], but in the absence of overt neuronal loss and without the formation of NFTs [20-22]. In

addition, it has been shown that the presence of both 3R and 4R isoforms, instead of a single isoform, enhance tau pathology and neurodegeneration [23]. Importantly, in mouse models that show the formation of NFTs, neurodegeneration is not observed [5, 20, 24, 25]. Furthermore, reducing the endogenous expression of tau slows the disease progression [5, 26] and ameliorates memory impairments caused by β-amyloid (Aβ) [27]. These data suggest a crucial role of tau accumulation and toxic tau oligomer formation in neurodegeneration and memory loss [5].

*Drosophila* models of tauopathies have certainly provided evidences and supported that non-fibrillar tau oligomers are the primary toxic species. First, there is evidence that apoptosis (characterized by TUNEL-positive cells) occurs in models expressing WT human tau in neurons and glia, which gives rise to the well-characterized "rough-eye phenotype" as an indicator of neurodegeneration [28, 29]. More importantly, in nearly all *Drosophila* models of tauopathy, neurodegeneration occurs in the absence of insoluble tau aggregate formation, implying that dysfunction and toxicity may be caused by soluble tau oligomers and other cellular processes [6, 30-35]. These models provide insights into the mechanism by which tau causes dysfunction early in the disease process [6, 34] and have also been applied as a platform for drug screening [36]. Another widely used model of tauopathy is the nematode *C. elegans* expressing human tau. Although tau oligomerization and aggregation are not well characterized [37, 38], *C. elegans* expressing human WT tau result in neuronal dysfunction, defective locomotion [39-41], and tau spreading [42].

In terms of cellular assays, treatment of human cells with either synthetic tau oligomers (that are either β-sheet positive or negative) or fibrils made from exogenously purified tau proteins has led to multiple reports of cell cytotoxicity [8, 43-47]. These purified tau oligomers are made with a high concentration of the tau proteins or through the aid of exogenous aggregation inducers such as heparin or Aβ oligomers [48-54]. Despite the ability to induce toxicity, these systems do not recapitulate the cellular environment, lacking the numerous chaperone proteins that may be required to produce the ensemble of tau oligomers that populate the fibrillogenesis cascade [55, 56]. Hence, there is a need to shift to the cellular systems which contain these molecular constituents. However, there has been conflicting evidences of the toxicity of tau in the cellular overexpression systems. In some studies, overexpression of both mutant tau [57-62] and WT tau [63-66] results in cell death. Specifically, it has been reported that the overexpression of non-endogenous human WT tau in cultured murine neurons can cause synapse loss and mitochondria trafficking deficits [63], as well as disruption in mitochondrial dynamics and functions [64]. On the other hand, several other studies have reported that overexpression of WT tau does not cause cell cytotoxicity, despite tau hyperphosphorylation and formation of aggregates [55, 61, 62, 67-69]. It has been proposed that the inconsistencies across these cellular studies are due to the utilization of different cell lines. In addition, the different outcomes in cell cytotoxicity may also be due to co-expression of different isoforms or an imbalance in the normal tau isoform ratios (between 3R and 4R) [23, 70-72]. Furthermore, it has been suggested that the conformations of tau oligomers formed by WT tau may represent those that are observed in mutant tau and can inform the targeting of both toxic WT and mutant tau oligomers [61]. Regardless, abnormally modified tau intermediates or early-stage spontaneously formed tau oligomers have been suggested to be more neurotoxic than fibrillary species. However, it remains to be clarified which tau intermediates and which mechanisms are critical for neurodegeneration and AD pathology.

**Formation of tau oligomers**

Tau oligomers exist as an ensemble of distinct assemblies which include both toxic and non-toxic, on- and off-pathway species along the fibrillogenesis cascade [73-79]. It is therefore imperative to understand WT tau oligomerization from the biochemical and

biophysical perspectives. WT tau has not been a focus in the field in the past decades mainly because of the initial perception that the fibrillar species of tau is the toxic species and that WT tau is shown to be incapable of spontaneously forming fibrils by themselves [80-83]. However, it has been widely shown that addition of aggregation inducers such as heparin to WT tau proteins will induce the formation of oligomers and fibrils both in purified proteins and in cells [82, 84]. Conventionally, treatment of purified tau proteins with aggregation inducers such as heparin, arachidonic acid, Congo Red, and tau fibrils as seeds results in the formation of insoluble and thioflavin-T (ThT) positive β-sheet fibrils, as characterized by circular dichroism and electron microscopy [85].

Recently, soluble and ThT positive β-sheet oligomers have been reported to be more toxic than fibrils. These soluble and ThT positive β-sheet oligomers can be generated by treatment of tau proteins with heparin (at different conditions to that of fibril formation), arachidonic acid, hexafluorisopropanol, and Aβ oligomers as seeds [86-97]. The main distinct feature of oligomers that differentiates them from fibrils is the lack of an obvious insoluble elongated fibrillar species, and soluble oligomers can typically be resolved by size exclusion chromatography to identify the number of monomers involved. In addition, these oligomers can also be made through highly concentrated tau proteins followed by centrifugation [98, 99]. On the other hand, other studies have illustrated tau toxicity related to soluble and ThT negative non-β-sheet oligomers [100-104]. These oligomers are typically formed spontaneously by disulfide bonds or through direct isolations from mouse brains, and they typically form dimers or trimers [101-104]. In contrast to the purified protein approach, tau oligomerization has also been studied in cells through engineering of tau cellular biosensors, primarily by fluorescence resonance energy transfer (FRET) [105] and biomolecular fluorescence complementation (BiFC) [106]. FRET is a phenomenon observed when a pair of fluorophores with spectral overlap are in proximity due to the interaction of their fused proteins of interest, in this case, tau oligomerization or aggregation [61, 107, 108]. On the other hand, split fluorescent or luciferase proteins are fused to tau in the BiFC approach, and fluorescence or luciferase is observed when tau is oligomerized or self-associated [109-112]. Overexpression of WT tau in living cells results in FRET and BiFC signals, recapitulating tau oligomerization.

Several factors determine the degree of oligomerization (number of self-assembled monomers) of WT tau, including protein concentration, incubation time, as well as different tau isoforms. Although there is clearly a concentration-dependent effect in tau oligomerization [98, 112], several studies have proposed that dimeric and trimeric tau oligomers are the main toxic species under physiological conditions [46, 101-103]. There are other studies that propose a formation of hexamers [113-115] or decamers [116, 117], but no specific toxic tau oligomer species has been isolated or identified to date. The exact number of monomers to oligomerize and induce toxicity remains unclear [14, 118, 119]. In addition, when aggregation inducers are used, it is important to control the concentration of proteins and the amount of inducers used, so as to avoid generating fibrils or a mixture of oligomer/fibril populations that may result in challenges in purification and difficulty in data interpretations. Most studies have shown a range of incubation times, between 12 to 96 hours in cellular systems with overexpressed tau [61] and up to 144 hours in purified proteins [98]. The peak of tau oligomerization is generally between 24-48 hours in both systems (particularly with inducers in purified proteins). Some studies show that oligomerization decreases with time due to dissociation [110], while most studies show the transition of oligomers into fibrils with time. Interestingly, it has been postulated that the formation of fibrils reduces toxic tau oligomers by sequestering them [61, 120, 121]. Most studies focus on investigating homo-oligomers (oligomers made up of same isoforms) [61, 110].

However, several studies have tested the effect of oligomerization with hetero-oligomers made up of different isoforms, and they have suggested that hetero-oligomers have a higher tendency to oligomerize or aggregate [122, 123] and affect cellular functions differently [70, 124]. Further research still needs to be conducted to find out how different tau isoforms, post-translation modifications, and mutations alter the conformations of tau oligomers. Lastly, the specific tau species that determines the toxicity remains to be investigated.

**Cell-to-cell spreading**

WT tau aggregation and related functions may not accurately predict the molecular and cellular mechanisms. Furthermore, WT tau aggregation may not provide a total understanding of the mechanisms that drive tau pathology in AD. Therefore, we have to look into other specific events involved in the progression of the pathology, including cell-to-cell migration of tau [125-127] and age-dependent tau spreading [128], that induce toxicity and affect neuronal cell death [96]. The cell-to-cell spreading phenomenon has been investigated both in vitro, by the ability of cells to secrete and uptake tau, and in vivo. Tau secretion is typically monitored by the amount of tau released into the cell culture medium in the naked form [129, 130], as well as through other vesicles such as exosomes [131] and other membrane vesicles [132]. In both human and mice, there is a very low concentration of extracellular tau. For example, in healthy control cerebral spinal fluid (CSF), the concentration of tau is ~0.16 ng/mL , while the concentration is ~0.85 ng/mL in AD patients [133]. Likewise, the concentration of tau in wild-type mouse interstitial fluid (ISF) is ~30–40 ng/mL [134]. This small amount of tau secretion is typically measured and quantified by highly sensitive affinity assays such as enzyme-linked immunosorbent assays (ELISA). On the other hand, cellular uptake of tau is analyzed by fluorescent assays using purified tau proteins stained with fluorescent probes or dyes that can be tracked via fluorescence microscopy.

In terms of cell-to-cell propagation of tau, it has been demonstrated that isolated WT human tau oligomers or filaments/seeds from AD brain can induce tau aggregation in human neurons without tau overexpression or pathological mutations, and also in other neuronal cells overexpressing WT tau [135-139]. As a result of tau spreading, observations consistent with AD tau pathology have been reported, including an increase in phosphorylated tau, changes in tau conformation [140], and induction of neuronal cell death [96]. Although all forms of tau have the ability to spread and induce further aggregation, some studies have shown that tau fibrils [140] and tau monomers [141] have reduced spreading capability. To monitor the cellular release, uptake, and propagation of tau at physiological concentrations and in real-time, previously discussed FRET and BiFC assays have been employed. For example, it has been shown that the unlabeled repeat domain (RD) aggregates are released from one cell population (expressing RD aggregates) to recipient tau FRET biosensor cells, and inducing aggregation (as illustrated through an increase in FRET). This indicates the propagation of seeds and the seeded aggregation between cells [108, 142-144]. In BiFC assays, split-luciferase tagged tau proteins illustrate increased luciferase signals with increasing tau concentrations of 0.01–1000 ng/mL, supporting that tau oligomers can be actively released and taken up by cells and neurons in vitro [110]. In animal studies, recent data illustrate that the injection or intracellular inoculation of synthetic or brain-derived tau oligomers and aggregates (or brain extracts) into WT mice may induce tau pathology and propagation [136, 138, 145, 146]. Additionally, transfer of tau aggregates can take place between cells in vivo [138, 147-151]. Functionally, propagation of tau oligomers and aggregates in mice results in inhibition of long-term potentiation (LTP), memory impairments [15, 152, 153], mitochondria dysfunction, and neuronal death.

The requirement of tau and its key role in cell-to-cell spreading have been illustrated by studies showing that no inclusions are formed and no pathology is observed when the recipient mice do not contain tau or when tau is depleted from the extracts prior to injection [150]. In terms of

the propagation mechanism, studies have shown that there is a trans-synaptic transfer of WT human tau proteins even at distant brain regions [154]. In addition, WT tau spreads further than mutated tau which resides near the immunosynapse [154, 155], although it is suggested that transmission of tauopathy strains is independent of their isoform composition [156]. It is also crucial to note that isolated tau tangles from patients possess the strongest seeding ability, followed by aggregated tau extracted from transgenic mouse brain, which induces inclusion formation at a higher efficiency than aggregated recombinant human tau [138, 157-159]. Most importantly, it remains to be answered which tau species plays the major role in cell-to-cell propagation and what concentrations are required to initiate the spreading.

## Conclusion

Tau proteins play key roles in physiological functions, but they are also involved in AD and tauopathy disease mechanisms. Recently, WT tau has received increasing attention, as spontaneously formed tau oligomers made up of tau proteins with less fibrillization tendency (e.g. WT tau), rather than large fibrillar aggregates, have been proposed to be the primary toxic species. This suggests the need to target WT tau for therapeutic discovery and biomarker development. In addition, each of the tauopathy models, both in vitro and in vivo, have their own advantages and limitations that should be taken into account when choosing the appropriate models for studies [160]. Many questions remain about the role of WT tau in toxicity, formation of oligomers, and cell-to-cell propagation. These questions include (1) What comprises the toxic tau species, and do they involve a specific population of tau monomers, dimers, or oligomers (or a combination of them); (2) Are the neurotoxicity effects of soluble tau species due to an abnormal tau accumulation, or do they play actual functions; and (3) Do these soluble tau species represent signs of early stage of AD pathogenesis.

## Author contributions

C.H.L. is credited with conceiving the idea and writing the manuscript. J.N.S. provided edits and comments to the manuscript. Authors approve the final version of this manuscript and declare no competing interests.

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