Tau Oligomers

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Prediction of Non-fibrillar Aggregates of Tau Protein

Neurofibrillary tangles (NFTs), a pathological hallmark of Alzheimer's disease (AD), are composed of filamentous polymers of tau protein [1]. NFTs are insoluble and resistant to proteases. Thus, even after neurons are lost, NFTs remain as "tombstones" of the NFT-bearing neurons and are called ghost tangles. In AD, the number of neurons lost and the number of NFT/ghost tangles should be the same if all of the neurons were lost after NFT formation. But they aren't. More neurons are lost than ghost tangles remain [2, 3]. Although the number of NFTs, neurons lost, and the severity of the disease all correlate well with each other [3], several findings point to a missing element. NFT formation and neuronal loss have been reported to be distinct events. Suppression of human tau (hTau) expression in an hTau transgenic mouse model did not block tau filament formation but reduced neuronal loss [4], and NFT-bearing neurons were functionally intact in hTau transgenic mice [5]. In an hTau *Drosophila* model, hTau over-expression induced neuronal loss without NFT formation [6]. Therefore, over-expression of tau, at least, induces neuronal toxicity in an animal model, but the toxic species of tau was not the tau filament itself, but something produced in the process of tau aggregation. In that sense, granular tau oligomers, the intermediate form of tau filament, meet this criterion for the toxic tau species.

Tau Oligomer as an Intermediate Species of Tau Filament

Tau is highly hydrophilic and does not aggregate by itself. The core of the tau filament, the microtubule binding domain (MBD), is positively charged, and that charge prevents intermolecular interactions of tau. Under physiological conditions, the positively charged residues of tau interact with negatively charged residues of tubulin [1]. Under pathological conditions, tau is highly phosphorylated, and the negative charge of phosphor residues is thought to neutralize the positive change of the MBD, induce detachment of tau from tubulin, and allow tau-tau interactions [1].

Polyanionic compounds, such as RNA or heparin, induce aggregation of recombinant tau probably by neutralizing the positive charges of tau [7–9]. Lipids, such as arachidonic acid, also induce tau aggregation above the critical micelle concentration because the surfaces of lipid micelles are negatively charged [10]. In an

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in vitro tau aggregation assay, non-filamentous tau aggregates called granular tau oligomers were found [11]. The non-filamentous tau aggregates could be separated from tau monomers and filaments by sucrose gradient centrifugation (Fig. 27.1). Tau filaments do not form in vitro without aggregation inducers. However, simply concentrating tau oligomers induces tau filament formation without additional heparin, and under atomic force microscopy (AFM), filaments formed in vitro or purified and AD brain degraded to granular tau structures [11] (Fig. 27.2). This suggested that the tau oligomer is an intermediate species of the tau filament. In addition, tau oligomers were found in animal models and human brains [12–14] (Fig. 27.3). The amino acid sequences critical for tau filament formation, PHF6 and PHF6* [15], are also reported to be key for tau oligomerization by western blots (WBs) and nuclear magnetic resonance analysis [16, 17]. In human brains, the number of tau oligomers was increased in the frontal cortex of Braak stage I patients, when NFTs have yet to form. Thus, tau oligomers form before NFTs [12–14].

Various Types of Non-filamentous Tau Aggregates

Definition and preparation of tau oligomers vary among researchers. For example, Maeda et al. induced tau aggregation by mixing recombinant tau with heparin and defined tau oligomers as granular structures under AFM [11]. The Davies group reported non-filamentous tau species that were extracted by a conformation-dependent antibody, MC1 [18]. The non-filamentous tau species formed filaments after concentration,

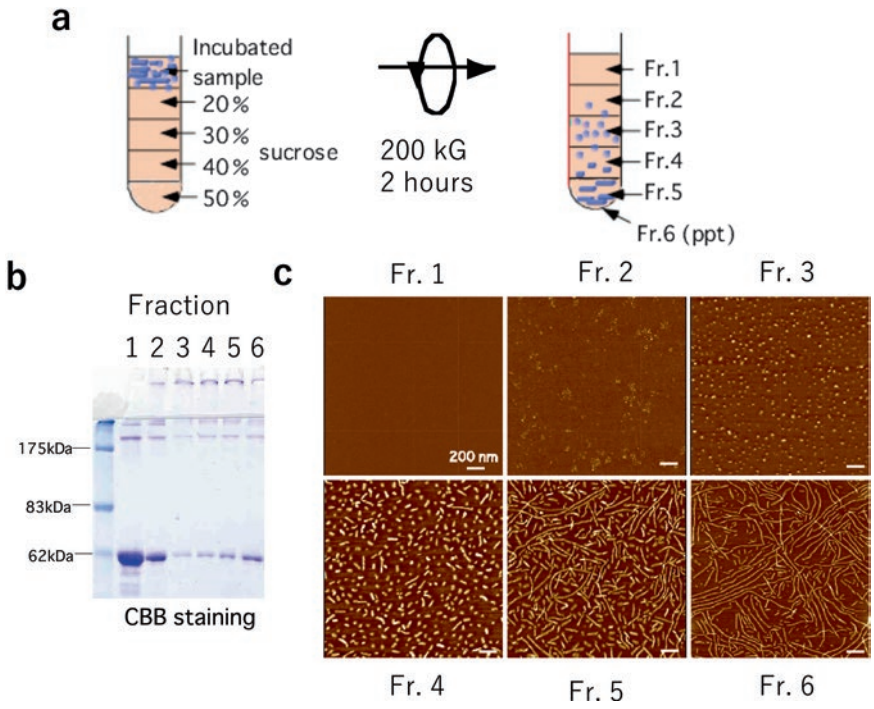

Fig. 27.1 The purification of granular tau oligomers using sucrose step gradient centrifugation. (**a**) Tau proteins were aggregated in vitro and layered onto 20–50% sucrose step gradients and centrifuged at 200,000 × G for 2 h to separate non-aggregated tau, granular tau oligomers, and tau filaments. (**b**, **c**) Staining with Coomassie brilliant blue (CBB) (**b**) and AFM images of all fractions (**c**) are shown. Granular tau oligomers could be recovered in fraction 3 as indicated (**b**, **c**). In fraction 1, tau monomers and multimers were collected (**b**), but no aggregated structure were observed under AFM (**c**). The amount of tau in fraction 3 was less than that in fraction 1 (**b**), but granular structures were detected under AFM (**c**). Longer filaments were collected in fractions 4–6 (**c**) [11]

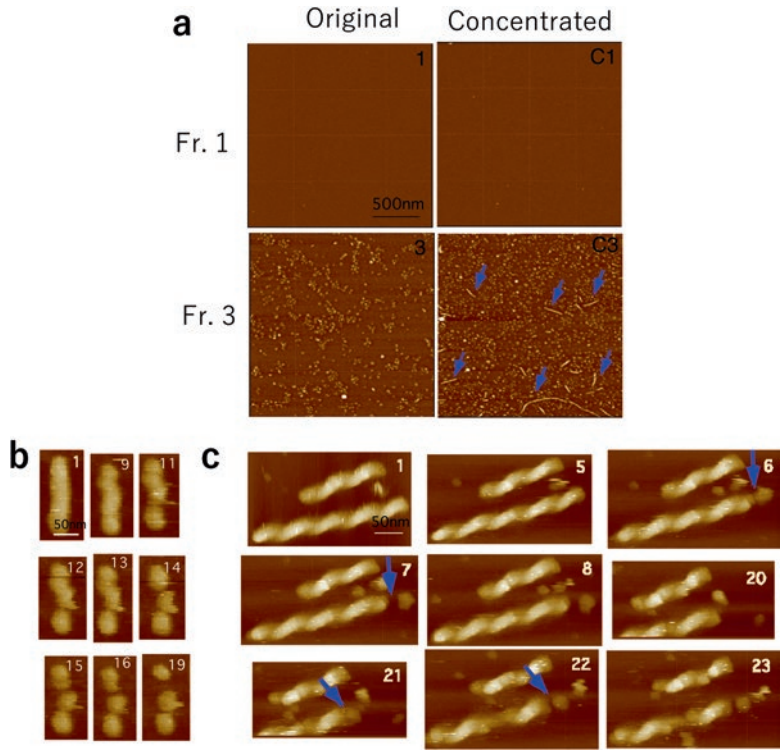

Fig. 27.2 The formation and degradation of tau filaments. (**a**) Granular tau oligomers in fraction 3 and non-aggregated tau in fraction 1 were concentrated without adding heparin. Filaments were observed by AFM in concentrated fraction 3 (C3) but not in the concentrated fraction 1 (C1). Blue arrows indicate the generated filaments in C3. (**b**, **c**) Structures were exposed to mechanical damage by AFM tips. Continuous AFM observation revealed that mechanical damage degraded tau filaments formed in vitro (**b**) or purified from an AD brain (**c**) to granular tau structures. The numbers at the top right indicate the order of the images. It took about 9 min to take an image [11]. Blue arrows indicate the breaking points of the tau filament

indicating that the oligomers extracted here are identical with the oligomers described above. Berger et al. reported a correlation of tau multimers and behavioral scores in an hTau transgenic mouse model [19]. Multimers were defined by the molecular mass by WB (140- and 170-kDa bands). The multimer can be a component of higher order aggregates, such as globular oligomers or tau filaments, but it degrades to a multimeric form under WB denaturing conditions. Thus, one component of tau oligomers may be the 140-/170-kDa multimers. Multimers might also be complexes of tau and other molecules, but another group reported that similar multimers may form only from recombinant tau [16]. Mandelkow's group induced tau oligomers using recombinant protein produced in insect cells (i.e., Sf9 cells) because highly phosphorylated tau proteins can be extracted, whereas recombinant tau protein produced in *E. coli* had no post-translational modifications [20]. They confirmed that phosphorylation enhanced tau aggregation [20, 21]. The Kayed group generated tau oligomers by cross-seeding with amyloid beta (Aβ) oligomers [22]. Those oligomers induced cell death when added exogenously to cells [22, 23]. Anti-tau oligomer antibodies were generated using the cross-seeded tau oligomers, and the antibodies blocked tau-induced neurodegeneration in hTau transgenic mouse models that lack Aβ aggregates and could not form Aβ seeds [24, 25]. Thus, tau aggregates, like tau oligomers seeded by Aβ aggregates, can be induced in the absence of Aβ aggregates. Binder's group [26]

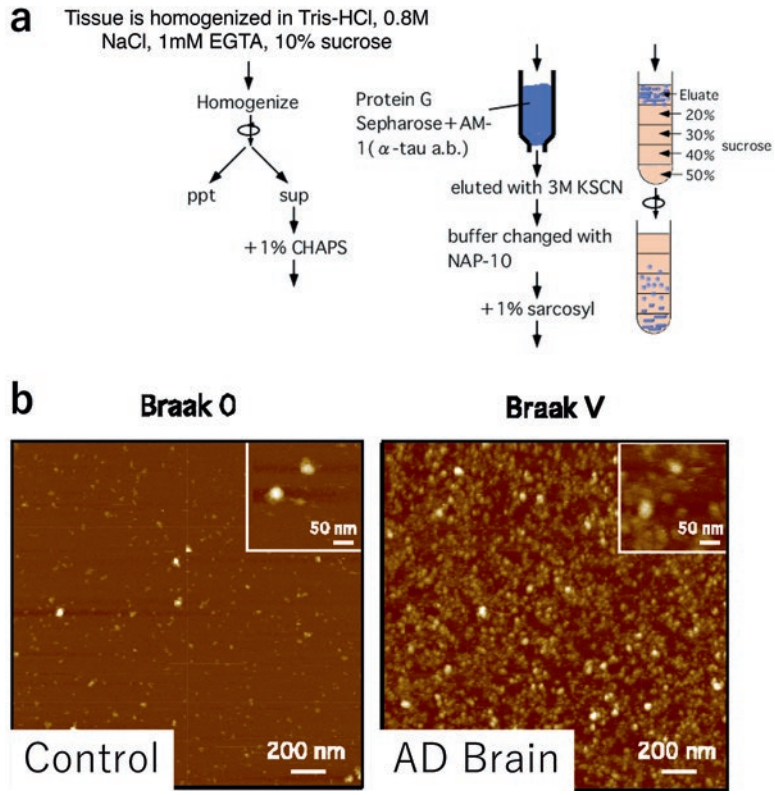

Fig. 27.3 Purification of granular tau oligomers from human brains. (**a**) Granular tau oligomers in human brains were purified in a combination of immune-affinity column chromatography with a pan-tau antibody and sucrose step gradient centrifugation [12]. (**b**) AD brains (Braak stage V) contained more granular tau oligomers than control brains (Braak stage 0) [12]. Inserts show the magnified images of granular tau oligomers purified from AD or control brains

stabilized tau aggregates with a chemical cross linker and found that, by WB, the tau dimer is a component of tau aggregates and that cross-linked tau dimers form short filaments and oligomeric globular structures but not long filaments.

Tau Oligomer Detection Methods EM and Oligomer Antibodies

Granular tau oligomers can be detected by AFM and electron microscopy (EM) [11, 22, 26], but not by other methods. To expand their ability to study tau, researchers generated antibodies specific for tau oligomers.

The Davies group generated two conformation-dependent antibodies, Alz50 and MC1 [27], that react with tau filaments purified from AD brains. Alz50 recognizes discontinuous sequences at the N-terminus and MBD. During abnormal conformation changes, inter- or intramolecular attachment of the N-terminus to the MBD may generate the Alz50 epitope [28]. MC1 is a second-generation conformation-dependent antibody that was raised against tau aggregates purified with an Alz50 immunoaffinity column. MC1 reacts with aggregated tau species more specifically than Alz50 [27, 29] and detects both tau filaments and oligomers [2]. With a combination of sucrose step gradients and the MC1 antibody, oligomeric species can be detected even in mouse tissue lysates [14]. However, the requirement for sucrose step gradient centrifugation limits the ability to do mechanistic studies of tau oligomer-dependent pathogenesis.

Researchers next sought to distinguish tau oligomers from tau filaments without gradient centrifugation. They generated more specific antibodies against tau oligomers than Alz50 and MC1 antibodies. Binder's group found the 180-kDa tau species in AD brain lysates [26]. To examine the pathogenesis of this tau species, they cross-linked tau dimers to obtain stable lower-order tau aggregates. When incubated with arachidonic acid, cross-linked tau dimers formed granular tau oligomer but not long fibrils. The

researchers immunized tau-knockout mice with the cross-linked tau dimers and obtained the Tau Oligomeric Component-1 (TOC1) antibody [26]. TOC1 preferentially labels granular tau oligomers and the end of tau filaments, supporting the idea that tau oligomers are an intermediate species of tau filament and the attachment of tau oligomer to tau filament will elongate the filament [11]. Unlike another tau-conformation dependent antibody, Alz50 that recognizes discontinuous tau sequences, amino acids 2–10 and 312–342, TOC1 recognizes amino acids 209–224 of tau.

TNT1 is another conformation-dependent antibody generated by the Binder group [30]. Its epitope is the tau phosphatase-activating domain (PAD) in the N-terminal domain. The N-terminus attaches to the MBD under physiological conditions. It is detached by aggregation or phosphorylation and impairs axonal transport via phosphatase activation, GSK-3β activation, and kinesin light chain phosphorylation [30, 31]. As with all other tau oligomer antibodies, reactivity depends on conformation. Notably, the PAD sequence lacks the endogenous mouse tau sequence, and thus, TNT1 cannot detect mouse tau even though mouse tau aggregates like human tau [32]. Both TOC1 and TNT1 are pan-tau antibodies in WB because their epitopes are freely accessible even under denatured conditions [33].

The Kayed group raised antibodies against the cross-seeding oligomeric species of tau and obtained the T22 (rabbit polyclonal) and TOMA (mouse monoclonal) antibodies [25, 34]. For unknown reasons, the epitopes of these antibodies are preserved even in WB, whereas other conformation-dependent antibodies function as pan-tau antibodies in WB because all sequences of tau protein are accessible to the antibodies. Normal tau immunization induced neurologic deficits in normal mice [35]. However, immunization with these antibodies blocked tau-induced neuronal dysfunction in hTau transgenic mice as mentioned above, suggesting that granular tau oligomers, not tau monomers, should be explored as therapeutic targets for tauopathies [24, 25].

Tau Oligomerization Enhancers, Blockers, and the Toxic Mechanism

Not all FTDP-17 mutations increase tau filament formation [36, 37]. However, all FTDP-17 tau mutations examined so far for tau oligomerization enhanced tau oligomerization. Notably, the P301L mutation decreases the size and increases the number of tau oligomers [14].

Tau aggregates (mainly filaments) have been suggested to spread from one brain region to another trans-synaptically [38]. The spreading may be mediated by the tau aggregates themselves, which are called prion-like tau species, but not by the dysfunction of projecting neurons [38]. Although it is not clear that the soluble fraction has prion-like activity [39, 40], tau oligomers may mediate the propagation [41]. They may function as a template for newly formed tau oligomers that can be amplified by adding non-aggregated tau [22]. Thus, the tau oligomer itself may increase tau oligomer numbers.

Heat shock proteins (HSPs) are involved in tau oligomerization [42]. HSPs, including Hsp90 and 27 that block tau aggregation, are inversely correlated with tau oligomer levels in human brains [16]. Thus, HSPs are an intriguing target for therapies to prevent tau pathogenesis [43, 44]. Other small molecules also block tau oligomerization. A screen of a library of natural compound derivatives for tau-binding compounds revealed several positives. For example, 1,2-dihydroxybenzene blocked tau oligomerization, and DL-isoproterenol reduced tau aggregation and neuronal cell loss in human tau transgenic mice [45]. These findings also support the idea that tau oligomer is a culprit of tau-mediated pathogenesis.

Tau aggregates accumulate inside of neurons. Thus, to assess their toxicity, tau oligomers must be introduced into neurons. However, tau oligomers are thought to be incorporated into cells [46] and to induce synaptotoxicity and Ca dysregulation [20, 47]. Surprisingly, the synaptotoxicity may be separate from cell viability, even though neuronal cell loss correlates well with the NFT formation as mentioned above. Ca dysregulation

by tau oligomers may be mediated by M1 and M3 muscarinic receptors [48], even though aggregated tau species showed less toxicity than monomeric non-aggregated tau in that system.

The mechanism of tau toxicity is unknown, but a hint might be provided by its conformation. Tau is reported to have a paper-clip conformation: the N-terminus is bent over to MBD in native state [49]. Tau aggregation disrupt that conformation and exposes the N-terminus. The exposure allows the PAD domain to induce the impairment of axonal trafficking [30].

Conclusion

Tau aggregation is toxic to cells. Thus, many researchers have visualized tau aggregation in their experimental models to search for a common feature between AD patients and the models. The exact mechanism of tau aggregation and toxicity and the targets of tau aggregates are still open issues. The discrepancy of tau filaments from neuronal cell loss implicates tau oligomers as the culprit of tau-mediated pathogenesis. Researchers have characterized tau oligomers by various methods. However, to directly examine their toxicity mechanisms, we will need methods to enhance or block tau oligomerization inside neurons. Also, to develop drugs that target tau oligomers, we will need tau oligomer probes that can be used for the target engagement in human live imaging. Antibodies specific for tau oligomers were used to show that tau oligomers have a structure distinct from other tau species. Thus, it might be possible to develop tau oligomer–specific probes for positron emission tomography. Those probes would be a powerful tool in combination with similar probes for tau filaments [50].

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