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The complexity of tau in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is characterized by two major pathological lesions in the brain, amyloid plaques and neurofibrillary tangles (NFTs) composed mainly of amyloid-β (Aβ) peptides and hyperphosphorylated tau, respectively. Although accumulation of toxic Aβ species in the brain has been proposed as one of the important early events in AD, continued lack of success of clinical trials based on Aβ-targeting drugs has triggered the field to seek out alternative disease mechanisms and related therapeutic strategies. One of the new approaches is to uncover novel roles of pathological tau during disease progression. This review will primarily focus on recent advances in understanding the contributions of tau to AD.

Keywords

Alzheimer's disease; Tauopathies; Tau; Neurodegeneration; Tau aggregation and propagation; Acetylation; Phosphorylation; Synaptic dysfunction; Glia; Neuroinflammation

1. Introduction

1.1. A brief historical review

NFTs were first described as one of the major brain lesions in AD by Alois Alzheimer in 1907 [1]. It wasn't until 1985 that the primary component of NFTs was identified as tau, a microtubule associated protein that is expressed primarily in neurons [2–10]. Hyperphosphorylation of tau in NFTs was documented soon after [11–14], and autosomal dominant mutations in *MAPT*, the gene encoding for tau, were found to cause frontotemporal dementia with parkinsonism (FTDP-17) [15–18]. See Fig. 1 for a historical timeline of tau associated with neurodegenerative diseases.

The importance of tau in AD progression has been recognized by clinical studies of the close correlation between AD development with tau-positive NFTs and neuropil threads, defined as tau-tangle filaments in areas of the brain that are high in neuronal and glial processes but lacking in cell bodies [19]. Both NFTs and neuropil threads begin in the transentorhinal

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region in the medial temporal lobar structures and progress to the neocortex and allocortex [20]. The number of NFT-positive cells correlates with disease stages, as measured by clinical parameters for cognitive decline and disease severity [20–24]. On the other hand, senile plaque density does not correlate with stages [25–27].

Besides AD, NFTs have been identified in over 20 different neurodegenerative diseases collectively termed “tauopathies” [28,29]. With the exception of AD, most of these diseases occur without amyloid deposition, and many are associated with tau mutations, suggesting that tau dysfunction and/or tangle formation contributes to the etiology of disease.

1.2. Characteristics of tau

Tau is encoded on chromosome 17 by the *MAPT* gene, which produces an overall hydrophilic protein with large natively unfolded regions enriched in the axons of developing and mature neurons [30–33]. Alternative splicing of 8 of the total 16 exons yields 6 isoforms in the central nervous system (CNS) and 6 additional isoforms in the peripheral nervous system (PNS), ranging from 58 kDa to 66 kDa and one 110 kDa isoform [34–37]. Tau protein is comprised of four primary domains (Fig. 2). Alternative splicing primarily affects the N-terminal projection region and microtubule-binding domain (MBD), producing 4-repeat (4R) and 3-repeat (3R) tau. These two isoforms are maintained in a balanced ratio (1:1) in adult human brains with 3R tau being primarily produced during development and the 4R tau isoforms being produced in adulthood [38]. 4R tau demonstrates a stronger activity in promoting microtubule assembly than 3R tau does [39,40]. Disruption of 3R and 4R ratio has been implicated in AD as well as other tauopathies and extensively reviewed elsewhere [41,42]. In brief, the ratio of 4R to 3R tau is increased in progressive supranuclear palsy [43,44], corticobasal degeneration [45], FTDP-17 [38,46,47] and argyrophilic grain disease [48], but decreased in Pick’s disease [49,50]. No clear pattern has emerged in AD [44,49,51] as vulnerable areas of the brain containing tau tangles show increased 4R tau isoforms in some cases [52,53] and 3R tau in others [44,54].

The most studied function of tau is its role in promoting microtubule assembly and stability, mainly supported by studies using in vitro cell-free systems [55]. However, knockout or knockdown of tau in mouse models and in primary neurons does not impair microtubule assembly or axonal transport [56–58]. The knockout mice do not have a severe phenotype, suggesting that the normal functions of tau might be compensated by various microtubule associated proteins (e.g., MAP1A, MAP1B, MAP2, etc.) [59–61]. Similar to tau knockout mouse brains (specifically axons) that develop normally, humans bearing disease-causing tau mutations or complete disruption are also developmentally normal [62]. In light of these unclear phenotypes in mice, in humans, a few individuals with microdeletions of the chromosome region containing *MAPT* and a few other genes, resulting in a 50% reduction in tau levels, do exhibit some delayed developmental issues in the CNS [63].

Nevertheless, a clear neuron-specific function for this protein is yet to emerge. The field would benefit from identifying non-redundant tau functions that are not developmentally important but can either 1) contribute to long-term cell survival functions that are essential for non-dividing cells like neurons, or 2) set off a cascade of events that may lead to neuronal death later in life. To date, over 60 disease-causing mutations in tau have been

identified, accounting for ~5% of all FTD cases [64,65]. These mutations, which are numbered by their locations in 2N4R human tau [66], are believed to cause disease via a toxic gain-of-function because tau is not required for neuronal survival, and mutations that affect alternative splicing of tau yet still produce wild type tau are also pathogenic [34]. Studies of these mutations show that they directly impact tau post-translational modifications, protein folding and aggregation, likely leading to toxic gain-of-function. We will discuss tau toxicity by reviewing recent advances in the consequences of tau post-translational modifications, particularly in the context of synaptic dysfunction, aggregation and propagation of tau. We will also discuss the emerging roles of glia in tauopathy, new 3D modeling systems for studying tau, and the development of tau positron emission tomography (PET) tracers.

2. Tau and synaptic function

Memory deficits in AD are highly associated with synaptic defects in the hippocampus [67–69]. Tau, as a promoter of axonal microtubule assembly, has been proposed to play a role in maintaining neuronal projections and affecting synaptic function. Loss of tau binding to microtubules may therefore contribute to synaptic dysfunction. Although tau knockout mice and flies do not exhibit any overt phenotypes [59,61,70–72], impairment of synaptic potentials and defects in spatial reverse learning have been observed in tau-null mice [73,74]. Consistently, tau knockdown in the adult hippocampus impairs motor coordination and causes morphological synaptic defects [75]. Tau hyperphosphorylation and aggregation are associated with impaired long-term synaptic plasticity and short-term plasticity. In the hippocampus of numerous transgenic tau mouse models expressing human wild type tau (hTau and triple transgenic PLB1), tau mutants (including P301 L, K257 T/P301S, $Tau_{RD}\Delta K280$ expressing pro-aggregated 4R fragment K18) or a model of genetically-induced tau hyperphosphorylation by the PP2A inhibitor CIP2A, long-term potentiation (LTP) is reduced at an age correlated with an increase in tau phosphorylation and aggregation [76–85]. Furthermore, LTP is reduced in mouse hippocampal slices by tau oligomers extracted from AD patient brains independent of soluble Aβ oligomers [86]. Reducing tau phosphorylation by inhibiting tau kinases restores tau-dependent LTP deficits and attenuates synaptic loss in tau transgenic mice [85,87].

It is unclear how tau mechanistically maintains synaptic plasticity, or how pathogenic versions of tau impair it. Several possible mechanisms might be involved. At the pre-synapse, pathogenic tau may interfere with normal synaptic vesicle release. Although tau protein was not found in the murine synaptic vesicle proteome by mass spectrometry [88], hyperphosphorylated tau was found to form more stable interactions with synaptic vesicles purified from AD brains but not in normal control brains [89–92]. This interaction may be mediated through the synaptic vesicle-anchored transmembrane protein synaptogyrin-3 [89,93,94]. The outcome of this pathogenic association may cluster F-actin at the pre-synapse and physically impede synaptic vesicle release, resulting in decreased neurotransmission [93].

On the other side of the synapse, normal tau is found to be involved in normal synaptic activity in the postsynaptic compartment [95]. Normal tau mainly associates with

microtubules in axons, but it can be recruited to dendrites and at the post-synapse under physiological or pathological conditions (recently reviewed by Ittner & Ittner, 2018) [96]. Synaptic activity drives tau to postsynaptic densities, where tau interacts with postsynaptic density proteins [95]. Dendritic tau is mostly hyperphosphorylated [78,97–100], unbound to microtubules and associated with dendritic spine loss [101]. In AD or other taupathies, these dendritic tau species play important roles in dendritic loss, aberant postsynaptic activity and cognitive dysfunction [102–104]. The molecular mechanisms likely involve regulation of NMDA or AMPA receptors, for example, dendritic tau has been shown to mediate Aβ-dependent excitotoxicity by complexing with Fyn kinase to trigger NMDA receptor phosphorylation [100]. In tau models, AMPA-mediated currents are suppressed in dendritic spines [102,105]. This defect may be attributed to hyperacetylated tau, which disrupts AMPA receptor trafficking during plasticity by reducing KIBRA levels at synapses [106]. It remains unclear whether hyperphosphorylated tau disrupts AMPA receptor stability at synapses.

3. Post-translational modifications of tau

3.1. Phosphorylation

Tau phosphorylation has been heavily implicated in AD and extensively studied, mainly because NFTs purified from AD brains are enriched with highly phosphorylated tau species. Biochemical characterization of tau phosphorylation at disease-related sites demonstrates that phosphorylation reduces tau's ability to bind to microtubules [107–110] and induces tau's self-assembly into tangles/filaments [111], presumably by altering the charge and structure within the MBD [112,113]. Mass spectrometry analysis of tau filaments led to identification of numerous pathological tau phospho-sites [114,115]. To date, approximately 45 out of 85 potential phosphorylation sites in tau have been reported experimentally. Some of these sites are differentially phosphorylated in AD or FTD brains but not in controls. Tau phosphorylation in the context of AD and other tauopathies has been extensively reviewed elsewhere, and therefore is not discussed further here [116–118].

3.2. Acetylation

Tau is a lysine-rich protein, particularly in the region spanning the MBD. Acetylation of tau was first described by Min and colleagues as a novel post-translational modification [119]. Tau acetylation at some specific lysine residues is associated with AD pathology in patient brains even at early Braak stages [119–121]. Multiple lysine residues in endogenous mouse tau have been identified to be acetylated by mass spectrometry analysis in both wild type and APP transgenic mice [122]. The histone acetyltransferases (HAT) p300 [119,123–125] and CREB binding protein (CBP) [126] acetylate tau, while SIRT1 [119,123] and HDAC6 deacetylate tau in the brain [124,127,128].

Protein acetylation at lysine residues serves as an important regulatory mechanism for enzymatic activity, protein-protein interaction and protein stability [129–131]. Mimicking tau acetylation with glutamine (tauKQ) at lysines 174 and 280 slows down total tau turnover in PS19 transgenic mice and transgenic *Drosophila*, respectively, without altering soluble

and insoluble tau levels in the latter [120,132], suggesting that one of the outcomes of tau acetylation is to regulate its turnover.

The relationship between tau acetylation and phosphorylation has been heavily investigated. However, the interplay between these two kinds of modifications is complex, possibly residue-dependent and disease-specific. The distribution of acetylated tau resembles that of hyperphosphorylated tau in AD brains [133]. Although phosphorylation is generally assumed to precede acetylation in AD pathology, acetylation of lysine 280 actually precedes phosphorylation in chronic traumatic encephalopathy [121]. Acetylation of tau at certain lysines (164, 174, 180 and 280) is associated with decreased phospho-tau degradation and thus increased phospho-tau levels [119,132], while simultaneous pseudo-acetylation at multiple lysines (163, 280, 281 and 369) or in other regions (in the KIGS motif or at lysine 321) is associated with decreased tau phosphorylation [124,134,135].

The influence of tau acetylation on aggregation is not conclusive yet and also seems residue-specific. Recent studies propose that acetylation precedes aggregation, yet it is unclear if acetylation promotes, protects against, or is unrelated to aggregation propensity, as acetylation within the MBD alters the structure of tau such that it may be either more or less prone to aggregation [136]. Acetylation at certain residues promotes tau aggregation and makes it more vulnerable to template-directed misfolding [137]. Acetylated tau at lysine 280 within the MBD is specifically associated with insoluble tau in AD brain and both PS19 and PS19/PDAPP mouse models [133,138], suggesting that acetylation promotes aggregation [128]. On the other hand, acetylation of tau is associated with decreased aggregation in some models. For example, CBP-mediated acetylation at lysine 321 inhibits recombinant tau fibril formation [126,135], and acetylation of recombinant tau at lysines 280 and 311 by p300 prevents tau aggregation by disfavoring liquid-liquid phase separation [125]. These findings are consistent with one of the earlier studies that tau aggregation is prevented by acetylation in the KIGS motif, which is hypoacetylated and hyperphosphorylated in AD brain and the P301L mouse model; therefore, loss of acetylation at this site is detrimental [124].

Tau acetylation may be harmful by accounting for a possible loss-of-function mechanism. Tau acetylation may disrupt microtubule assembly by altering the structure and charge within the MBD [125,134,135,137]. In support, pharmacological HDAC6 inhibition increases tau acetylation [124,127] and causes a minor reduction in affinity for microtubules [127]. Another detrimental outcome of tau acetylation is synaptic dysfunction. A *Drosophila* model of tau acetylation (K163/280/281/369Q) and a mouse model of Aβ-induced tau acetylation exhibit memory impairment and locomotor dysfunction [123,134]. Double acetyl-mimic at AD-related sites lysines 274 and 281 leads to tau mislocalization to somatodendritic compartments in primary cultures [139], and results in LTP deficits and impairment of memory formation in mice [106]. Tau acetyl-mimics induce loss of postsynaptic protein KIBRA and reduce AMPA receptor trafficking, which may imply the underlying molecular mechanism [106]. The effect of acetylated tau on synaptic deficits has been reviewed by Tracy and Gan [105].

4. Pathological aggregation and propagation of tau

Tau aggregation is the overt pathological hallmark of tauopathies. It still needs to be clarified whether the toxic species are the insoluble aggregates, pre-fibril soluble tau oligomers, fragments of already-formed aggregates, or the loss of soluble tau that is leeched into aggregates. The lengthy period of cognitive decline in AD indicates that toxicity is a slow, cumulative process. Likewise, formation of the initial aggregates occurs slowly, but subsequent fragmentation greatly facilitates formation of more aggregates [140].

NFTs are concentrated in the brainstem nuclei, especially the substantia nigra and locus coeruleus, in several tauopathies. There is variable involvement of the basal ganglia, thalamus and cortex in various neurodegenerative diseases that present with tauopathy [141–144]. In AD, tau pathology may appear at a younger age than senile plaques do [145], though this timeline remains debatable. Braak suggests that tau pathology begins in the locus coeruleus and then spreads to other brainstem nuclei and to the entorhinal cortex. Since the development of tau pathology in AD brain correlates well with the brain regions related to cognitive impairment, the Braak stages of AD are classified into stages I–VI using the spreading pattern of tau pathologies as one of the important criterion [20].

Similar to the Braak stages, stereotypical temporospatial spreading of tau inclusions also occurs in other tauopathies such as argyrophilic grain disease. A key difference between these tauopathies is that the spread of tau progresses in different directions and to different brain regions [146–148].

Aberrant tau pathology follows a progressive pattern of spread in AD. However, no clear mechanism of cell-to-cell tau spread has been elucidated. Many studies over the past decade have demonstrated that tau is capable of spreading from one neuron to another. Today, the study of tau aggregation is focusing on the structure of these aggregates, as well as the mechanisms of tau secretion, uptake and aggregate seeding by distinct pathological tau strains.

4.1. Aggregation

Intracellular tau aggregate formation is believed to be mediated by the MBD, spanning between Ser214 and Glu372 [149]. The MBD binds tightly to MTs and tethers tubulin dimers together [109]. The third repeat, which contains the hexapeptide motif VQIVYK, is the most important for fibril assembly [150]. This motif, along with a second hexapeptide motif (VQIINK), allows for formation of β-sheet structures that are necessary for tau aggregation [151–154]. FTD mutations in tau that destabilize local structure around VQIVYK trigger spontaneous aggregation [155]. In support, structure-based inhibitors that target VQIINK, or introduction of β-sheet-breaking prolines in the MBD, prevent tau aggregate formation [156,157].

Paired helical filaments and straight filaments in AD are morphologically heterogeneous but generally range in diameter from 22 to 24 nm as determined by electron microscopy [158–160]. Advancements in structure-based technologies helped finally solve high-resolution structures of tau filaments. Cryogenic electron microscopy revealed that a combined cross-β/

β-helix structure consisting of residues 306–378 within the MBD makes up the core of tau filaments derived from an AD patient brain [161]. Variations in inter-protofilament packing between paired helical and straight filaments suggests that tau can adopt distinct folds in the human brain in different diseases [162].

Multiple factors including tau phosphorylation and cleavage are early steps that precede aggregation. One of the most significant findings regarding tau aggregation recently is that phosphorylation of tau promotes liquid-liquid phase separation under cellular protein conditions, resulting in molecular crowding of amyloid-promoting regions within the MBD that drives electrostatic amyloid-favoring coacervation [163]. Tau can be cleaved by many proteases, which may promote tau aggregation [164–166]. Aβ plaques are also capable of enhancing the aggregation of AD brain-derived tau injected into mouse brains [167]. As Aβ plaques and tau tangles are spatially distinct in AD brain, both regionally in the brain and topologically across membranes, the question remains as to how exactly Aβ drives tau pathology.

Chaperone machinery provides a molecular mechanism involved in tau aggregation and degradation. A class of chaperones, such as DnaJA2, Hsp60, clusterin, Hsp104 and Hsc70, demonstrates activities in inhibiting tau aggregation and seeding-capacity of tau aggregates [168]. However, Hsp90, the most abundant chaperone in cells, shows a distinct function by promoting pathological tau stability and aggregation in the diseased state [169]. It remains unclear whether these chaperones are able to reverse already-formed tau fibrils [168,170].

4.2. Propagation

Early in 1997, an AD case study revealed that a disconnected frontal cortex tissue due to surgical removal in brain was completely lack of tau positive tangles or neuropil threads, indicating that the development of tau pathology involves cortico-cortical fibers [171]. The spreading of tau from one cell to another long fibers conflicts with the biology of tau as an intracellular microtuble-binding protein. More and more recent studies have shown that tau can be secreted from neurons [172–175]. Tau is physiologically present in the cerebrospinal fluid (CSF) of normal, healthy individuals [176]. Tau is also detectable in the extracellular interstitial fluid from the brains of live mice using microdialysis technology, with a relatively long half-life of up to 11 h [177]. Using co-culture systems, it was found that extracellular tau fibrils induce transmissible aggregation in recipient cells [178–180]. The nature of secreted tau has not been fully characterized with consistent observations [172,181–184]. The secretion of tau is dependent upon neuronal activity and varies between different tau isoforms [185]. Paradoxically, FTD mutations reduce tau secretion [175,186].

Nevertheless, inoculation of pathological tau in tau transgenic mouse brains clearly demonstrates the transmission of tau pathology from one region to another [187]. Tau oligomers derived from AD patients that are injected into wild type mouse hippocampus cause memory impairments and the spread of phospho-tau to other regions of the brain including the cortex, corpus callosum and hypothalamus [188]. Confined expression of pro-aggregation P301 L tau in the entorhinal cortex using genetic approaches leads to anterograde spread to the dentate gyrus, CA1 and CA3 regions in two regulatable tau mouse models [189,190]. These mice suffer from loss of excitatory neurons in the medial

entorhinal cortex which are associated with spatial memory [191]. The spreading patterns in these tau transgenic mouse brains strongly suggest that propagation of tau in mouse brain follows the connectivity of neurons in the brain.

How tau can move from one neuron to another is not well understood. Several recent findings started to explore the potential underlying mechanisms, including exosome release, synaptic release and other unconventional mechanisms of release as discussed in the following sections.

4.2.1. Exosomes—Exosomes are membrane-bound vesicles released by mammalian cells from intracellular multivesicular compartments. They play important functions in intercellular communication, as exosomes are potential vehicles for delivering cellular contents from origin cells to recipient cells [192]. Detection of tau in exosomes isolated from CSF [193] or plasma [194] of human AD patients suggests that tau is transported via exosomes. Tau secretion in association with exosomes was first observed in HEK293 cells [195]. However, other studies reported failures to detect tau in exosomes isolated from other cell lines [186] or cultured primary neurons [196]. These contradictory studies were re-examined recently. It was found that tau is present only in exosomes from mature (older than DIV14) but not immature neurons [182]. Furthermore, only a minor fraction of secreted tau is actually associated with exosomes [174,182,197–200]. Therefore, the sensitivity of the assay matters for the detection of exosomal tau [198]. Using ultra-sensitive immunoassays specific for full-length and mid-region tau based on Simoa (named for single molecule array), the majority of free-floating tau secreted from human induced pluripotent stem cell (iPSC)-derived neurons was found to be mostly truncated [198]. However, the ratio of full-length to truncated tau is higher in exosomes than in free-floating fractions [198]. A possible explanation is that exosomes are released from multivesicular bodies, where tau is captured for degradation by autophagy, before tau can be degraded. Exosomal tau is phosphorylated (at T181 and possibly other sites) and oligomerized [182,198]. Exosomes containing tau are capable of seeding tau aggregation in neighboring cells, including neurons and microglia [182]. Interestingly, recent studies showed that microglia take up extracellular tau and promote tau propagation via exosome secretion, and knockout of nSMase2, a key regulator of exosome release, in vivo blocks exosome-mediated tau propagation [201–205]. However, there is still a debate whether there is a significant difference in exosome-associated tau in CSF between AD patients and non-dementia controls [182,198], raising the concern of using exosomal tau as a useful biomarker for AD. Thus, the functional contribution of exosomal tau to AD still needs more investigation.

4.2.2. Synaptic release—Tau spread through neural networks may be due to a trans-synaptic mechanism of release. Phosphorylated soluble tau oligomers are enriched in synapses from AD brains and may propagate along neuronal connections [177,206]. Intracerebral injections of tau seeds in P301S mice are associated with pathological spread via functionally connected neuroanatomical pathways: Injection into the entorhinal cortex leads to decreased synaptic plasticity in the CA1 region, while injection into the basal ganglia leads to motor deficits indicative of neurodegeneration [207]. Tau derived from

either AD, CBD or PSP patient brains that was injected into different brain regions spreads along neural networks independent of tau origin [208].

Spread through the neural connectome may depend upon neuronal activity. AMPA receptor activation stimulates release of tau in cultured neurons [172]. Similarly, reverse microdialysis of K^+ into mouse brains increases tau secretion [175]. Chemogenetic or optogenetic activation of neuronal activity increases tau release in primary neurons and is associated with brain hippocampus atrophy and tau pathology in P301 L mice [209]. Seemingly in contradiction, stimulating neuronal activity in organotypic slices stimulates tau release in wild type but not 3xTg slices [181]. However, basal tau release is increased in 3xTg organotypic slices compared to wild type. It is unknown if whether increased secretion is due to higher network activity in the tau transgenic mice compared to wild type [181]. It is possible that the 3xTg slices have enhanced network activity at baseline that could drive this increase in tau release. In this case, the additional tau release induced by adding high KCl could be occluded in 3xTg slices. In accordance with this idea, densely connected brain regions that have higher tau burden are more vulnerable to neurodegeneration in AD and progressive supranuclear palsy [210], potentially supporting the idea that these hubs may be centers of greater trans-synaptic tau spread.

4.2.3. Unconventional secretion—Other unconventional secretion pathways provide alternative avenues for non-vesicular tau release [211] including direct translocation across the plasma membrane. In several early studies, tau was observed to associate with the plasma membrane [212–214] as well as form pore-like annular protofibrils in vivo [215]. in vitro studies also revealed that interaction of tau with the lipid bilayer induces membrane disruption [216,217]. These studies indicate that tau may directly penetrate the membrane. Two recent papers showed that tau is secreted directly through plasma membrane, occurring in specific membrane micro-domains and depending on some specific lipids like cholesterol and sphingomyelin [197,200]. Both studies revealed that cell surface heparan sulfate proteoglycans (HSPGs) facilitate this unconventional tau secretion, likely by helping tau to be released from membranes at the end of the penetration process. The role of HSPGs has been reported for unconventional secretion of other proteins [218,219]. Importantly, tau phosphorylation and oligomerization is necessary for this secretion mechanism and these unconventionally secreted tau species can spread to adjacent cells and induce aggregation [197]. These studies did not rule out other forms of secretion of free tau. For example, a non-canonical secretion pathway mediated by Hsc70/DnaJ complex and SNAP-23 can also facilitate release of proteins into the extracellular space [220,221]. Further investigations will help us understand the roles of these secretory pathways in tau spreading.

4.2.4. Tau uptake—Mounting evidences demonstrate that tau can be taken up by neuronal cells by receptor-mediated endocytosis or micropinocytosis [179,222–227]. Just as the topological conundrum plagues the poorly-defined mechanisms of tau release, the same paradox applies for tau to cross the membrane and enter the cytosol of recipient cells. If tau is secreted with exosomes, extracellular exosomes must somehow deliver tau seeds directly into the cytosol. However, direct fusion of exosomes with the plasma membrane is yet to be reported. Another potential mechanism for tau uptake into the cytosol is through direct

translocation across the plasma membrane, which has recently been shown to mediate tau release [197,200]. Again, no evidence directly supports this route in the literature so far. Many studies consistently show that internalized tau proteins enter through endosomes and can remain in a low-pH compartment for a long time [228]. Tau aggregates can also be internalized at axonal terminals and retrogradely transported toward the cell soma [227]. An unbiased CRISPRi screen of 3200 genes further found that extracellular tau is taken up by micropinocytosis via the HSPG biosynthetic pathway [229] that has been shown to mediate uptake of prion proteins [218,219,230,231]. Tau uptake and tau fibril seeding ability can be blocked chemically by inhibiting binding to HSPGs using heparin, chlorate or heparinase, or genetically by knocking down genes encoding enzymes involved in HSPG synthesis in neuroglioma cells, iPSC-derived neurons and mouse brain slice cultures [226,229,232]. Combining these studies, it seems that a two-step process is involved in tau entry, allowing for tau to act as a seed for aggregation in recipient cells: entering cells via a membrane-based route followed by crossing the membrane boundary of these compartments and enter the cytosol in order to trigger aggregation. Exactly how tau escapes from those membranes remains to be resolved. Finally, further investigation should help clarify whether monomeric and aggregated tau species behave similarly in this entry process [197].

4.2.5. Seeding of aggregates by distinct strains—

Tau is a highly soluble protein due to its flexible, hydrophilic composition. In other terms, it may either adopt many conformations or no particular conformation at all. Recent evidence suggests that pathogenic tau may form multiple, distinct structures [233].

Two different strains with seeding ability that were isolated from the brains of P301S mice [234] add to the growing list of protocols for generating or extracting tau fibrils [235]. Unique strains of tau that are associated with different tauopathies can be stably passaged in dividing cells, injected into mice, and then passaged back into cells, all while retaining the same unique conformation [236]. Although different tau strains are associated with different pathologies in various cell types and brain regions [237], they seem not to have effect on the direction of tau propagation [208]. There is tremendous variability in tau structure within each tauopathy, yet post-translational modifications and truncation have minimal effects on tau filament morphology [238]. Instead, phosphorylation may be more critical in the early steps of dissociating tau from microtubules rather than directly causing aggregation.

Tau monoclonal antibodies are capable of distinguishing tau aggregates in AD brains from those in other tauopathies [239]. One possible explanation for the selectivity of these antibodies is that there is an AD-specific tau strain. Another possibility is that these antibodies only recognize AD-specific post-translational modifications that do not occur in other tauopathies. Further study is required to determine if tau does acquire various morphologies and whether or not they are physiologically and pathologically relevant.

5. Role of glia and inflammation in tauopathy

Several pieces of data demonstrate the association between glia and tau pathology. Activated glia cells were observed near neurons containing hyperphosphorylated tau in postmortem tauopathy brains [240,241], and oligomeric tau colocalizes with glia cells in animal models

as well as in AD and FTD brains [242]. Clinically, an elevation of immune biomarkers such as soluble immune gene TREM2 and YKL-40 were observed in the cerebrospinal fluid of AD and other tauopathy patients, and these increases are correlated with CSF tau and phospho-tau levels [243–245]. In tau transgenic models, activated microglia and elevated inflammatory mediators in P301S tau models are associated with tau pathology [246–248]. These early observations suggest that tau pathology may contribute to the activation of glia cells and the development of neuroinflammation in AD and other tauopathies [249]. Genome-wide transcriptome studies in different tau transgenic models revealed that alterations in microglial phenotypes are driven by tau dysfunction: specifically, the inflammatory changes can be reversed by suppression of the tau transgene [250,251]. Furthermore, transcriptome analysis of isolated microglia cells from tau transgenic mouse brains revealed an age-dependent neurodegeneration-specific molecular signature involving the interferon-related pathway and innate immune pathways in tau animal models [252]. Recently, longitudinal gene expression changes were assessed in isolated microglia from tau transgenic animals, which revealed that NF-κB signaling and cytokinecytokine receptor interaction pathways may be the first to be activated in tau transgenic mouse brains, likely driven by the key upstream regulators RELA, STAT1 and STAT6 [253]. With the application of the new tools for single cell transcriptomics, mass cytometry and bioinformatic analyses [254–258], the spatial and temporal heterogeneity of microglia activation states in response to tau pathology would be better captured and understood. Lastly, how pathogenic tau activates microglia at the cellular and molecular level is unclear. A recent study demonstrates that aggregated tau, following microglia uptake and lysosomal sorting, can activate the NLRP3-ASC inflammasome, an important sensor of innate immunity [259], providing some initial insight into the mechanism involved in this process.

The impact of glia activation and neuroinflammation on tau pathology is not fully understood. Accumulating evidence suggests that these factors exacerbate tau pathology, likely through a non-cell autonomous impact on neuronal signaling via cytokine secretion [260], or by directly impacting features of brain tau metabolism such as tau degradation, aggregation and spreading [201,261–263]. Modulation of tau pathology by microglia is further supported by recent findings revealing the functions of two genetic risk factors, APOE and microglia-specific gene TREM2, in tau pathology by influencing microglia-dependent inflammation [264–267]. The complement pathway, a tau-associated molecular signature, seems to influence tau pathology too. Inhibiting the complement C3ar pathway significantly reduces tau pathology in tauopathy animal models [268]. A recent proteomics study identified that C1q protein accumulates in the postsynaptic density of P301S mice and AD patients, and mediates microglial-dependent synapse engulfment, adding another dimension to the contribution of microglia in tau pathology-triggered neurodegeneration [269]. Finally, new topics such as the contribution of microglia senescence to the development of tau pathology during aging are emerging [270], providing us with more novel perspectives for the functions of microglia in tauopathies. Overall, active research in this area will bring more clarity to the roles of glia and neuroinflammation on tauopathy [271].

6. New models for tau study: 3D culture and organoids

Developing technologies in 3D human neural cultures and cerebral organoids provide new systems for creating more relevant AD models. Although these new AD model systems that develop Aβ plaques and tau pathology are still being characterized, one significant advantage of 3D cultures for studying tau pathology is that they dramatically increase the expression of 4R adult tau isoforms compared to 2D cultures, which mainly express 3R tau isoforms [272]. A balanced expression of 3R and 4R isoforms is essential for recapitulating tauopathy from human brains. Consequently, high levels of detergent-resistant, silver-positive aggregates of phosphorylated tau as well as filamentous tau are detectable in the soma and neurites of 3D-differentiated neuronal cells expressing fAD mutations [272], which have not been observed in either 2D cultures or animal models expressing human wild type tau [273]. Additionally, 3D cultures can incorporate various human cell-types, including neurons, astrocytes and microglia [274]. These improved 3D cell culture systems can be used to study intracellular tau aggregation and the consequences of tau modifications, as well as the function(s) of microglial on tau pathology [272,274,275] because tau aggregation can be quickly triggered by application of exogenous synthetic tau fibrils in 3D cultures [276]. Therefore, the ability to form tau pathology in AD patient-derived 3D cultures provides an accessible cell culture platform that more closely resembles physiological conditions than 2D cultures do [277].

3D cerebral organoids can be derived from human pluripotent stem cells and thus directly from AD patients [278,279]. Brain organoids derived from fAD patients recapitulate Aβ aggregation, tau hyperphosphorylation and aggregation [280,281]. They uniquely provide a platform for genetically manipulating human brain-like tissue and studying downstream effects such as tau phosphorylation state and tau spreading [87]. Although organoids lack endogenous microglia, human iPSC-derived microglial-like cells can be implanted and integrated into brain organoids, where they are capable of phagocytosing brain-derived tau oligomers [282]. It remains to be seen whether implanted induced microglia are capable of regulating existing tau pathology in organoids. Therefore, with further characterization and development of these new models, we will be equipped with more powerful tools to understand the mechanism for tau pathogenesis in AD.

7. Therapeutic strategies and diagnostic tools centered on tau

Tau is emerging as a marker and therapeutic target for AD and other dementias. Recent development of PET tracers targeting tau has allowed researchers to confirm in patients the spread of tau as characterized by Braak staging [283,284], as well as the correlation of tau but not Aβ with cognitive decline [283,285–288]. Recent efforts to improve live tau imaging in patients have led to progress in the development and characterization of several tracers [289]. The tracers PBB3, flortaucipir (formally known as T807 and ^{18}F-AV-1451), THK-5351 and MK-6240 are capable of detecting tau [290–294]. Some are better than others for detecting aggregated, phosphorylated or soluble tau species. Using tau PET imaging, it was found that Aβ deposition precedes tau accumulation in fAD presenilin-1 (PSEN1) cases in a long-term study in a Colombian community containing cognitively unimpaired and impaired carriers of the PSEN1 E280 A mutation. Elevated tau deposition in

the neocortex was associated with mild cognitive impairment and worse scores on cognitive tests [287]. It remains to be investigated whether this timeline holds in sporadic AD cases. Importantly, this study demonstrates that tau PET imaging may be useful as a biomarker to distinguish individuals at high risk to develop the clinical symptoms of AD and to track disease progression.

8. Conclusion

Recent works have advanced scientists' understanding of the consequences of pathogenic tau. Targeting pathways such as synaptic activity, inflammation, tau protein stability, or post-translational modifications/modifiers of tau may provide valid therapeutic strategies. En route toward that goal, the tauopathy field would benefit from exploring the elusive function(s) of tau other than its role in promoting microtubule-assembly.

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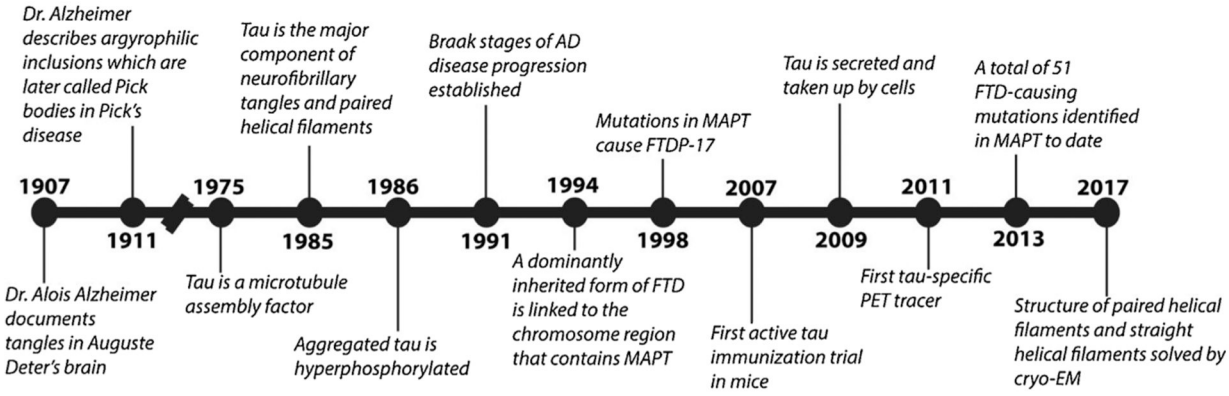

Fig. 1.
A brief history of tau.

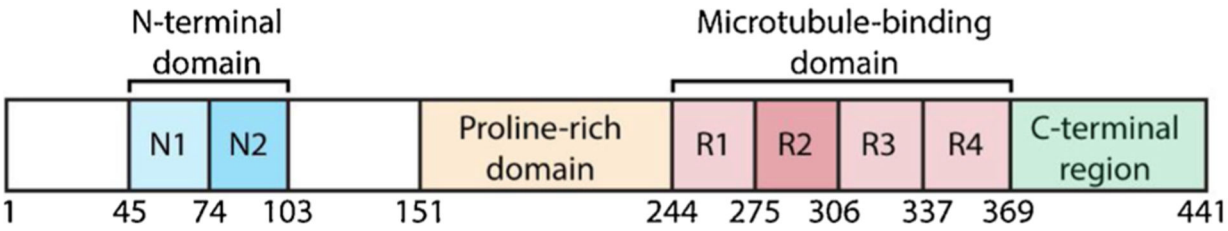

Fig. 2. Domains of 2N4R tau.

Tau protein is comprised of four primary domains, the N-terminal domain (blue), the proline-rich domain (tan), the microtubule-binding domain (pink), and the C-terminal region (green). Alternative splicing of the N-terminal and microtubule-binding domains yields six isoforms in the CNS. Repeat domains R1, R3 and R4 (light pink) are constitutive, while R2 (dark pink) is incorporated only in the three 4R isoforms. N1 and/or N2 may be skipped, but inclusion of N2 requires that N1 also be included. The final variants become: 0N3R, 1N3R, 2N3R, 0N4R, 1N4R, and 2N4R tau, the last of which is depicted here.