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Propagation of Tau Aggregates and Neurodegeneration

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Annu. Rev. Neurosci. 2017. 40:189–210

The *Annual Review of Neuroscience* is online at neuro.annualreviews.org

https://doi.org/10.1146/annurev-neuro-072116-031153

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Keywords

Alzheimer's disease, amyloid, cell-to-cell spreading, disease propagation, Pick's disease, prion-like, protein strains, Tau, Tauopathies, toxicity

Abstract

A pathway from the natively unfolded microtubule-associated protein Tau to a highly structured amyloid fibril underlies human Tauopathies. This ordered assembly causes disease and represents the gain of toxic function. In recent years, evidence has accumulated to suggest that Tau inclusions form first in a small number of brain cells, from where they propagate to other regions, resulting in neurodegeneration and disease. Propagation of pathology is often called prion-like, which refers to the capacity of an assembled protein to induce the same abnormal conformation in a protein of the same kind, initiating a self-amplifying cascade. In addition, prion-like encompasses the release of protein aggregates from brain cells and their uptake by neighboring cells. In mice, the intracerebral injection of Tau inclusions induces the ordered assembly of monomeric Tau, followed by its spreading to distant brain regions. Conformational differences between Tau aggregates from transgenic mouse brain and in vitro assembled recombinant protein account for the greater seeding potency of brain aggregates. Short fibrils constitute the major species of seed-competent Tau in the brains of transgenic mice. The existence of multiple human Tauopathies with distinct fibril morphologies has led to the suggestion that different molecular conformers (or strains) of aggregated Tau exist.

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INTRODUCTION

Alois Alzheimer and Oskar Fischer used Bielschowsky silver to reveal by light microscopy the inclusions of Alzheimer's and Pick's diseases (AD and PiD) (Alzheimer 1907, 1911; Fischer 1907). These inclusions are amyloid plaques and neurofibrillary lesions in AD and Pick bodies in PiD. Although Alzheimer is best known for his description of the clinicopathological characteristics of the disease that bears his name, he was also the first to describe the inclusions that define the disease, later named after Arnold Pick (Gans 1922). **Figure 1** shows entry 728 from the autopsy book of the Royal Psychiatric Clinic in Munich. Therese Mühlich was one of two individuals with temporal lobe atrophy that Alzheimer studied (Onari & Spatz 1926, Stertz 1926). The diagnosis reads "Pikscher Fall" (Pik's case), with Pick's name misspelled (the handwriting appears to be that of Alzheimer). Alzheimer's diagnosis thus predated the naming of Pick's disease by some 12 years.

In the 1960s, electron microscopy was used to show that neurofibrillary lesions and Pick bodies are made of abnormal filaments (Kidd 1963, Rewcastle & Ball 1968). In the 1980s, Tau protein (**Figure 2*a***) was identified as the major component of the neurofibrillary lesions of AD and Pick bodies of PiD (Lee et al. 2001, Goedert 2015, Arendt et al. 2016). Abundant glial Tau inclusions are found alongside neuronal inclusions in some diseases, such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). In white matter Tauopathy with globular glial inclusions, also known as globular glial Tauopathy (GGT), oligodendroglial Tau inclusions predominate. Abundant filamentous Tau inclusions are characteristic of many human neurodegenerative diseases (see the sidebar titled Neurodegenerative Diseases with Abundant Tau Inclusions).

Small numbers of Tau inclusions form as a function of age in nerve cells (Ulrich 1985, Braak & Braak 1991) and some glial cells, chiefly astrocytes (Kovacs et al. 2016). Their stereotypical appearance in nerve cells underlies Braaks' stages of AD (Braak & Braak 1991, Braak & Del Tredici 2011), according to which inclusions form first in subcortical regions, transentorhinal cortex, and entorhinal cortex (stages I and II). They then appear in the hippocampal formation and some parts of the neocortex (stages III and IV), followed by most of the neocortex (stages V and VI).

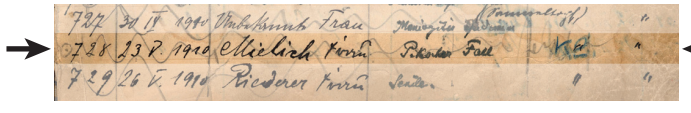

Figure 1

Entry 728 from the autopsy book of the Royal Psychiatric Clinic in Munich, where Alois Alzheimer worked. Therese Mühlich (written as Mielich Frau) died on May 23, 1910. The diagnosis was Pikscher Fall (Pik's case), with Arnold Pick's surname misspelled.

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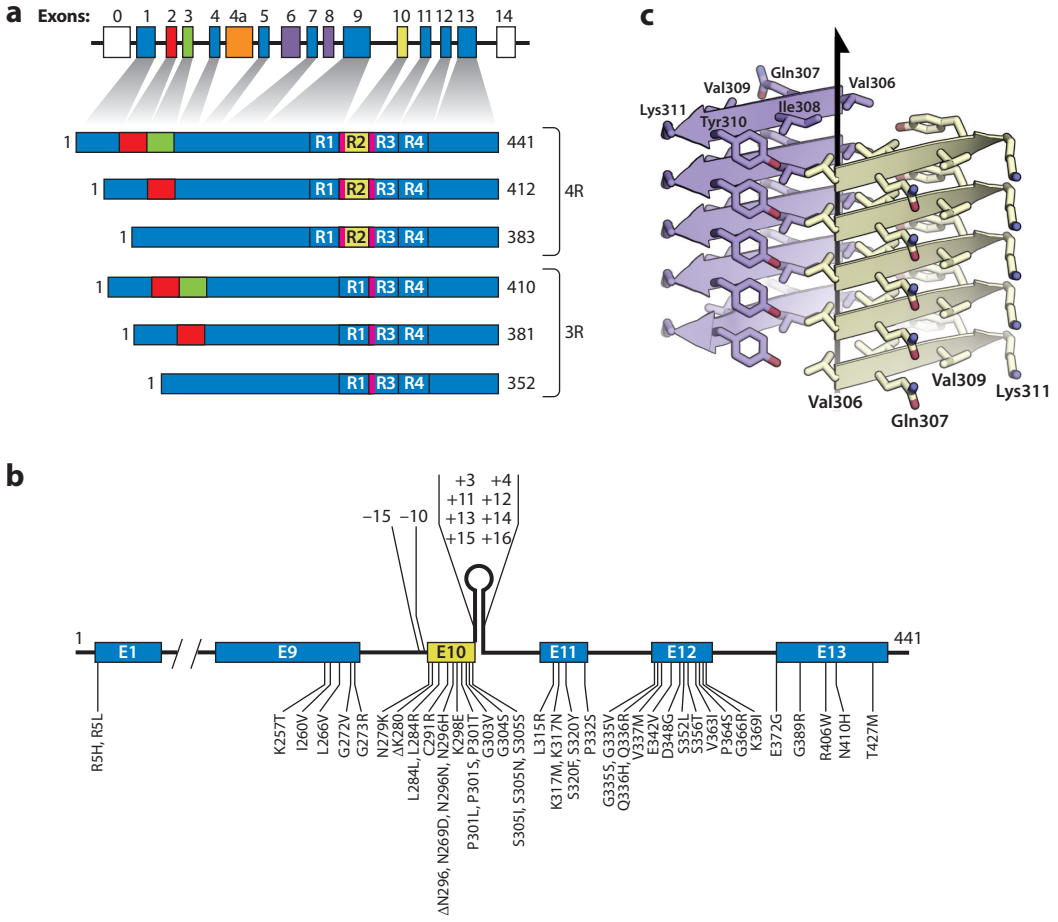

Figure 2

Human brain Tau isoforms, *MAPT* mutations, and crystal structure of residues 306–311 of Tau. (*a*) *MAPT* and the six Tau isoforms expressed in adult human brain. *MAPT* consists of 16 exons (E). Alternative mRNA splicing of E2 (*red*), E3 (*green*), and E10 (*yellow*) gives rise to the six Tau isoforms (352–441 amino acids). The constitutively spliced exons (E1, E4, E5, E7, E9, E11, E12, and E13) are shown in blue. E0, which is part of the promoter, and E14 are noncoding (*white*). E6 and E8 (*violet*) are not transcribed in human brain. E4a (*orange*) is expressed only in the peripheral nervous system. The repeats of Tau (R1–R4) are shown, with three isoforms having four repeats each (4R) and three isoforms having three repeats each (3R). The hexapeptide sequences VQIINK (residues 275–280, at the beginning of R2) and VQIVYK (residues 306–311, at the beginning of R3), which are required for Tau aggregation, are shown in magenta. The exons and introns are not drawn to scale. (*b*) Mutations in *MAPT* in cases of frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17T). Forty-nine coding-region mutations and 10 intronic mutations flanking E10 are shown. (*c*) Steric-zipper crystal structure of the hexapeptide VQIVYK (residues 306–311) from the core of Tau filaments (Sawaya et al. 2007), which is required for aggregation. Two β-sheets are shown (*violet* and *tan*), with the β-strands being parallel within each sheet and antiparallel between sheets. The peptide backbones are shown as arrows. Protruding from each sheet are the amino acid side chains. The black arrow marks the filament axis. Adapted from Goedert (2015) with permission from AAAS.

Individuals at stages I and II are asymptomatic, whereas those at stages V and VI have AD, with some individuals at stages III and IV showing signs of memory impairment. These findings are compatible with the existence of a long presymptomatic phase. When positron emission tomography was used, Tau tracer retention showed similar stages (Johnson et al. 2016, Schöll et al. 2016).

NEURODEGENERATIVE DISEASES WITH ABUNDANT TAU INCLUSIONS

This list includes only diseases for which the isoform composition of Tau inclusions has been established. Asterisks indicate diseases mentioned in the text.

3R + 4R Tauopathies

- Alzheimer's disease (AD)*
- Amyotrophic lateral sclerosis/parkinsonism-dementia complex
- Anti-IgLON5-related Tauopathy
- Chronic traumatic encephalopathy (CTE)*
- Diffuse neurofibrillary tangles with calcification
- Down's syndrome
- Familial British dementia
- Familial Danish dementia
- Gerstmann-Sträussler-Scheinker disease
- Niemann-Pick disease, type C
- Non-Guamanian motor neuron disease with neurofibrillary tangles
- Postencephalitic parkinsonism*
- SLC9A6-related parkinsonism
- Tangle-only dementia (TD)*
- Familial frontotemporal dementia and parkinsonism (some *MAPT* mutations, such as V337M and R406W)*

3R Tauopathies

- Pick's disease (PiD)*
- Familial frontotemporal dementia and parkinsonism (some *MAPT* mutations, such as G272V and Q336R)*

4R Tauopathies

- Argyrophilic grain disease (AGD)*
- Corticobasal degeneration (CBD)*
- Guadeloupean parkinsonism
- Globular glial Tauopathy (GGT)*
- Huntington's disease
- Progressive supranuclear palsy (PSP)*
- Tau astrogliopathy*
- Familial frontotemporal dementia and parkinsonism (some *MAPT* mutations, such as P301S, all known intronic mutations, and many coding region mutations in exon 10)*

Common human neurodegenerative diseases are characterized by the presence of abundant inclusions with the properties of amyloid fibrils (Eisenberg & Jucker 2012). Each inclusion has a single protein as its major component, with amyloid-β (Aβ), Tau, and α-synuclein being the most commonly involved. Most neurodegenerative diseases are defined by a single type of inclusion. AD, the most prevalent of these diseases, is characterized by two types of inclusions, abundant extracellular Aβ deposits and intraneuronal Tau aggregates.

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Aβ, Tau, and α-synuclein undergo a transformation from a soluble to an insoluble filamentous amyloid state, with several intermediates. Most cases of disease are sporadic, but a small percentage of cases are inherited, often in a dominant manner. The latter are caused by mutations in the genes encoding the proteins that make up the inclusions, or proteins that increase their production, underscoring the importance of inclusion formation for neurodegeneration. The finding that the three genes, mutations in which cause familial AD [Aβ precursor protein (APP), presenilin-1, and presenilin-2], influence APP processing, and are involved in the production of Aβ peptides, led to the formulation of the amyloid cascade hypothesis (Hardy & Selkoe 2002). Mutations in *MAPT* (**Figure 2*b***), the microtubule-associated protein Tau gene, give rise to an inherited form of frontotemporal dementia and parkinsonism with abundant filamentous Tau inclusions in brain, in the absence of Aβ deposits (Goedert 2015). Although APP dysfunction may initiate a cascade of events, it appears to be the dysfunction of Tau that is the efficient cause of neurodegeneration.

Until recently, cell autonomous mechanisms were believed to account for sporadic human neurodegenerative diseases, implying that the same aggregation events occur independently in many brain cells, resulting in degeneration. At death, protein inclusions are present in thousands of postmitotic nerve cells. Alternatively, the first inclusions may form in a localized fashion, from where they propagate to normal cells through cell nonautonomous mechanisms, resulting in degeneration.

Propagation is consistent with staging schemes, which have postulated that Tau inclusions progress from a few sites in a predictable manner [locus coeruleus and transentorhinal cortex in AD, frontotemporal cortex in PiD, ambient gyrus in argyrophilic grain disease (AGD), and cortical sulci in chronic traumatic encephalopathy (CTE)] (Braak & Braak 1991, Saito et al. 2004, McKee et al. 2013, Irwin et al. 2015). However, staging is also compatible with brain regions being affected sequentially, without aggregate transfer. Propagation is supported by the absence of Tau inclusions in the disconnected frontal cortex of an individual with AD who had undergone an operation to remove a meningioma 27 years earlier (Duyckaerts et al. 1997). Although there was abundant Tau pathology in limbic and isocortical regions, there was none in the disconnected frontal cortex.

Over the past eight years, experimental studies in mice have shown that the injection of Tau inclusions induces nerve cells to form intracellular inclusions at the injection sites, from where they can spread to distant brain regions (Clavaguera et al. 2009). Provided these findings are related to what happens in human brain, cell nonautonomous mechanisms and spreading must also be at work in human neurodegenerative diseases.

Propagation of pathology is often called prion-like, referring to the formation of ordered protein assemblies and their intercellular spread. The acronym prion stands for proteinaceous infectious particle, encompassing the formation of ordered assemblies, intercellular propagation, and interorganismal transmission (Prusiner 1982). There is no evidence to suggest that human Tauopathies can transfer between individuals, hence our use of prion-like. Propagation of aggregates requires their release into the extracellular space, uptake by connected cells and seeded aggregation of soluble proteins. Studying the underlying mechanisms may lead to the identification of novel therapeutic targets.

TAU ISOFORMS

Tau is expressed predominantly in the central and peripheral nervous systems, where it is most abundant in nerve cell axons. It can be divided into an N-terminal projection domain, a proline-rich region, a repeat region, and a C-terminal domain.

Six Tau isoforms ranging from 352 to 441 amino acids are expressed in adult human brain (**Figure 2*a***) (Goedert et al. 1989), produced by alternative mRNA splicing of transcripts from

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MAPT on chromosome 17q21.31 (Neve et al. 1986). They differ by the presence or absence of inserts of 29 or 58 amino acids in the N-terminal half, and the inclusion, or not, of the 31 amino acid repeat encoded by exon 10 of *MAPT* in the C-terminal half. Inclusion of exon 10 results in the production of three Tau isoforms with four repeats each (4R) and its exclusion in a further three isoforms with three repeats each (3R). The repeats comprise residues 244–368 or 252–376, depending on the alignment, in the numbering of the 441 amino acid isoform. Together with some adjoining sequences, they constitute the microtubule-binding domains of Tau (Kadavath et al. 2015).

Single molecule tracking in the processes of differentiated PC12 cells has revealed a kiss-and-hop mechanism, with a dwell time of Tau on individual microtubules of only about 40 ms (Janning et al. 2014). Isoform differences did not influence this interaction significantly (Niewidok et al. 2016). Despite these rapid dynamics, Tau promoted microtubule assembly. It remains to be seen if microtubules were also stabilized. In brain, Tau is subject to posttranslational modifications, including phosphorylation, acetylation, methylation, glycation, isomerization, *O*-GlcNAcylation, nitration, sumoylation, ubiquitination, and truncation (Spillantini & Goedert 2013, Morris et al. 2015). Big Tau, which carries an additional large exon in the N-terminal half, is expressed in the peripheral nervous system (Couchie et al. 1992, Goedert et al. 1992b).

Tau protein is natively unfolded. However, this does not preclude global order. Single-molecule Förster resonance energy transfer has shown the presence of long-range contacts between N and C termini, as well as between both termini and the repeats, giving rise to an S-shaped fold (Elbaum-Garfinkle & Rhoades 2012).

Similar amounts of 3R and 4R Tau are expressed in the cerebral cortex of adults (Goedert & Jakes 1990). In developing human brain, only the shortest Tau isoform is present. 3R, 4R, and 5R Tau isoforms are found in the brains of adult chickens (Yoshida & Goedert 2002), whereas most adult rodents express only 4R Tau (Götz et al. 1995). What is conserved is the expression of one hyperphosphorylated 3R Tau isoform lacking N-terminal inserts during vertebrate development. The genomes of *Caenorhabditis elegans* and *Drosophila melanogaster* each encode one protein with Tau-like repeats (Goedert et al. 1996a, Heidary & Fortini 2001). Similar repeats are present in the high-molecular-weight proteins MAP2 and MAP4 (Lewis et al. 1988, Aizawa et al. 1990). MAP4 may derive from a nonvertebrate ancestor, whereas MAP2 and Tau may have shared a more recent common ancestor (Sündermann et al. 2016).

TAU AGGREGATION

Full-length Tau assembles into filaments through its repeats, with the N-terminal half and the C terminus forming the fuzzy coat (Goedert et al. 1988; Wischik et al. 1988a,b). Tau filaments from human brain and those assembled from expressed protein have a cross-β structure characteristic of amyloid fibrils (Berriman et al. 2003), with their cores consisting of approximately 90 amino acids. The region that binds to microtubules also forms the core of Tau filaments, suggesting that physiological function and pathological assembly are mutually exclusive.

Phosphorylation of Tau negatively regulates its ability to interact with microtubules, and filamentous Tau is invariably abnormally hyperphosphorylated (Iqbal et al. 2016). However, whether phosphorylation is a trigger for aggregation remains to be proved. Alternatively, a conformational change in Tau arising from assembly may cause its hyperphosphorylation. There is no strong evidence to suggest that the activities of protein kinases, phosphatases, or both are changed in human Tauopathies. Other posttranslational modifications may also be involved. Many publications equate Tau phosphorylation with aggregation. This is probably not correct. Although aggregated Tau is heavily phosphorylated in human brain, not all phosphorylated Tau is aggregated or on the

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way to aggregation. For instance, researchers have shown that highly phosphorylated Tau forms during hibernation (Arendt et al. 2003). This was not associated with the formation of filaments and was reversible upon arousal.

In AD, CTE, postencephalitic parkinsonism, and several other Tauopathies, all six isoforms are present in the disease filaments (see the sidebar titled Neurodegenerative Diseases with Abundant Tau Inclusions) (Goedert et al. 1992a,b; Buée-Scherrer et al. 1997; Schmidt et al. 2001). In AD, they are either paired helical or straight, with both types of filaments sharing a common structural subunit (Crowther 1991). In other diseases—such as PSP, CBD, AGD, GGT, and aging-related Tau astrogliopathy—only isoforms with 4R Tau are found in the filaments (see the sidebar titled Neurodegenerative Diseases with Abundant Tau Inclusions) (Flament et al. 1991; Ksiezak-Reding et al. 1994; Togo et al. 2002; Kovacs et al. 2008, 2016). In PiD, 3R Tau isoforms predominate in the inclusions (see the sidebar titled Neurodegenerative Diseases with Abundant Tau Inclusions) (Delacourte et al. 1996). Unlike AD, these diseases lack Aβ deposits. The morphologies of Tau filaments in different diseases vary, even when they are made of the same isoforms (**Figure 3**) (Crowther & Goedert 2000). These differences can also be detected by silver staining (Uchihara et al. 2005). Inclusions made of all six Tau isoforms stain with Gallyas-Braak and Campbell-Switzer. Those made of 4R Tau are positive only with Gallyas-Braak, whereas those made of 3R Tau stain only with Campbell-Switzer.

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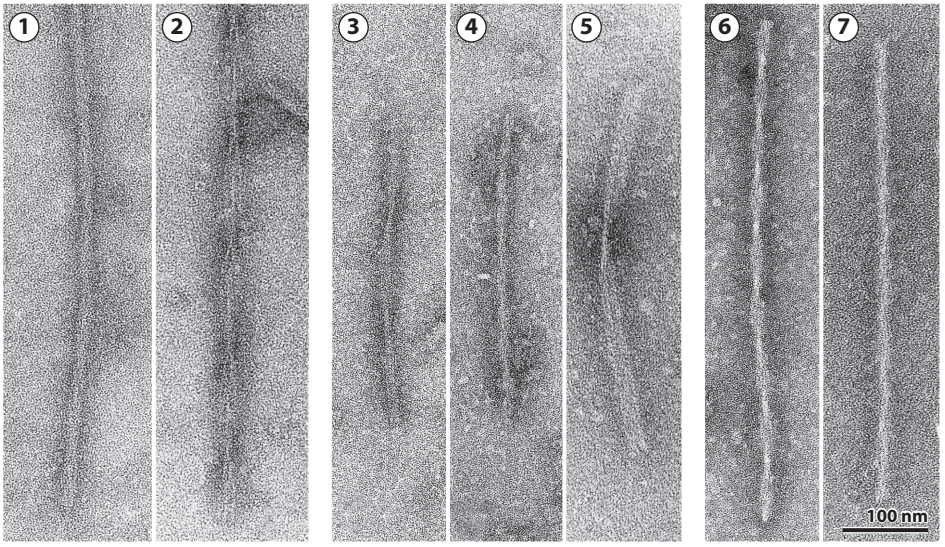

Figure 3

Tau filaments from cases of frontotemporal dementia and parkinsonism linked to chromosome 17 caused by *MAPT* mutations (FTDP-17T). (① and ②) Neuronal Tau filaments from a case with abundant Pick body–like inclusions and a G389R mutation in *MAPT* (from Murrell et al. 1999). ① Straight filaments form the majority species, and ② strongly stranded twisted filaments are in the minority. (③–⑤) Tau filaments from cases with neuronal and glial inclusions and a P301L mutation in *MAPT* or an intronic mutation (from Spillantini et al. 1997, 1998a). ③ Narrow twisted ribbons and ④ occasional rope-like filaments. ⑤ Familial multiple system Tauopathy with presenile dementia and other cases caused by *MAPT* mutations in the intron after E10 are characterized by wide twisted ribbons and neuronal and glial Tau inclusions. The filaments in ③–⑤ are made of 4R Tau. (⑥ and ⑦) Tau filaments from a case with a V337M mutation in *MAPT* (from Spillantini et al. 1996). ⑥ Paired helical and ⑦ straight filaments are present as in Alzheimer's disease. Tau inclusions are largely neuronal, and filaments in ⑥ and ⑦ are made of 3R and 4R Tau. Adapted from Goedert (2015) with permission from AAAS.

Research suggests that patients with AD-type neurofibrillary degeneration restricted to hippocampus and medial temporal lobe, who lack Aβ deposits, suffer from primary age-related Tauopathy (PART), a condition that differs from AD (Crary et al. 2014). Tangle-only dementia (TD) (Ulrich et al. 1992), a rare form of dementia, may also represent a severe form of PART. However, the view that PART is different from AD has been challenged (Duyckaerts et al. 2015), because PART is clinically and neuropathologically similar to what appear to be the early stages of AD.

In AD, following the death of tangle-bearing cells, Tau filaments can remain in the extracellular space as ghost tangles, which consist largely of Tau repeats that have lost their fuzzy coat through proteolysis (Bondareff et al. 1994). In PiD, PSP, CBD, and most cases caused by *MAPT* mutations, Tau filaments do not accumulate to a significant extent in the extracellular space following the death of aggregate-bearing cells. The reasons why Tau filaments from AD brains are less soluble remain to be established.

Overexpression of human wild-type Tau in mouse brain does not result in the formation of abundant filamentous inclusions (Götz et al. 1995, Probst et al. 2000). By contrast, overexpression of human Tau with disease-causing mutations, such as P301L and P301S, gives rise to disease models that reproduce the essential molecular and cellular characteristics of human Tauopathies, including the formation of abundant Tau filaments and extensive neurodegeneration (Lewis et al. 2000, Allen et al. 2002).

The interaction in vitro between unphosphorylated, full-length, recombinant Tau and some negatively charged compounds, such as sulfated glycosaminoglycans, results in filament assembly (Goedert et al. 1996b, Pérez et al. 1996). Heparin probably induces dimerization of Tau, with filaments growing through monomer addition (Ramachandran & Udgaonkar 2011). Filaments are decorated by antibodies directed against the N and C termini of Tau but not by an antibody directed against the repeats. These findings, which indicate that the repeat region is inaccessible to the antibody, are identical to those obtained previously in AD (Goedert et al. 1992a). Synthetic Tau filament morphologies are similar to those in human Tauopathies (Goedert et al. 1996b, Morozova et al. 2013). The mechanisms leading to filament formation inside brain cells in sporadic human Tauopathies remain to be identified. Heparin is probably not involved.

Hexapeptide sequences in R2 (amino acids 275–280, VQIINK) and R3 (amino acids 306–311, VQIVYK) are essential for filament assembly and render Tau aggregation competent (**Figure 2*a***) (Von Bergen et al. 2000, 2001). Solid-state nuclear magnetic resonance spectroscopy of filaments assembled from three Tau repeats (R1, R3, and R4) showed the presence of three beta-strands, one from each repeat (Andronesi et al. 2008). The core region of Tau filaments corresponded to residues 306–324 located in R3 (Daebel et al. 2012). Microcrystals of residues 306–311 formed steric zippers (**Figure 2*c***) (Sawaya et al. 2007). Residues 310–313 in Tau (YKPV) differ from the equivalent residues in MAP2 (TKKI). When the latter were changed to YKPV, MAP2c also assembled into filaments (Xie et al. 2015).

GENETICS OF *MAPT*

The link between Tau dysfunction and neurodegeneration was established through human genetics. First, a dominantly inherited form of frontotemporal dementia and parkinsonism was linked to chromosome 17q21-22 (FTDP-17) (Wilhelmsen et al. 1994). In June 1998, mutations in *MAPT* were reported in this and other families with FTDP-17 (Hutton et al. 1998, Poorkaj et al. 1998, Spillantini et al. 1998b). Fifty-nine pathogenic *MAPT* mutations had been identified by October 2016 (**Figure 2*b***; see also the sidebar titled Neurodegenerative Diseases with Abundant Tau Inclusions). Behavioral symptoms are the most common clinical sign. However, in some cases,

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MAPT mutations have been associated with parkinsonism. In addition, neurological syndromes similar to PSP, CBD, PiD, and motor neuron disease have been described. The ages of disease onset are variable but can be as early as in the third decade. *MAPT* mutations are associated with abundant Tau inclusions predominantly in nerve cells (exons 9, 11, 12, and 13) or in both nerve cells and glial cells (exons 1 and 10, introns 9 and 10) (Ghetti et al. 2015).

Mutations in *MAPT* account for about 5% of cases of frontotemporal dementia. They are concentrated in exons 9–12 (encoding R1–R4) and the introns flanking exon 10. Mutations can be divided into those with a primary effect at the protein level and those affecting the alternative splicing of Tau pre-mRNA. Mutations that act at the protein level change or delete single amino acids, reducing the ability of Tau to interact with microtubules. Some mutations also promote the assembly of Tau into filaments. Mutations with a primary effect at the RNA level are intronic or exonic and increase the alternative mRNA splicing of exon 10 of *MAPT*. This affects the ratio of 3R to 4R isoforms, resulting in the relative overproduction of 4R Tau and its assembly into filaments.

Aggregated Tau can show different isoform patterns, depending on the mutations in *MAPT* (Ghetti et al. 2015). Mutations V337M in exon 12 and R406W in exon 13 give rise to insoluble Tau bands of 60, 64, and 68 kDa and a weaker band of 72 kDa. Following dephosphorylation, six bands are present that align with recombinant Tau, like what is seen in AD. The brains of many individuals with missense *MAPT* mutations in exons 9–13 (K257T, L266V, S305N, G272V, L315R, S320F, S320Y, P332S, Q336H, Q336R, K369I, E372G, and G389R) are characterized by abundant Pick bodies made predominantly of 3R Tau. As in sporadic PiD, insoluble Tau shows strong bands of 60 and 64 kDa. However, variable amounts of the 68 and 72 kDa bands are also observed. A third pattern is characteristic of *MAPT* mutations that affect the alternative mRNA splicing of exon 10 (intronic mutations and exonic mutations N279K, ΔK280, L284L, L284R, ΔN296, N296D, N296H, N296N, S305I, S305N, and S305S). Insoluble Tau runs as two strong bands of 64 and 68 kDa and a weaker band of 72 kDa; following dephosphorylation, three bands are present that align with recombinant 4R Tau (isoforms of 383, 412, and 441 amino acids). A similar pattern of pathological Tau bands is observed for mutations in exon 10, such as P301S, which have their primary effects at the protein level. Aggregation of 4R Tau has also been described for mutations I260V in exon 9, K317N in exon 11, E342V in exon 12, and N410H in exon 13, showing that it is possible to alter 3R and 4R Tau mRNAs through mutations located outside exon 10.

The effects of *MAPT* mutations can be varied. Thus, neighboring mutations in exon 12 (G335S, G335V, Q336H, Q336R, and V337M) give rise to structurally distinct filamentous Tau aggregates and exert different functional effects. Mutation G335S is characterized by the presence of abundant filamentous Tau inclusions in nerve cells and glial cells, in the absence of Pick bodies (Spina et al. 2007). Mutations Q336H and Q336R give rise to what is a familial form of PiD, with abundant Pick bodies in nerve cells (Pickering-Brown et al. 2004, Tacik et al. 2015), whereas mutation V337M produces a neuronal filamentous Tau pathology indistinguishable from that of AD (Spillantini et al. 1996, Poorkaj et al. 1998). These findings on *MAPT* mutations in three adjacent codons reinforce the view that the mechanisms resulting in the formation of neurofibrillary lesions and Pick bodies are closely related. Recombinant Tau with the G335S, G335V (Neumann et al. 2005), or V337M mutation shows a greatly reduced ability to promote microtubule assembly. By contrast, mutations Q336H and Q336R increase the ability of Tau to promote microtubule assembly. Mutations G335V and V337M fail to increase heparin-induced assembly of Tau into filaments significantly. By contrast, mutations Q336H and Q336R selectively increase the assembly of 3R Tau.

MAPT in populations of European descent is characterized by two haplotypes that result from a 900-kb inversion (H1) or noninversion (H2) polymorphism (Stefansson et al. 2005). Inheritance of the H1 haplotype is a risk factor for PSP (Conrad et al. 1997, Baker et al. 1999), CBD

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(Houlden et al. 2001), and Parkinson's disease (PD) (Pastor et al. 2000). This has been confirmed in genome-wide association studies (Satake et al. 2009, Simón-Sánchez et al. 2009, Höglinger et al. 2011, Kouri et al. 2015). The association with PD is particularly surprising, as PD is not characterized by the presence of Tau inclusions.

For PSP and CBD, researchers have also found an association with an allele at the *MOBP/SLC25A38* locus, which results in elevated levels of appoptosin, a protein that activates caspase-3, which can cleave Tau (Zhao et al. 2015). This may result in increased aggregation of 4R Tau. Additional loci were unique to PSP or CBD. The association of the H1 *MAPT* haplotype with PSP had a higher odds ratio than that between apolipoprotein E epsilon 4 (APOEε4) and AD (Höglinger et al. 2011). APOEε4 is the major risk factor allele for late-onset AD (Corder et al. 1993). The H2 haplotype is associated with increased expression of exon 3 of *MAPT* in gray matter, suggesting that inclusion of exon 3 is protective (Caffrey et al. 2008). Reduced expression of 1N4R has also been associated with the H2 haplotype (Valenca et al. 2016). Tau isoforms containing exons 2 and 10 promote aggregation, whereas exon 3–containing isoforms are inhibitory (Zhong et al. 2012).

Even though all six Tau isoforms form the paired helical and straight filaments of AD, no known mutations in *MAPT* give rise to AD. Investigators have reported that Tau with an A152T substitution may be a risk factor for AD (Coppola et al. 2012), as well as for PSP, CBD, and unusual Tauopathies (Kovacs et al. 2011, Coppola et al. 2012, Kara et al. 2012; but see also Pastor et al. 2015).

PROPAGATION OF TAU AGGREGATES

The assembly of Tau into filaments can be initiated or accelerated by the addition of seeds. If mechanisms for the intercellular transfer of seeds exist, then human Tauopathies can propagate through the brain. Since 2009, much evidence has been adduced to suggest that Tau assemblies, when applied extracellularly, can seed the formation of aggregates (Clavaguera et al. 2009, Frost et al. 2009). This is followed by the spreading of Tau aggregates. Because Tau is an intracellular protein, its propagation requires seeding as well as aggregate uptake and release. Despite the fact that monomeric Tau is taken up by cells, from which it can be released, it is probably not able to seed aggregation. Expressed Tau can only be seeded when it is aggregation competent (Falcon et al. 2015). Thus, deletion of amino acids 275–280 in R2 and 306–311 in R3 abolished the seeding activity of full-length Tau. Aggregation inhibitors may thus be able to reduce Tau-induced seeding and spreading.

Uptake of ordered Tau assemblies depends on the presence of heparan sulfate proteoglycans at the cell surface and may occur through macropinocytosis, at least in cultured cells (Holmes et al. 2013). The seeds probably escape from endosomal vesicles to induce the assembly of cytoplasmic Tau. Following assembly, Tau aggregates are released from cells through ill-defined mechanisms (**Figure 4**). Intracellular Tau might transfer between cells through tunneling nanotubes. Alternatively, Tau could be released into the extracellular space, either freely or inside vesicles. It has been detected in the interstitial fluid of transgenic mice (Yamada et al. 2011).

Microglial cells may promote Tau propagation through exosome-dependent mechanisms (Asai et al. 2015). Another study concluded that Tau was released from cells through an exosome-independent pathway that required heat shock cognate 70, its cochaperone DnaJ, and synaptosomal-associated protein 23 (Fontaine et al. 2016). Most of this work probably described the release of aggregation-incompetent soluble Tau. By contrast, optogenetic and chemogenetic approaches in transgenic mouse models have shown that an increase in neural activity can accelerate Tauopathy (Wu et al. 2016).

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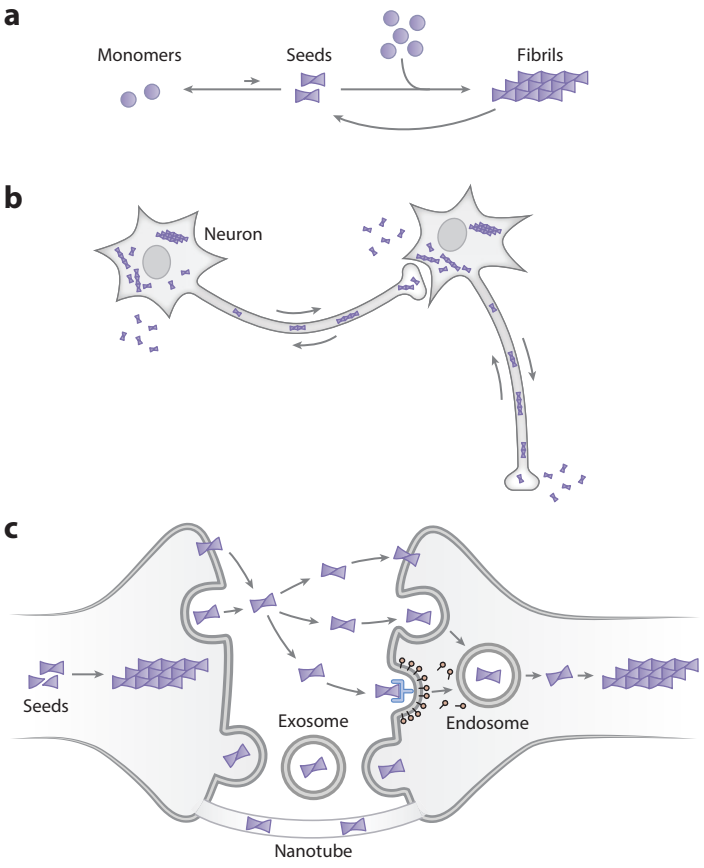

Figure 4

Intercellular transfer of protein aggregates. (*a*) A pathological pathway leading from native monomers to amyloid fibrils underlies the most common human neurodegenerative diseases. The formation of seeds from monomers is slow and energetically unfavorable. By contrast, the growth of fibrils from seeds through the addition of protein monomers is rapid. Fibrils can in turn give rise to additional seeds through fragmentation. (*b*,*c*) Possible mechanisms of intercellular aggregate transfer. Seeds can be released into the extracellular space in a free form or within membrane-bound vesicles, such as exosomes. Free seeds may penetrate the plasma membrane of a recipient neuron or enter the neuron by fluid-phase or receptor-mediated endocytosis. Exosomes will fuse with the plasma membrane of a recipient neuron. The intercellular transfer of seeds may also occur through nanotubes that connect the cytoplasm of two adjoining cells. In the cytoplasm of recipient cells, seeds will grow into fibrils through the addition of protein monomers. The transfer of aggregates may be bidirectional (*arrows*). This drawing is schematic; Tau aggregates can spread between connected neurons, but it is unclear if their release is (entirely) through synaptic mechanisms. Adapted from Goedert et al. (2014) with permission from Springer.

Phosphorylation of Tau seeds is not required, even though seeded Tau aggregates are hyperphosphorylated (Falcon et al. 2015). Tau fibrils may grow by incorporating unphosphorylated Tau that then undergoes a conformational change and becomes hyperphosphorylated. It remains to be seen if phosphorylation of Tau can influence seeded aggregation.

The intracerebral injection of brain extracts from mice expressing human P301S Tau with inclusions (Allen et al. 2002) into mice transgenic for wild-type human Tau lacking inclusions (line ALZ17) (Probst et al. 2000) induced the assembly of wild-type Tau into filaments and its

spreading to distant brain regions (Clavaguera et al. 2009). No inclusions formed when Tau was immunodepleted from the extracts prior to injection.

Subsequently, several groups studied the spreading of pathological Tau along the entorhinal cortex/hippocampal pathway. They used mouse models that apparently expressed human P301L Tau only in the entorhinal cortex (de Calignon et al. 2012, Harris et al. 2012, Liu et al. 2012; but see also Yetman et al. 2016). Several months after the appearance of Tau inclusions in entorhinal cortex, hippocampal neurons also developed Tau pathology. This was followed by the formation of Tau inclusions in connected areas of neocortex and amygdala. Over time, activated microglia and astrocytes accumulated in the medial entorhinal cortex, where nerve cell loss was observed at late time points (Fu et al. 2016). This is consistent with previous findings in mice transgenic for human P301S Tau, suggesting that glial activation and neuroinflammation are downstream of Tau aggregation (Bellucci et al. 2004). In mice transgenic for human mutant amyloid precursor protein, presenilin-1, and/or mutant Tau, neuroinflammatory changes must be secondary, even though they may influence the development of neurodegeneration. Primary microgliopathies, such as Nasu-Hakola disease (Paloneva et al. 2000) and hereditary diffuse leucoencephalopathy with spheroids (Rademakers et al. 2012), are not characterized by Tauopathy.

Aggregated recombinant human Tau induced inclusion formation, but with a lower efficiency than aggregated Tau from transgenic mouse brain (Clavaguera et al. 2013b, Iba et al. 2013). Similar differences have been described for prions, Aβ, α-synuclein, and reactive serum amyloid A assemblies (Meyer-Luehmann et al. 2006, Zhang et al. 2008, Luk et al. 2012, Stöhr et al. 2012, Prusiner 2013, Recasens et al. 2014). Recombinant Tau aggregates were more resistant to disaggregation by guanidine hydrochloride and digestion by proteinase K than Tau aggregates from transgenic mouse brain, consistent with the view that more stable aggregates possess lower seeding activity. Recombinant aggregated Tau was also more stable than Tau filaments from AD brain.

Distinct conformations accounted for differences in seeding potency (Falcon et al. 2015). Thus, Tau filaments formed from recombinant P301S Tau following seeding with aggregated Tau from transgenic mouse brain (in the absence of heparin) showed resistance to guanidine hydrochloride, which was similar to that of Tau seeds from the brains of mice transgenic for human P301S Tau. The seeding potency of Tau filaments was like that of brain-derived aggregated Tau.

When presymptomatic P301S Tau transgenic mice were intracerebrally injected with brain extracts from symptomatic animals (Ahmed et al. 2014), Tau inclusions formed rapidly at the injection sites. Contralateral and caudorostral propagation was evident in nuclei with strong afferent and efferent connections to the injection sites, indicating that the spread of pathology was dependent on connectivity, not proximity.

Virally mediated expression of Tau has also been used to study propagation. Several groups observed Tau aggregates in dentate gyrus following adeno-associated virus-mediated expression of P301L Tau in entorhinal cortex (Siman et al. 2013, Asai et al. 2015, Wegmann et al. 2015). Spreading of wild-type Tau was also observed when lentiviral vectors were used (Dujardin et al. 2014).

The intraperitoneal injection of brain extracts from symptomatic P301S Tau transgenic mice into presymptomatic mice promoted the formation of cerebral Tau inclusions (Clavaguera et al. 2014). Aggregated Tau can thus promote inclusion formation in the central nervous system of transgenic mice following peripheral administration. Similar findings have been reported for prions, assembled Aβ, and assembled α-synuclein (Eisele et al. 2010, Prusiner 2013, Sacino et al. 2014).

We dissected the molecular characteristics of seed-competent Tau from the brains of symptomatic P301S Tau transgenic mice (Jackson et al. 2016). Sucrose gradient fractions caused aggregation in transfected cells only when large Tau aggregates (>10 mers) were present. The same fractions induced the formation and spreading of filamentous Tau in presymptomatic transgenic

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mice, whereas fractions containing monomers and small Tau aggregates were inactive. Immunoelectron microscopy showed that seed-competent sucrose gradient fractions contained aggregated Tau species including ring-like structures and small fibrils.

Cells may interact with particles, not the monomeric proteins that make up those particles (Pieri et al. 2012). Because Tau oligomers may be made of 50–100 monomers and fibrils of thousands of monomers, at an equal concentration, many more oligomers than fibrils were injected. It will be important to determine if similar species of aggregated Tau underlie seeding, spreading, and neurodegeneration in AD and other human Tauopathies.

Assuming that intracellular aggregation requires seeds moving from one cell to another, it follows that inhibition of seed uptake, seeding, and release provides novel therapeutic opportunities. Antibodies may be able to target what is an obligatory extracellular stage, provided that Tau aggregates are not contained within membranous structures. Anti-Tau antibodies have been shown to reduce the amount of hyperphosphorylated and aggregated Tau in transgenic mice (Yanamandra et al. 2014, Sankaranarayanan et al. 2015). When Tau assemblies enter cells, they can be detected and neutralized via a danger response mediated by bound anti-Tau antibodies and the cytosolic Fc receptor tripartite motif protein 21 (TRIM21) (McEwan et al. 2017). Tau seeds are neutralized by TRIM21 through the activity of the proteasome and the AAA ATPase p97/valosin-containing protein, in a manner similar to that of infectious viruses. Most studies have used transfected nonneuronal cells, some of which were of human origin, or primary nerve cells from rodents. However, human neurons derived from induced pluripotent stem cells also took up seeds and exhibited seed-induced Tau aggregation (Usenovic et al. 2015, Verheyen et al. 2015).

Taken together, it thus appears that the spread of Tau pathology in transgenic mouse brain is linked to the connectivity of neurons rather than to their proximity (Ahmed et al. 2014). Equally, in human brain, the lack of Tau aggregate spread to disconnected frontal cortex (Duyckaerts et al. 1997) strongly suggests that connectivity is central to spreading, as does the stereotypical staging of Tau pathology in AD (Braak & Braak 1991). Increased neural activity stimulates the release of Tau (Pooler et al. 2013, Yamada et al. 2014) and can accelerate Tauopathy (Wu et al. 2016). Synaptic contacts appear to be important for the transmission of Tau from cell to cell (Calafate et al. 2015). These observations strongly support a model in which the principal mode of spreading of pathology in brain occurs by transport of Tau aggregates, their release at synapses, and their uptake by recipient cells, where they act as seeds for the next round of propagation (**Figure 4*b*,*c***).

STRAINS OF AGGREGATED TAU

The intracerebral injection of brain homogenates from humans with pathologically confirmed Tauopathies led to the formation of neuronal and glial Tau inclusions in ALZ17 mice (Clavaguera et al. 2013a). Inclusions formed after inoculation of brain homogenates from all cases of AD, TD, PiD, AGD, PSP, and CBD. Brain homogenates from patients with AGD, PSP, and CBD produced lesions similar to those of the human disorders. With the exception of PiD, the inclusions of the Tauopathies used were made of either 4R Tau (AGD, PSP, and CBD) or a mixture of 3R and 4R Tau (AD and TD).

Injection of PSP homogenates into ALZ17 mice gave rise to silver-positive neuronal and glial Tau aggregates; the latter resembled tufted astrocytes, the hallmark lesion of PSP. The injection of CBD homogenates produced neuronal inclusions and silver-positive structures reminiscent of astrocytic plaques. With AGD homogenates, argyrophilic grains and silver-negative astrocytic Tau inclusions were seen, like in the human disease. With the exception of PiD, Tau inclusions propagated over time to connected brain regions. Similar, although fewer, inclusions formed after the intracerebral injection into nontransgenic mice of brain homogenates from human Tauopathies.

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Some of these findings were replicated when AD and CBD brain homogenates were injected into a mouse line transgenic for human P301S Tau (Boluda et al. 2015).

Induced Tau pathology propagated serially when brain homogenates from ALZ17 mice that had received bilateral injections of brain extracts from human P301S Tau transgenic mice 18 months earlier were injected into 3-month-old ALZ17 mice (Clavaguera et al. 2013a). In a different experiment, homogenates were prepared from the brains of nontransgenic mice that had been injected bilaterally with AGD brain homogenates 18 months earlier. Twelve months after the intracerebral injection of these homogenates into ALZ17 mice, many neuropil threads and Tau aggregates were present at the injection sites.

Morphologically different Tau assemblies made of four Tau repeats formed in human embryonic kidney (HEK) cells. Inoculation of these assemblies into the hippocampus of young transgenic mice induced pathologies that were stable through serial transmission. When HEK cells expressing four Tau repeats were seeded with homogenates from these brains, inclusions formed that were identical to those present initially (Sanders et al. 2014).

These observations suggest that different strains of aggregated Tau may exist, but additional work is required. In particular, it will be important to see if a given Tau strain possesses unique structural features. Fibril heterogeneity may arise from packing polymorphisms, segmental polymorphisms, or both (Wiltzius et al. 2009). Packing polymorphisms refer to differences in the packing of β-sheets, whereas segmental polymorphisms arise from the presence of multiple amyloidogenic segments in the same protein, with each segment forming a different type of fibril. Network connectivity studies have provided evidence that different Tauopathies, which show filaments with different morphologies (**Figure 3**) (Crowther & Goedert 2000), may be caused by distinct molecular conformers of assembled Tau (Zhou et al. 2012). This may explain (at least in part) selective neuronal vulnerability. Host factors, including different turnover rates of proteins between nerve cells, different levels of arborization, and different numbers of active mitochondria, may also play an important role (Walsh & Selkoe 2016).

TAU TOXICITY

Aggregation of Tau into amyloid fibrils is a defining feature of AD and other Tauopathies. In the human diseases, nerve cells and glial cells become dysfunctional and die, giving rise to disease symptoms. The molecular nature of toxic Tau species is an important issue for future work.

In human Tauopathies, only full-length Tau can be detected in the sarkosyl-insoluble fraction (Goedert et al. 1992a), suggesting that bulk truncation, if it occurs, happens after assembly. However, some Tau truncation cannot be excluded in early aggregation, toxicity, or both. In mice transgenic for human mutant P301L Tau (line JPNL3), activation of calpains gave rise to toxic forms of Tau (Rao et al. 2014). It was accelerated because of a marked depletion of calpastatin, an endogenous calpain inhibitor. In a separate study, coexpression of human (151–421) 3R and full-length 4R Tau (wild-type or P301S) in mice led to a failure of axonal transport, clumping of mitochondria, disruption of the Golgi apparatus, and missorting of synaptic proteins (Ozcelik et al. 2016). There was extensive nerve cell dysfunction and paralysis by three weeks of age, but sarkosyl-insoluble Tau and Tau filaments were not present. Thus, sarkosyl-soluble, aggregated Tau can cause neurotoxicity in the absence of filaments. When the expression of truncated Tau was halted, most mice recovered.

These observations support the postulated importance of oligomeric, sarkosyl-soluble Tau for the pathogenesis of human Tauopathies. They suggest that early stages of toxicity may be reversible. The future will tell if a reversible toxic phase precedes an irreversible neurodegenerative phase in human Tauopathies.

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Tau oligomers have been detected in the brains of patients with AD (Maeda et al. 2006, Lasagna-Reeves et al. 2012). In transgenic mouse models of Tauopathies, nerve cell loss and memory deficits can apparently precede detectable filamentous Tau pathology (Andorfer et al. 2003). Moreover, nerve cell loss has been reported in the absence of filaments in human Tau–overexpressing *Drosophila* (Wittmann et al. 2001), suggesting that the events that lead from Tau accumulation to neurodegeneration may not necessarily involve filament formation.

Mouse lines transgenic for human mutant P301S Tau develop sarkosyl-insoluble Tau inclusions, neurodegeneration, and paralysis (Allen et al. 2002). Inclusions form only when animals heterozygous for the transgene are over 12 months old. However, in the rTg4510 mouse model, which massively overexpresses human mutant P301L Tau in a largely reversible manner, researchers have described a dissociation between the processes that lead to memory loss and neurodegeneration and those that result in Tau filament formation (SantaCruz et al. 2005). Thus, nerve cell loss stopped when transgene expression was reduced in animals older than four months, but the number of tangles kept increasing. Moreover, nerve cell loss occurred in the dentate gyrus of the hippocampus without the formation of Tau filaments, whereas in the striatum only a small degree of cell loss was observed, despite large numbers of Tau filaments (Spires et al. 2006). A subsequent study showed that memory loss correlated with the presence of soluble Tau oligomers (Berger et al. 2007).

Nonfilamentous Tau aggregates are therefore apparently more toxic than filaments. It remains to be seen if this also applies to human brain, where nerve cells with neurofibrillary tangles can survive for many years (Morsch et al. 1999). Filamentous Tau aggregates may be space-occupying, biologically inert lesions that slowly suffocate and kill nerve cells and their processes while surviving the death of these cells in AD. This would be consistent with the known correlation between the presence of Tau fibrils and neurodegeneration.

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CONCLUSION

The ordered assembly of Tau proteins represents the gain of toxic function that causes human Tauopathies. Downstream of assembly, Tau propagation and neurodegeneration take place. Small Tau fibrils are the major species responsible for propagation. The molecular Tau species responsible for neurodegeneration remain to be identified.

DISCLOSURE STATEMENT

D.S.E. is chair of the Scientific Advisory Board of ADRx, Inc., a company seeking therapies for amyloid diseases. The authors are not aware of any other affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We thank Hans Kretzschmar (1953–2014) for **Figure 1**. Janine Goedert and Claude D. Conter helped us to decipher Alzheimer's handwriting. M.G. is an Honorary Professor in the Department of Clinical Neurosciences at the University of Cambridge. He is supported by the United Kingdom Medical Research Council (MC_U105184291) and the European Union Joint Program–Neurodegenerative Disease Research. D.S.E. is an Investigator of the Howard Hughes Medical Institute and is supported by US National Institutes of Health grants AG 02943 and AG 04812.

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Annual Review of Neuroscience

Volume 40, 2017

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