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Tau and Tauopathies

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Abstract

Tauopathies are age-related neurodegenerative diseases that are characterized by the presence of aggregates of abnormally phosphorylated tau. As tau was originally discovered as a microtubule-associated protein, it has been hypothesized that neurodegeneration results from a loss of the ability of tau to associate with microtubules. However, tau has been found to have other functions aside from the promotion and stabilization of microtubule assembly. It is conceivable that such functions may be affected by the abnormal phosphorylation of tau and might have consequences for neuronal function or viability. This chapter provides an overview of tau structure, functions, and its involvement in neurodegenerative diseases.

Keywords

Tau; Alzheimer's disease; tauopathies; phosphorylation; SH3 domain; microtubule

Tau was discovered as a microtubule-associated protein from porcine brain that promoted microtubule assembly *in vitro* [1]. The tau protein sequence determined from murine cDNA was the first to be reported for a microtubule-associated protein [2] and subsequently, antisense treatment of primary neuronal cultures indicated a critical role for tau in axonal development [3]. While studies of two independently generated tau knockout mouse models suggested that mice lacking tau appeared to develop normally, neurons cultured from one such mouse showed detectable slowing in axonal maturation [4; 5]. In addition, the defects in neuronal development exhibited by a MAP1B knockout mouse were exacerbated when tau was also deleted [6]. These studies underline the fact that several microtubule-associated proteins exist in the brain and suggest that each might have their own distinct functions during development and in the adult. In fact, while tau shares significant sequence homology with microtubule-associated proteins MAP2 and MAP4 in the carboxyl terminus microtubule binding domain, it shares very little homology in the amino terminal "projection domain" [7; 8].

The idea that different microtubule-associated proteins each have distinct functions is clearly illustrated by the fact that only tau has been associated with neurofibrillary tangles in age-related neurodegenerative diseases such as Alzheimer's disease (AD) [9; 10; 11]. Moreover, mutations in the tau gene, MAPT, cause autosomal dominant neurodegenerative diseases such as frontotemporal dementia with Parkinsonism linked to chromosome 17 [12; 13; 14], and transgenic mouse models expressing mutant tau exhibit neuronal loss (reviewed by [15; 16; 17; 18]). A mechanistic understanding of the route by which tau leads to neurodegeneration is still unclear. However, alongside hypotheses based on the loss of tau's ability to stabilize microtubules are other possibilities based on new functions and interactions that have been described for tau. This chapter will summarize recent studies on

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the interaction of tau with microtubules in addition to investigations indicating that the function of tau extends beyond its actions on microtubules. Much like its microtubule-binding properties, these alternative functions of tau may be regulated by phosphorylation. Therefore, such functions might be altered in the disease state where tau is abnormally phosphorylated and play a role in neuropathological processes.

I. Tau gene and isoforms

Tau is encoded by a single gene, *MAPT*, located on chromosome 17q21 [19]. *MAPT* is over 50 kb in size and comprises two haplotypes, H1 and H2, with multiple variants of each [20; 21]. Several tau isoforms are generated by alternative splicing, creating both high and low molecular weight isoforms. The human central nervous system expresses six low molecular-weight isoforms that range in size from 352 to 441 amino acids (Fig. 1). These isoforms are differentiated by the presence or absence of sequences encoded by *MAPT* exons 2, 3, and 10 [22]. Exons 9, 10, 11, and 12 each encode a microtubule binding motif. The four motifs are imperfect copies of an 18 amino acid sequence termed a “repeat,” and each repeat is separated by a 13–14 amino acid inter-repeat sequence [2]. Isoforms that include exon 10 are commonly referred to as four-repeat or 4R tau isoforms while those that exclude exon 10 are referred to as three-repeat or 3R tau isoforms. Alternative splicing of tau is developmentally regulated, with exons 2, 3, and 10 being expressed only post-natally [22]. Human adult tau has approximately equal representation of 3R and 4R tau isoforms, with the 1N3R and 1N4R being the most abundant forms [23; 24]. Alternative splicing of human tau differs from that of rodent tau, as adult rodent tau is predominantly 4R tau [25]. Comparison of the tau sequence from mouse, rat, cow, monkey, goat, and chicken shows high conservation of the microtubule binding repeats across species [2; 25; 26; 27; 28]. Tau-like sequences have also been found in frog, nematode, and zebrafish [29; 30; 31].

Because 4R tau isoforms contain a fourth microtubule binding repeat, adult tau interacts with microtubules more strongly [32; 33; 34]. Tau alternative splicing can also affect its phosphorylation, which influences the interaction between tau and microtubules [35]. Phosphorylation is generally higher in fetal tau [36]. When a single tau cDNA is expressed by transfection in cells, several differentially phosphorylated species can be generated.

While mice with a disrupted tau gene are viable, microarray analysis performed on the brains of such mice showed alterations in gene expression relative to *wild type* mice [37]. The genes with the highest levels of change did not involve the cytoskeleton, suggesting that the most critical function of tau may not be related to microtubule binding. For example, adult tau knockout mice had increased muscle weakness [38] and were protected against experimentally induced seizures [39]. The idea that tau might play a role in processes other than axonal development is supported by the fact that tau is expressed in non-neuronal cells. Tau expression has been reported in muscle, liver, kidney, and other tissues [40; 41]. It has also been found in human breast, prostate, gastric, and pancreatic cancer cell lines and tissues [42; 43; 44; 45; 46], as well as in the muscle cells of individuals with inclusion body myositis [47]. The function of tau in non-neuronal cells remains to be elucidated and functions outside of the cytoskeleton may have significance for neurodegenerative disease.

II. Tau in neurodegenerative disease

While the discovery of tau predated its connection to AD, its importance in neurodegenerative disease has attracted a large community of investigators. AD is characterized by two neuropathological features, senile plaques and neurofibrillary tangles, and tau is the primary component of the neurofibrillary tangles (NFT, reviewed by [48; 49]). Senile plaques are made of amyloid β-protein (Aβ) and the gene encoding Aβ has been connected to AD (reviewed by [50]). However, *MAPT* has not been genetically linked to AD.

Nevertheless, cultured neurons exposed to Aβ do not undergo cell death in the absence of tau [51]. Likewise, genetically removing tau from animal models that exhibited amyloid plaques lessened the deficits induced by the amyloid [39]. These findings underline a critical role for tau in the neurodegenerative process. Moreover, tau pathology is found in several other age-related neurodegenerative diseases such as progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's disease, argyrophilic grain disease (AGD), and frontotemporal dementia. Tau pathology involving 4R tau is found in PSP, CBD, and AGD, with tau aggregates being found in the medial temporal lobe, cortex, basal ganglia, subthalamic nucleus, and substantia nigra. Besides neurons, oligodendrocytes and astrocytes can also display tau pathology. Pick's disease has 3R tau in the Pick bodies that are found in the hippocampus and dentate fascia. The clinical presentation of these diseases includes dementia, Parkinsonism, and focal cortical syndrome (reviewed by [52; 53; 54; 55]).

The importance of tau in neurodegeneration has been verified by the discovery of *MAPT* mutations in families with frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17; reviewed by [56; 57; 58]). Mutations in the tau gene are responsible for ≈30% of inherited FTD. These mutations are autosomal dominant and can be located in either coding or non-coding regions. More than 90% of the mutations in coding regions are located in the carboxyl terminal end of tau, with P301L being the most prevalent (Table 1). Mutations in non-coding regions are mainly within the intron separating exons 10 and 11. These mutations modulate alternative splicing of the *MAPT* mRNA, resulting in higher than normal levels of 4R tau relative to 3R tau [59]. In addition, the tau haplotype H1c has been linked to progressive supranuclear palsy [21; 60].

Tauopathy models

Transgenic animals expressing mutant tau cDNAs exhibit tau pathology that increases with age. While these models have shown a variety of traits, perhaps owing to the variety of mutations and gene promoters employed, a striking feature has been neuronal loss and behavioral deficits (reviewed by [16; 17; 61]). Mouse models expressing only mutant genes involved in amyloid production showed amyloid plaques, but did not acquire neurofibrillary tangles or suffer neuronal loss [62]. Therefore, inclusion of a mutant tau cDNA in addition to mutant genes involved in amyloid production was integral in creating a triple transgenic mouse model that exhibited both the plaques and tangles characteristic of AD [63].

Cell culture models that reproduce tau filament formation have been reported [64; 65]. However, the polymerization of *E. coli*-synthesized tau in vitro, induced by either arachidonic acid or heparin, has enabled a more extensive analysis of the structural features of tau that are involved in polymerization (reviewed by [66; 67; 68]). These studies have led to the identification of specific motifs in the tau repeat region that facilitate the formation of tau filaments [69]. In such assays, FTDP-17-associated missense mutations or tau truncation at Asp421 increased filament formation [70; 71; 72]. These results suggest that filament formation in the human neuroblastoma cell culture model may have involved the cleavage of tau at Asp421, as conversion of the neighboring Ser422 to Ala or Glu led to a loss of filament formation in cells [64]. Lastly, the in vitro assays have indicated that several phosphomimicking mutations slowed filament formation [73; 74; 75], although some facilitated formation [76].

Despite the evidence that tau filaments are a hallmark feature of classic AD pathology, some models hint at the possibility that tau filaments may not be a prerequisite for neurodegeneration. Studies of a mouse model with inducible tau expression have shown that down-regulation of tau expression, without a decrease in tangle burden, was sufficient to ameliorate behavioral deficits [77]. Moreover, tauopathy mouse models exist where behavioral deficits were exhibited without the presence of tangles or neuronal loss [78; 79]. In addition, in

Drosophila and nematode tauopathy models, neuronal loss and behavioral deficits occurred without the formation of tau filaments [80; 81]. Taken together, these studies have suggested that tau, in its soluble form, may have unidentified roles in the mechanisms underlying both neuronal cell function and disease. Tau oligomers that occur in advance of tau filaments have been proposed as a critical entity in the neurodegenerative process (reviewed by [82]). These observations, in combination with other recent studies, have raised the possibility that tau filament formation may be a protective mechanism initiated by cells to sequester abnormal tau (reviewed by [83; 84; 85]).

In neurodegenerative disease, the phosphorylation state of tau in NFTs and other tau lesions is abnormal, meaning that there is an increase in both the overall number of sites phosphorylated and the level of phosphorylation at particular sites relative to normal adult brain tau. Tau phosphorylation is complex. The 441 residue tau protein has 45 Ser, 35 Thr, and 5 Tyr residues, presenting a multitude of phosphorylation sites. In addition, phosphorylation at some sites facilitates the subsequent phosphorylation of other sites. The effect of phosphorylation depends on the location of the site modified (See Section IV below). Both kinases and phosphatases have been implicated in the appearance of abnormally phosphorylated tau, and despite differences in the morphology of tau lesions among tauopathies, abnormal tau phosphorylation is a common denominator. Interestingly, many sites that are phosphorylated in disease correspond to sites that are phosphorylated during normal brain development [86; 87; 88]. The regulation of tau phosphorylation and tau kinases in both development and disease, as well as the functional significance of tau phosphorylation, has been the subject of much investigation. Because of the prevalence of abnormal tau phosphorylation during neurodegeneration, reducing tau phosphorylation as a therapeutic strategy has been investigated (reviewed by [89; 90]). A significant challenge has been limiting the action of kinase inhibitors to tau phosphorylation.

The abnormal phosphorylation of tau also occurred in tau transgenic mouse models that express either FTDP-17 mutant or wild type tau (reviewed by [91]) and reducing tau phosphorylation in one such model lessened aggregated tau and axonal degeneration [92]. Experiments in *Drosophila* tauopathy models have demonstrated that tau phosphorylation is required for neuronal loss [93]. This same study also showed that cell cycle genes were required for tau-induced neurodegeneration, supporting the hypothesis that neurons die because they are receiving signals to divide (reviewed by [94; 95]). The presence of “mitotic” phospho-epitopes in “disease tau”, characteristic of the tau expressed during development, had first led to this hypothesis [96; 97; 98; 99] and the presence of tetraploid neurons in AD brain has strengthened the hypothesis [100].

III. Interactions with the cytoskeleton

Microtubule binding and assembly

Tau was originally discovered through its ability to promote microtubule assembly, which stems from its ability to modulate the dynamic instability of microtubules [33; 101]. The interaction between tau and microtubules depends on the tau microtubule-binding repeats, as well as on the flanking regions upstream and downstream of the repeats. Defining the role of the flanking regions was largely accomplished by investigating the ability of truncated or point-mutated tau proteins to either associate with microtubules [102; 103; 104; 105] or to decrease dynamic instability [33].

Most recently, the physical interaction between tau and microtubules has been delineated using nuclear magnetic resonance spectroscopy (NMR). Comparison of the NMR spectra of tau in the presence and absence of microtubules indicated that while all repeats contacted the microtubules, there were specific sequences that were strongly involved in the

interaction[34; 106]. These sequences included [240] KSRLQTAPV[248], [275]VQIINKKLDLS[285], and [297]IKHV[300]. In addition, residues in the flanking regions as far upstream as Ser214 and as far downstream as Lys375 were also involved [107], with [225] KVAVVRT[231] and [370]KIETHK[375] having especially strong interactions [34]. These data indicate that in the presence of microtubules, the molecular environment around the tau regions flanking the microtubule repeats changed. Although the simplest explanation is that a direct interaction occurred between these tau areas and the microtubule, one cannot rule out the possibility that flanking regions were involved in intramolecular interactions and that in the presence of microtubules, such interactions were altered [108].

[275]VQIINKKLDLS[285] and [297]IKHV[300] are both in exon 10, a fact that may explain why 4R tau isoforms interact with microtubules more strongly than do 3R tau isoforms. Interestingly, in comparing 4R and 3R tau, it has been found that 4R tau could decrease microtubule shortening during dynamic fluctuations in microtubule length whereas 3R tau had no effect in this regard [109]. In addition, 4R tau and 3R tau showed qualitative differences with respect to their actions on the microtubule growth rate and on the behavior of growing microtubule populations [110]. These differences have significance towards both the function of microtubules over the course of development and the consequences of the change in the 4R:3R tau ratio brought on by intronic tau mutations. Lastly, the binding of tau to microtubules has been visualized by cryo-EM, showing that tau bound along individual protofilaments [111]. Synchrotron x-ray scattering data has suggested that tau altered the shape of the protofilament, resulting in changes in the curvature of microtubules and a shift from 13 to 14 microtubules per protofilament [112].

Several studies have demonstrated that some FTDP-17 missense mutations reduced the ability of tau to promote microtubule assembly [24; 113; 114; 115]. Additional insights have been gained through NMR data [116], analysis of microtubule dynamics in cells [117], and experiments utilizing *Xenopus* oocytes to assess microtubule function [118]. While these investigations have shown that some mutations attenuated the ability of tau to bind to microtubules and to regulate the dynamic instability of microtubules, missense mutations outside of the microtubule repeat region did not replicate these effects, suggesting that different FTDP-linked tau mutations affect tau function in different ways.

The interaction between tau and microtubules is greatly decreased by tau phosphorylation at Ser262 and Ser356, and phospho-mimicking replacements at these positions effectively reduce microtubule association *in vitro* and in cells [119]. Other phosphorylation sites shown to have some effects on microtubule association are Ser205, Ser212, Ser214, Thr231, Ser235, Ser396, and Ser404 [33; 75; 98; 120; 121; 122]. On tubulin, the tau-interacting site is located at the carboxyl terminal end, which is highly acidic. Therefore, the interaction between the basic tau repeat regions and microtubules is thought to be primarily electrostatic in nature. This is consistent with the ability of salt to affect the binding between tau and microtubules. Thus, it is not surprising that the addition of an acidic phosphate group to tau would attenuate its association with microtubules, provided the location of the phosphate was appropriate. A reduction in the microtubule-binding or assembly-promoting ability of tau has been a recurrent theme in hypotheses regarding the role of hyperphosphorylation in mechanisms of neurodegeneration (reviewed by [123]). As a result, development of therapeutics aimed at preserving microtubules has been undertaken (for instance, see [124]).

Axonal transport

Fast axonal transport (FAT) is significantly impaired in a number of neurodegenerative diseases, including tauopathies, and these defects have been linked to alterations in the normal function of tau (reviewed in [125]). For example, in cellular models where tau was over-expressed, a disruption in the trafficking of membranous vesicles and mitochondria

was found [126; 127; 128; 129; 130]. Similarly, various mouse models of tauopathy where wild type or mutant tau was expressed also demonstrated impaired axonal transport [131; 132]. The ability of tau to interfere with axonal transport may arise through direct interactions between tau and transport motor complexes. In fact, tau was able to associate with kinesin as demonstrated by immunofluorescence and co-immunoprecipitation experiments [133; 134]. In vitro experiments have further identified a direct interaction between tau and kinesin [135; 136], and between tau and the p150 protein in the dynein-dynactin motor complex [137]. Moreover, these direct interactions between tau and motors decreased the ability of kinesin to attach to microtubules [138] and increased the rate of motor detachment from microtubules [139; 140], although the above studies also reported conflicting data concerning whether tau altered overall cargo transport rates. As these results have shown, the effects of tau on axonal transport may be more complex than simply blocking motor access to the microtubules. For instance, an interaction between tau and c-Jun N-terminal kinase-interacting protein 1 (JIP1) has been proposed to affect the kinesin-I motor complex, causing a re-localization of JIP1 and impaired axonal transport [141]. Also, in *Aplysia*, tau overexpression was capable of causing both a complete stop in transport and a reorganization of microtubule polarity within the axon [142]. The conformation of tau may influence FAT as well since studies performed using squid axoplasm showed that soluble, monomeric tau did not affect transport [143] whereas tau filaments or N-terminal fragments significantly reduced transport using a mechanism involving PP1, GSK-3β and the light chain of the kinesin motor [144].

In spite of the abundance of data that has implicated tau in the inhibition of FAT, a study showing similar rates of axonal transport in wild type, tau transgenic, and tau depleted mice has argued against the ability of tau to significantly affect this process [145]. These discrepancies may originate from differences in tau phosphorylation between the experimental systems, differences in the experimental methods used to measure FAT, or differences in the cellular sources used. Further studies are needed to clarify the role of tau in the inhibition of FAT in neurodegenerative diseases.

Interactions with actin

Shortly after it was reported as a microtubule-associated protein, tau was also found to associate with actin *in vitro* [146; 147]. The interaction site was subsequently mapped to the microtubule binding domain, and then specifically to the repeats [148; 149]. The functional implications of this interaction have remained obscure, although tau depletion in cultured neurons altered actin morphology in growth cones [150] and inactivation of tau in the growth cones caused collapse of lamellipodia [151]. More recently, the C-terminus of tau was found to co-localize with actin in the growing neurite tips of NGF-differentiated PC12 cells [152]. Nevertheless, *E. coli* tau failed to bind to actin *in vitro* [153], suggesting that these previously reported associations might require specific tau phosphorylation or involve intermediates. An association with actin may explain why tau phosphorylated on Ser262, a modification that decreases the affinity of tau for microtubules, had a role in neurite outgrowth [119; 154]. Other reports have suggested that tau may affect actin remodeling indirectly. Tau expression antagonized the action of Gem GTPase, a negative regulator of Rho [37]. Rho activation is critical for neurite outgrowth, therefore tau could affect neurite outgrowth by lessening the inhibition of Rho by Gem GTPase. In addition, in fibroblasts treated with platelet-derived growth factor, tau expression delayed actin stress fiber recovery, wherein tau-expressing cells maintained the “high Rac, low Rho” actin morphology characteristic of activated cells [155]. Given the many interactions that have been described for tau (see Section V), as well as its known localization in the axonal growth cone [156; 157], it is probable that tau has a role in orchestrating actin remodeling in response to signaling during neurite outgrowth.

An interaction between tau and actin has also been described in animal models of tauopathy. Actin aggregates analogous to Hirano bodies were found when human mutant tau was

expressed in *Drosophila* and actin aggregates were also identified in mouse tauopathy models [158]. Moreover, actin and actin-related proteins appear in the neuropathology of Alzheimer's disease [159].

IV. Phosphorylation and other post-translational modifications

The phosphorylation of tau on serines and threonines is developmentally regulated. Table 2 lists the phosphorylated residues that have been identified in fetal and adult rat tau either by mass spectrometry [36; 160] or by phospho-specific antibody probes [98; 161; 162]. These experiments demonstrate that fetal tau is more highly phosphorylated than adult tau. The phosphorylation of tau in AD includes all of the sites shown in Table 2 [160; 161]. Table 3 lists some commonly used tau antibodies, several of which detect specific phosphorylated sites. In AD, tau is phosphorylated either at sites that are not normally phosphorylated in adult tau or at a higher level at sites that are normally phosphorylated in adult tau.

The phosphorylation of tau causes conformational changes that result in a slowing of its electrophoretic migration, and early structural studies found that tau became more elongated upon phosphorylation [163]. Fluorescence resonance energy transfer studies have suggested that tau normally exists in a conformation in which both the amino and carboxyl termini fold inward. This allowed the carboxyl terminus to simultaneously interact with both the microtubule repeat domain and the amino terminus [108]. Phosphomimicking mutations altered this conformation and generated reactivity to a conformation-specific tau antibody [164]. Such conformational changes may underlie the effects of tau phosphorylation on its interactions with other proteins. Phosphorylation of tau could also affect its proteolytic cleavage [165].

Several Ser/Thr kinases act on tau (recently reviewed by [49]). Among the best studied are the proline-directed kinases GSK3β, cdk5, MAPK (ERK), JNK (SAPK), and p38. Non-proline directed kinases MARK, casein kinase I (CKI), PKA, CaMKII, and PKC also phosphorylate tau. In some cases, tau phosphorylation at one site facilitated phosphorylation at another site, known as "priming." This has been demonstrated by the requirement of cdk5− or GSK3β-mediated phosphorylation of residue Ser235 prior to phosphorylation of Thr231 by GSK3β [122; 166]. FTDP-17 mutations also promoted phosphorylation *in vitro* [167]. Many studies have been performed either *in vitro* with purified kinases or brain extracts, or in transfected cells where both tau and kinases were overexpressed. A significant challenge, though not unique to tau, has been to identify the kinases that are responsible for the phosphorylation of the endogenous protein in neuronal cells.

The regulation of tau phosphorylation during development is of significant interest as several of the sites phosphorylated in disease appear normally during early development. In neuroblastoma cells, Ser214 and Ser262, in addition to several proline directed sites such as Ser202, Thr205, Thr231, Ser235, Ser396, and Ser404 become highly phosphorylated during mitosis [96; 97; 98]. These findings suggest that in developing neurons, tau phosphorylation can be regulated by cell cycle mechanisms. Changes in tau phosphorylation occurring when neuronal cells were treated with Aβ also have been investigated [168]. These findings have implicated both GSK3β and MAPK [169; 170] as kinases involved in the abnormal phosphorylation of tau during AD pathogenesis. The phosphorylation of tau has also been investigated in mouse models of tauopathy as well as in mouse models where kinases or phosphatases were expressed (reviewed by [91]).

Phosphatases also act on tau, and phosphatase inhibition has been suggested as one mechanism by which tau acquires its hyperphosphorylated state during the neurodegenerative process [171]. Both PP1 and PP2A associate with and dephosphorylate tau [172; 173; 174; 175], with PP2A accounting for 70% of the tau phosphatase activity in

brain [176]. FTDP-17 mutations reduced the interaction between PP2A and tau, suggesting another route by which these mutations would result in hyperphosphorylation and disease [177].

Tau contains five potential sites for tyrosine phosphorylation and Src family tyrosine kinases (Fyn, Src, and Lck), Syk, Abl, and tau-tubulin kinase phosphorylate tau. Direct interactions between tau and the SH3 domains of Fyn, Src, and Lck have been demonstrated [178], and tau also interacts with Abl and Syk [179; 180]. Fyn, Src, and Syk phosphorylate tau at Tyr18 [180; 181], while Abl phosphorylates Tyr394 [179]. Phosphorylated Tyr18 and Tyr394 have been found in early development, in tauopathy mouse models, and in AD brain, reproducing the behavior seen with disease-related Ser/Thr phosphorylated sites [179; 181; 182; 183]. Phospho-Tyr197, a modification that can be generated by tau tubulin kinase [184], has been identified along with phospho-Tyr394 in the tau filaments isolated from a tauopathy mouse model. It also occurs in AD brain [182]. The phosphorylation of tyr29 by Lck has also been reported [185]. Functional implications for the tyrosine phosphorylation of tau have yet to be elucidated. However, the presence of these modifications in tau pathology, and data implicating Fyn in AD [186; 187; 188], suggests that activated tyrosine kinases will also be a part of the neuropathogenic process.

In addition to being phosphorylated, tau can be O-GlcNAcylated, nitrated, and ubiquitinated. Because O-linked GlcNAcylation of tau occurs on Ser and Thr residues [189], it has the potential to indirectly regulate tau phosphorylation [190]. Tau nitration on Tyr29 has been found in AD and other tauopathies [191], and the presence of nitration, which is catalyzed by reactive nitrogen species, is consistent with an elevation of oxidative stress during neurodegeneration. Ubiquitination of tau is readily seen following co-transfection of tau and the E3 ubiquitin ligase CHIP (carboxy terminus of Hsp70-interacting protein) into non-neuronal cells [192; 193; 194]. The presence of ubiquitinated tau is well established in AD [195] and the specific lysines modified in abnormal tau from AD brain have been identified as Lys254, Lys311, and Lys353 [196]. Ubiquitination of tau has been shown to increase soluble tau levels, and to target tau for proteasomal degradation [192; 193; 197]. Tau can also undergo sumoylation, a ubiquitin-like modification, at Lys340 [198].

V. Other interactions

Phospho-serine/threonine-based interactions

Tau interacts with Pin1, a prolyl-isomerase that changes the conformation of phospho-Ser/Thr-pro bonds from cis to trans conformation. This interaction was initially shown to involve the WW domain of pin1 that recognizes phospho-Ser/Thr residues, and the phospho-Thr231 residue of tau [199]. Subsequently, an interaction between pin1 and the phospho-Thr212 residue of tau was also uncovered by NMR [200]. The presence of pin1 restored microtubule-polymerizing properties to tau lost following cdc2-mediated phosphorylation [199] and reduced the levels of tau phosphorylation in tau transgenic mice [201; 202]. These observations have been attributed to an increase in the susceptibility of tau to phosphatases in the presence of pin1 [203; 204]. The opposing effects of pin1 on *wild-type* versus FTDP-17 mutant tau has presented more evidence for the potential importance of the interaction [201; 202]. Also contributing to the interest in the pin1-tau interaction is the finding that the pin1-knockout mice exhibited age-dependent neurodegeneration, increased tau phosphorylation, and neuropathology [204].

14-3-3 is a signal transduction protein that exists in several isoforms, of which the 14-3-3ζ isoform has been identified as a tau interactor [205]. 14-3-3ζ has been shown to increase PKA-mediated tau phosphorylation [205; 206], while its effect on GSK3β-mediated tau phosphorylation is less clear [207; 208; 209]. The phospho-Ser214 residue on tau is thought to

be the primary binding site for 14-3-3ζ [210], with the added presence of phospho-Ser235 strengthening the interaction [211]. While the impact of 14-3-3ζ on tau phosphorylation in neuronal cells remains to be investigated, evidence that the interaction is influenced by both the phosphorylation state and the isoform of tau [212] suggests that the interaction could potentially have implications for both development and disease.

Tau is able to enhance growth factor-induced MAPK signaling through a mechanism that required the phosphorylation of tau at Thr231 [213]. Tau was phosphorylated on Thr231 in response to nerve growth factor (NGF) and tau depletion attenuated MAPK activation as well as AP-1 activation [213]. The effect of tau on signaling was independent of an interaction between tau and microtubules. Interestingly, these findings may have significant implications for the role of tau in neurodegenerative disease as the early appearance of phospho-Thr231-tau [214; 215], as well as an abnormal activation of MAPK, occurs in AD [216; 217; 218]. One could speculate that abnormal MAPK signaling induced by various upstream triggers such as Aβ accumulation, oxidative stress, and aberrant growth factor activity, would be potentiated by hyperphosphorylated tau, leading to a positive feedback loop where MAPK would phosphorylate tau further. Faulty MAPK signaling might also drive the cell cycle and culminate in neuronal cell death.

SH3 domain interactions

Within tau exons 7 and 9, upstream of the first microtubule-binding repeat, lies a proline-rich domain containing >20% proline. This region contains seven PXXP motifs that can potentially interact with the Src homology 3 (SH3) domains commonly found in tyrosine kinases and adapter proteins. *In vitro* binding assays have demonstrated that a PXXP in tau interacted with the SH3 domain of Src family kinases [178] and tau also interacted with the SH3 domains of phosphatidylinositol-3 kinase (PI3K), grb2, and phospholipase Cγ PLCγ) [219]. Co-immunoprecipitation experiments have confirmed that tau interacted with Fyn, PI3K and PLCγ in cells [43; 178; 220]. A possible functional significance of the tau-Fyn interaction is the upregulation of Fyn kinase activity by tau [155], a known consequence of SH3 domain interactions for Src family tyrosine kinases. The presence of tau also increased PLCγ activity, though the involvement of the SH3 domain interaction has not been demonstrated [221]. The involvement of the tau-Fyn SH3 interaction in directing the tyrosine phosphorylation of tau has been shown [222].

Tau phosphorylation affects SH3 domain interactions [219; 222; 223], leading to the speculation that these interactions are regulated during development and may have a role in disease. The finding that FTDP-17 tau mutations increased the tau-Fyn SH3 interaction [222] also supports a role for the interaction during neuropathogenesis.

Molecular chaperone interactions

Tau interacts with both the stress induced heat shock protein hsp70 and the constitutively expressed heat shock cognate protein hsc70 [193; 224; 225]. Both interactions promote the ubiquitination of tau by CHIP and the proteasome-mediated degradation of tau [192; 193; 194; 197; 225]. The interaction with heat shock proteins may also have a role in the degradation of tau via the autophagy-lysosomal pathway [226; 227]. Previous studies have demonstrated that phosphorylation of tau increased both its ubiquitination [193] and its degradation [228]. In addition, hsp27 and hsp90 recognize phosphorylated tau and facilitate its proteasome-mediated degradation [193; 229]. These results raise the possibility that, in response to disease-related phosphorylation modifications, the cell attempts to eliminate tau by a mechanism involving interactions with heat-shock proteins.

The tau motifs that bind to hsc70 and hsp70 have been identified and correspond to the VQI(I/V) sequences in exons 9 and 10 [224], the motifs that have been found to mediate the β-sheet conformation involved in tau filament formation [69]. Therefore, in addition to potentially directing the degradation of disease tau, the association between hsc70/hsp70 and tau could also be neuroprotective by preventing tau filament formation. The ability of hsp70 to inhibit tau filament formation *in vitro* supports this possibility [230].

Non-microtubule localizations for tau

Given that certain tau modifications result in a reduced affinity for microtubules, one would predict that non-microtubule localizations for tau exist. In fact, the association of tau with two non-microtubule structures within cells, the nucleoli and polysomes [231; 232; 233], has long been known. Phosphorylation has been proposed to regulate the localization of tau to the nucleus [234] and the direct association of tau with nucleic acid *in vitro* has also been reported [235]. It has recently been suggested that tau may contribute to chromosome instability [236].

Tau that is phosphorylated at Thr231 associated with the microtubule-organizing center [122] and tau that is dephosphorylated at Ser199/Ser202, Ser396/Ser404, or Thr231 associated with the plasma membrane [156; 237; 238]. Tau dephosphorylated at Ser199/Ser202 was also enriched in the growth cone of primary cultured neurons [156; 239]. Moreover, tau associated with lipid rafts, membrane microdomains implicated in signal transduction and growth cone function [240; 241; 242; 243]. Evidence indicating that tau-Fyn complexes existed in lipid rafts has also been reported [240].

The existence of extracellular tau has been recently reported, with the amino terminus being critical for the extracellular localization [244]. Also, an interaction between extracellular tau and muscarinic M1 and M3 receptors has been reported, suggesting that extracellular tau is capable of inducing changes in intracellular calcium [245]. These findings raise the possibility that interneuronal propagation of neurodegenerative disease may involve extracellular tau. The ability of extracellular tau to induce pathology has been explored in mouse and cell culture models [246; 247].

Amino terminus of tau

Investigations into the properties of truncated tau, terminating in exon 9, have revealed that the amino terminus of tau was capable of associating with the plasma membrane and affecting NGF-mediated neurite outgrowth [156]. Similarly, the amino terminus of tau negatively affected neurite outgrowth in oligodendrocytes [248]. Interestingly, the amino terminus of tau participated in Aβ-oligomer-activated signal transduction pathways where microtubules were disrupted [249]. Because the truncated tau used in these studies contained the proline rich region, it is conceivable that interactions with proteins such as Src family tyrosine kinases or PI3K may underlie these reported effects. Moreover, by expressing the amino terminus of tau in mice, it has been demonstrated that the localization of Fyn was shifted from the postsynaptic area to the cell soma, due to its interaction with the amino terminus of tau in the soma [250]. As a result, the association of the NMDA receptor with the postsynaptic density was reduced and susceptibility to seizure was also reduced. These data strongly argue for the amino terminus having critical functions in the neuron. Moreover, the expression of the amino terminus of tau was able to lessen the deficits of an APP transgenic mouse model, similar to that achieved when a $tau^{-/-}$ trait was introduced [39; 250].

As a separate consideration, alternative splicing of tau is capable of generating an amino terminal fragment of tau, owing to alternative splice sites in exon 6 that create frameshifts and stop codons [251]. Such tau fragments inhibited fast axonal transport [144]. In addition, a

toxic amino terminal fragment of tau, generated by calpain cleavage, has been described in neurons treated with Aβ [252]. The production of this fragment increased in aged primary neuronal cultures and decreased if membrane cholesterol was lowered [253]. Taken together, these observations provide more evidence that non-microtubule-associated tau plays an important role in both normal and diseased cells.

VI. Reflections

The idea that tau is more than a microtubule-associated protein is borne out by the fact that tau exists in forms that do not associate with microtubules and interact with many other proteins besides microtubules. And although tau knockout mice do not exhibit gross defects in brain development, their blunted response to excitotoxic stimuli suggest that tau is important for neuronal function in ways that are not yet understood. In fact, the two genes whose expression was increased the most in tau knockout mouse neurons were c-fos and fosB (Data supplement [37]), transcription factors critical for regulating transcription of a diverse range of genes. Such data strongly suggests that tau has a critical role in basic cell growth. It is not possible at present to determine whether this role stems from a function in neuronal or non-neuronal cells.

Three-dimensional structural information for tau would greatly contribute to the understanding of phosphorylation and protein conformation in tau function and the effect of FTDP-17 missense mutations and alternative splicing on tau structure. Because tau has unusual physical properties, obtaining structural data has been challenging. Recent analyses of tau using NMR indicates its potential to provide more information about tau structure [254].

The ability of tau to interact with a number of signal transduction proteins suggests a possible role for tau in signaling. Tau may participate in the mTor and JNK pathways [93; 255] and we have obtained evidence that tau potentiates NGF-induced MAPK activation [213]. However, despite available co-immunoprecipitation data for some interactions, the specific molecular complexes that engage tau as a signal transduction protein remain to be identified. Also, the functional significance of both the tyrosine phosphorylation of tau and its increased phosphorylation during development remain unclear.

While the microtubule associated functions of tau are important, its function in signaling may be equally important and it is unclear which functions are most critical during the neurodegenerative process. Establishing new functions for tau would lead to new hypotheses regarding the connection between tau and neurodegenerative disease. If a non-filamentous form of hyperphosphorylated tau is responsible for early behavioral deficits, understanding the role of phosphorylated tau during development and in signal transduction may provide clues to pathways that are mis-regulated during the disease process.

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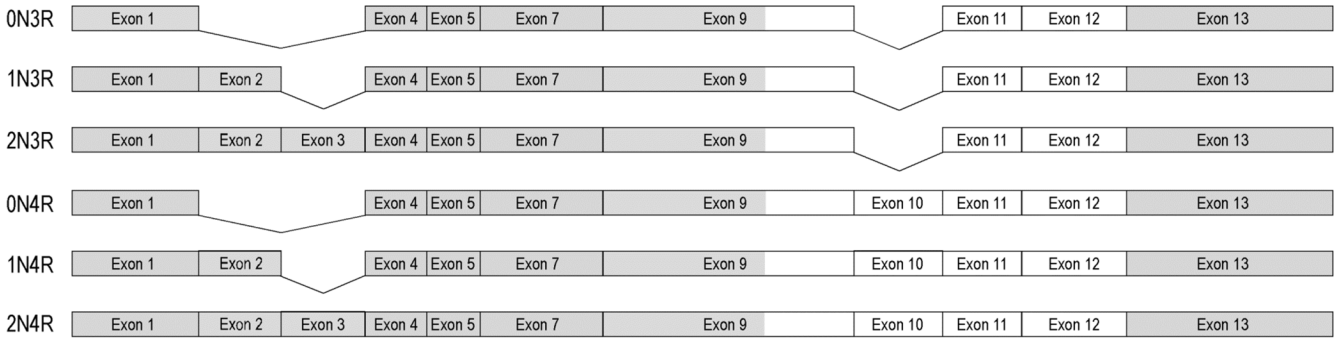

Fig. 1.

Tau schematic, drawn to scale, showing the six tau isoforms present in human brain. Exons 2, 3, and 10 are only expressed in the adult. Clear areas each contain a microtubule binding motif (e.g., exon 10-containing isoforms contain four microtubule binding motifs).

Table 1

Missense mutations in tau causing frontotemporal dementia (reviewed by [56; 57; 58])

Exon 1	Exon 9	Exon 10	Exon 11	Exon 12	Exon 13
R5H, R5L	K257T	N279K	L315R	G335V, G335S	G389R
	I260V	ΔK280	K317M	Q336R	R406W
	L266V	L284L	S320F, S320Y	V337M	T427M
	G272V	N296H, N296N, ΔN296		E342V	
	G273R	P301L, P301S, P301T		S352L	
		G303V		V363I	
		S305N, S305S		K369I	

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Table 2

Phosphorylated Ser and Thr sites in fetal and adult tau, numbered according to 441 amino acid human isoform (2N4R) of tau. Residues in bold indicate that mass spec data has been obtained for the residue. Asterisk indicates that fetal tau phosphorylation of the residue occurs at a higher level. (References: [161; 162; 184; 256; 257; 258; 259; 260])

		Possible kinases													
Fetal site	**Adult site**	**CamKII**	**CKI**	**Cdc2**	**Cdk2**	**Cdk5**	**Dyrk1a**	**GSK3β**	**JNK**	**MAPK**	**MARK**	**p38**	**PKA**	**PKB/Akt**	**TTKI**
Thr181	**Thr181***						●		●	●		●			
Ser 198								●					●		●
Ser199	**Ser199***						●	●		●					●
Ser202	**Ser202***		●		●	●	●		●	●		●			●
Thr205	Thr205*		●	●	●	●			●	●			●		
Thr212				●		●	●	●	●	●			●		
Ser214	Ser214*					●		●					●	●	
Thr217	Thr217*						●	●	●	●					
Thr231	**Thr231**			●		●	●	●	●	●					
Ser235				●		●		●	●	●					
Ser262		●						●			●		●		
Ser356		●									●	●	●		
Ser396	Ser396		●	●	●	●	●	●	●	●		●			
Ser400							●	●							
Ser404	**Ser404***		●	●		●	●	●	●	●		●			
Ser409	Ser409*	●											●		
Ser413								●		●					
Ser416		●											●		
Ser422		●					●		●			●			●

Table 3

Monoclonal tau antibodies (others are also available) Polyclonal antibodies are also commercially available.

Name	Epitope	Notes
Alz50	Involves amino terminus and MTBR	Conformation specific [261]
Tau12	Amino acids 9–18	Human specific, total tau [262]
Tau1	Amino acids 189–207	Dephosphorylation specific [263]
Tau5	Amino acids 210–230	Total tau, rodent>human [261]
AT8	Phospho-Ser202/Ser205	[264]
CP13	Phospho-Ser202	[265]
AT100	Phospho-Thr212/Ser214	
CP3	Phospho-Ser214	[265]
AT180	Phospho-Thr231	[266]
CP17	Phospho-Thr231	[267]
TG3	Phospho-Thr231	Conformation specific[268]
CP9	Phospho-Thr231	[265]
12E8	Phospho-Ser262/Ser356	[162]
PG5	Phospho-Ser409	[265]
PHF-1	Phospho-Ser396/Ser404	[269]
9G3	Phospho-Tyr18	[181]