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The role of tau phosphorylation and cleavage in neuronal cell death

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1. ABSTRACT

The microtubule-associated protein tau is the primary component of the intracellular filamentous deposits found in Alzheimer's disease (AD) brain and also in a family of neurodegenerative diseases called 'tauopathies', where tau pathology is the primary, defining characteristic with little or no amyloid-beta (Abeta) pathology. It has been demonstrated that tau modifications such as hyperphosphorylation and truncation might be important events in the process leading to tau intracellular aggregation and neuronal cell death. The discovery of tau gene mutations in frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) reinforced the predominant role attributed to tau proteins in the pathogenesis of neurodegenerative disorders. This review highlights recent findings concerning the normal metabolism and function of tau, as well as the abnormal processing and function of tau in AD and in the tauopathies.

2. INTRODUCTION

Tau is a family of microtubule-associated proteins (MAPs) that are abundant in the central nervous system (CNS), where it is expressed predominantly in axons (1). Although tau is mainly found in neurons, nonneuronal cells can express trace amounts. For instance, tau proteins are found in glial cells and oligodendrocytes (2, 3) and also in several peripheral tissues such as heart, kidney, lung, muscle, pancreas, testis, and in fibroblasts (4-6). Tau proteins play a fundamental role in stablilizing the neuronal cytoskeleton and facilitating neurite formation and stability. In addition to its role in stabilizing microtubules, over the past several years other tau functions such as roles in vesicular transport and axonal polarity have been identified and clearly indicate that tau is a multifunctional protein (7-9). Although the underlying mechanisms contributing to the pathological processing of tau in neurodegenerative conditions have not been fully elucidated, it is clear that tau becomes characteristically

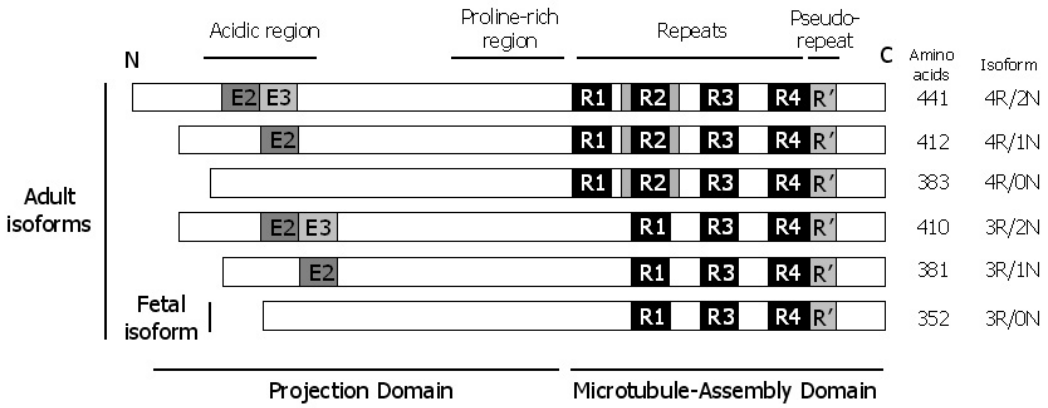

Figure 1. Schematic representation of six predominant isoforms and domains of tau found in human brain. The number of amino acids in each isoform and its abbreviation are indicated at the right. The six isoforms are generated by splicing in or out exons 2 and 3 (E2 and E3) in the N-terminal region and exon 10 (R2 and flanking gray boxes) in the C-terminal region. E2 and E3 encode respective 29-amino acid insert and each microtubule-binding repeat, designated to R1 to R4, is 18-amino acid long. Psuedorepeat region R', K369-S400 in 4R/2N tau isoform, is followed by microtubule-binding repeats. The splicing in or out exon 10 results in a tau form with or without R2, to yield isoforms with four (4R) or three (3R) microtubule-binding domains, respectively. Six isoforms of tau are present in adult human brain whereas only the shortest isoform (3R/0N) of tau is present in fetal brain. The N-terminal projection domain includes the acidic and proline-rich domains, and the C-terminal microtubule-assembly domain includes microtubule-binding repeats, pseudorepeat, and C-terminal tail part.

altered both functionally and structurally in Alzheimer's disease (AD) and other tauopathies. The 1998 discovery that tau gene mutations cause frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) increased interest in the mechanisms underlying the tau pathology in tau-related disorders (10-14). Although formation of filamentous intracellular aggregates of tau is a common pathological hallmark of these tau-related disorders, the role of insoluble filamentous aggregates as a toxic mediator in neuronal dysfunction and death is still not clear. Given that the correlation between aggregate presence and the incidence of disease does not necessarily dictate a causal relationship, the focus has been shifting to identify the toxic tau species during the entire fibrillogenic process from the soluble monomers through oligomers to the insoluble mature aggregates. There is increasing evidence that posttranslational processing of tau such as phosphorylation and limited proteolysis is driving forces in the formation of filamentous deposits. Due to these alterations, tau undergoes conformational changes as it transforms from an unfolded monomer to the structured polymer characteristic of aggregates. This review will cover recent advances in modifications of tau and their biological consequences.

3. TAU GENE AND ALTERNATIVE SPLICING

Human tau proteins are encoded by a single gene on chromosome 17q21 that consists of 16 exons. The majority of the tau isoforms in the CNS contain 8-11 exons due to alternative mRNA splicing of exons 2, 3, and 10 generating six tau isoforms ranging from 352 to 441 amino acids in length (Figure 1) (15, 16). The interaction between tau and microtubules is mediated by three or four C-terminal imperfect repeat domains (R1-R4, 31-32 amino acids each) encoded by exons 9-12 (15, 17, 18). Although the microtubule binding repeats are the functional portion of tau in terms of stabilizing the microtubules, the domains that flank these repeats play a critical role in regulating the ability of tau to bind to the microtubules. The proline-rich domain and pseudorepeat C-terminal domain R', which are upstream and downstream of the repeats, respectively, strongly enhance the tau's microtubule binding affinity (17, 19).

Alternative splicing of exon 10 produces tau isoforms with either three (exon 10-) or four (exon 10+) repeat domains, known as 3R and 4R tau, respectively (Figure 1). These three- or four-repeat domains contain imperfect 18-amino acid repeats separated by 13- or 14-amino acid-long inter-repeat sequences (20). In addition, alternative splicing of exons 2 and 3 results in 3R and 4R isoforms without (0N) or with either 29 (1N) or 58 (2N) amino acid inserts. Exon 3 never appears independently of exon 2 (21). These two additional inserts are highly acidic and are followed by a basic proline-rich region. The N-terminal part is referred to as the projection domain since it projects from the microtubule surface where it may interact with other cytoskeletal elements and plasma membrane (22-24). Projection domains may determine spacing between microtubules in the axon and may increase axonal diameter (25). In peripheral neurons, which often project a very long axon with a large diameter, an additional N-terminal tau sequence encoded by exon 4a is present generating a specific tau isoform called 'big tau' (26, 27), suggesting that the N-terminal region of tau is crucial in the stabilization and organization of certain types of axons. In adult human brain, the ratio of 3R tau to 4R tau isoforms is about one and the 1N, 0N, and 2N isoforms comprise about 54%, 37%, and 9%, respectively, of total tau (28). In addition, the alternative splicing of tau is developmentally regulated such that only the shortest tau isoform (3R/0N) is

expressed in fetal brain, whereas all six isoforms appear in the postnatal period of the human brain (29). It has been demonstrated that adult tau isoforms with 4R are more efficient at promoting microtubule assembly than the fetal isoform with 3R (17, 28, 30). Interestingly, the inter-region between repeats 1 and 2 (R1-R2 inter-region) and more specifically the peptide ^{274}WVQIINKK^{281} within this sequence, is the most potent inducer of microtubule polymerization. This R1-R2 inter-region is unique to 4R tau, which is adult-specific. The absence of this region in 3R, which is the only form expressed early in development, likely contributes to the cytoskeletal plasticity required of immature neurons (24, 31). As mentioned above, in the peripheral nervous system (PNS), inclusion of exon 4a in the amino-terminus results in the expression of 110 kDa tau protein termed 'big tau', or 'high molecular weight tau' (32-34). Novel isoforms of tau that lack the microtubule-binding domains have been reported, which are due to the use of additional 3' splice sites of exon 6 (35). Utilization of two additional splice sites results in frameshifts and produces tau molecules lacking the microtubule binding domains (35, 36). Exon 8 has so far only been found in bovine tau mRNA (37, 38).

4. CONFORMATIONAL STRUCTURES OF TAU PROTEINS

Tau is normally highly soluble and is one of the longest natively unfolded proteins, lacking significant amounts of secondary structure over a sequence of 441 amino acids in the longest human CNS isoform. Tau is an unusual protein that has long stretches of charged regions that are not conducive for intermolecular hydrophobic association (39). However, in AD brain as well as in other neurodegenerative disorders tau self-assembles into filamentous structures. Of the four microtubule binding repeats in tau, the predicted amino acids having beta-structure are concentrated in R2 and R3 and can self-assemble into filaments *in vitro* (40). Two hexapeptides within this region of tau, ^{275}VQIINK^{280} and ^{306}VQIVYK^{311}, are capable of undergoing a conformational change from a random coil to a beta sheet structure (41). Recently, it has been reported that repeat domains R2-R4 contain residual beta-structure, which has the potential to serve as nucleation seeds for aggregation of tau into PHFs (42). However, it has been also reported that PHFs are comprised of alpha-helices (43).

Truncation at both the amino- and carboxy-termini has been demonstrated to directly influence the conformation into which the molecule folds and hence the ability of tau to polymerize into fibrils, at least *in vitro*. In order to aggregate into filaments, the tau molecule must undergo a shift from an essentially unfolded random coil configuration to more compact status called the Alz50 state, where its amino-terminus comes into close proximity of the microtubule-binding repeats (44), suggesting that N-terminal domain can facilitate the formation of fibrils. Conversely, the carboxy tail of the tau molecule inhibits filament formation (45). Tau constructs lacking the carboxy tail assembled much faster and to a greater extent than wild type. Tau truncated at Asp421, the site at which caspase 3 cleaves tau, assembled more readily than the full-length tau (46, 47).

Besides the truncation of the C-terminal domain, phosphorylation at Ser396/404 greatly enhances the rates of tau filament formation *in vitro* (45). In addition, it has been reported that *in vitro* abnormal hyperphosphorylation promotes the self-assembly of tau in to tangles of paired helical filaments (PHFs) and straight filaments by neutralizing the inhibitory basic charges of the flanking regions (48). Recently, it has been demonstrated that pseudophosphorylation (in which a Ser/Thr is mutated to an Asp or Glu to mimic phosphorylation (49, 50)) in the N-terminal portion of tau up to amino acid 208 mainly suppressed tau aggregation, whereas mutations in the C-terminal region mainly lead to enhanced aggregation (51). In particular, pseudophosphorylation of Ser422 significantly facilitated the tau aggregation (51). In disease conditions where pathological alterations of tau occur in the form of abnormal phosphorylation, truncation, and/or mutations, tau can adopt a partial beta-structure, which then leads to the highly ordered morphology of the PHFs (41, 52, 53).

5. PHYSIOLOGICAL ROLE OF TAU

5.1. Microtubule binding

It has been unequivocally demonstrated that tau suppresses the dynamic instability of microtubules and thus promotes microtubule stability. The phosphorylation of tau at specific sites is the predominant mechanism by which tau function is regulated (54). It is becoming increasingly apparent that phosphorylation of a few specific sites plays a significant role in regulating tau-microtubule interactions. Phosphorylation of the KXGS motifs within the microtubule-binding repeats of tau strongly reduces the binding of tau to microtubules *in vitro* (55) and probably *in vivo* (56, 57). Since site-specific phosphorylation clearly modulates the function and intracellular localization of tau, inappropriate phosphorylation is probably a key event in the development of tau pathology. It has been demonstrated that phosphorylation of Ser262 significantly attenuates the ability of tau to bind microtubules *in vitro* (55). However *in situ*, phosphorylation of two or more KXGS motifs (especially Ser262 and Ser356) is required to decrease microtubule binding and facilitate the formation of cell processes (56). Microtubule-affinity-regulating kinase (MARK), cAMP-dependent protein kinase (PKA), and calcium/calmodulin-dependent protein kinase II might contribute to the phosphorylation of these sites *in vivo* (57-62). Phosphorylation of Thr231 also plays a significant role in regulating tau-microtubule interactions. Thr231 is a primed glycogen synthase kinase 3 beta (GSK3beta) site on tau, which means that Ser235 must be phosphorylated first to get efficient phosphorylation of Thr231 (63). Phosphorylation of Thr231 greatly diminishes the ability of tau to bind microtubules *in situ* (64). Furthermore, when cell lysates were separated into soluble cytosolic and insoluble cytoskeletal fractions, almost all the tau phosphorylated at the Thr231 epitope was present in the soluble fraction (64, 65). In addition, phosphorylation of Thr231 inhibits the ability of tau to stabilize microtubules

in the cell as indicated by a reduction in the levels of acetylated tubulin, a marker of microtubule stability (66). By contrast, phosphorylation of tau at Ser396 and/or Ser404 did not significantly affect the ability of tau to bind microtubules (64). Phosphorylation of Thr231 thus appears to play a key role in regulating tau function *in vivo*. A significant consequence of tau hyperphosphorylation is a reduction in its ability to interact with microtubules. It has been demonstrated that the pool of tau able to bind to microtubules is significantly reduced in AD brain and the degree of impairment in microtubule binding correlates with the extent of tau pathology (67). Overall, although the phosphorylation of specific sites does significantly decrease tau's ability to stabilize microtubules, it must be emphasized that phosphorylation of every site on tau does not equally affect tau's microtubule-binding affinity. These data indicate that abnormal phosphorylation rather than hyperphosphorylation appears to play a key role in regulating tau function in microtubule binding. In addition, the majority of FTDP-17 missense mutations disrupt tau-microtubule interactions reducing the ability of tau to promote microtubule assembly (68-71).

As indicated above 4R tau binds microtubules more efficiently and more effectively stabilizes microtubules than 3R tau (17, 18, 28, 30). Further, it has been demonstrated that 4R tau not only binds microtubules with a greater affinity, but can also displace 3R tau from microtubules *in situ* suggesting that 4R tau preferentially associates with microtubules and outcompetes 3R tau for microtubule binding sites (72). *In vivo*, it has been shown that the developmentally regulated transition in expression from 3R to 4R tau correlates with increased microtubule stability and decreased cytoskeletal plasticity (29, 73). However, the preferential binding of 4R tau over 3R tau to microtubules may not simply due to the addition of one more repeat domain in 4R tau (31). The inter-repeat (IR) domain, which is located between microtubule binding domains 1 and 2 and present only in 4R, has been reported to provide a unique microtubule binding site with more than twice the binding affinity of any individual repeat through distinct binding sites from those bound by the repeats, suggesting that R1-R2 IR may establish an adult-specific, high affinity anchor, which tethers the otherwise mobile tau to the tubulin to increase microtubule stability (31).

5.2. Neurite outgrowth

Tau likely plays a key role in the axonal growth and in the establishment of neuronal polarity (74). Tau strongly promotes neurite outgrowth during differentiation (7, 75-77), and even in nonneuronal cells tau induces cell processes with a cytoskeletal organization reminiscent of neurites (56, 78-80). Early studies demonstrated that suppression of tau expression in cultured cerebellar neurons by using antisense oligonucleotides significantly attenuated neurite outgrowth (7, 81). However, a tau knockout mouse has no overt phenotype except for a decrease in the number of microtubules in small-caliber axons (82). This lack of phenotype is probably due to a redundancy of function and/or compensatory upregulation of other microtubule-associated proteins (82, 83). Indeed, knocking out both MAP-1B and tau results in a severe dysgenesis of axonal tracts (corpus callosum, anterior commissure, etc), delayed neuronal migration resulting in a disruption of neuronal layer formation and disorganization of microtubules in growth cones (84). Furthermore, primary cultures of hippocampal neurons lacking tau exhibit decreased rates of neurite extension and inhibited neuronal polarization (i.e. the development of axons and dendrites) (83), defects that are more pronounced in the tau-MAP-1B double knockout model (84). During axonogenesis, tau function appears to be locally regulated by phosphorylation. Interestingly, there is a proximodistal gradient in tau phosphorylation at Ser199/202 and Thr205 along the nascent axon: tau in the cell body and proximal axon is ~80% phosphorylated at these sites (85). Furthermore, neurite outgrowth seems to require tau phosphorylation at KXGS motifs in a specific spatial and temporal manner, probably by MARK or PKA, resulting in the detachment of tau from microtubules and their destabilization (56, 86). The formation of neurites can be blocked if MARK2 is inactivated in N2a neuroblastoma cells (86). Further, neurite formation can be blocked if the target KXGS motifs on tau are rendered nonphosphorylatable by point mutations. Recently, it has been reported that overexpression of tau resulted in the stimulation of neurite outgrowth upon cAMP treatment in neuroblastoma cells (87). In contrast, there is indirect evidence that GSK3-mediated tau phosphorylation might facilitate neurite retraction (88). Interestingly, in support of tau's involvement in neurite outgrowth, it has been reported that tau mediates neurite outgrowth by torsinA protein, which is an AAA+ ATPase (89, 90). GAG deletion mutations of torsinA results in the primary early-onset torsion dystonia (91, 92).

5.3. Axonal transport

Tau proteins regulate axonal traffic (8, 9). There is increasing evidence that tau may modulate motor-based transport along microtubules. Tau appears to interfere with the binding of kinesin and kinesin-like motors to microtubules leading to a preferential inhibition of plus-end directed transport (8). In mouse models in which tau is overexpressed in the central nervous system, there is almost always axonopathy, predominantly in spinal cord neurons (93-95). In these tau-overexpression mouse models, there is invariable evidence of axonal and myelin degeneration with axonal swellings that contain cytoskeletal elements (93-95). In addition, overexpression of the shortest human tau isoform significantly inhibits fast axonal transport in ventral root axons (95). Tau can inhibit kinesin-dependent fast axonal transport in cell culture models (8, 96), and this is probably the case *in vivo* when tau is overexpressed. The primary mechanism by which tau inhibits kinesin-dependent transport is by reducing the attachment frequency of the motors. Tau has no effect on the speed or run length of kinesin once it is attached to the microtubules (97). Phosphorylation of tau modulates its affinity for microtubules and thus its ability to regulate motor activity. Overexpression of GSK3beta in mice transgenic for human tau significantly increases the phosphorylation state of tau and reduces the axonopathy compared with that in mice that overexpress human tau only. In the double-transgenic mice, there is also less motor impairment when compared

with the transgenics overexpressing the human tau alone (98, 99). This is probably because the increase in tau phosphorylation due to overexpression of GSK3beta decreases the affinity of tau for microtubules. This should make the tau in the GSK3beta-human tau double-transgenic mice less effective at competing with kinesin for binding sites, the net result being greater kinesin binding and a restoration of anterograde axonal transport. It has been demonstrated that in cell culture models, GSK3beta-mediated tau phosphorylation is associated with proper anterograde organelle transport (100), providing further evidence that the control of axonal transport by tau is regulated by GSK3beta-mediated phosphorylation. Recently, it has been also demonstrated that overexpression of tau disrupts axonal transport causing vesicle aggregation and loss of locomotor function (101). However, co-expression of constitutively active GSK-3beta enhances and GSK3beta inhibitors reverse both the axon transport and locomotor phenotypes, suggesting that the pathological effects of tau are phosphorylation-dependent (101).

5.4. Signal transduction

The interaction between tau and src family non-receptor tyrosine kinases suggests that tau may play a role in signal transduction (102-104). The proline-rich domain of tau binds to SH3 domains from the src family non-receptor tyrosine kinases such as src, fyn, and lck (104). Mapping the site of interaction on tau identified the PXXP sequence at ^{233}Pro-Lys-Ser-Pro^{236} as the region for interaction with the fyn SH3 domain. Phosphorylation is likely to regulate the interaction, as peptide-binding data has shown that phosphorylation of tau at Thr231 decreased the its binding with fyn (105). Further, interaction of fyn and tau results in the tyrosine phosphorylation of tau at Tyr18. It has been demonstrated that in mouse Tyr18 is phosphorylated early in neuronal development but is not phosphorylated in the adult. Tyrosine phosphorylated tau has also been reported in human fetal brain (106). In contrast to the phosphorylation of tau on some serines and threonines, the Tyr18 phosphorylation did not impact on its microtubule association properties (107). Moreover, tyrosine phosphorylation is closely associated with highly regulated and dynamic signal transduction processes. In neuronal cells, the importance of tyrosine phosphorylation in growth cone function is well established (108, 109). Growth cones contain src and fyn (110, 111) and neurons cultured from mice deficient in either src or fyn were defective in neurite outgrowth in a substrate-dependent manner (112, 113). The tyrosine phosphorylation of tau leads to the speculation that tau may have a role in neuronal signal transduction. Since src family non-receptor kinases associate with lipid rafts through their N-terminal modifications of myristoylation and palmitoylation (114, 115), it is conceivable that the SH3 domain interaction has a role in directing tau to lipid rafts. In oligodendrocytes, tau-fyn complexes have been found in lipid rafts and when the lipid rafts were abolished through the inhibition of sphingolipid synthesis by fumonisin B1, process outgrowth was inhibited suggesting a role for tau-fyn interaction in process outgrowth (102). However, it remains to be proven that the fyn-tau interaction is required for the lipid raft localization of tau. In addition, recruitment of tau to activated fyn in rafts appears to be an important step in myelination of oligodendrocytes (102). Indeed, tau mRNA is actively transported into the processes of oligodendrocytes and enriched at the turning and branching points, as well as in some growing tips (116), suggesting an essential role for tau in oligodendrocyte maturation.

6. POSTTRANSLATIONAL MODIFICATIONS

6.1.Phosphorylation

6.1.1.Sites of phosphorylation

There are 80 serine or threonine residues and 5 tyrosine residues in the longest tau isoform found in the human CNS; therefore, almost 20% of the molecule has the potential to be phosphorylated (29). Using phosphorylation-dependent monoclonal antibodies against tau, mass spectrometry and sequencing, at least 30 phosphorylation sites on tau have been reported including tyrosine residues (24, 117, 118). As described, phosphorylation of tau at specific sites clearly affects its function. Below we highlight the kinases and phosphatases that may be involved in dynamically modulating the phosphorylation states of tau, and how an imbalance in site specific phosphorylation result in a pathological change in the conformation of tau.

6.1.2.Kinases

Although many potential kinases have been examined, only a few are considered to be good candidates for *in vivo* tau kinases. One likely tau kinase is GSK3beta (119). GSK3beta is expressed at high levels in brain (120), where it localizes to neurons (121), and thus is in an appropriate compartment to access tau. GSK3beta associates with microtubules (122) and, when this kinase is overexpressed in cells, the phosphorylation statue of tau dramatically increases at numerous sites (64, 123, 124). Immunoblot analyses have revealed that modest (20-50%) increases in expression of GSK3beta in the brains of transgenic mice result in increased tau phosphorylation at several sites (98, 125). Furthermore, treatment of cells with lithium, a selective inhibitor of GSK3, significantly attenuates tau phosphorylation (126-128). Chronic lithium treatment also decreases tau phosphorylation in mouse models in which mutant FTDP-17 tau is overexpressed (129, 130). These and other findings provide extremely strong evidence that tau is an *in vivo* substrate of GSK3beta, and that abnormal phosphorylation of tau by GSK3beta might contribute to the pathogenic processes in AD brain. However, GSK3beta phosphorylates and regulates numerous other proteins (131), and therefore the possibility remains that GSK3beta indirectly regulates tau phosphorylation *in vivo*. Nonetheless, of all the protein kinases known to phosphorylate tau *in vitro*, the strongest evidence so far is for tau being a substrate of GSK3beta *in vivo*.

Another possible *in vivo* tau kinase is cyclin-dependent kinase 5 (Cdk5). Cdk5 is a unique member of the Cdk family that is activated by interaction with the non-cyclins, p35 and p39, which are regulatory proteins that are expressed almost exclusively in postmitotic neurons (132, 133). P35 and p39 can be proteolyzed by the calcium-

dependent protease calpain (134, 135), resulting in p25 and p29, respectively, which are more stable than p35 or p39 and thus cause a more prolonged activation of Cdk5 (134-137). *In vitro*, tau is a substrate of Cdk5, and most, if not all, of the sites on tau that are phosphorylated by Cdk5 are also phosphorylated by GSK3beta (138-141). Overexpression of Cdk5 and p25, but not p35, results in increased tau phosphorylation at specific sites (65, 137). However, other studies have found that upregulation of Cdk5 and p25 increases Cdk5 activity but does not significantly increase tau phosphorylation *in situ* (142, 143). In addition, inhibition of Ckd5 in primary cortical neurons increases tau phosphorylation (144). Furthermore, in a p35 knockout mouse in which Cdk5 activity was significantly decreased, tau phosphorylation was increased. It is also interesting to note that in this p35 knockout mouse model GSK3beta activity was increased, suggesting that GSK3beta may be regulated by Cdk5 (145). Therefore, the role of Cdk5 in regulating tau phosphorylation *in vivo* needs to be evaluated further.

Although the majority of sites on tau that are phosphorylated are Ser/Thr-Pro sites, Ser and Thr sites not followed by Pro residues are also phosphorylated. Data indicate that tau is phosphorylated by PKA *in vivo*. For example, treatment of brain slices (146) or cultured cells (147) with forskolin (an adenylyl cyclase activator) and rolipram (a cAMP phosphodiesterase inhibitor) results in a pronounced increase in tau phosphorylation. Activation of endogenous PKA can thus increase tau phosphorylation. Furthermore, many of the sites on tau that are phosphorylated in brain slices in response to increases in cAMP levels are those that are phosphorylated by PKA *in vitro* (146).

MARK also likely regulates tau phosphorylation *in vivo*. MARK selectively phosphorylates a KXGS motif, which is present in each microtubule binding repeat of tau, as well as other microtubule-associated proteins (57, 148). Because tau is phosphorylated at KXGS motifs *in vivo* (Ser262 being the most prominently phosphorylated KXGS motif) (149), and MARK probably phosphorylates these epitopes more efficiently *in situ* than do other protein kinases (86), MARK could be an important *in vivo* tau kinase. In cultured cell models, MARK appears to regulate tau phosphorylation (86) and, in AD brain, MARK is associated with NFTs and co-localizes with phospho-Ser262 staining (150). Although the ability of MARK to phosphorylate tau in a mouse model has not been examined directly, MARK phosphorylates tau at KXGS motifs in retinal ganglion cell axons (151). Furthermore, it has been recently showed that the Ser/Thr kinase PAR-1 kinase phosphorylates tau *in vivo* in flies (152). Microtubule-affinity regulating kinase (MARK) is the mammalian homolog of *Drosophila* PAR-1. PAR-1/MARK has been demonstrated to be required for neurite outgrowth and neuronal polarity (86, 153).

Overall, it is clear that GSK3beta, Cdk5, PKA, and MARK probably modulate tau phosphorylation *in vivo* at some level, either directly or indirectly. Many other kinases can increase tau phosphorylation in non-neuronal cell model systems when they are overexpressed. However, without validation in a true neuronal system in which the proteins are expressed in the appropriate context, the role of these kinases in modulating tau phosphorylation *in vivo* remain to be established.

6.1.3. Phosphatases

Phosphatases counterbalance the action of kinases. *In vitro*, tau is readily dephosphorylated by numerous protein phosphatases, including protein phosphatase 1 (PP1), 2A (PP2A), 2B (PP2B, calcineurin) and 5 (PP5) (154). PP1 is targeted to microtubules by tau (155) and PP5 has been shown to dephosphorylate tau both *in vitro* and *in situ* when over-expressed in PC12 cells (156). Tau proteins from brain tissue or neuroblastoma cells are rapidly dephosphorylated by endogenous phosphatases (157-159). Given the fact that PP2A is directly linked to the microtubules by ionic interactions (160), the majority of studies have focused on the role of PP2A in regulating tau phosphorylation. The predominant brain isoform of PP2A, ABalphaC, binds directly to tau and is likely a major tau phosphatase (160, 161). It is also of interest to note that is has been hypothesized that Pin-1 regulates phosphorylation of Thr231 by selectively binding to this site and facilitating the conversion of the *cis* pThr-Pro motif to a *trans* conformation thus allowing dephosphorylation of the site by the predominant Pro-directed PP2A (162). This is an interesting hypothesis; however, it should be noted that phosphorylation of peptides from this region of tau did not alter the equilibrium of *cis-trans* isomers (163). There is also data to suggest that there is reduced binding of PP2A to tau with FTDP-17 mutations, which could contribute to the increase in tau phosphorylation that occurs in FTDP-17 cases (164).

6.1.4. Balance between kinases and phosphatases

The state of phosphorylation of a phosphoprotein is a function of the balance between the activities of the protein kinases and the protein phosphatases that regulate its phosphorylation (52). Dynamic and site-specific phosphorylation of tau is essential for its proper functioning (54). These dynamic phosphorylation and dephosphorylation events at particular sites are achieved by a fine balance between the activities of specific kinases and phosphatases. There is increasing evidence that inappropriate phosphorylation of tau, which leads to tau dysfunction, results in decreased cell viability. Indeed, in all neurodegenerative diseases in which tau pathology has been observed, the tau is abnormally phosphorylated (53). These diseases include the FTDP-17 cases, which are caused by mutations in the tau gene (11-13). Immunohistochemical studies have shown increased expression of several kinases, including Ca^{++}/calmodulin-dependent kinase, GSK3, PKA, Cdk-5, MAPK/ERK, SAPK/JNK, and casein kinase I, and co-localization with hyperphosphorylated tau deposits and NFTs in neurons in AD (58-62, 165). In addition, it has been reported that the expression and activities of some phosphatases are decreased in the affected area of AD brain (166-171). In particular, the activities of PP2A and PP1 are reduced by ~20-30% in AD brain (168, 172). Interestingly, inhibition of PP2A activity by okadaic acid in cultured cells and in

metabolically active rat brain slices results in abnormal hyperphosphorylation of tau at several of the same sites as in AD, not only directly by a decrease in tau dephosphorylation, but also indirectly by promoting the activities of specific kinases (173-176). These observations suggest that a disturbance of the balance between the kinases and phosphatases in AD brain might underlie the abnormal hyperphosphorylation of tau and other neuronal proteins.

6.1.5. Effects of phosphorylation of tau on its aggregate formation

The tau that forms the fibrillar structures of the neurofilbrillary tangles (NFTs), is abnormally phosphorylated. Analysis of PHFs purified from AD brains has revealed that filamentous tau from AD brain contains all six CNS tau isoforms (34). In AD, tau filaments consist primarily of PHFs, with straight filaments being a minority species (48, 177, 178). As indicated above, phosphorylation at specific sites can significantly increase the tendency of tau to aggregate. For example, pseudophosphorylation of Ser396 and Ser404 causes tau to be more fibrillogenic (45), and a tau construct in which Ser422 is mutated to Glu shows a significantly increased propensity to aggregate (51). Recently, it has been also reported that pseudophosphorylation of tau at Ser205, Thr205, and Thr212 enhances polymerization of tau into filaments (50, 179). In contrast, it has also been demonstrated that phosphorylation of tau at Ser262 and Ser214 does not prime tau for PHF assembly, but rather inhibits it, suggesting that abnormal phosphorylation of these sites on tau is not directly responsible for the pathological aggregation into PHFs (180). Along with the phosphorylation of specific residues, a number of FTDP-17 mutations may promote aggregation of tau proteins, including R5L, K257T, I260V, G272V, deltaK280, P301L, P301S, Q336R, V337M, and R406W (181-187). The tau fibrillization pathway can be subdivided based on key steps. First, the microtubule binding function of tau must be neutralized so that tau protein can accumulate intracellularly in an assembly competent form (188), suggesting that aggregation of tau may be concentration-dependent. Second, tau molecules must self-associate through their microtubule binding repeat regions to form the beta-sheet enriched filaments observed in tissue. When the critical concentration of tau molecules is achieved, unfolded monomer tau molecules, which have no substantial secondary structures, oligomerize leading to a conformational change to a beta-sheet enriched structure. The earliest secondary structure detectable with fluorescent dyes corresponds to tau aggregates associated with membranous structures (189, 190), suggesting that the folding of tau protein into beta-sheet containing species may be facilitated by interaction with intracellular membranes and organelles. The third step involves the nucleation of tau filaments and formation of mature NFTs. Filaments gradually replace amorphous deposits to dominate the tau immunostaining of cells (189, 190). Whereas some lesions develop predominantly straight filaments, late stage disease is dominated by PHF morphology, which may represent a minimal energy conformation (191). It has been reported that in biopsy specimens, individual PHFs appear in endwise association with membranes, consistent with surface-mediated nucleation and polar extension from stable tau-membrane complexes (192). Final steps include the loss of cell viability and formation of “ghost tangles”, which appear as extracellular fibrillar aggregates that retain the ability to bind the small molecule fluorophores thioflavin S and Congo red, and thiazine red (193-195). In the transition, NFTs undergo proteolytic modifications (196) and become highly insoluble (197). Together these data are consistent with an assembly pathway involving amorphous aggregation followed by facilitated fibrillization, with a role for phosphorylation and mutations from the earliest stage. The first detectable step for NFTs by immunohistochemistry using antibodies to different phosphorylated and non-phosphorylated tau epitopes involves the aggregation of tau protein into non-fibrillar deposits (198), called ‘pretangles’, which display a punctate staining pattern in the cytoplasm and are not reactive with beta-sheet-sensitive dyes such as thioflavin S or thiazine red (190).

Although the PHFs, which are made up of abnormally phosphorylated tau, are one of the characteristic hallmarks of tauopathies, the role of aggregates as toxic mediators of neuronal dysfunction and death is still not clear. Indeed, the correlation between NFT presence and the incidence of disease does not necessarily dictate a causal relationship, and therefore the focus has been shifting to identify the toxic tau species during the entire fibrillogenic process from the soluble monomers through oligomers to the insoluble mature tangles (NFTs). Given that several animal models show cognitive deficits and impaired axonal transport in the absence of NFTs (9, 199, 200), small soluble oligomers may be the toxic species leading to neuronal dysfunction and degeneration (201). A recent study supported this idea by demonstrating that suppression of transgenic tau expression restored memory function and stabilized neuronal cell populations whereas NFTs continued to accumulate, suggesting that NFTs are not sufficient to cause cognitive decline or neuronal death (202). Furthermore, other studies suggested that NFTs might represent a protective compensatory response aimed at reducing reactive oxygen species (ROS)-associated damage (203). However, although benign and/or protective at the beginning, established NFTs may secondarily sequester normal cellular proteins, thus directly altering cellular physiology leading to secondary neuronal damage. This may be a nonspecific process because protein aggregates are inherently sticky. Whether the monomers, oligomers, or NFTs (mature filaments) are the important toxic moieties, the question of what causes tau to aggregate and what kinetic profile is responsible must be addressed.

6.2. Proteolysis

Proteolysis is a key mechanism for maintaining the intracellular environment relatively free of misfolded proteins (204). Although, *in vitro*, tau has been reported to be a substrate for a number of proteases such as trypsin, chymotrypsin, cathepsin D, calpains, caspases, proteasomal proteases, double-stranded DNA-stimulated protease, and thrombin (205-211), the proteases that degrade tau in brain

are still unclear. Although tau in AD and other tauopathies is present predominantly as an intact full-length molecule (212-216), tau in AD NFTs has been shown to be truncated both at Glu391 and Asp421 (47, 217). However, what percentage of tau is truncated at these sites at what stage of neurofibrillary pathology in AD brain has not been reported. It has been suggested that truncated tau, albeit not a large amount, may play a significant role in the neuronal cell death and PHF formation given that truncated tau at Asp421 (due to caspase-cleavage) have been shown to be associated with apoptosis in cultured cells (218, 219), and that truncated tau at Glu391 was shown to be the major constituent of the minimal PHF core (189, 220-223) and is present in AD brains but not in age-matched controls (222).

A candidate family of proteases that may play a significant role in abnormal proteolysis of tau are the caspases. It has been demonstrated that caspases play a critical role in Aβ-induced neuronal apoptosis (224, 225) and are activated in apoptotic neurons in AD brain (226-231). In addition, the cleavage of tau at Asp421 by caspase-3 has been detected both in neurons treated with pre-aggregated Aβ and in AD brains (47, 232). Truncated tau at Asp421 has been demonstrated to cause neuronal death and also play a significant role in the nucleation-dependent filament formation of tau (219).

Another possible *in vivo* tau protease family is the calpains, which are calcium-activated proteases. It has been previously shown that calpain may be abnormally activated in AD patients compared with age-matched controls (233). In addition, activated calpain-2 colocalized with tau filaments in AD and frontotemporal dementia brains (234). Recently, it has been reported that pre-aggregated Abeta induced the generation of 17 kDa tau fragment *in vitro* and in cultured hippocampal neurons and that inhibitors of calpain completely prevented the formation of the 17 kDa fragment and significantly reduced Abeta-induced neuronal death (235). It is also reported that thrombin can cleave human recombinant tau at multiple arginine and lysine sites (205), but the role of this protease in degrading tau *in vivo* remains unclear.

Recently, it has been demonstrated that truncation at both the amino- and carboxy-termini directly influences fibril formation of tau, and the aggregation of tau appears to involve an ordered series of phosphorylation and cleavage events (44). During the process of neurofibrillary tangle evolution, it has been proposed that tau undergoes conformational changes and becomes progressively truncated at both its amino- and carboxy-termini. The Alz50 conformation of tau, which is a folded state of tau in which the N-terminal part of tau interacts with the microtubule-binding domains, appears first in pretangle neurons but persists in neurons containing NFTs as well (236). Subsequently, both carboxy and amino truncation events ensue. Many Alz50-positive NFTs are also reactive to Tau-C3, the antibody that specifically recognizes tau truncated at Asp421 (237). Tau-C3 reactivity also co-localizes with Tau-66-positive structures, which recognize a conformation of tau that requires N-terminal cleavage. Once in the Tau-66 state, tau is cleaved even more extensively in the NFTs, becoming positive for MN423, an antibody that reacts with tau truncated at Glu391. A high incidence of colocalization of MN423 and Tau-66 suggests that the more extensive C-terminal truncation is a somewhat later event (237). However, the presence of C-terminally Asp421-trucated tau in pretangle neurons suggests a role for caspase cleavage in the initiation of polymer formation (238).

The effect of phosphorylation of tau on its proteolysis is still not well understood. PHF-tau is more resistant to proteolysis by calpain than normal tau and fetal tau, indicating that phosphorylation decreases the sensitivity of tau to calpain (209, 239). On the other hand, fetal tau is more vulnerable to proteolysis by cathepsin D than unmodified recombinant tau, suggesting that phosphorylation increases susceptibility of tau to cathepsin D (208). Phosphorylation of tau by PKA attenuates calpain-mediated proteolysis of tau *in vitro* (240), and there is evidence that this the case *in situ* (147). It has also been reported that phosphorylation of recombinant tau with a double-stranded DNA-dependent protein kinase accelerates thrombin-mediated proteolysis (241).

In vitro, tau proteins can be directly degraded by the proteasome without being ubiquitylated (242) and proteasomal processing of tau is bi-directional, proceeding from both N- and C-termini (210). However, it also has been reported that tau is not normally degraded by the proteasome (243). There have been no reports thus far indicating that tau under normal conditions becomes ubiquitylated. However, SDS-insoluble PHFs contain ubiquitin (244) and ubiquitin is found in the filamentous components of several neurodegenerative diseases such as AD, Parkinson's disease, Pick's disease, and progressive supranuclear palsy, all of which involve abnormalities in cytoskeletal structures (245). It has been reported that there is a several fold increase in ubiquitin levels in the cortex of AD patients' brains and ubiquitin levels correlated strongly with the extent of neurofibrillary pathology in the cortex. In contrast, the cerebellum, which does not undergo significant neurofibrillary changes, contained normal levels of ubiquitin in AD (246). The accumulation of ubiquitylated of tau appears to be a late event in the development of neurofibrillary pathology, as it occurs after the formation of NFTs (247, 248). In addition, most PHF-tau is mono-ubiquitylated (247), which is not a signal for ubiquitin-mediated degradation (249, 250).

Refolding and elimination of unfolded or misfolded protein is mediated by molecular chaperones such as Hsc/Hsp70 and Hsp90. The ubiquitin-proteasome system (UPS) is mediated by an energy-dependent process and concerted action of a number of molecules including specific ubiquitin ligases (251-253). A dysfunction of the UPS has been proposed in numerous neurological disorders such as AD, Huntington's disease, Parkinson's disease, and Angelman's syndrome (254-259). A dysfunction of the UPS in AD brains has been suggested, given the data that proteasome activity is decreased in AD brains (260) and that PHF-tau extracted from AD brains has been shown to be able to inhibit the proteasome *in vitro* (261). It has been

demonstrated that tau extracted from AD brains is a target of the E3 ubiquitin ligase carboxyl terminus of the heat shock cognate (Hsc)-70-interacting protein (CHIP) (262) and of the E2 ubiquitin-conjugating enzyme (Ubc) H5B (263). CHIP binds to the constitutively expressed Hsc70, the heat-inducible Hsp70, and also to Hsp90 through multiple tetratricopeptide (TPR) repeats and inhibits the folding activity of the chaperones (251, 264). CHIP possesses a U box motif, which cooperates with an E2 ubiquitin-conjugating enzyme and an E3 ubiquitin ligase in the formation of multiubiquitin chains, indicating that the CHIP participates in ubiquitylation reactions. The CHIP protein has been reported to act as a key regulator to target misfolded proteins from chaperones to the proteasome (265, 266). In fact, CHIP promotes the ubiquitination of chaperone substrates including tau and stimulates their degradation by the UPS (251, 263, 267). It has been reported that CHIP associates with tau through the microtubule-binding domain (263). In a cell culture model expressing GSK3beta and tau, the amount of cell death was significantly decreased with the co-expression of CHIP, and ubiquitylated phosphorylated tau was most abundant in CHIP-co-expressing cells whereas phosphorylated non-ubiquitylated tau was most abundant in CHIP-deficient cells. These results suggest that accumulation of soluble phosphorylated tau is toxic, while insoluble ubiquitylated phosphorylated tau is less toxic. CHIP appears to ubiquitylate phosphorylated-tau not only for degradation in the proteasome, but also to move tau into a segregated insoluble fraction, possibly for prevention of cell death (263, 268).

6.3. Other modifications

6.3.1. Glycosylation and other modifications

O-glycosylation is a dynamic and abundant posttranslational modification that consists of the addition of an O-linked N-acetylglucosamine (O-GlcNAc) residue on Ser or Thr residues in the proximity of Pro residues (269). Although the functional significance of O-GlcNAc modification is not yet fully understood, it is implicated in transcriptional regulation, protein degradation, cell activation, cell cycle regulation, and the proper assembly of mutimeric protein complexes (270). This modification is often reciprocal to phosphorylation (271). It occurs in neurofilaments (272) and microtubule-associated proteins including MAP2 and tau proteins (273-275). The number of O-GlcNAcylated sites on tau proteins is lower than the number of phosphorylation sites. Site-specific or stoichiometric changes in O-GlcNAcylation may modulate tau function. In fact, phosphorylation and O-GlcNAcylation may have opposite effects. For instance, O-GlcNAcyation of tau proteins and other microtubule-associated proteins suggests a role for O-GlcNAc in mediating their interactions with tubulin. O-GlcNAcylation may also play a role in subcellular localization and degradation of tau proteins (271, 273, 274). It has also been reported that hyperphosphorylated tau proteins in AD brain are N-glycosylated (in contrast to O-glycosylation) and that glycan(s) may maintain the helicity of PHF or facilitate the subsequent abnormal hyperphosphorylation of tau in AD brain (206, 276, 277).

There is also evidence that the enzyme transglutaminase II can incorporate polyamines into tau both *in vitro* and *in situ* (278). Polyamination of tau had no effect on microtubule binding even though one of the major Gln residues that are modified by transglutaminase lies within the microtubule-binding domain (279). However, tau that is polyaminated by transglutaminase is significantly less susceptible to degradation by the calpain (278). PHF-tau can undergo deamidation (a reaction that transglutaminases can catalyze (280)) and contains the amino acid isomer L-isoaspartate (281, 282). Since protein isomerization can enhance the aggregation process, this modification could contribute to the pathogenesis of AD (283, 284). Protein L-isoaspartyl methyltransferase (PIMT), which may be involved in the repair of isomerized proteins, colocalizes with NFTs in AD brain. These findings suggest a possible role of protein isomerization in the abnormal aggregation of tau in AD (281-284).

7. TAU IN ALZHEIMER'S DISEASE

AD is characterized clinically by a progressive loss of memory and cognitive functions, resulting in a severe dementia. Neuropathologically, AD is defined by the accumulation of two types of insoluble fibrous materials, which are the extracellular Abeta protein in the form of senile plaques and intracellular NFTs made of abnormally and hyperphosphorylated tau. Although these two lesions are often present in the same area of the AD brain, the relationship between the two pathologies has not been clearly established. Recently, it has been demonstrated that Abeta-induced caspase activation leads to tau cleavage and generates tangle-like morphology, suggesting that Abeta accumulation is an early event that may precede PHF formation of tau (219). A potential link between senile plaques and NFTs involves the Abeta-induced activation of putative tau kinases leading to tau phosphorylation. Indeed, tau hyperphosphorylation has been attributed to the increased activity of kinases, such GSK3beta or MAP kinase, in either young or mature hippocampal neurons treated with pre-aggregated Abeta (285-287). Neurons from tau knockout mice are resistant to Abeta-induced neurotoxicity (288) and suppression of tau overexpression in transgenic mice prevents further declines in memory function (202), suggesting that tau plays a fundamental role in the pathogenic events that occur in AD brain. Although the role of NFTs as a toxic mediator in neuronal dysfunction and death in AD is still not clear, the tau aggregation is closely related with the pathology of AD (203), and there is increasing data to suggest that a conformational change in tau that precedes the formation of PHFs and NFTs may be the toxic entity as described above (9, 199-202).

8. TAU IN FTDP-17

FTDP-17 describes a collection of autosomal dominant inherited tauopathies with overlapping clinical and pathological characteristics. Common clinical features include behavioral changes, disinhibition, language deficits, dementia, and progressive parkinsonism with an adult-age onset (289-293). These symptoms are neuropathologically

Table 1. Tau mutations identified in FTDP-17

Mutation	Type	Location	E10 splicing	MT assembly	Reference
R5H	Missense	E1	No change	Decreased	307
R5L	Missense	E1	No change	Decreased	308
K257T	Missense	E9, R1	No change	Decreased	309, 310
I260V	Missense	E9, R1	No change	ND	187
L266V	Missense	E9, R1	No change	Decreased	311
G272V	Missense	E9, R1	No change	Decreased	11
E9+33	Intronic	I9	ND	ND	71
N279K	Missense	E10, IR1-2	Increased	No effect	14, 312, 313
deltaK280	Deletion	E10, IR1-2	Decreased	Decreased	71
L284L	Silent	E10, IR1-2	Increased	No effect	314
N296N	Silent	E10, R2	Increased	No effect	315
deltaN296	Deletion	E10, R2	Increased	Decreased	316, 317
N296H	Missense	E10, R2	Increased	Decreased	317, 318
P301L	Missense	E10, R2	No change	Decreased	11, 319
P301S	Missense	E10, R2	No change	Decreased	320, 321
S305N	Missense	E10, IR2-3	Increased	No effect	313, 314, 322
S305S	Silent	E10, IR2-3	Increased	No effect	323, 324
E10+3	Intronic	I10	Increased	No effect	13
E10+11	Intronic	I10	Increased	No effect	325
E10+12	Intronic	I10	Increased	No effect	326
E10+13	Intronic	I10	Increased	No effect	11
E10+14	Intronic	I10	Increased	No effect	11
E10+16	Intronic	I10	Increased	No effect	11
L315R	Missense	E11	No change	Decreased	327

accompanied by frontal and temporal lobe atrophy with major neuronal loss, gray and white matter gliosis and superficial laminar spongiosis and by the presence of abundant filamentous tau pathology in nerve cells and for some in glial cells (13, 294). To date, all analyzed cases of FTDP-17 are characterized by the presence of an abundant filamentous pathology, consisting of hyperphosphorylated tau protein. However, the morphology, isoform composition, and distribution of tau filaments and deposits appear to vary according to the type of mutation (Table 1).

The vast majority of tau mutations are missense, deletion or silent mutations in the coding region, or intronic mutations located close to the splice-donor site of the intron following exon 10. Most coding-region mutations are located in exons 9-12 or in exon 13 near the microtubule-binding region and two mutations in exon 1 of tau (R5H and R5L). Mutations in exon 1 (R5H and R5L), exon 9 (K257T, I260V, L266V and G272V), exon 11 (L315R, S320R), exon 12 (V337M, E342V, S352L and K369I) and exon 13 (G389R and R406W) affect all six tau isoforms. By contrast, mutants in exon 10 (N279K, deltaK280, L284L, N296N, deltaN296, N296H, P301L, P301S, S305N and S305S) affect only 4R tau isoforms or their expression levels. The intronic mutations identified to date are located in the intron following exon 10 at positions +3, +11, +12, +13, +14, +16, +19 and +29 (with the first nucleotide of the splice-donor site designated +1) that alter their regulation of exon 10 splicing and thus the ratio of 4R/3R tau proteins. Mutations in the tau gene result in one of three effects on tau. The first effect is to decrease the ability of tau to interact with microtubules, thereby hindering its ability to stabilize microtubules and promote microtubule assembly. The second effect of certain tau mutations is to alter exon 10 splicing, with the majority of mutations resulting in increased exon 10 splicing (inclusion into tau mRNA), thereby increasing the synthesis of 4R tau. However, one mutation, deltaK280, has been reported to decrease exon 10 splicing (71). Lastly, missense mutations, as well as deltaK280 increase tau filament formation *in vitro* (181, 186, 295). For example the deltaK280 and P301L mutations directly influence tau aggregation by augmenting the formation of beta-structures around ^{306}VQIVYK^{311} and ^{275}VQIINK^{280} tau motifs (181). Tau mutations that inhibit microtubule assembly generally are missense mutations in or near the highly conserved microtubule-binding repeat domains. Mutations of tau gene and their involvement in FTDP-17 emphasize the fact that abnormal tau proteins may play a central role in the etiopathogenesis of neurodegenerative disorders, without any Abeta involvement. Although the etiology, clinical symptoms, pathologic findings and the biochemical composition of tau inclusions in AD and FTDP-17 are different, substantial similarities in the tau alterations exists between these tauopathies.

9. TAU IN OTHER NEURODEGENERATIVE DISEASES

Intraneuronal neurofibrillary lesions, which are made of tau, are also the defining characteristic of a number of other neurodegenerative diseases and the most prominent of which are progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and Pick's disease (PiD) (53, 296). Like FTDP-17, the major pathology in these disorders is the formation of intranuclear NFTs in the

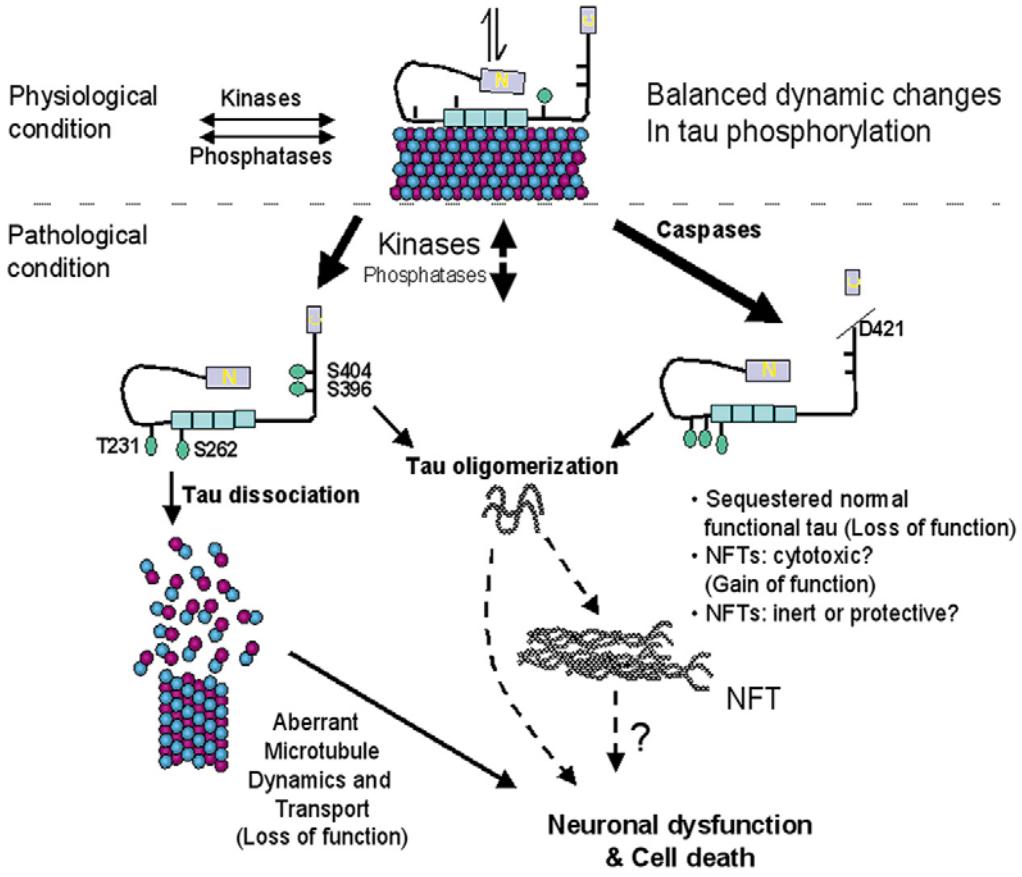

Figure 2. Role of abnormal phosphorylation and truncation of tau in neuronal cell death. In normal brain where the majority of tau is associated with microtubules, there are balanced and dynamic changes in tau phosphorylation allowing for appropriate neuronal function. Several protein kinases and phosphatases likely work in concert to appropriately regulate tau phosphorylation. In particular, phosphorylation at Ser262 and Thr231 likely play key roles in regulating tau-microtubule interactions. However, in pathological conditions such as AD and other tauopathies, tau becomes abnormally hyperphosphorylated. Dysregulation in the balance of the activities of specific kinases and phosphatases may be one of the causes of hyperphosphorylation of tau. Especially, phosphorylation of the critical microtubule regulatory sites significantly leads to the increased levels of free tau that is not bound to microtubules. Free tau could undergo further inappropriate phosphorylation events at fibrillogenic sites such as Ser396/404. Cleavage by caspases at Asp421 increases the fibrillogenic properties of tau. Furthermore, N-glycosylation of tau, which is found in AD brain, makes tau a more favorable substrate for further phosphorylation by other protein kinases and resistant for dephosphorylation by phosphatases. The resultant abnormally hyperphosphorylated tau exerts detrimental effects; it is not only unable to bind to microtubule but also sequesters normal tau leading to the inhibition of assembly and disruption of microtubules (loss of function). The breakdown of the microtubule network compromises vital cellular functions such as axonal transport, neurite outgrowth, and signal transduction. In addition, abnormal hyperphosphorylation and caspase cleavage of tau significantly facilitate tau-tau interactions leading to the formation of oligomers and subsequently tau filaments (PHFs). Although still controversial, oligomers are considered to mediate cytotoxic effects of abnormal tau by sequestering intracellular components and hindering cellular transport leading to the dysfunction of affected neurons (gain of function) whereas PHFs are inert or even cytoprotective. Accordingly, it is considered that abnormal phosphorylation and proteolysis of tau result in the impairment of neuronal function and eventually cell death through complex events.

absence of Abeta-deposits. However, contrary to FTDP-17, which is a family of genetic disorders, these tauopathies are sporadic in nature. For a more thorough review of tauopathies see Lee et al. (53, 296).

10. SUMMARY AND PERSPECTIVE

Over the past several years, substantial progress has been made in our understanding of how modifications of tau affect tau function. Figure 2 illustrates the proposed stepwise changes in tau modifications that may contribute to the demise of the affected neurons (Figure 2). It is evident that specific, coordinated phosphorylation events are crucial for the appropriate functioning of tau. However, it still remains to be determined which protein kinases phosphorylate tau *in vivo* and how the dynamics of these processes are regulated. It is also evident that tau is abnormally modified when tau pathology occurs in a neurodegenerative disease. Given that the phosphorylation of specific sites on tau can inhibit its ability to bind

microtubules efficiently and increase its ability to polymerize and that amino- and carboxy-terminal truncation of tau modulate its filament formation, it is likely the abnormal post-translational events play a key role in tau pathogenic processes. It has been suggested that the modification-induced loss of function (i.e. impairment of microtubule-binding), as well as the toxic gain of function (i.e. an increased propensity to oligomerize), synergize to reduce the levels of functional tau and thus disrupt normal microtubule-based functions, which could contribute to the demise of the cell. Given the previous findings that transgenic mice expressing human tau have consistently demonstrated neurological deficits and that neuron loss, and that the burden of NFTs correlates well with the progression of the disease in humans with AD (95, 297-300), the deleterious effects of tau pathology were thought to be responsible to a toxic gain of function by neurofibrillary tangles. However, a recent study suggested that the neurodegenerative sequellae of pathological tau may not primarily due to the formation of NFTs (202). The authors generated an inducible tau transgenic mouse model in which the expression of human tau with the P301L FTDP-17 mutation was regulated by tetracycline. With the expression of mutant tau, these transgenic mice developed memory impairments, overt pathological tau deposits and gross brain atrophy with abundant neurofibrillary tangles. However, when the P301L mutant tau expression was turned off, mice showed improved memory function and a rescue of neurological loss, but the accumulation of neurofibrillary tangles continued, suggesting that toxic gain of function of NFTs is not sufficient to explain cognitive decline or neuronal death in this model of tauopathy (202). Recently, it has been reported that the tau-mediated neuronal cell death is caused by the inability of affected cells to properly regulate their microtubule dynamics due to misregulation by tau (301, 302), favoring the alternative loss of function hypothesis in tau-mediated neuronal cell death (303). It has also been demonstrated that mutations leading to the reduced tau activity or, at the other extreme, to overly active tau activity resulted in the under- or over-stabilized microtubules, respectively, which in turn invariably lead to the neuronal cell death, suggesting that improperly regulated microtubules cannot perform their normal essential cellular functions (303). Increased microtubule dynamics can be observed in taxol-resistant cells (304), in the FTDP-17 missense mutations (303), and in cells expressing hyperphosphorylated tau (18, 305). In addition, overly suppressed microtubule dynamics can be observed in the FTDP-17 RNA splicing mutations in which 4R is over-expressed and 3R is under-expressed (18, 306). It is evident that abnormal modifications such as phosphorylation and truncation play a key role in the pathogenesis of AD and other tauopathies. What remains unclear are the specific protein kinases and phosphatases that mediate abnormal phosphorylation in tau, and the specific proteases that produce amino- and carboxy-terminal truncated tau. What also remains to be elucidated are the specific functional changes in tau that are responsible for the pathological outcomes. Is it the phosphorylation-induced deficits in microtubule binding, the increased presence of tau fibrils, or other changes in tau localization and binding partners? Clearly, more work is needed to fully elucidate the role of site-specific phosphorylation in the normal functioning of tau and how these processes are perturbed and contribute to a pathogenic chain of events in the disease state.

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12. REFERENCE

1. Binder, L. I., A. Frankfurter & L. I. Rebhun: The distribution of tau in the mammalian central nervous system. *J Cell Biol*, 101, 1371-8 (1985)
2. Richter-Landsberg, C. & N. G. Bauer: Tau-inclusion body formation in oligodendroglia: the role of stress proteins and proteasome inhibition. *Int J Dev Neurosci*, 22, 443-51 (2004)
3. Chin, S. S. & J. E. Goldman: Glial inclusions in CNS degenerative diseases. *J Neuropathol Exp Neurol*, 55, 499-508 (1996)
4. Ingelson, M., E. Vanmechelen & L. Lannfelt: Microtubule-associated protein tau in human fibroblasts with the Swedish Alzheimer mutation. *Neurosci Lett*, 220, 9-12 (1996)
5. Gu, Y., F. Oyama & Y. Ihara: Tau is widely expressed in rat tissues. *J Neurochem*, 67, 1235-44 (1996)
6. Vanier, M. T., P. Neuville, L. Michalik & J. F. Launay: Expression of specific tau exons in normal and tumoral pancreatic acinar cells. *J Cell Sci*, 111 (Pt 10), 1419-32 (1998)
7. Caceres, A. & K. S. Kosik: Inhibition of neurite polarity by tau antisense oligonucleotides in primary cerebellar neurons. *Nature*, 343, 461-3 (1990)
8. Ebneth, A., R. Godemann, K. Stamer, S. Illenberger, B. Trinczek & E. Mandelkow: Overexpression of tau protein inhibits kinesin-dependent trafficking of vesicles, mitochondria, and endoplasmic reticulum: implications for Alzheimer's disease. *J Cell Biol*, 143, 777-94 (1998)
9. Stamer, K., R. Vogel, E. Thies, E. Mandelkow & E. M. Mandelkow: Tau blocks traffic of organelles, neurofilaments, and APP vesicles in neurons and enhances oxidative stress. *J Cell Biol*, 156, 1051-63 (2002)
10. Dumanchin, C., A. Camuzat, D. Campion, P. Verpillat, D. Hannequin, B. Dubois, P. Saugier-Veber, C. Martin, C. Penet, F. Charbonnier, Y. Agid, T. Frebourg & A. Brice: Segregation of a missense mutation in the microtubule-associated protein tau gene with familial frontotemporal dementia and parkinsonism. *Hum Mol Genet*, 7, 1825-9 (1998)
11. Hutton, M., C. L. Lendon, P. Rizzu, M. Baker, S. Froelich, H. Houlden, S. Pickering-Brown, S. Chakraverty, A. Isaacs, A. Grover, J. Hackett, J. Adamson, S. Lincoln, D. Dickson, P. Davies, R. C. Petersen, M. Stevens, E. de Graaff, E. Wauters, J. van Baren, M. Hillebrand, M. Joosse, J. M. Kwon, P. Nowotny, L. K. Che, J. Norton, J. C. Morris, L. A. Reed, J. Trojanowski, H. Basun, L. Lannfelt, M. Neystat, S. Fahn, F. Dark, T. Tannenberg, P. R. Dodd, N. Hayward, J. B. Kwok, P. R. Schofield, A. Andreadis, J. Snowden, D. Craufurd, D. Neary, F. Owen, B. A. Oostra, J. Hardy, A. Goate, J. van Swieten, D. Mann, T. Lynch & P.

Heutink: Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature*, 393, 702-5 (1998)
12. Poorkaj, P., T. D. Bird, E. Wijsman, E. Nemens, R. M. Garruto, L. Anderson, A. Andreadis, W. C. Wiederholt, M. Raskind & G. D. Schellenberg: Tau is a candidate gene for chromosome 17 frontotemporal dementia. *Ann Neurol*, 43, 815-25 (1998)
13. Spillantini, M. G., J. R. Murrell, M. Goedert, M. R. Farlow, A. Klug & B. Ghetti: Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. *Proc Natl Acad Sci U S A*, 95, 7737-41 (1998)
14. Clark, L. N., P. Poorkaj, Z. Wszolek, D. H. Geschwind, Z. S. Nasreddine, B. Miller, D. Li, H. Payami, F. Awert, K. Markopoulou, A. Andreadis, I. D'Souza, V. M. Lee, L. Reed, J. Q. Trojanowski, V. Zhukareva, T. Bird, G. Schellenberg & K. C. Wilhelmsen: Pathogenic implications of mutations in the tau gene in pallido-ponto-nigral degeneration and related neurodegenerative disorders linked to chromosome 17. *Proc Natl Acad Sci U S A*, 95, 13103-7 (1998)
15. Goedert, M., C. M. Wischik, R. A. Crowther, J. E. Walker & A. Klug: Cloning and sequencing of the cDNA encoding a core protein of the paired helical filament of Alzheimer disease: identification as the microtubule-associated protein tau. *Proc Natl Acad Sci U S A*, 85, 4051-5 (1988)
16. Neve, R. L., P. Harris, K. S. Kosik, D. M. Kurnit & T. A. Donlon: Identification of cDNA clones for the human microtubule-associated protein tau and chromosomal localization of the genes for tau and microtubule-associated protein 2. *Brain Res*, 387, 271-80 (1986)
17. Gustke, N., B. Trinczek, J. Biernat, E. M. Mandelkow & E. Mandelkow: Domains of tau protein and interactions with microtubules. *Biochemistry*, 33, 9511-22 (1994)
18. Trinczek, B., J. Biernat, K. Baumann, E. M. Mandelkow & E. Mandelkow: Domains of tau protein, differential phosphorylation, and dynamic instability of microtubules. *Mol Biol Cell*, 6, 1887-902 (1995)
19. Mandelkow, E. M., J. Biernat, G. Drewes, N. Gustke, B. Trinczek & E. Mandelkow: Tau domains, phosphorylation, and interactions with microtubules. *Neurobiol Aging*, 16, 355-62; discussion 362-3 (1995)
20. Lee, G., R. L. Neve & K. S. Kosik: The microtubule binding domain of tau protein. *Neuron*, 2, 1615-24 (1989)
21. Andreadis, A., W. M. Brown & K. S. Kosik: Structure and novel exons of the human tau gene. *Biochemistry*, 31, 10626-33 (1992)
22. Brandt, R., J. Leger & G. Lee: Interaction of tau with the neural plasma membrane mediated by tau's amino-terminal projection domain. *J Cell Biol*, 131, 1327-40 (1995)
23. Hirokawa, N., Y. Shiomura & S. Okabe: Tau proteins: the molecular structure and mode of binding on microtubules. *J Cell Biol*, 107, 1449-59 (1988)
24. Sergeant, N., A. Delacourte & L. Buee: Tau protein as a differential biomarker of tauopathies. *Biochim Biophys Acta*, 1739, 179-97 (2005)
25. Chen, J., Y. Kanai, N. J. Cowan & N. Hirokawa: Projection domains of MAP2 and tau determine spacings between microtubules in dendrites and axons. *Nature*, 360, 674-7 (1992)
26. Andreadis, A.: Tau gene alternative splicing: expression patterns, regulation and modulation of function in normal brain and neurodegenerative diseases. *Biochim Biophys Acta*, 1739, 91-103 (2005)
27. Georgieff, I. S., R. K. Liem, D. Couchie, C. Mavilia, J. Nunez & M. L. Shelanski: Expression of high molecular weight tau in the central and peripheral nervous systems. *J Cell Sci*, 105 (Pt 3), 729-37 (1993)
28. Goedert, M. & R. Jakes: Expression of separate isoforms of human tau protein: correlation with the tau pattern in brain and effects on tubulin polymerization. *Embo J*, 9, 4225-30 (1990)
29. Goedert, M., M. G. Spillantini, R. Jakes, D. Rutherford & R. A. Crowther: Multiple isoforms of human microtubule-associated protein tau: sequences and localization in neurofibrillary tangles of Alzheimer's disease. *Neuron*, 3, 519-26 (1989)
30. Butner, K. A. & M. W. Kirschner: Tau protein binds to microtubules through a flexible array of distributed weak sites. *J Cell Biol*, 115, 717-30 (1991)
31. Goode, B. L. & S. C. Feinstein: Identification of a novel microtubule binding and assembly domain in the developmentally regulated inter-repeat region of tau. *J Cell Biol*, 124, 769-82 (1994)
32. Couchie, D., C. Mavilia, I. S. Georgieff, R. K. Liem, M. L. Shelanski & J. Nunez: Primary structure of high molecular weight tau present in the peripheral nervous system. *Proc Natl Acad Sci U S A*, 89, 4378-81 (1992)
33. Georgieff, I. S., R. K. Liem, W. Mellado, J. Nunez & M. L. Shelanski: High molecular weight tau: preferential localization in the peripheral nervous system. *J Cell Sci*, 100 (Pt 1), 55-60 (1991)
34. Goedert, M., M. G. Spillantini & R. A. Crowther: Cloning of a big tau microtubule-associated protein characteristic of the peripheral nervous system. *Proc Natl Acad Sci U S A*, 89, 1983-7 (1992)
35. Luo, M. H., S. W. Tse, J. Memmott & A. Andreadis: Novel isoforms of tau that lack the microtubule-binding domain. *J Neurochem*, 90, 340-51 (2004)
36. Wei, M. L. & A. Andreadis: Splicing of a regulated exon reveals additional complexity in the axonal microtubule-associated protein tau. *J Neurochem*, 70, 1346-56 (1998)
37. Chen, W. T., W. K. Liu & S. H. Yen: Expression of tau exon 8 in different species. *Neurosci Lett*, 172, 167-70 (1994)
38. Himmler, A.: Structure of the bovine tau gene: alternatively spliced transcripts generate a protein family. *Mol Cell Biol*, 9, 1389-96 (1989)
39. Ruben, G. C., K. Iqbal, I. Grundke-Iqbal, H. M. Wisniewski, T. L. Ciardelli & J. E. Johnson, Jr.: The microtubule-associated protein tau forms a triple-stranded left-hand helical polymer. *J Biol Chem*, 266, 22019-27 (1991)
40. von Bergen, M., P. Friedhoff, J. Biernat, J. Heberle, E. M. Mandelkow & E. Mandelkow: Assembly of tau protein into Alzheimer paired helical filaments depends on a local sequence motif ((306)VQIVYK (311)) forming beta structure. *Proc Natl Acad Sci U S A*, 97, 5129-34 (2000)
41. von Bergen, M., S. Barghorn, J. Biernat, E. M. Mandelkow & E. Mandelkow: Tau aggregation is driven by a transition from random coil to beta sheet structure. *Biochim Biophys Acta*, 1739, 158-66 (2005)

42. Mukrasch, M. D., J. Biernat, M. von Bergen, C. Griesinger, E. Mandelkow & M. Zweckstetter: Sites of tau important for aggregation populate {beta}-structure and bind to microtubules and polyanions. *J Biol Chem*, 280, 24978-86 (2005)
43. Sadqi, M., F. Hernandez, U. Pan, M. Perez, M. D. Schaeberle, J. Avila & V. Munoz: Alpha-helix structure in Alzheimer's disease aggregates of tau-protein. *Biochemistry*, 41, 7150-5 (2002)
44. Binder, L. I., A. L. Guillozet-Bongaarts, F. Garcia-Sierra & R. W. Berry: Tau, tangles, and Alzheimer's disease. *Biochim Biophys Acta*, 1739, 216-23 (2005)
45. Abraha, A., N. Ghoshal, T. C. Gamblin, V. Cryns, R. W. Berry, J. Kuret & L. I. Binder: C-terminal inhibition of tau assembly *in vitro* and in Alzheimer's disease. *J Cell Sci*, 113 Pt 21, 3737-45 (2000)
46. Berry, R. W., A. Abraha, S. Lagalwar, N. LaPointe, T. C. Gamblin, V. L. Cryns & L. I. Binder: Inhibition of tau polymerization by its carboxy-terminal caspase cleavage fragment. *Biochemistry*, 42, 8325-31 (2003)
47. Gamblin, T. C., R. W. Berry & L. I. Binder: Tau polymerization: role of the amino terminus. *Biochemistry*, 42, 2252-7 (2003)
48. Alonso, A., T. Zaidi, M. Novak, I. Grundke-Iqbal & K. Iqbal: Hyperphosphorylation induces self-assembly of tau into tangles of paired helical filaments/straight filaments. *Proc Natl Acad Sci U S A*, 98, 6923-8 (2001)
49. Eidenmuller, J., T. Fath, A. Hellwig, J. Reed, E. Sontag & R. Brandt: Structural and functional implications of tau hyperphosphorylation: information from phosphorylation-mimicking mutated tau proteins. *Biochemistry*, 39, 13166-75 (2000)
50. Necula, M. & J. Kuret: Site-specific pseudophosphorylation modulates the rate of tau filament dissociation. *FEBS Lett*, 579, 1453-7 (2005)
51. Haase, C., J. T. Stieler, T. Arendt & M. Holzer: Pseudophosphorylation of tau protein alters its ability for self-aggregation. *J Neurochem*, 88, 1509-20 (2004)
52. Iqbal, K., C. Alonso Adel, S. Chen, M. O. Chohan, E. El-Akkad, C. X. Gong, S. Khatoon, B. Li, F. Liu, A. Rahman, H. Tanimukai & I. Grundke-Iqbal: Tau pathology in Alzheimer disease and other tauopathies. *Biochim Biophys Acta*, 1739, 198-210 (2005)
53. Lee, V. M., M. Goedert & J. Q. Trojanowski: Neurodegenerative tauopathies. *Annu Rev Neurosci*, 24, 1121-59 (2001)
54. Johnson, G. V. & W. H. Stoothoff: Tau phosphorylation in neuronal cell function and dysfunction. *J Cell Sci*, 117, 5721-9 (2004)
55. Biernat, J., N. Gustke, G. Drewes, E. M. Mandelkow & E. Mandelkow: Phosphorylation of Ser262 strongly reduces binding of tau to microtubules: distinction between PHF-like immunoreactivity and microtubule binding. *Neuron*, 11, 153-63 (1993)
56. Biernat, J. & E. M. Mandelkow: The development of cell processes induced by tau protein requires phosphorylation of serine 262 and 356 in the repeat domain and is inhibited by phosphorylation in the proline-rich domains. *Mol Biol Cell*, 10, 727-40 (1999)
57. Drewes, G., B. Trinczek, S. Illenberger, J. Biernat, G. Schmitt-Ulms, H. E. Meyer, E. M. Mandelkow & E. Mandelkow: Microtubule-associated protein/microtubule affinity-regulating kinase (p110mark). A novel protein kinase that regulates tau-microtubule interactions and dynamic instability by phosphorylation at the Alzheimer-specific site serine 262. *J Biol Chem*, 270, 7679-88 (1995)
58. Pei, J. J., E. Braak, H. Braak, I. Grundke-Iqbal, K. Iqbal, B. Winblad & R. F. Cowburn: Distribution of active glycogen synthase kinase 3beta (GSK-3beta) in brains staged for Alzheimer disease neurofibrillary changes. *J Neuropathol Exp Neurol*, 58, 1010-9 (1999)
59. Pei, J. J., I. Grundke-Iqbal, K. Iqbal, N. Bogdanovic, B. Winblad & R. F. Cowburn: Accumulation of cyclin-dependent kinase 5 (cdk5) in neurons with early stages of Alzheimer's disease neurofibrillary degeneration. *Brain Res*, 797, 267-77 (1998)
60. Perry, G., H. Roder, A. Nunomura, A. Takeda, A. L. Friedlich, X. Zhu, A. K. Raina, N. Holbrook, S. L. Siedlak, P. L. Harris & M. A. Smith: Activation of neuronal extracellular receptor kinase (ERK) in Alzheimer disease links oxidative stress to abnormal phosphorylation. *Neuroreport*, 10, 2411-5 (1999)
61. Jicha, G. A., C. Weaver, E. Lane, C. Vianna, Y. Kress, J. Rockwood & P. Davies: cAMP-dependent protein kinase phosphorylations on tau in Alzheimer's disease. *J Neurosci*, 19, 7486-94 (1999)
62. Xiao, J., G. Perry, J. Troncoso & M. J. Monteiro: alpha-calcium-calmodulin-dependent kinase II is associated with paired helical filaments of Alzheimer's disease. *J Neuropathol Exp Neurol*, 55, 954-63 (1996)
63. Goedert, M., R. Jakes, R. A. Crowther, P. Cohen, E. Vanmechelen, M. Vandermeeren & P. Cras: Epitope mapping of monoclonal antibodies to the paired helical filaments of Alzheimer's disease: identification of phosphorylation sites in tau protein. *Biochem J*, 301 (Pt 3), 871-7 (1994)
64. Cho, J. H. & G. V. Johnson: Glycogen synthase kinase 3beta phosphorylates tau at both primed and unprimed sites. Differential impact on microtubule binding. *J Biol Chem*, 278, 187-93 (2003)
65. Hamdane, M., A. V. Sambo, P. Delobel, S. Begard, A. Violleau, A. Delacourte, P. Bertrand, J. Benavides & L. Buee: Mitotic-like tau phosphorylation by p25-Cdk5 kinase complex. *J Biol Chem*, 278, 34026-34 (2003)
66. Cho, J. H. & G. V. Johnson: Primed phosphorylation of tau at Thr231 by glycogen synthase kinase 3beta (GSK3beta) plays a critical role in regulating tau's ability to bind and stabilize microtubules. *J Neurochem*, 88, 349-58 (2004)
67. Brandt, R., M. Hundelt & N. Shahani: Tau alteration and neuronal degeneration in tauopathies: mechanisms and models. *Biochim Biophys Acta*, 1739, 331-54 (2005)
68. Hasegawa, M., M. J. Smith & M. Goedert: Tau proteins with FTDP-17 mutations have a reduced ability to promote microtubule assembly. *FEBS Lett*, 437, 207-10 (1998)
69. Hong, M., V. Zhukareva, V. Vogelsberg-Ragaglia, Z. Wszolek, L. Reed, B. I. Miller, D. H. Geschwind, T. D. Bird, D. McKeel, A. Goate, J. C. Morris, K. C. Wilhelmsen, G. D. Schellenberg, J. Q. Trojanowski & V. M. Lee: Mutation-specific functional impairments in distinct tau isoforms of hereditary FTDP-17. *Science*, 282, 1914-7 (1998)
70. Dayanandan, R., M. Van Slegtenhorst, T. G. Mack, L. Ko, S. H. Yen, K. Leroy, J. P. Brion, B. H. Anderton, M.

Hutton & S. Lovestone: Mutations in tau reduce its microtubule binding properties in intact cells and affect its phosphorylation. *FEBS Lett*, 446, 228-32 (1999)
71. Rizzu, P., J. C. Van Swieten, M. Joosse, M. Hasegawa, M. Stevens, A. Tibben, M. F. Niermeijer, M. Hillebrand, R. Ravid, B. A. Oostra, M. Goedert, C. M. van Duijn & P. Heutink: High prevalence of mutations in the microtubule-associated protein tau in a population study of frontotemporal dementia in the Netherlands. *Am J Hum Genet*, 64, 414-21 (1999)
72. Lu, M. & K. S. Kosik: Competition for microtubule-binding with dual expression of tau missense and splice isoforms. *Mol Biol Cell*, 12, 171-84 (2001)
73. Kosik, K. S., L. D. Orecchio, S. Bakalis & R. L. Neve: Developmentally regulated expression of specific tau sequences. *Neuron*, 2, 1389-97 (1989)
74. Smith, M. A., S. L. Siedlak, P. L. Richey, P. Mulvihill, J. Ghiso, B. Frangione, F. Tagliavini, G. Giaccone, O. Bugiani, D. Praprotnik & et al.: Tau protein directly interacts with the amyloid beta-protein precursor: implications for Alzheimer's disease. *Nat Med*, 1, 365-9 (1995)
75. Hirokawa, N., T. Funakoshi, R. Sato-Harada & Y. Kanai: Selective stabilization of tau in axons and microtubule-associated protein 2C in cell bodies and dendrites contributes to polarized localization of cytoskeletal proteins in mature neurons. *J Cell Biol*, 132, 667-79 (1996)
76. Leger, J. G., R. Brandt & G. Lee: Identification of tau protein regions required for process formation in PC12 cells. *J Cell Sci*, 107 (Pt 12), 3403-12 (1994)
77. Esmaeli-Azad, B., J. H. McCarty & S. C. Feinstein: Sense and antisense transfection analysis of tau function: tau influences net microtubule assembly, neurite outgrowth and neuritic stability. *J Cell Sci*, 107 (Pt 4), 869-79 (1994)
78. Barlow, S., M. L. Gonzalez-Garay, R. R. West, J. B. Olmsted & F. Cabral: Stable expression of heterologous microtubule-associated proteins (MAPs) in Chinese hamster ovary cells: evidence for differing roles of MAPs in microtubule organization. *J Cell Biol*, 126, 1017-29 (1994)
79. Kanai, Y., R. Takemura, T. Oshima, H. Mori, Y. Ihara, M. Yanagisawa, T. Masaki & N. Hirokawa: Expression of multiple tau isoforms and microtubule bundle formation in fibroblasts transfected with a single tau cDNA. *J Cell Biol*, 109, 1173-84 (1989)
80. Knops, J., K. S. Kosik, G. Lee, J. D. Pardee, L. Cohen-Gould & L. McConlogue: Overexpression of tau in a nonneuronal cell induces long cellular processes. *J Cell Biol*, 114, 725-33 (1991)
81. Caceres, A., S. Potrebic & K. S. Kosik: The effect of tau antisense oligonucleotides on neurite formation of cultured cerebellar macroneurons. *J Neurosci*, 11, 1515-23 (1991)
82. Harada, A., K. Oguchi, S. Okabe, J. Kuno, S. Terada, T. Ohshima, R. Sato-Yoshitake, Y. Takei, T. Noda & N. Hirokawa: Altered microtubule organization in small-calibre axons of mice lacking tau protein. *Nature*, 369, 488-91 (1994)
83. Dawson, H. N., A. Ferreira, M. V. Eyster, N. Ghoshal, L. I. Binder & M. P. Vitek: Inhibition of neuronal maturation in primary hippocampal neurons from tau deficient mice. *J Cell Sci*, 114, 1179-87 (2001)
84. Takei, Y., J. Teng, A. Harada & N. Hirokawa: Defects in axonal elongation and neuronal migration in mice with disrupted tau and map1b genes. *J Cell Biol*, 150, 989-1000 (2000)
85. Mandell, J. W. & G. A. Banker: Microtubule-associated proteins, phosphorylation gradients, and the establishment of neuronal polarity. *Perspect Dev Neurobiol*, 4, 125-35 (1996)
86. Biernat, J., Y. Z. Wu, T. Timm, Q. Zheng-Fischhofer, E. Mandelkow, L. Meijer & E. M. Mandelkow: Protein kinase MARK/PAR-1 is required for neurite outgrowth and establishment of neuronal polarity. *Mol Biol Cell*, 13, 4013-28 (2002)
87. Yoshizaki, C., M. Tsukane & T. Yamauchi: Overexpression of tau leads to the stimulation of neurite outgrowth, the activation of caspase 3 activity, and accumulation and phosphorylation of tau in neuroblastoma cells on cAMP treatment. *Neurosci Res*, 49, 363-71 (2004)
88. Sayas, C. L., J. Avila & F. Wandosell: Regulation of neuronal cytoskeleton by lysophosphatidic acid: role of GSK-3. *Biochim Biophys Acta*, 1582, 144-53 (2002)
89. Ferrari-Toninelli, G., S. Paccioretti, S. Francisconi, D. Uberti & M. Memo: TorsinA negatively controls neurite outgrowth of SH-SY5Y human neuronal cell line. *Brain Res*, 1012, 75-81 (2004)
90. Toninelli, G. F., P. Spano & M. Memo: TorsinA, microtubules and cell polarity. *Funct Neurol*, 18, 7-10 (2003)
91. Ozelius, L. J., J. Hewett, P. Kramer, S. B. Bressman, C. Shalish, D. de Leon, M. Rutter, N. Risch, M. F. Brin, E. D. Markova, S. A. Limborska, I. A. Ivanova-Smolenskaya, M. K. McCormick, S. Fahn, A. J. Buckler, J. F. Gusella & X. O. Breakefield: Fine localization of the torsion dystonia gene (DYT1) on human chromosome 9q34: YAC map and linkage disequilibrium. *Genome Res*, 7, 483-94 (1997)
92. Ozelius, L. J., C. E. Page, C. Klein, J. W. Hewett, M. Mineta, J. Leung, C. Shalish, S. B. Bressman, D. de Leon, M. F. Brin, S. Fahn, D. P. Corey & X. O. Breakefield: The TOR1A (DYT1) gene family and its role in early onset torsion dystonia. *Genomics*, 62, 377-84 (1999)
93. Spittaels, K., C. Van den Haute, J. Van Dorpe, K. Bruynseels, K. Vandezande, I. Laenen, H. Geerts, M. Mercken, R. Sciot, A. Van Lommel, R. Loos & F. Van Leuven: Prominent axonopathy in the brain and spinal cord of transgenic mice overexpressing four-repeat human tau protein. *Am J Pathol*, 155, 2153-65 (1999)
94. Probst, A., J. Gotz, K. H. Wiederhold, M. Tolnay, C. Mistl, A. L. Jaton, M. Hong, T. Ishihara, V. M. Lee, J. Q. Trojanowski, R. Jakes, R. A. Crowther, M. G. Spillantini, K. Burki & M. Goedert: Axonopathy and amyotrophy in mice transgenic for human four-repeat tau protein. *Acta Neuropathol (Berl)*, 99, 469-81 (2000)
95. Ishihara, T., M. Hong, B. Zhang, Y. Nakagawa, M. K. Lee, J. Q. Trojanowski & V. M. Lee: Age-dependent emergence and progression of a tauopathy in transgenic mice overexpressing the shortest human tau isoform. *Neuron*, 24, 751-62 (1999)
96. Mandelkow, E. M., K. Stamer, R. Vogel, E. Thies & E. Mandelkow: Clogging of axons by tau, inhibition of axonal

traffic and starvation of synapses. *Neurobiol Aging*, 24, 1079-85 (2003)
97. Seitz, A., H. Kojima, K. Oiwa, E. M. Mandelkow, Y. H. Song & E. Mandelkow: Single-molecule investigation of the interference between kinesin, tau and MAP2c. *Embo J*, 21, 4896-905 (2002)
98. Spittaels, K., C. Van den Haute, J. Van Dorpe, H. Geerts, M. Mercken, K. Bruynseels, R. Lasrado, K. Vandezande, I. Laenen, T. Boon, J. Van Lint, J. Vandenheede, D. Moechars, R. Loos & F. Van Leuven: Glycogen synthase kinase-3beta phosphorylates protein tau and rescues the axonopathy in the central nervous system of human four-repeat tau transgenic mice. *J Biol Chem*, 275, 41340-9 (2000)
99. Nuydens, R., G. Van Den Kieboom, C. Nolten, C. Verhulst, P. Van Osta, K. Spittaels, C. Van den Haute, E. De Feyter, H. Geerts & F. Van Leuven: Coexpression of GSK-3beta corrects phenotypic aberrations of dorsal root ganglion cells, cultured from adult transgenic mice overexpressing human protein tau. *Neurobiol Dis*, 9, 38-48 (2002)
100. Tatebayashi, Y., N. Haque, Y. C. Tung, K. Iqbal & I. Grundke-Iqbal: Role of tau phosphorylation by glycogen synthase kinase-3beta in the regulation of organelle transport. *J Cell Sci*, 117, 1653-63 (2004)
101. Mudher, A., D. Shepherd, T. A. Newman, P. Mildren, J. P. Jukes, A. Squire, A. Mears, J. A. Drummond, S. Berg, D. MacKay, A. A. Asuni, R. Bhat & S. Lovestone: GSK-3beta inhibition reverses axonal transport defects and behavioural phenotypes in Drosophila. *Mol Psychiatry*, 9, 522-30 (2004)
102. Klein, C., E. M. Kramer, A. M. Cardine, B. Schraven, R. Brandt & J. Trotter: Process outgrowth of oligodendrocytes is promoted by interaction of fyn kinase with the cytoskeletal protein tau. *J Neurosci*, 22, 698-707 (2002)
103. Lee, G.: Tau and src family tyrosine kinases. *Biochim Biophys Acta*, 1739, 323-30 (2005)
104. Lee, G., S. T. Newman, D. L. Gard, H. Band & G. Panchamoorthy: Tau interacts with src-family non-receptor tyrosine kinases. *J Cell Sci*, 111 (Pt 21), 3167-77 (1998)
105. Zamora-Leon, S. P., G. Lee, P. Davies & B. Shafit-Zagardo: Binding of Fyn to MAP-2c through an SH3 binding domain. Regulation of the interaction by ERK2. *J Biol Chem*, 276, 39950-8 (2001)
106. Williamson, R., T. Scales, B. R. Clark, G. Gibb, C. H. Reynolds, S. Kellie, I. N. Bird, I. M. Varndell, P. W. Sheppard, I. Everall & B. H. Anderton: Rapid tyrosine phosphorylation of neuronal proteins including tau and focal adhesion kinase in response to amyloid-beta peptide exposure: involvement of Src family protein kinases. *J Neurosci*, 22, 10-20 (2002)
107. Lee, G., R. Thangavel, V. M. Sharma, J. M. Litersky, K. Bhaskar, S. M. Fang, L. H. Do, A. Andreadis, G. Van Hoesen & H. Ksiezak-Reding: Phosphorylation of tau by fyn: implications for Alzheimer's disease. *J Neurosci*, 24, 2304-12 (2004)
108. Bixby, J. L. & P. Jhabvala: Tyrosine phosphorylation in early embryonic growth cones. *J Neurosci*, 13, 3421-32 (1993)
109. Goldberg, D. J. & D. Y. Wu: Tyrosine phosphorylation and protrusive structures of the growth cone. *Perspect Dev Neurobiol*, 4, 183-92 (1996)
110. Maness, P. F., M. Aubry, C. G. Shores, L. Frame & K. H. Pfenninger: c-src gene product in developing rat brain is enriched in nerve growth cone membranes. *Proc Natl Acad Sci U S A*, 85, 5001-5 (1988)
111. Helmke, S. & K. H. Pfenninger: Growth cone enrichment and cytoskeletal association of non-receptor tyrosine kinases. *Cell Motil Cytoskeleton*, 30, 194-207 (1995)
112. Beggs, H. E., P. Soriano & P. F. Maness: NCAM-dependent neurite outgrowth is inhibited in neurons from Fyn-minus mice. *J Cell Biol*, 127, 825-33 (1994)
113. Ignelzi, M. A., Jr., D. R. Miller, P. Soriano & P. F. Maness: Impaired neurite outgrowth of src-minus cerebellar neurons on the cell adhesion molecule L1. *Neuron*, 12, 873-84 (1994)
114. van't Hof, W. & M. D. Resh: Rapid plasma membrane anchoring of newly synthesized p59fyn: selective requirement for NH2-terminal myristoylation and palmitoylation at cysteine-3. *J Cell Biol*, 136, 1023-35 (1997)
115. Webb, Y., L. Hermida-Matsumoto & M. D. Resh: Inhibition of protein palmitoylation, raft localization, and T cell signaling by 2-bromopalmitate and polyunsaturated fatty acids. *J Biol Chem*, 275, 261-70 (2000)
116. Gorath, M., T. Stahnke, T. Mronga, O. Goldbaum & C. Richter-Landsberg: Developmental changes of tau protein and mRNA in cultured rat brain oligodendrocytes. *Glia*, 36, 89-101 (2001)
117. Buee, L., T. Bussiere, V. Buee-Scherrer, A. Delacourte & P. R. Hof: Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. *Brain Res Brain Res Rev*, 33, 95-130 (2000)
118. Derkinderen, P., T. M. Scales, D. P. Hanger, K. Y. Leung, H. L. Byers, M. A. Ward, C. Lenz, C. Price, I. N. Bird, T. Perera, S. Kellie, R. Williamson, W. Noble, R. A. Van Etten, K. Leroy, J. P. Brion, C. H. Reynolds & B. H. Anderton: Tyrosine 394 is phosphorylated in Alzheimer's paired helical filament tau and in fetal tau with c-Abl as the candidate tyrosine kinase. *J Neurosci*, 25, 6584-93 (2005)
119. Doble, B. W. & J. R. Woodgett: GSK-3: tricks of the trade for a multi-tasking kinase. *J Cell Sci*, 116, 1175-86 (2003)
120. Woodgett, J. R.: Molecular cloning and expression of glycogen synthase kinase-3/factor A. *Embo J*, 9, 2431-8 (1990)
121. Leroy, K. & J. P. Brion: Developmental expression and localization of glycogen synthase kinase-3beta in rat brain. *J Chem Neuroanat*, 16, 279-93 (1999)
122. Ishiguro, K., A. Shiratsuchi, S. Sato, A. Omori, M. Arioka, S. Kobayashi, T. Uchida & K. Imahori: Glycogen synthase kinase 3 beta is identical to tau protein kinase I generating several epitopes of paired helical filaments. *FEBS Lett*, 325, 167-72 (1993)
123. Lovestone, S., C. L. Hartley, J. Pearce & B. H. Anderton: Phosphorylation of tau by glycogen synthase kinase-3 beta in intact mammalian cells: the effects on the organization and stability of microtubules. *Neuroscience*, 73, 1145-57 (1996)
124. Wagner, U., M. Utton, J. M. Gallo & C. C. Miller: Cellular phosphorylation of tau by GSK-3 beta influences tau binding to microtubules and microtubule organisation. *J Cell Sci*, 109 (Pt 6), 1537-43 (1996)

125. Lucas, J. J., F. Hernandez, P. Gomez-Ramos, M. A. Moran, R. Hen & J. Avila: Decreased nuclear beta-catenin, tau hyperphosphorylation and neurodegeneration in GSK-3beta conditional transgenic mice. *Embo J*, 20, 27-39 (2001)
126. Hong, M., D. C. Chen, P. S. Klein & V. M. Lee: Lithium reduces tau phosphorylation by inhibition of glycogen synthase kinase-3. *J Biol Chem*, 272, 25326-32 (1997)
127. Lovestone, S., D. R. Davis, M. T. Webster, S. Kaech, J. P. Brion, A. Matus & B. H. Anderton: Lithium reduces tau phosphorylation: effects in living cells and in neurons at therapeutic concentrations. *Biol Psychiatry*, 45, 995-1003 (1999)
128. Stambolic, V., L. Ruel & J. R. Woodgett: Lithium inhibits glycogen synthase kinase-3 activity and mimics wingless signalling in intact cells. *Curr Biol*, 6, 1664-8 (1996)
129. Noble, W., E. Planel, C. Zehr, V. Olm, J. Meyerson, F. Suleman, K. Gaynor, L. Wang, J. LaFrancois, B. Feinstein, M. Burns, P. Krishnamurthy, Y. Wen, R. Bhat, J. Lewis, D. Dickson & K. Duff: Inhibition of glycogen synthase kinase-3 by lithium correlates with reduced tauopathy and degeneration *in vivo*. *Proc Natl Acad Sci U S A*, 102, 6990-5 (2005)
130. Perez, M., F. Hernandez, F. Lim, J. Diaz-Nido & J. Avila: Chronic lithium treatment decreases mutant tau protein aggregation in a transgenic mouse model. *J Alzheimers Dis*, 5, 301-8 (2003)
131. Jope, R. S. & G. V. Johnson: The glamour and gloom of glycogen synthase kinase-3. *Trends Biochem Sci*, 29, 95-102 (2004)
132. Shelton, S. B. & G. V. Johnson: Cyclin-dependent kinase-5 in neurodegeneration. *J Neurochem*, 88, 1313-26 (2004)
133. Dhavan, R. & L. H. Tsai: A decade of CDK5. *Nat Rev Mol Cell Biol*, 2, 749-59 (2001)
134. Patzke, H. & L. H. Tsai: Calpain-mediated cleavage of the cyclin-dependent kinase-5 activator p39 to p29. *J Biol Chem*, 277, 8054-60 (2002)
135. Kusakawa, G., T. Saito, R. Onuki, K. Ishiguro, T. Kishimoto & S. Hisanaga: Calpain-dependent proteolytic cleavage of the p35 cyclin-dependent kinase 5 activator to p25. *J Biol Chem*, 275, 17166-72 (2000)
136. Patrick, G. N., P. Zhou, Y. T. Kwon, P. M. Howley & L. H. Tsai: p35, the neuronal-specific activator of cyclin-dependent kinase 5 (Cdk5) is degraded by the ubiquitin-proteasome pathway. *J Biol Chem*, 273, 24057-64 (1998)
137. Patrick, G. N., L. Zukerberg, M. Nikolic, S. de la Monte, P. Dikkes & L. H. Tsai: Conversion of p35 to p25 deregulates Cdk5 activity and promotes neurodegeneration. *Nature*, 402, 615-22 (1999)
138. Hashiguchi, M., T. Saito, S. Hisanaga & T. Hashiguchi: Truncation of CDK5 activator p35 induces intensive phosphorylation of Ser202/Thr205 of human tau. *J Biol Chem*, 277, 44525-30 (2002)
139. Lund, E. T., R. McKenna, D. B. Evans, S. K. Sharma & W. R. Mathews: Characterization of the *in vitro* phosphorylation of human tau by tau protein kinase II (cdk5/p20) using mass spectrometry. *J Neurochem*, 76, 1221-32 (2001)
140. Liu, F., K. Iqbal, I. Grundke-Iqbal & C. X. Gong: Involvement of aberrant glycosylation in phosphorylation of tau by cdk5 and GSK-3beta. *FEBS Lett*, 530, 209-14 (2002)
141. Anderton, B. H., J. Betts, W. P. Blackstock, J. P. Brion, S. Chapman, J. Connell, R. Dayanandan, J. M. Gallo, G. Gibb, D. P. Hanger, M. Hutton, E. Kardalinou, K. Leroy, S. Lovestone, T. Mack, C. H. Reynolds & M. Van Slegtenhorst: Sites of phosphorylation in tau and factors affecting their regulation. *Biochem Soc Symp*73-80 (2001)
142. Kerokoski, P., T. Suuronen, A. Salminen, H. Soininen & T. Pirttila: Influence of phosphorylation of p35, an activator of cyclin-dependent kinase 5 (cdk5), on the proteolysis of p35. *Brain Res Mol Brain Res*, 106, 50-6 (2002)
143. Shelton, S. B., P. Krishnamurthy & G. V. Johnson: Effects of cyclin-dependent kinase-5 activity on apoptosis and tau phosphorylation in immortalized mouse brain cortical cells. *J Neurosci Res*, 76, 110-20 (2004)
144. Morfini, G., G. Szebenyi, H. Brown, H. C. Pant, G. Pigino, S. DeBoer, U. Beffert & S. T. Brady: A novel CDK5-dependent pathway for regulating GSK3 activity and kinesin-driven motility in neurons. *Embo J*, 23, 2235-45 (2004)
145. Hallows, J. L., K. Chen, R. A. DePinho & I. Vincent: Decreased cyclin-dependent kinase 5 (cdk5) activity is accompanied by redistribution of cdk5 and cytoskeletal proteins and increased cytoskeletal protein phosphorylation in p35 null mice. *J Neurosci*, 23, 10633-44 (2003)
146. Fleming, L. M. & G. V. Johnson: Modulation of the phosphorylation state of tau *in situ*: the roles of calcium and cyclic AMP. *Biochem J*, 309 (Pt 1), 41-7 (1995)
147. Litersky, J. M., G. V. Johnson, R. Jakes, M. Goedert, M. Lee & P. Seubert: Tau protein is phosphorylated by cyclic AMP-dependent protein kinase and calcium/calmodulin-dependent protein kinase II within its microtubule-binding domains at Ser-262 and Ser-356. *Biochem J*, 316 (Pt 2), 655-60 (1996)
148. Drewes, G., A. Ebneth, U. Preuss, E. M. Mandelkow & E. Mandelkow: MARK, a novel family of protein kinases that phosphorylate microtubule-associated proteins and trigger microtubule disruption. *Cell*, 89, 297-308 (1997)
149. Seubert, P., M. Mawal-Dewan, R. Barbour, R. Jakes, M. Goedert, G. V. Johnson, J. M. Litersky, D. Schenk, I. Lieberburg, J. Q. Trojanowski & et al.: Detection of phosphorylated Ser262 in fetal tau, adult tau, and paired helical filament tau. *J Biol Chem*, 270, 18917-22 (1995)
150. Chin, J. Y., R. B. Knowles, A. Schneider, G. Drewes, E. M. Mandelkow & B. T. Hyman: Microtubule-affinity regulating kinase (MARK) is tightly associated with neurofibrillary tangles in Alzheimer brain: a fluorescence resonance energy transfer study. *J Neuropathol Exp Neurol*, 59, 966-71 (2000)
151. Mandelkow, E. M., E. Thies, B. Trinczek, J. Biernat & E. Mandelkow: MARK/PAR1 kinase is a regulator of microtubule-dependent transport in axons. *J Cell Biol*, 167, 99-110 (2004)
152. Nishimura, I., Y. Yang & B. Lu: PAR-1 kinase plays an initiator role in a temporally ordered phosphorylation process that confers tau toxicity in Drosophila. *Cell*, 116, 671-82 (2004)
153. Guo, S. & K. J. Kemphues: par-1, a gene required for establishing polarity in C. elegans embryos, encodes a putative Ser/Thr kinase that is asymmetrically distributed. *Cell*, 81, 611-20 (1995)

154. Tian, Q. & J. Wang: Role of serine/threonine protein phosphatase in Alzheimer's disease. *Neurosignals*, 11, 262-9 (2002)
155. Liao, H., Y. Li, D. L. Brautigan & G. G. Gundersen: Protein phosphatase 1 is targeted to microtubules by the microtubule-associated protein Tau. *J Biol Chem*, 273, 21901-8 (1998)
156. Gong, C. X., F. Liu, G. Wu, S. Rossie, J. Wegiel, L. Li, I. Grundke-Iqbal & K. Iqbal: Dephosphorylation of microtubule-associated protein tau by protein phosphatase 5. *J Neurochem*, 88, 298-310 (2004)
157. Soulie, C., J. Lepagnol, A. Delacourte & M. L. Caillet-Boudin: Dephosphorylation studies of SKNSH-SY 5Y cell Tau proteins by endogenous phosphatase activity. *Neurosci Lett*, 206, 189-92 (1996)
158. Matsuo, E. S., R. W. Shin, M. L. Billingsley, A. Van deVoorde, M. O'Connor, J. Q. Trojanowski & V. M. Lee: Biopsy-derived adult human brain tau is phosphorylated at many of the same sites as Alzheimer's disease paired helical filament tau. *Neuron*, 13, 989-1002 (1994)
159. Buee-Scherrer, V., O. Condamines, C. Mourton-Gilles, R. Jakes, M. Goedert, B. Pau & A. Delacourte: AD2, a phosphorylation-dependent monoclonal antibody directed against tau proteins found in Alzheimer's disease. *Brain Res Mol Brain Res*, 39, 79-88 (1996)
160. Sontag, E., V. Nunbhakdi-Craig, G. Lee, R. Brandt, C. Kamibayashi, J. Kuret, C. L. White, 3rd, M. C. Mumby & G. S. Bloom: Molecular interactions among protein phosphatase 2A, tau, and microtubules. Implications for the regulation of tau phosphorylation and the development of tauopathies. *J Biol Chem*, 274, 25490-8 (1999)
161. Sontag, E., V. Nunbhakdi-Craig, G. Lee, G. S. Bloom & M. C. Mumby: Regulation of the phosphorylation state and microtubule-binding activity of Tau by protein phosphatase 2A. *Neuron*, 17, 1201-7 (1996)
162. Zhou, X. Z., O. Kops, A. Werner, P. J. Lu, M. Shen, G. Stoller, G. Kullertz, M. Stark, G. Fischer & K. P. Lu: Pin1-dependent prolyl isomerization regulates dephosphorylation of Cdc25C and tau proteins. *Mol Cell*, 6, 873-83 (2000)
163. Daly, N. L., R. Hoffmann, L. Otvos, Jr. & D. J. Craik: Role of phosphorylation in the conformation of tau peptides implicated in Alzheimer's disease. *Biochemistry*, 39, 9039-46 (2000)
164. Goedert, M., S. Satumtira, R. Jakes, M. J. Smith, C. Kamibayashi, C. L. White, 3rd & E. Sontag: Reduced binding of protein phosphatase 2A to tau protein with frontotemporal dementia and parkinsonism linked to chromosome 17 mutations. *J Neurochem*, 75, 2155-62 (2000)
165. Kuret, J., G. S. Johnson, D. Cha, E. R. Christenson, A. J. DeMaggio & M. F. Hoekstra: Casein kinase 1 is tightly associated with paired-helical filaments isolated from Alzheimer's disease brain. *J Neurochem*, 69, 2506-15 (1997)
166. Loring, J. F., X. Wen, J. M. Lee, J. Seilhamer & R. Somogyi: A gene expression profile of Alzheimer's disease. *DNA Cell Biol*, 20, 683-95 (2001)
167. Lian, Q., C. J. Ladner, D. Magnuson & J. M. Lee: Selective changes of calcineurin (protein phosphatase 2B) activity in Alzheimer's disease cerebral cortex. *Exp Neurol*, 167, 158-65 (2001)
168. Gong, C. X., T. J. Singh, I. Grundke-Iqbal & K. Iqbal: Phosphoprotein phosphatase activities in Alzheimer disease brain. *J Neurochem*, 61, 921-7 (1993)
169. Liu, F., I. Grundke-Iqbal, K. Iqbal & C. X. Gong: Contributions of protein phosphatases PP1, PP2A, PP2B and PP5 to the regulation of tau phosphorylation. *Eur J Neurosci*, 22, 1942-50 (2005)
170. Vogelsberg-Ragaglia, V., T. Schuck, J. Q. Trojanowski & V. M. Lee: PP2A mRNA expression is quantitatively decreased in Alzheimer's disease hippocampus. *Exp Neurol*, 168, 402-12 (2001)
171. Sontag, E., C. Hladik, L. Montgomery, A. Luangpirom, I. Mudrak, E. Ogris & C. L. White, 3rd: Downregulation of protein phosphatase 2A carboxyl methylation and methyltransferase may contribute to Alzheimer disease pathogenesis. *J Neuropathol Exp Neurol*, 63, 1080-91 (2004)
172. Gong, C. X., S. Shaikh, J. Z. Wang, T. Zaidi, I. Grundke-Iqbal & K. Iqbal: Phosphatase activity toward abnormally phosphorylated tau: decrease in Alzheimer disease brain. *J Neurochem*, 65, 732-8 (1995)
173. An, W. L., R. F. Cowburn, L. Li, H. Braak, I. Alafuzoff, K. Iqbal, I. G. Iqbal, B. Winblad & J. J. Pei: Up-regulation of phosphorylated/activated p70 S6 kinase and its relationship to neurofibrillary pathology in Alzheimer's disease. *Am J Pathol*, 163, 591-607 (2003)
174. Pei, J. J., C. X. Gong, W. L. An, B. Winblad, R. F. Cowburn, I. Grundke-Iqbal & K. Iqbal: Okadaic-acid-induced inhibition of protein phosphatase 2A produces activation of mitogen-activated protein kinases ERK1/2, MEK1/2, and p70 S6, similar to that in Alzheimer's disease. *Am J Pathol*, 163, 845-58 (2003)
175. Bennecib, M., C. X. Gong, I. Grundke-Iqbal & K. Iqbal: Inhibition of PP-2A upregulates CaMKII in rat forebrain and induces hyperphosphorylation of tau at Ser 262/356. *FEBS Lett*, 490, 15-22 (2001)
176. Tanaka, T., J. Zhong, K. Iqbal, E. Trenkner & I. Grundke-Iqbal: The regulation of phosphorylation of tau in SY5Y neuroblastoma cells: the role of protein phosphatases. *FEBS Lett*, 426, 248-54 (1998)
177. Iqbal, K. & I. Grundke-Iqbal: Metabolic/signal transduction hypothesis of Alzheimer's disease and other tauopathies. *Acta Neuropathol (Berl)*, 109, 25-31 (2005)
178. Kidd, M.: Paired helical filaments in electron microscopy of Alzheimer's disease. *Nature*, 197, 192-3 (1963)
179. Rankin, C. A., Q. Sun & T. C. Gamblin: Pseudo-phosphorylation of tau at Ser202 and Thr205 affects tau filament formation. *Brain Res Mol Brain Res*, 138, 84-93 (2005)
180. Schneider, A., J. Biernat, M. von Bergen, E. Mandelkow & E. M. Mandelkow: Phosphorylation that detaches tau protein from microtubules (Ser262, Ser214) also protects it against aggregation into Alzheimer paired helical filaments. *Biochemistry*, 38, 3549-58 (1999)
181. von Bergen, M., S. Barghorn, L. Li, A. Marx, J. Biernat, E. M. Mandelkow & E. Mandelkow: Mutations of tau protein in frontotemporal dementia promote aggregation of paired helical filaments by enhancing local beta-structure. *J Biol Chem*, 276, 48165-74 (2001)
182. Barghorn, S., Q. Zheng-Fischhofer, M. Ackmann, J. Biernat, M. von Bergen, E. M. Mandelkow & E.

Mandelkow: Structure, microtubule interactions, and paired helical filament aggregation by tau mutants of frontotemporal dementias. *Biochemistry*, 39, 11714-21 (2000)
183. Goedert, M., R. Jakes & R. A. Crowther: Effects of frontotemporal dementia FTDP-17 mutations on heparin-induced assembly of tau filaments. *FEBS Lett*, 450, 306-11 (1999)
184. Nacharaju, P., J. Lewis, C. Easson, S. Yen, J. Hackett, M. Hutton & S. H. Yen: Accelerated filament formation from tau protein with specific FTDP-17 missense mutations. *FEBS Lett*, 447, 195-9 (1999)
185. Pickering-Brown, S. M., M. Baker, T. Nonaka, K. Ikeda, S. Sharma, J. Mackenzie, S. A. Simpson, J. W. Moore, J. S. Snowden, R. de Silva, T. Revesz, M. Hasegawa, M. Hutton & D. M. Mann: Frontotemporal dementia with Pick-type histology associated with Q336R mutation in the tau gene. *Brain*, 127, 1415-26 (2004)
186. Gamblin, T. C., M. E. King, H. Dawson, M. P. Vitek, J. Kuret, R. W. Berry & L. I. Binder: *In vitro* polymerization of tau protein monitored by laser light scattering: method and application to the study of FTDP-17 mutants. *Biochemistry*, 39, 6136-44 (2000)
187. Grover, A., E. England, M. Baker, N. Sahara, J. Adamson, B. Granger, H. Houlden, U. Passant, S. H. Yen, M. DeTure & M. Hutton: A novel tau mutation in exon 9 (1260V) causes a four-repeat tauopathy. *Exp Neurol*, 184, 131-40 (2003)
188. Kuret, J., C. N. Chirita, E. E. Congdon, T. Kannanayakal, G. Li, M. Necula, H. Yin & Q. Zhong: Pathways of tau fibrillization. *Biochim Biophys Acta*, 1739, 167-78 (2005)
189. Mena, R., P. C. Edwards, C. R. Harrington, E. B. Mukaetova-Ladinska & C. M. Wischik: Staging the pathological assembly of truncated tau protein into paired helical filaments in Alzheimer's disease. *Acta Neuropathol (Berl)*, 91, 633-41 (1996)
190. Galvan, M., J. P. David, A. Delacourte, J. Luna & R. Mena: Sequence of neurofibrillary changes in aging and Alzheimer's disease: A confocal study with phospho-tau antibody, AD2. *J Alzheimers Dis*, 3, 417-425 (2001)
191. Turner, M. S., R. W. Briehl, F. A. Ferrone & R. Josephs: Twisted protein aggregates and disease: the stability of sickle hemoglobin fibers. *Phys Rev Lett*, 90, 128103 (2003)
192. Gray, E. G., M. Paula-Barbosa & A. Roher: Alzheimer's disease: paired helical filaments and cytomembranes. *Neuropathol Appl Neurobiol*, 13, 91-110 (1987)
193. Uchihara, T., A. Nakamura, M. Yamazaki & O. Mori: Evolution from pretangle neurons to neurofibrillary tangles monitored by thiazin red combined with Gallyas method and double immunofluorescence. *Acta Neuropathol (Berl)*, 101, 535-9 (2001)
194. Schwab, C., J. C. Steele, H. Akiyama, E. G. McGeer & P. L. McGeer: Relationship of amyloid beta/A4 protein to the neurofibrillary tangles in Guamanian parkinsonism-dementia. *Acta Neuropathol (Berl)*, 90, 287-98 (1995)
195. Defossez, A. & A. Delacourte: Transformation of degenerating neurofibrils into amyloid substance in Alzheimer's disease: histochemical and immunohistochemical studies. *J Neurol Sci*, 81, 1-10 (1987)
196. Bondareff, W., C. Harrington, C. M. Wischik, D. L. Hauser & M. Roth: Immunohistochemical staging of neurofibrillary degeneration in Alzheimer's disease. *J Neuropathol Exp Neurol*, 53, 158-64 (1994)
197. Iqbal, K., T. Zaidi, C. H. Thompson, P. A. Merz & H. M. Wisniewski: Alzheimer paired helical filaments: bulk isolation, solubility, and protein composition. *Acta Neuropathol (Berl)*, 62, 167-77 (1984)
198. Bancher, C., C. Brunner, H. Lassmann, H. Budka, K. Jellinger, G. Wiche, F. Seitelberger, I. Grundke-Iqbal, K. Iqbal & H. M. Wisniewski: Accumulation of abnormally phosphorylated tau precedes the formation of neurofibrillary tangles in Alzheimer's disease. *Brain Res*, 477, 90-9 (1989)
199. Tanzi, R. E. & L. Bertram: New frontiers in Alzheimer's disease genetics. *Neuron*, 32, 181-4 (2001)
200. Gotz, J., J. R. Streffer, D. David, A. Schild, F. Hoerndli, L. Pennanen, P. Kurosinski & F. Chen: Transgenic animal models of Alzheimer's disease and related disorders: histopathology, behavior and therapy. *Mol Psychiatry*, 9, 664-83 (2004)
201. Caughey, B. & P. T. Lansbury: Protofibrils, pores, fibrils, and neurodegeneration: separating the responsible protein aggregates from the innocent bystanders. *Annu Rev Neurosci*, 26, 267-98 (2003)
202. Santacruz, K., J. Lewis, T. Spires, J. Paulson, L. Kotilinek, M. Ingelsson, A. Guimaraes, M. DeTure, M. Ramsden, E. McGowan, C. Forster, M. Yue, J. Orne, C. Janus, A. Mariash, M. Kuskowski, B. Hyman, M. Hutton & K. H. Ashe: Tau suppression in a neurodegenerative mouse model improves memory function. *Science*, 309, 476-81 (2005)
203. Lee, H. G., G. Perry, P. I. Moreira, M. R. Garrett, Q. Liu, X. Zhu, A. Takeda, A. Nunomura & M. A. Smith: Tau phosphorylation in Alzheimer's disease: pathogen or protector? *Trends Mol Med*, 11, 164-9 (2005)
204. Sherman, M. Y. & A. L. Goldberg: Cellular defenses against unfolded proteins: a cell biologist thinks about neurodegenerative diseases. *Neuron*, 29, 15-32 (2001)
205. Arai, T., J. P. Guo & P. L. McGeer: Proteolysis of non-phosphorylated and phosphorylated tau by thrombin. *J Biol Chem*, 280, 5145-53 (2005)
206. Wang, J. Z., I. Grundke-Iqbal & K. Iqbal: Glycosylation of microtubule-associated protein tau: an abnormal posttranslational modification in Alzheimer's disease. *Nat Med*, 2, 871-5 (1996)
207. Ksiezak-Reding, H. & S. H. Yen: Structural stability of paired helical filaments requires microtubule-binding domains of tau: a model for self-association. *Neuron*, 6, 717-28 (1991)
208. Kenessey, A., P. Nacharaju, L. W. Ko & S. H. Yen: Degradation of tau by lysosomal enzyme cathepsin D: implication for Alzheimer neurofibrillary degeneration. *J Neurochem*, 69, 2026-38 (1997)
209. Mercken, M., F. Grynspan & R. A. Nixon: Differential sensitivity to proteolysis by brain calpain of adult human tau, fetal human tau and PHF-tau. *FEBS Lett*, 368, 10-4 (1995)
210. David, D. C., R. Layfield, L. Serpell, Y. Narain, M. Goedert & M. G. Spillantini: Proteasomal degradation of tau protein. *J Neurochem*, 83, 176-85 (2002)

211. Olesen, O. F.: Proteolytic degradation of microtubule associated protein tau by thrombin. *Biochem Biophys Res Commun*, 201, 716-21 (1994)
212. Iqbal, K., I. Grundke-Iqbal, T. Zaidi, P. A. Merz, G. Y. Wen, S. S. Shaikh, H. M. Wisniewski, I. Alafuzoff & B. Winblad: Defective brain microtubule assembly in Alzheimer's disease. *Lancet*, 2, 421-6 (1986)
213. Grundke-Iqbal, I., K. Iqbal, Y. C. Tung, M. Quinlan, H. M. Wisniewski & L. I. Binder: Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. *Proc Natl Acad Sci U S A*, 83, 4913-7 (1986)
214. Grundke-Iqbal, I., K. Iqbal, M. Quinlan, Y. C. Tung, M. S. Zaidi & H. M. Wisniewski: Microtubule-associated protein tau. A component of Alzheimer paired helical filaments. *J Biol Chem*, 261, 6084-9 (1986)
215. Lee, V. M., B. J. Balin, L. Otvos, Jr. & J. Q. Trojanowski: A68: a major subunit of paired helical filaments and derivatized forms of normal Tau. *Science*, 251, 675-8 (1991)
216. Goedert, M.: Tau protein and the neurofibrillary pathology of Alzheimer's disease. *Ann N Y Acad Sci*, 777, 121-31 (1996)
217. Novak, M., R. Jakes, P. C. Edwards, C. Milstein & C. M. Wischik: Difference between the tau protein of Alzheimer paired helical filament core and normal tau revealed by epitope analysis of monoclonal antibodies 423 and 7.51. *Proc Natl Acad Sci U S A*, 88, 5837-41 (1991)
218. Fasulo, L., G. Ugolini, M. Visintin, A. Bradbury, C. Brancolini, V. Verzillo, M. Novak & A. Cattaneo: The neuronal microtubule-associated protein tau is a substrate for caspase-3 and an effector of apoptosis. *J Neurochem*, 75, 624-33 (2000)
219. Rissman, R. A., W. W. Poon, M. Blurton-Jones, S. Oddo, R. Torp, M. P. Vitek, F. M. LaFerla, T. T. Rohn & C. W. Cotman: Caspase-cleavage of tau is an early event in Alzheimer disease tangle pathology. *J Clin Invest*, 114, 121-30 (2004)
220. Garcia-Sierra, F., N. Ghoshal, B. Quinn, R. W. Berry & L. I. Binder: Conformational changes and truncation of tau protein during tangle evolution in Alzheimer's disease. *J Alzheimers Dis*, 5, 65-77 (2003)
221. Ugolini, G., A. Cattaneo & M. Novak: Co-localization of truncated tau and DNA fragmentation in Alzheimer's disease neurones. *Neuroreport*, 8, 3709-12 (1997)
222. Novak, M., J. Kabat & C. M. Wischik: Molecular characterization of the minimal protease resistant tau unit of the Alzheimer's disease paired helical filament. *Embo J*, 12, 365-70 (1993)
223. Novak, M.: Truncated tau protein as a new marker for Alzheimer's disease. *Acta Virol*, 38, 173-89 (1994)
224. Troy, C. M., S. A. Rabacchi, W. J. Friedman, T. F. Frappier, K. Brown & M. L. Shelanski: Caspase-2 mediates neuronal cell death induced by beta-amyloid. *J Neurosci*, 20, 1386-92 (2000)
225. Gervais, F. G., D. Xu, G. S. Robertson, J. P. Vaillancourt, Y. Zhu, J. Huang, A. LeBlanc, D. Smith, M. Rigby, M. S. Shearman, E. E. Clarke, H. Zheng, L. H. Van Der Ploeg, S. C. Ruffolo, N. A. Thornberry, S. Xanthoudakis, R. J. Zamboni, S. Roy & D. W. Nicholson: Involvement of caspases in proteolytic cleavage of Alzheimer's amyloid-beta precursor protein and amyloidogenic A beta peptide formation. *Cell*, 97, 395-406 (1999)
226. Chan, S. L., W. S. Griffin & M. P. Mattson: Evidence for caspase-mediated cleavage of AMPA receptor subunits in neuronal apoptosis and Alzheimer's disease. *J Neurosci Res*, 57, 315-23 (1999)
227. Cotman, C. W. & J. H. Su: Mechanisms of neuronal death in Alzheimer's disease. *Brain Pathol*, 6, 493-506 (1996)
228. Smale, G., N. R. Nichols, D. R. Brady, C. E. Finch & W. E. Horton, Jr.: Evidence for apoptotic cell death in Alzheimer's disease. *Exp Neurol*, 133, 225-30 (1995)
229. Selznick, L. A., D. M. Holtzman, B. H. Han, M. Gokden, A. N. Srinivasan, E. M. Johnson, Jr. & K. A. Roth: *In situ* immunodetection of neuronal caspase-3 activation in Alzheimer disease. *J Neuropathol Exp Neurol*, 58, 1020-6 (1999)
230. Selznick, L. A., T. S. Zheng, R. A. Flavell, P. Rakic & K. A. Roth: Amyloid beta-induced neuronal death is bax-dependent but caspase-independent. *J Neuropathol Exp Neurol*, 59, 271-9 (2000)
231. Masliah, E., M. Mallory, M. Alford, S. Tanaka & L. A. Hansen: Caspase dependent DNA fragmentation might be associated with excitotoxicity in Alzheimer disease. *J Neuropathol Exp Neurol*, 57, 1041-52 (1998)
232. Chung, C. W., Y. H. Song, I. K. Kim, W. J. Yoon, B. R. Ryu, D. G. Jo, H. N. Woo, Y. K. Kwon, H. H. Kim, B. J. Gwag, I. H. Mook-Jung & Y. K. Jung: Proapoptotic effects of tau cleavage product generated by caspase-3. *Neurobiol Dis*, 8, 162-72 (2001)
233. Saito, K., J. S. Elce, J. E. Hamos & R. A. Nixon: Widespread activation of calcium-activated neutral proteinase (calpain) in the brain in Alzheimer disease: a potential molecular basis for neuronal degeneration. *Proc Natl Acad Sci U S A*, 90, 2628-32 (1993)
234. Adamec, E., P. Mohan, J. P. Vonsattel & R. A. Nixon: Calpain activation in neurodegenerative diseases: confocal immunofluorescence study with antibodies specifically recognizing the active form of calpain 2. *Acta Neuropathol (Berl)*, 104, 92-104 (2002)
235. Park, S. Y. & A. Ferreira: The generation of a 17 kDa neurotoxic fragment: an alternative mechanism by which tau mediates beta-amyloid-induced neurodegeneration. *J Neurosci*, 25, 5365-75 (2005)
236. Braak, E., H. Braak & E. M. Mandelkow: A sequence of cytoskeleton changes related to the formation of neurofibrillary tangles and neuropil threads. *Acta Neuropathol (Berl)*, 87, 554-67 (1994)
237. Guillozet-Bongaarts, A. L., F. Garcia-Sierra, M. R. Reynolds, P. M. Horowitz, Y. Fu, T. Wang, M. E. Cahill, E. H. Bigio, R. W. Berry & L. I. Binder: Tau truncation during neurofibrillary tangle evolution in Alzheimer's disease. *Neurobiol Aging*, 26, 1015-22 (2005)
238. Trojanowski, J. Q. & V. M. Lee: Phosphorylation of paired helical filament tau in Alzheimer's disease neurofibrillary lesions: focusing on phosphatases. *Faseb J*, 9, 1570-6 (1995)
239. Yang, L. S. & H. Ksiezak-Reding: Calpain-induced proteolysis of normal human tau and tau associated with paired helical filaments. *Eur J Biochem*, 233, 9-17 (1995)
240. Litersky, J. M. & G. V. Johnson: Phosphorylation by cAMP-dependent protein kinase inhibits the degradation of tau by calpain. *J Biol Chem*, 267, 1563-8 (1992)

241. Wang, X., S. An & J. M. Wu: Specific processing of native and phosphorylated tau protein by proteases. *Biochem Biophys Res Commun*, 219, 591-7 (1996)
242. Layfield, R., J. R. Cavey & J. Lowe: Role of ubiquitin-mediated proteolysis in the pathogenesis of neurodegenerative disorders. *Ageing Res Rev*, 2, 343-56 (2003)
243. Feuillette, S., O. Blard, M. Lecourtois, T. Frebourg, D. Campion & C. Dumanchin: Tau is not normally degraded by the proteasome. *J Neurosci Res*, 80, 400-5 (2005)
244. Mori, H., J. Kondo & Y. Ihara: Ubiquitin is a component of paired helical filaments in Alzheimer's disease. *Science*, 235, 1641-4 (1987)
245. Manetto, V., G. Perry, M. Tabaton, P. Mulvihill, V. A. Fried, H. T. Smith, P. Gambetti & L. Autilio-Gambetti: Ubiquitin is associated with abnormal cytoplasmic filaments characteristic of neurodegenerative diseases. *Proc Natl Acad Sci U S A*, 85, 4501-5 (1988)
246. Wang, G. P., S. Khatoon, K. Iqbal & I. Grundke-Iqbal: Brain ubiquitin is markedly elevated in Alzheimer disease. *Brain Res*, 566, 146-51 (1991)
247. Morishima-Kawashima, M., M. Hasegawa, K. Takio, M. Suzuki, K. Titani & Y. Ihara: Ubiquitin is conjugated with amino-terminally processed tau in paired helical filaments. *Neuron*, 10, 1151-60 (1993)
248. Bancher, C., I. Grundke-Iqbal, K. Iqbal, V. A. Fried, H. T. Smith & H. M. Wisniewski: Abnormal phosphorylation of tau precedes ubiquitination in neurofibrillary pathology of Alzheimer disease. *Brain Res*, 539, 11-8 (1991)
249. Gregori, L., M. S. Poosch, G. Cousins & V. Chau: A uniform isopeptide-linked multiubiquitin chain is sufficient to target substrate for degradation in ubiquitin-mediated proteolysis. *J Biol Chem*, 265, 8354-7 (1990)
250. Chau, V., J. W. Tobias, A. Bachmair, D. Marriott, D. J. Ecker, D. K. Gonda & A. Varshavsky: A multiubiquitin chain is confined to specific lysine in a targeted short-lived protein. *Science*, 243, 1576-83 (1989)
251. Connell, P., C. A. Ballinger, J. Jiang, Y. Wu, L. J. Thompson, J. Hohfeld & C. Patterson: The co-chaperone CHIP regulates protein triage decisions mediated by heat-shock proteins. *Nat Cell Biol*, 3, 93-6 (2001)
252. Schneider, C., L. Sepp-Lorenzino, E. Nimmesgern, O. Ouerfelli, S. Danishefsky, N. Rosen & F. U. Hartl: Pharmacologic shifting of a balance between protein refolding and degradation mediated by Hsp90. *Proc Natl Acad Sci U S A*, 93, 14536-41 (1996)
253. Wickner, S., M. R. Maurizi & S. Gottesman: Posttranslational quality control: folding, refolding, and degrading proteins. *Science*, 286, 1888-93 (1999)
254. Snyder, H., K. Mensah, C. Theisler, J. Lee, A. Matouschek & B. Wolozin: Aggregated and monomeric alpha-synuclein bind to the S6' proteasomal protein and inhibit proteasomal function. *J Biol Chem*, 278, 11753-9 (2003)
255. Kishino, T., M. Lalande & J. Wagstaff: UBE3A/E6-AP mutations cause Angelman syndrome. *Nat Genet*, 15, 70-3 (1997)
256. Kitada, T., S. Asakawa, N. Hattori, H. Matsumine, Y. Yamamura, S. Minoshima, M. Yokochi, Y. Mizuno & N. Shimizu: Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature*, 392, 605-8 (1998)
257. Leroy, E., R. Boyer, G. Auburger, B. Leube, G. Ulm, E. Mezey, G. Harta, M. J. Brownstein, S. Jonnalagada, T. Chernova, A. Dehejia, C. Lavedan, T. Gasser, P. J. Steinbach, K. D. Wilkinson & M. H. Polymeropoulos: The ubiquitin pathway in Parkinson's disease. *Nature*, 395, 451-2 (1998)
258. Bence, N. F., R. M. Sampat & R. R. Kopito: Impairment of the ubiquitin-proteasome system by protein aggregation. *Science*, 292, 1552-5 (2001)
259. Hope, A. D., R. de Silva, D. F. Fischer, E. M. Hol, F. W. van Leeuwen & A. J. Lees: Alzheimer's associated variant ubiquitin causes inhibition of the 26S proteasome and chaperone expression. *J Neurochem*, 86, 394-404 (2003)
260. Keller, J. N., K. B. Hanni & W. R. Markesbery: Impaired proteasome function in Alzheimer's disease. *J Neurochem*, 75, 436-9 (2000)
261. Keck, S., R. Nitsch, T. Grune & O. Ullrich: Proteasome inhibition by paired helical filament-tau in brains of patients with Alzheimer's disease. *J Neurochem*, 85, 115-22 (2003)
262. Shimura, H., D. Schwartz, S. P. Gygi & K. S. Kosik: CHIP-Hsc70 complex ubiquitinates phosphorylated tau and enhances cell survival. *J Biol Chem*, 279, 4869-76 (2004)
263. Petrucelli, L., D. Dickson, K. Kehoe, J. Taylor, H. Snyder, A. Grover, M. De Lucia, E. McGowan, J. Lewis, G. Prihar, J. Kim, W. H. Dillmann, S. E. Browne, A. Hall, R. Voellmy, Y. Tsuboi, T. M. Dawson, B. Wolozin, J. Hardy & M. Hutton: CHIP and Hsp70 regulate tau ubiquitination, degradation and aggregation. *Hum Mol Genet*, 13, 703-14 (2004)
264. Ballinger, C. A., P. Connell, Y. Wu, Z. Hu, L. J. Thompson, L. Y. Yin & C. Patterson: Identification of CHIP, a novel tetratricopeptide repeat-containing protein that interacts with heat shock proteins and negatively regulates chaperone functions. *Mol Cell Biol*, 19, 4535-45 (1999)
265. Wiederkehr, T., B. Bukau & A. Buchberger: Protein turnover: a CHIP programmed for proteolysis. *Curr Biol*, 12, R26-8 (2002)
266. Demand, J., S. Alberti, C. Patterson & J. Hohfeld: Cooperation of a ubiquitin domain protein and an E3 ubiquitin ligase during chaperone/proteasome coupling. *Curr Biol*, 11, 1569-77 (2001)
267. Meacham, G. C., C. Patterson, W. Zhang, J. M. Younger & D. M. Cyr: The Hsc70 co-chaperone CHIP targets immature CFTR for proteasomal degradation. *Nat Cell Biol*, 3, 100-5 (2001)
268. Kosik, K. S. & H. Shimura: Phosphorylated tau and the neurodegenerative foldopathies. *Biochim Biophys Acta*, 1739, 298-310 (2005)
269. Haltiwanger, R. S., S. Busby, K. Grove, S. Li, D. Mason, L. Medina, D. Moloney, G. Philipsberg & R. Scartozzi: O-glycosylation of nuclear and cytoplasmic proteins: regulation analogous to phosphorylation? *Biochem Biophys Res Commun*, 231, 237-42 (1997)
270. Hart, G. W., L. K. Kreppel, F. I. Comer, C. S. Arnold, D. M. Snow, Z. Ye, X. Cheng, D. DellaManna, D. S. Caine, B. J. Earles, Y. Akimoto, R. N. Cole & B. K. Hayes: O-GlcNAcylation of key nuclear and cytoskeletal proteins: reciprocity with O-phosphorylation and putative roles in protein multimerization. *Glycobiology*, 6, 711-6 (1996)

271. Kamemura, K. & G. W. Hart: Dynamic interplay between O-glycosylation and O-phosphorylation of nucleocytoplasmic proteins: a new paradigm for metabolic control of signal transduction and transcription. *Prog Nucleic Acid Res Mol Biol*, 73, 107-36 (2003)
272. Dong, D. L., Z. S. Xu, G. W. Hart & D. W. Cleveland: Cytoplasmic O-GlcNAc modification of the head domain and the KSP repeat motif of the neurofilament protein neurofilament-H. *J Biol Chem*, 271, 20845-52 (1996)
273. Lefebvre, T., M. L. Caillet-Boudin, L. Buee, A. Delacourte & J. C. Michalski: O-GlcNAc glycosylation and neurological disorders. *Adv Exp Med Biol*, 535, 189-202 (2003)
274. Lefebvre, T., S. Ferreira, L. Dupont-Wallois, T. Bussiere, M. J. Dupire, A. Delacourte, J. C. Michalski & M. L. Caillet-Boudin: Evidence of a balance between phosphorylation and O-GlcNAc glycosylation of Tau proteins--a role in nuclear localization. *Biochim Biophys Acta*, 1619, 167-76 (2003)
275. Arnold, C. S., G. V. Johnson, R. N. Cole, D. L. Dong, M. Lee & G. W. Hart: The microtubule-associated protein tau is extensively modified with O-linked N-acetylglucosamine. *J Biol Chem*, 271, 28741-4 (1996)
276. Liu, F., K. Iqbal, I. Grundke-Iqbal, G. W. Hart & C. X. Gong: O-GlcNAcylation regulates phosphorylation of tau: a mechanism involved in Alzheimer's disease. *Proc Natl Acad Sci U S A*, 101, 10804-9 (2004)
277. Sato, Y., Y. Naito, I. Grundke-Iqbal, K. Iqbal & T. Endo: Analysis of N-glycans of pathological tau: possible occurrence of aberrant processing of tau in Alzheimer's disease. *FEBS Lett*, 496, 152-60 (2001)
278. Tucholski, J., J. Kuret & G. V. Johnson: Tau is modified by tissue transglutaminase *in situ*: possible functional and metabolic effects of polyamination. *J Neurochem*, 73, 1871-80 (1999)
279. Murthy, S. N., J. H. Wilson, T. J. Lukas, J. Kuret & L. Lorand: Cross-linking sites of the human tau protein, probed by reactions with human transglutaminase. *J Neurochem*, 71, 2607-14 (1998)
280. Lorand, L. & R. M. Graham: Transglutaminases: crosslinking enzymes with pleiotropic functions. *Nat Rev Mol Cell Biol*, 4, 140-56 (2003)
281. Watanabe, A., K. Takio & Y. Ihara: Deamidation and isoaspartate formation in smeared tau in paired helical filaments. Unusual properties of the microtubule-binding domain of tau. *J Biol Chem*, 274, 7368-78 (1999)
282. Shimizu, T., A. Watanabe, M. Ogawara, H. Mori & T. Shirasawa: Isoaspartate formation and neurodegeneration in Alzheimer's disease. *Arch Biochem Biophys*, 381, 225-34 (2000)
283. Lim, J. & K. P. Lu: Pinning down phosphorylated tau and tauopathies. *Biochim Biophys Acta*, 1739, 311-22 (2005)
284. Chen, F., D. David, A. Ferrari & J. Gotz: Posttranslational modifications of tau--role in human tauopathies and modeling in transgenic animals. *Curr Drug Targets*, 5, 503-15 (2004)
285. Ferreira, A., Q. Lu, L. Orecchio & K. S. Kosik: Selective phosphorylation of adult tau isoforms in mature hippocampal neurons exposed to fibrillar A beta. *Mol Cell Neurosci*, 9, 220-34 (1997)
286. Ekinci, F. J., K. U. Malik & T. B. Shea: Activation of the L voltage-sensitive calcium channel by mitogen-activated protein (MAP) kinase following exposure of neuronal cells to beta-amyloid. MAP kinase mediates beta-amyloid-induced neurodegeneration. *J Biol Chem*, 274, 30322-7 (1999)
287. Takashima, A., K. Noguchi, K. Sato, T. Hoshino & K. Imahori: Tau protein kinase I is essential for amyloid beta-protein-induced neurotoxicity. *Proc Natl Acad Sci U S A*, 90, 7789-93 (1993)
288. Rapoport, M., H. N. Dawson, L. I. Binder, M. P. Vitek & A. Ferreira: Tau is essential to beta -amyloid-induced neurotoxicity. *Proc Natl Acad Sci U S A*, 99, 6364-9 (2002)
289. Wszolek, Z. K., R. F. Pfeiffer, M. H. Bhatt, R. L. Schelper, M. Cordes, B. J. Snow, R. L. Rodnitzky, E. C. Wolters, F. Arwert & D. B. Calne: Rapidly progressive autosomal dominant parkinsonism and dementia with pallido-ponto-nigral degeneration. *Ann Neurol*, 32, 312-20 (1992)
290. Foster, N. L., K. Wilhelmsen, A. A. Sima, M. Z. Jones, C. J. D'Amato & S. Gilman: Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. Conference Participants. *Ann Neurol*, 41, 706-15 (1997)
291. Di Maria, E., M. Tabaton, T. Vigo, G. Abbruzzese, E. Bellone, C. Donati, E. Frasson, R. Marchese, P. Montagna, D. G. Munoz, P. P. Pramstaller, G. Zanusso, F. Ajmar & P. Mandich: Corticobasal degeneration shares a common genetic background with progressive supranuclear palsy. *Ann Neurol*, 47, 374-7 (2000)
292. Nasreddine, Z. S., M. Loginov, L. N. Clark, J. Lamarche, B. L. Miller, A. Lamontagne, V. Zhukareva, V. M. Lee, K. C. Wilhelmsen & D. H. Geschwind: From genotype to phenotype: a clinical pathological, and biochemical investigation of frontotemporal dementia and parkinsonism (FTDP-17) caused by the P301L tau mutation. *Ann Neurol*, 45, 704-15 (1999)
293. Wilhelmsen, K. C., T. Lynch, E. Pavlou, M. Higgins & T. G. Nygaard: Localization of disinhibition-dementia-parkinsonism-amyotrophy complex to 17q21-22. *Am J Hum Genet*, 55, 1159-65 (1994)
294. Crowther, R. A. & M. Goedert: Abnormal tau-containing filaments in neurodegenerative diseases. *J Struct Biol*, 130, 271-9 (2000)
295. Friedhoff, P., M. von Bergen, E. M. Mandelkow & E. Mandelkow: Structure of tau protein and assembly into paired helical filaments. *Biochim Biophys Acta*, 1502, 122-32 (2000)
296. Goedert, M.: Tau protein and neurodegeneration. *Semin Cell Dev Biol*, 15, 45-9 (2004)
297. Andorfer, C., Y. Kress, M. Espinoza, R. de Silva, K. L. Tucker, Y. A. Barde, K. Duff & P. Davies: Hyperphosphorylation and aggregation of tau in mice expressing normal human tau isoforms. *J Neurochem*, 86, 582-90 (2003)
298. Gotz, J., M. Tolnay, R. Barmettler, A. Ferrari, K. Burki, M. Goedert, A. Probst & R. M. Nitsch: Human tau transgenic mice. Towards an animal model for neuro- and glialfibrillary lesion formation. *Adv Exp Med Biol*, 487, 71-83 (2001)
299. Lewis, J., E. McGowan, J. Rockwood, H. Melrose, P. Nacharaju, M. Van Slegtenhorst, K. Gwinn-Hardy, M. Paul Murphy, M. Baker, X. Yu, K. Duff, J. Hardy, A. Corral, W. L. Lin, S. H. Yen, D. W. Dickson, P. Davies & M. Hutton:

Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein. *Nat Genet*, 25, 402-5 (2000)
300. Tatebayashi, Y., T. Miyasaka, D. H. Chui, T. Akagi, K. Mishima, K. Iwasaki, M. Fujiwara, K. Tanemura, M. Murayama, K. Ishiguro, E. Planel, S. Sato, T. Hashikawa & A. Takashima: Tau filament formation and associative memory deficit in aged mice expressing mutant (R406W) human tau. *Proc Natl Acad Sci U S A*, 99, 13896-901 (2002)
301. Bunker, J. M., L. Wilson, M. A. Jordan & S. C. Feinstein: Modulation of microtubule dynamics by tau in living cells: implications for development and neurodegeneration. *Mol Biol Cell*, 15, 2720-8 (2004)
302. Panda, D., J. C. Samuel, M. Massie, S. C. Feinstein & L. Wilson: Differential regulation of microtubule dynamics by three- and four-repeat tau: implications for the onset of neurodegenerative disease. *Proc Natl Acad Sci U S A*, 100, 9548-53 (2003)
303. Feinstein, S. C. & L. Wilson: Inability of tau to properly regulate neuronal microtubule dynamics: a loss-of-function mechanism by which tau might mediate neuronal cell death. *Biochim Biophys Acta*, 1739, 268-79 (2005)
304. Goncalves, A., D. Braguer, K. Kamath, L. Martello, C. Briand, S. Horwitz, L. Wilson & M. A. Jordan: Resistance to Taxol in lung cancer cells associated with increased microtubule dynamics. *Proc Natl Acad Sci U S A*, 98, 11737-42 (2001)
305. Ebneth, A., G. Drewes, E. M. Mandelkow & E. Mandelkow: Phosphorylation of MAP2c and MAP4 by MARK kinases leads to the destabilization of microtubules in cells. *Cell Motil Cytoskeleton*, 44, 209-24 (1999)
306. Delobel, P., S. Flament, M. Hamdane, R. Jakes, A. Rousseau, A. Delacourte, J. P. Vilain, M. Goedert & L. Buee: Functional characterization of FTDP-17 tau gene mutations through their effects on Xenopus oocyte maturation. *J Biol Chem*, 277, 9199-205 (2002)
307. Hayashi, S., Y. Toyoshima, M. Hasegawa, Y. Umeda, K. Wakabayashi, S. Tokiguchi, T. Iwatsubo & H. Takahashi: Late-onset frontotemporal dementia with a novel exon 1 (Arg5His) tau gene mutation. *Ann Neurol*, 51, 525-30 (2002)
308. Poorkaj, P., N. A. Muma, V. Zhukareva, E. J. Cochran, K. M. Shannon, H. Hurtig, W. C. Koller, T. D. Bird, J. Q. Trojanowski, V. M. Lee & G. D. Schellenberg: An R5L tau mutation in a subject with a progressive supranuclear palsy phenotype. *Ann Neurol*, 52, 511-6 (2002)
309. Pickering-Brown, S., M. Baker, S. H. Yen, W. K. Liu, M. Hasegawa, N. Cairns, P. L. Lantos, M. Rossor, T. Iwatsubo, Y. Davies, D. Allsop, R. Furlong, F. Owen, J. Hardy, D. Mann & M. Hutton: Pick's disease is associated with mutations in the tau gene. *Ann Neurol*, 48, 859-67 (2000)
310. Rizzini, C., M. Goedert, J. R. Hodges, M. J. Smith, R. Jakes, R. Hills, J. H. Xuereb, R. A. Crowther & M. G. Spillantini: Tau gene mutation K257T causes a tauopathy similar to Pick's disease. *J Neuropathol Exp Neurol*, 59, 990-1001 (2000)
311. Kobayashi, T., S. Ota, K. Tanaka, Y. Ito, M. Hasegawa, Y. Umeda, Y. Motoi, M. Takanashi, M. Yasuhara, M. Anno, Y. Mizuno & H. Mori: A novel L266V mutation of the tau gene causes frontotemporal dementia with a unique tau pathology. *Ann Neurol*, 53, 133-7 (2003)
312. Delisle, M. B., J. R. Murrell, R. Richardson, J. A. Trofatter, O. Rascol, X. Soulages, M. Mohr, P. Calvas & B. Ghetti: A mutation at codon 279 (N279K) in exon 10 of the Tau gene causes a tauopathy with dementia and supranuclear palsy. *Acta Neuropathol (Berl)*, 98, 62-77 (1999)
313. Hasegawa, M., M. J. Smith, M. Iijima, T. Tabira & M. Goedert: FTDP-17 mutations N279K and S305N in tau produce increased splicing of exon 10. *FEBS Lett*, 443, 93-6 (1999)
314. D'Souza, I., P. Poorkaj, M. Hong, D. Nochlin, V. M. Lee, T. D. Bird & G. D. Schellenberg: Missense and silent tau gene mutations cause frontotemporal dementia with parkinsonism-chromosome 17 type, by affecting multiple alternative RNA splicing regulatory elements. *Proc Natl Acad Sci U S A*, 96, 5598-603 (1999)
315. Spillantini, M. G. & M. Goedert: Tau mutations in familial frontotemporal dementia. *Brain*, 123 (Pt 5), 857-9 (2000)
316. Pastor, P., E. Pastor, C. Carnero, R. Vela, T. Garcia, G. Amer, E. Tolosa & R. Oliva: Familial atypical progressive supranuclear palsy associated with homozigosity for the delN296 mutation in the tau gene. *Ann Neurol*, 49, 263-7 (2001)
317. Yoshida, H., R. A. Crowther & M. Goedert: Functional effects of tau gene mutations deltaN296 and N296H. *J Neurochem*, 80, 548-51(2002)
318. Iseki, E., T. Matsumura, W. Marui, H. Hino, T. Odawara, N. Sugiyama, K. Suzuki, H. Sawada, T. Arai & K. Kosaka: Familial frontotemporal dementia and parkinsonism with a novel N296H mutation in exon 10 of the tau gene and a widespread tau accumulation in the glial cells. *Acta Neuropathol (Berl)*, 102, 285-92(2001)
319. Nagiec, E. W., K. E. Sampson & I. Abraham: Mutated tau binds less avidly to microtubules than wildtype tau in living cells. *J Neurosci Res*, 63, 268-75(2001)
320. Bugiani, O., J. R. Murrell, G. Giaccone, M. Hasegawa, G. Ghigo, M. Tabaton, M. Morbin, A. Primavera, F. Carella, C. Solaro, M. Grisoli, M. Savoiardo, M. G. Spillantini, F. Tagliavini, M. Goedert & B. Ghetti: Frontotemporal dementia and corticobasal degeneration in a family with a P301S mutation in tau. *J Neuropathol Exp Neurol*, 58, 667-77(1999)
321. Sperfeld, A. D., M. B. Collatz, H. Baier, M. Palmbach, A. Storch, J. Schwarz, K. Tatsch, S. Reske, M. Joosse, P. Heutink & A. C. Ludolph: FTDP-17: an early-onset phenotype with parkinsonism and epileptic seizures caused by a novel mutation. *Ann Neurol*, 46, 708-15(1999)
322. Iijima, M., T. Tabira, P. Poorkaj, G. D. Schellenberg, J. Q. Trojanowski, V. M. Lee, M. L. Schmidt, K. Takahashi, T. Nabika, T. Matsumoto, Y. Yamashita, S. Yoshioka & H. Ishino: A distinct familial presenile dementia with a novel missense mutation in the tau gene. *Neuroreport*, 10, 497-501(1999)
323. Stanford, P. M., G. M. Halliday, W. S. Brooks, J. B. Kwok, C. E. Storey, H. Creasey, J. G. Morris, M. J. Fulham & P. R. Schofield: Progressive supranuclear palsy pathology caused by a novel silent mutation in exon 10 of

the tau gene: expansion of the disease phenotype caused by tau gene mutations. *Brain*, 123 (Pt 5), 880-93(2000)
324. Wszolek, Z. K., Y. Tsuboi, R. J. Uitti, L. Reed, M. L. Hutton & D. W. Dickson: Progressive supranuclear palsy as a disease phenotype caused by the S305S tau gene mutation. *Brain*, 124, 1666-70(2001)
325. Miyamoto, K., A. Kowalska, M. Hasegawa, T. Tabira, K. Takahashi, W. Araki, I. Akiguchi & A. Ikemoto: Familial frontotemporal dementia and parkinsonism with a novel mutation at an intron 10+11-splice site in the tau gene. *Ann Neurol*, 50, 117-20(2001)
326. Yasuda, M., J. Takamatsu, I. D'Souza, R. A. Crowther, T. Kawamata, M. Hasegawa, H. Hasegawa, M. G. Spillantini, S. Tanimukai, P. Poorkaj, L. Varani, G. Varani, T. Iwatsubo, M. Goedert, D. G. Schellenberg & C. Tanaka: A novel mutation at position +12 in the intron following exon 10 of the tau gene in familial frontotemporal dementia (FTD-Kumamoto). *Ann Neurol*, 47, 422-9(2000)
327. van Herpen, E., S. M. Rosso, L. A. Serverijnen, H. Yoshida, G. Breedveld, R. van de Graaf, W. Kamphorst, R. Ravid, R. Willemsen, D. Dooijes, D. Majoor-Krakauer, J. M. Kros, R. A. Crowther, M. Goedert, P. Heutink & J. C. van Swieten: Variable phenotypic expression and extensive tau pathology in two families with the novel tau mutation L315R. *Ann Neurol*, 54, 573-81(2003)
328. Rosso, S. M., E. van Herpen, W. Deelen, W. Kamphorst, L. A. Severijnen, R. Willemsen, R. Ravid, M. F. Niermeijer, D. Dooijes, M. J. Smith, M. Goedert, P. Heutink & J. C. van Swieten: A novel tau mutation, S320F, causes a tauopathy with inclusions similar to those in Pick's disease. *Ann Neurol*, 51, 373-6(2002)
329. Lippa, C. F., V. Zhukareva, T. Kawarai, K. Uryu, M. Shafiq, L. E. Nee, J. Grafman, Y. Liang, P. H. St George-Hyslop, J. Q. Trojanowski & V. M. Lee: Frontotemporal dementia with novel tau pathology and a Glu342Val tau mutation. *Ann Neurol*, 48, 850-8(2000)
330. Nicholl, D. J., M. A. Greenstone, C. E. Clarke, P. Rizzu, D. Crooks, A. Crowe, J. Q. Trojanowski, V. M. Lee & P. Heutink: An English kindred with a novel recessive tauopathy and respiratory failure. *Ann Neurol*, 54, 682-6(2003)
331. Neumann, M., W. Schulz-Schaeffer, R. A. Crowther, M. J. Smith, M. G. Spillantini, M. Goedert & H. A. Kretzschmar: Pick's disease associated with the novel Tau gene mutation K369I. *Ann Neurol*, 50, 503-13(2001)
332. Murrell, J. R., M. G. Spillantini, P. Zolo, M. Guazzelli, M. J. Smith, M. Hasegawa, F. Redi, R. A. Crowther, P. Pietrini, B. Ghetti & M. Goedert: Tau gene mutation G389R causes a tauopathy with abundant pick body-like inclusions and axonal deposits. *J Neuropathol Exp Neurol*, 58, 1207-26(1999)
333. Perez, M., F. Lim, M. Arrasate & J. Avila: The FTDP-17-linked mutation R406W abolishes the interaction of phosphorylated tau with microtubules. *J Neurochem*, 74, 2583-9(2000)

Abbreviations: MAPs: microtubule-associated proteins; PHFs: paired helical filaments; NFTs: neurofilbrillary tangles; FTDP-17: frontotemporal dementia with parkinsonism linked to chromosome 17; AD: Alzheimer's disease; PSP: progressive supranuclear palsy; CBD: corticobasal degeneration; PiD: Pick's disease; GSK3beta: glycogen synthase kinase 3beta; MARK: Microtubule-affinity-regulating kinase; PKA: cAMP-dependent protein kinase; Cdk5: cyclin-dependent kinase 5; CHIP: carboxyl terminus of the heat shock cognate (Hsc)-70-interacting protein

Key Words: Tau, Tauopathy, Alzheimer's disease, FTDP-17, Phosphorylation, Microtubules; Kinases, Phosphatases, PHFs, Posttranslational modifications, Review

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