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The role of tau kinases in Alzheimer's disease

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Abstract

A principal feature of the progression of Alzheimer's disease (AD) is the appearance of aberrant phosphorylation of the microtubule-associated protein tau in the brains of affected individuals. Significant research efforts have been directed at identifying the kinases involved in this process, as well as developing pharmacological agents to inhibit these molecules. This review focuses on recent developments in both the physiological and pathological effects of tau phosphorylation, and the contribution of phosphorylation to tau toxicity and pathological progression in AD. The evolving concepts of the roles tau plays in cellular biology, and the mechanisms by which phosphorylation regulates tau function, is reshaping the framework for the development of therapeutics targeting tau to treat AD.

Keywords

Alzheimer's disease; axonal transport; β-amyloid; kinase; microtubule; phosphatase; phosphorylation; tau

Introduction

Tau is an alternatively spliced microtubule-binding protein that is predominantly expressed in neurons [1–3]. The abnormal accumulation of tau and the formation of neurofibrillary tangles (NFTs) composed primarily of this protein, as well as the formation of β-amyloid (Aβ) plaques, have been implicated in the progression of Alzheimer's disease (AD) [4–6]. The exact pathways and precipitating events leading to the abnormal accumulation of tau remain unclear, but phosphorylation has been postulated to be an important contributor [7].

In the human brain, tau exists primarily as six different isoforms, which vary in the presence or absence of one or two N-terminal acidic repeats, and in the presence or absence of the second of four microtubule-binding repeats [8], although other splice variants have been reported [9, 10]. The expression of tau is regulated developmentally, and the specific ratios of the tau isoforms differ in fetal and adult animals [11]. In 1984, Lindwall and Cole demonstrated that the dephosphorylation of tau isolated from bovine brains increases the ability of the protein to bind microtubules and to promote microtubule assembly, clearly demonstrating a functional

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outcome of phosphorylation, although the kinases involved were unknown [12]. Since this initial report, various studies have focused on delineating the kinases involved in tau phosphorylation, as well as identifying the specific sites on tau that are phosphorylated and their contribution to physiological, as well as pathological, processes.

Because aberrant phosphorylation and aggregation are a defining hallmark of tau in AD brains, and because the prominent belief is that abnormal phosphorylation results in tau dysfunction and pathological properties, significant research efforts have been focused on developing effective kinase inhibitor therapies (for a comprehensive review, see reference [13]). These potential therapeutics are directed at a wide variety of kinases, including glycogen synthase kinase 3β (GSK3β), cyclin-dependent kinase 5 (Cdk5), JNK and microtubule-associated regulatory kinase (MARK).

In this review, some of the processes that may contribute to alterations in tau phosphorylation in the context of AD, the effect that these phosphorylation events may have on neuronal physiology, and the possible contribution of different protein kinases, as well as protein phosphatases, are discussed.

Tau kinases and disease processes

Activation of tau kinases by *β*-amyloid

The exposure of cells or neurons to Aβ *in situ* leads to increases in tau phosphorylation at various sites as a result of the activation of different kinases. Early studies demonstrated that the treatment of neurons with Aβ fibrils increased the immunoreactivity of phosphorylated tau [14,15], and that this increase was lithium-sensitive, implicating GSK3β as the responsible kinase [16]. Moreover, studies focusing on the immediate downstream effects of Aβ *in vivo* demonstrated that the generation of Aβ leads to an increase in intraneuronal calcium levels [17], which can result in calpain activation and increased Cdk5 activity because of the cleavage of p35 to p25 [18,19]. This calcium increase is NMDA-dependent, and can be blocked by NMDA antagonists, such as MK-801 or memantine [20,21]. Correspondingly, treatment with memantine reduces the amount of phosphorylated tau in the CSF of humans with AD, as well as in rats [22–24]. However, the contribution of Cdk5 to tau phosphorylation is unclear, as p35-null mice exhibit a decrease in Cdk5 activity, but significant increases in tau phosphorylation, as well as GSK3β activity [25]. A more recent study also demonstrated that Cdk5 activity was not required for the pathological phosphorylation of tau in a mouse model of Niemann-Pick Type C disease; in fact, genetic ablation of p35 resulted in an increase in tau phosphorylation, as indicated by increases in AT8 (Ser^{199}/Ser^{202}/Thr^{205}) and PHF1 (Ser^{396}/Ser^{404}) immunoreactivity [26] (antibody epitopes are provided in Table 1). Therefore, the role of Cdk5 in the direct modulation of tau phosphorylation remains to be clarified, and this enzyme may have indirect effects.

In addition to its effects on calcium homeostasis, Aβ may modulate tau phosphorylation through other mechanisms. Aβ treatment can increase reactive oxygen species generation, leading to JNK activation and to an increase in tau phosphorylation [27,28]. Recent research has demonstrated that the Aβ-induced increase in JNK activation and tau phosphorylation in neurons can be blocked by treatment with the omega-3 fatty acid docosahexaenoic acid (DHA) and, also, that JNK activation and tau phosphorylation in AD mouse models, as well as correlated behavioral deficits, can be abrogated with a DHA/curcumin diet [29]. In addition, Aβ-catalyzed disruptions in phosphocholine metabolism have been suggested to cause Cdk5 upregulation and AT8 phosphorylation [30].

Aβ also activates tyrosine kinases [31,32]. For example, recent evidence indicated that c-Abl activity was increased in mutant amyloid-precursor protein (APP) mouse models [33]. In this

particular study [33], elevated c-Abl activity correlated with downstream Cdk5 activation and phosphorylation of tau at PHF1/AT8, although other studies have revealed that c-Abl, as well as the Abl-related gene (Arg) tyrosine kinase, can phosphorylate tau directly at Tyr^{394} [34, 35]. Tau phosphorylated at Tyr^{394} has been detected in paired helical filaments isolated from AD brains, suggesting a role in AD pathogenesis [35]. Tau is also phosphorylated at Tyr^{18} by Fyn, and it has been postulated that tau and Fyn function together to regulate microtubule structure [36].

A correlation between increased Aβ levels and the activation of tau kinases is also evident in some AD mouse models. Several transgenic models expressing APP or APP and presenilin with familial AD mutations displayed increases in tau phosphorylation [37,38] or the mislocalization of phosphorylated tau species [39], although NFTs did not develop. However, other mouse models expressing mutated APP/presenilin did not exhibit tau pathology, despite aggressive amyloid pathology, Cdk5 activation and cell loss [40]. A transgenic mouse model with five familial AD mutations has also provided an association between increased tau phosphorylation and the expression of the C-terminus of APP [41]. In addition, in another mouse model expressing an APP construct mutated to enhance Aβ oligomerization, an increase in phosphorylated tau (ie, PHF1 immunoreactivity) without fibrillization was demonstrated [42]. Combining a tau (P301L) transgene, a frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17) mutation in tau (FTDP-17 tau) and the APP (Swe)/PS1 (M146V) transgenes resulted in a substantial increase in the extent of tau phosphorylation and pathology [43,44]. However, overexpression of FTDP-17 tau alone resulted in increased phosphorylation and neurofibrillary pathology [45,46]. Combined, these and other studies indicate that there may not necessarily be direct associations between Aβ, kinase activation and tau phosphorylation in AD, although Aβ likely plays an indirect or modulatory role.

Insights into tau phosphorylation from insulin-resistant models

The existence of a correlation between type 2 diabetes and an increased risk for AD is still being debated [47]; however, this possible association has led to studies examining the relationships between tau phosphorylation, kinase activation and insulin dysfunction. An early hypothesis of the possible role of insulin resistance in aberrant tau phosphorylation stated that downregulation of the insulin receptor/PI3K/Akt pathway led to reduced inhibition of GSK3β and increased tau phosphorylation [48]. However, recent studies have provided data that suggest this may not be the primary mechanism by which insulin dysfunction contributes to increased tau phosphorylation, as described in the following paragraphs.

Systemic administration of streptozotocin (STZ), a compound that is selectively toxic toward insulin-producing β-cells in the islets of Langerhans, is often used to induce diabetes in rodent models of disease [49]. In wild-type mice, peripheral administration of STZ led to increased tau phosphorylation at various sites, but did not lead to the formation of insoluble aggregates [50]. In a mouse model expressing FTDP-17 tau, a similar treatment paradigm exacerbated tau pathology, including increasing the levels of AT8 immunoreactivity, dystrophic neurites and NFTs [51]. The mechanism responsible for the increase in tau phosphorylation in response to insulin deficiency is unlikely to be elevated GSK3β activity (in fact, a decrease in the active form of the kinase was observed); instead, the specific inactivation of protein phosphatase 2A (PP2A) may be responsible [50]. One potential mechanism for STZ-induced reduction of PP2A activity is through the induction of hypothermia [52]. Interestingly, anesthesia-induced hypothermia also results in increases in tau phosphorylation through the inhibition of phosphatase activity [53].

Central administration of STZ has been proposed to induce AD, as this agent induces behavioral and neuropathological changes that recapitulate the disease phenotype [54]. Although the mechanism of action of centrally administered STZ differs from that observed when the

compound is administered systemically, central administration of STZ results in reduced levels of both the insulin receptor and insulin in the brain [55]. In a recent study, STZ injected directly into the cerebral ventricles resulted in acute increases in tau phosphorylation at AD-related epitopes, as well as the expected increase in the levels of activated GSK3β [56]. Interestingly, a decrease in the levels of GluT1 was also observed, as well as a decrease in the levels of *O*-*N*-acetylglucosamine (*O*-GlcNAc) and *O*-GlcNAc transferase ([OGT], which catalyzes *O*-GlcNAcylation). A reciprocal relationship between phosphorylation and *O*-GlcNAcylation has been reported previously, and inhibition of phosphatase activity (resulting in increased tau phosphorylation) leads to decreased levels of *O*-GlcNAcylation of tau [57]. Therefore, this mechanistic link between impaired *O*-GlcNAcylation and impaired glucose metabolism presents an interesting pathway, resulting in tau hyperphosphorylation that is independent of increased tau kinase function. Indeed, compounds that inhibit O-GlcNAcase prevent tau hyperphosphorylation by inhibiting the removal of *O*-GlcNAc modifications [58].

Tau phosphorylation and Alzheimer's disease pathophysiology

Tau kinases and microtubule stability

Although increasing evidence suggests that tau has roles in the cell beyond its ability to regulate microtubule dynamics, the phosphorylation-regulated function of tau remains of primary interest in studies assessing the potential pathophysiological role of the protein in AD and other tauopathies (for a review, see reference [8]). Studies have clearly demonstrated that tau phosphorylation at various sites, by many different kinases, regulates the microtubule affinity of the protein, as well as its ability to regulate microtubule dynamics ([59], and reviewed in reference [60]). Phosphorylation of tau by GSK3β and Cdk5 [61] affects tau-microtubule interactions by reducing the microtubule affinity of tau; phosphorylation of Ser^{214} by PKA has also been demonstrated to have a similar effect [62]. Most notably, phosphorylation of the serines within the Lys-Xaa-Gly-Ser (KXGS) motifs (and particularly at the 12E8 [Ser^{262}/Ser^{356}] site) of the microtubule-binding domains (MTBDs) of tau consistently exerted a strong negative effect on tau-microtubule interactions; a prominent kinase that phosphorylates the KXGS motif is MARK [63]. A recent structural study of pseudo-phosphorylated tau indicated that phosphorylation at the KXGS motif introduces a destabilizing rigid turn to three residues adjacent to Ser^{262} that decouples tau from microtubules [64]. Given these and other findings, it is reasonable to speculate that the hyperphosphorylation of tau may contribute to the reported defects of microtubule integrity in AD brains [65].

The prevailing model of microtubule-related tau toxicity suggests that phosphorylation of tau precedes the dissociation of the protein from microtubules, and this event is followed by the aggregation of phosphorylated tau, leading to NFT formation in AD brains [66]. This model is supported by a study in which 12E8 phosphorylation promoted further phosphorylation at the possible GSK3β-phosphorylated epitopes AT8 and PHF1 [67]. This increased phosphorylation could be the result of a structural change induced by Ser^{262} phosphorylation that either renders tau more amenable to further phosphorylation or, potentially, less amenable to dephosphorylation by phosphatases. Notably, the tau binding site for PP2A has been localized to the MTBDs [68]. A crystallization study confirmed this localization, and also determined that a negatively charged pocket of PP2A interacted with tau, allowing dephosphorylation of Ser^{396} [69]. Therefore, the addition of an electronegative phosphate group to the binding tract of tau may interfere with the binding of PP2A to tau, allowing aberrant increases in tau phosphorylation because of decreased phosphatase activity.

However, separating the normal flux of tau phosphorylation and dephosphorylation, both of which are required for microtubule stability and neuronal health, from aberrant phosphorylation that leads to a pathogenic cascade is challenging. Complicating the phosphorylation/dephosphorylation model, an early study determined that, *in vitro*, tau

phosphorylated at Ser^{262}, which decreases the affinity of tau for microtubules, also prevented it from assembling into paired helical filaments (PHFs) [62]. More recently, in a *Drosophila* tauopathy model, tau that could not be phosphorylated at either two of the KXGS motifs, or at the 11 GSK3β-targeted sites, was expressed [70]. Unexpectedly, tau that could not be phosphorylated at the GSK3β-targeted sites, but could be phosphorylated at the KXGS motifs, was completely bound to the microtubules and, nevertheless, was the most toxic form of tau studied. In contrast, tau that could not be phosphorylated at the KXGS motifs, but could be phosphorylaed at all other sites, was present in the soluble fractions and was almost completely non-toxic. This study indicates that the relationship between phosphorylation and tau-microtubule interactions extends beyond the microtubule-binding regions, and that the relationship between microtubule binding and toxicity is likely to be more subtly complex than usually presumed.

Tau kinases and axonal transport

Defective axonal transport has long been considered to have a role in neurodegenerative diseases [71], including AD [72,73]. Tau's identity as a microtubule-associated protein has made it an attractive candidate in AD-associated axonal transport defects. Different mechanisms and protein complexes have been observed for the transport of various cargoes, and tau itself can be described as a substrate for axonal transport [74]. The binding of tau to the anterograde transport protein kinesin, as well as its rate of transport in the axons, is dependent on the degree of phosphorylation; suppression of GSK3β activity by lithium results in the suppression of kinesin-tau binding [75].

Similar to microtubule dynamics, phosphorylation of different tau sites can have opposing effects on axonal transport. A recent study demonstrated that increased GSK3β (and Cdk5) activity decreased the frequency of mitochondrial movement in neurons, and was accompanied by increases in PHF1 and AT270 (Thr^{181}) immunoreactivity [76]. A separate study demonstrated that tau overexpression decreased the quantity of moving mitochondria in the axons, and that this effect was reversed by the co-expression of MARK, implicating microtubule affinity in the regulation of mitochondrial movement by tau [77]. The relative expression of tau in these models should be considered carefully, as a study of fast axonal transport in which various low monomeric tau:tubulin ratios were investigated in a squid axoplasm model displayed no effect following the introduction of phosphorylated tau, although transport impediment was achieved at high tau:tubulin ratios [78]. In a more recent study using the same methodology, monomeric tau did not affect transport, but filamentous tau inhibited anterograde transport – an effect that was relieved by inhibiting GSK3β [79]. However, consideration of this latter finding needs to be tempered by results from an earlier study, which also used the squid axoplasm as well as other models, indicating that addition of active GSK3β (in the absence of tau) inhibited fast anterograde transport by phosphorylating kinesin [80].

An attractive alternative role for tau phosphorylation in the regulation of axonal transport has recently emerged. JNK-interacting protein 1 (JIP1) has been described as a regulator of axonal development and transport [81]. A promoter variant of this protein has also been associated with AD [82]. Tau phosphorylated at pathogenic residues (ie, AT8, AT180 [Thr^{231}/Ser^{235}] and PHF1) has recently been demonstrated to compete with the kinesin-1 complex for binding to JIP1, resulting in mislocalization of JIP1 from neurites to neuronal somata [83]. This interaction of abnormally phosphorylated tau with JIP1 may impair the axonal transport of specific cargoes in a tauopathy mouse model (in the absence of amyloid toxicity) [84], and could be a contributing factor to the documented axonal transport deficits observed in AD [71,83].

Although tau has been implicated as a causative agent in axonal transport deficits, recent data have alluded to a reverse sequence, whereby microtubular transport deficits cause tau

pathology. Falzone and colleagues described a kinesin light chain 1 (KLC-1)-null mouse model with predicted deficits in cargo transport [85]. The null mutation resulted in axonal structural defects and significant accumulation of tau that was phosphorylated at AD-associated epitopes (Ser^{202}/Thr^{205}) along the axonal tracts, and this accumulation correlated with aberrant activation of JNK [85]. The potential dual role of JNK in both tau-JIP1-mediated regulation of transport, as well as in the initiation of aberrant tau pathology by deficits in axonal transport, is intriguing and warrants further study.

Tau kinases and protein aggregation

The correlation between insoluble NFT formation and memory impairment in AD originally led to the hypothesis that insoluble tau is the pathogenic form of this protein [86]. Since the discovery that the tau present in NFTs is hyperphosphorylated [6,7,87], the kinases responsible for this hyperphosphorylation have been the focus of various studies. However, the results of recent studies have led to an emerging conceptual framework in which pre-aggregate, soluble tau species may be causative elements in tau pathology [88], and even that expression of potentially abnormally processed soluble tau, independent of its fibrillar state, may drive tau pathology. The key findings of several of the studies that have led to this developing hypothesis are described in this section.

In 2005, a doxycycline-repressible mouse model of tauopathy was used to demonstrate that suppressing the expression of tau, while leaving insoluble tau aggregates intact, led to improved memory function [89]. This result was confirmed in a more recent study in which soluble phosphorylated tau species were demonstrated to contribute to neurodegeneration in a *Drosophila* model of human tauopathies [90]. Soluble, non-PHF tau was also responsible for inhibiting microtubule dynamics [91]. Interestingly, studies on tau-tubulin kinase (TTBK), a serine/threonine kinase belonging to the casein kinase 1 family [92], also support these findings. For example, the TTBK2 isoform has been associated with spinocerebellar ataxia [93]. In addition, TTBK1 has been linked to tau phosphorylation at multiple AD-relevant sites [94], and, in a tauopathy mouse model, this phosphorylation occurred without the appearance of phosphorylated sarkosyl-insoluble aggregates, but with the emergence of proto-fibrillar tau oligomers [95]. The presence of activated GSK3β and Cdk5 was noted, highlighting the possibility that TTBK1 does not phosphorylate tau directly, but may mediate tau phosphorylation indirectly by the GSK3β and Cdk5 putative tau kinases.

These and other data are supportive of the hypothesis that insoluble tau may be protective by acting as a ‘sink’ for soluble pathological species. The concept that aggregates of pathological proteins may be protective has also been proposed for other neurodegenerative diseases. For example, data suggest that soluble mutant huntingtin (mhtt) may be more toxic than aggregated mhtt, as cells in which mhtt aggregates form survive significantly longer than cells in which the mhtt does not aggregate [96]. Although the hypothesis that ‘pre-aggregated’ tau is the toxic form is attractive, it still remains to be substantiated, as visualization methods for specifically detecting oligomeric or pre-aggregates of tau have not been developed, and analysis presently relies on time-consuming biochemical assays. The strongest evidence supporting the ‘soluble-tau’ hypothesis remains the presence of toxicity and hyperphosphorylation in the absence of microscopically visible aggregates.

Conclusion

There is still much to learn regarding the role of tau kinases in AD, and hypotheses and perspectives continue to evolve as new data arise. As an understanding of the role of tau phosphorylation in AD pathogenesis is gained, the field is becoming better equipped to develop therapeutic strategies to treat the disease. Although it is important to consider tau kinases in the AD pathological processes, identifying pathogenic events that occur prior to the onset of

memory deficits is of crucial importance and will undoubtedly be an ever-increasing area of investigation as effective therapeutic strategies are sought.

In addition, the possibility that inhibiting kinases in models of AD pathogenesis is having beneficial effects that are not related directly to a reduction in tau phosphorylation should not be discounted. For example, lithium inhibits GSK3β, reduces APP processing [97], acts as a neurotrophin [98] and lowers inflammatory activity [99]; the Cdk5 inhibitor seliciclib (Cyclacel Pharmaceuticals Inc) prevents Aβ-induced Golgi fragmentation [100]; and, in an unrelated model, the JNK inhibitor SP-600125 (Celgene Corp) reduces proinflammatory microglial activity [101]. The kinases targeted are all considered to be tau kinases, but the beneficial effects of the kinase inhibitors in *in vitro* and *in vivo* models could be the result of their effects on other pathways. Changes that occur in tau phosphorylation following treatment with these inhibitors may only represent a marker of kinase activity, and may not be related directly to the attenuation of pathogenic outcomes. An indicator of this possibility is the observation that the expression of an extensively pseudophosphorylated tau construct in a mouse model did not result in any obvious pathology, memory loss, changes in tau localization or alterations in dendritic spine density [102].

In addition to the search for tau kinase modifiers, there is a focus on developing strategies to reduce the levels of phosphorylated tau using immunotherapy. This approach has yielded promising results in a tangle mouse model [103], resulting in a reduction in the amounts of phosphorylated and total tau in neurons, as well as improvements in cognitive defects. A promising therapeutic strategy may be immunotherapy combined with modifiers of tau kinases.

More recent studies have focused on post-translational modifications other than tau phosphorylation that may be early facilitators of tau pathology. For example, a recent imaging study conducted in the brains of mice in a tauopathy model indicated that non-terminal caspase activation in neurons can result in tau cleavage at the C-terminus, and that this event may be one of the primary drivers of pathogenicity that is independent of phosphorylation, although the two events (phosphorylation and cleavage) may function together [104]. Overall, it is clear that site-specific phosphorylation of tau plays a crucial role in regulating the physiological functions of tau, and that dysregulation of tau phosphorylation, be it as a primary or a secondary event, is a hallmark of AD pathology. Therefore, further studies that increase the knowledge of kinases that phosphorylate tau are of crucial importance. The abundance of information regarding the role of inappropriate kinase activation and tau phosphorylation (as well as other important post-translational modifications of tau, such as cleavage and *O*-GlcNAcylation) in neuronal dysfunction and death has certainly helped determine the pathogenic processes involved in AD. It is also exciting to consider that as new data emerge, paradigm shifts regarding the relative contribution of tau phosphorylation and aggregates to AD pathogenesis are likely to occur.

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References

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1. Weingarten MD, Lockwood AH, Hwo SY, Kirschner MW. A protein factor essential for microtubule assembly. Proc Natl Acad Sci USA 1975;72(5):1858–1862. [PubMed: 1057175]

2. Mareck A, Fellous A, Francon J, Nunez J. Changes in composition and activity of microtubule-associated proteins during brain development. Nature 1980;284(5754):353–355. [PubMed: 7360270]
3. Francon J, Fellous A, Lennon AM, Nunez J. Requirement for 'factor(s)' for tubulin assembly during brain development. Eur J Biochem 1978;85(1):43–53. [PubMed: 639823]
4. Wolozin BL, Pruchnicki A, Dickson DW, Davies P. A neuronal antigen in the brains of Alzheimer patients. Science 1986;232(4750):648–650. [PubMed: 3083509]
5. Wood JG, Mirra SS, Pollock NJ, Binder LI. Neurofibrillary tangles of Alzheimer disease share antigenic determinants with the axonal microtubule-associated protein tau (tau). Proc Natl Acad Sci USA 1986;83(11):4040–4043. [PubMed: 2424015]
6. Kosik KS, Joachim CL, Selkoe DJ. Microtubule-associated protein tau (tau) is a major antigenic component of paired helical filaments in Alzheimer disease. Proc Natl Acad Sci USA 1986;83(11): 4044–4048. [PubMed: 2424016]
7. Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI. Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. Proc Natl Acad Sci USA 1986;83(13):4913–4917. [PubMed: 3088567]
8. Stoothoff WH, Johnson GV. Tau phosphorylation: Physiological and pathological consequences. Biochim Biophys Acta 2005;1739(2–3):280–297. [PubMed: 15615646]
9. Andreadis A, Brown WM, Kosik KS. Structure and novel exons of the human *tau* gene. Biochemistry 1992;31(43):10626–10633. [PubMed: 1420178]
10. Wei ML, Andreadis A. Splicing of a regulated exon reveals additional complexity in the axonal microtubule-associated protein tau. J Neurochem 1998;70(4):1346–1356. [PubMed: 9523550]
11. Goedert M, Spillantini MG, Jakes R, Rutherford D, Crowther RA. Multiple isoforms of human microtubule-associated protein tau: Sequences and localization in neurofibrillary tangles of Alzheimer's disease. Neuron 1989;3(4):519–526. [PubMed: 2484340]
12. Lindwall G, Cole RD. Phosphorylation affects the ability of tau protein to promote microtubule assembly. J Biol Chem 1984;259(8):5301–5305. [PubMed: 6425287]
13• . Savage MJ, Gingrich DE. Advances in the development of kinase inhibitor therapeutics for Alzheimer's disease. Drug Dev Res 2009;70(2):125–144. A comprehensive review of the development of tau kinase inhibitors for the treatment of AD.
14. Busciglio J, Lorenzo A, Yeh J, Yankner BA. β-amyloid fibrils induce tau phosphorylation and loss of microtubule binding. Neuron 1995;14(4):879–888. [PubMed: 7718249]
15. Ferreira A, Lu Q, Orecchio L, Kosik KS. Selective phosphorylation of adult tau isoforms in mature hippocampal neurons exposed to fibrillar Aβ. Mol Cell Neurosci 1997;9(3):220–234. [PubMed: 9245504]
16. Alvarez G, Munoz-Montano JR, Satrustegui J, Avila J, Bogonez E, Diaz-Nido J. Lithium protects cultured neurons against β-amyloid-induced neurodegeneration. FEBS Lett 1999;453(3):260–264. [PubMed: 10405156]
17. Mattson MP, Cheng B, Davis D, Bryant K, Lieberburg I, Rydel RE. β-Amyloid peptides destabilize calcium homeostasis and render human cortical neurons vulnerable to excitotoxicity. J Neurosci 1992;12(2):376–389. [PubMed: 1346802]
18. Lopes JP, Oliveira CR, Agostinho P. Neurodegeneration in an Aβ-induced model of Alzheimer's disease: The role of Cdk5. Aging Cell 2010;9(1):64–77. [PubMed: 19895631]
19. Lee MS, Kwon YT, Li M, Peng J, Friedlander RM, Tsai LH. Neurotoxicity induces cleavage of p35 to p25 by calpain. Nature 2000;405(6784):360–364. [PubMed: 10830966]
20. De Felice FG, Velasco PT, Lambert MP, Viola K, Fernandez SJ, Ferreira ST, Klein WL. Aβ oligomers induce neuronal oxidative stress through an *N*-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine. J Biol Chem 2007;282(15):11590–11601. [PubMed: 17308309]
21. Weiss JH, Pike CJ, Cotman CW. Ca^{2+} channel blockers attenuate β-amyloid peptide toxicity to cortical neurons in culture. J Neurochem 1994;62(1):372–375. [PubMed: 8263540]
22. Degerman Gunnarsson M, Kilander L, Basun H, Lannfelt L. Reduction of phosphorylated tau during memantine treatment of Alzheimer's disease. Dement Geriatr Cogn Disord 2007;24(4):247–252. [PubMed: 17700020]

23. Li L, Sengupta A, Haque N, Grundke-Iqbal I, Iqbal K. Memantine inhibits and reverses the Alzheimer type abnormal hyperphosphorylation of tau and associated neurodegeneration. FEBS Lett 2004;566 (1–3):261–269. [PubMed: 15147906]
24. Song MS, Rauw G, Baker GB, Kar S. Memantine protects rat cortical cultured neurons against β-amyloid-induced toxicity by attenuating tau phosphorylation. Eur J Neurosci 2008;28(10):1989–2002. [PubMed: 19046381]
25• • . Hallows JL, Chen K, DePinho RA, Vincent I. 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 2003;23(33):10633–10644. Reported the presence of increased tau phosphorylation in p35-null mice. Also suggested the possibility that Cdk5 is not a primary tau kinase in vivo. [PubMed: 14627648]
26. Hallows JL, Iosif RE, Biasell RD, Vincent I. p35/p25 is not essential for tau and cytoskeletal pathology or neuronal loss in Niemann-Pick type C disease. J Neurosci 2006;26(10):2738–2744. [PubMed: 16525053]
27. Tamagno E, Robino G, Obbili A, Bardini P, Aragno M, Parola M, Danni O. H_2O_2 and 4-hydroxynonenal mediate amyloid β-induced neuronal apoptosis by activating JNKs and p38MAPK. Exp Neurol 2003;180(2):144–155. [PubMed: 12684028]
28. Tamagno E, Parola M, Guglielmotto M, Santoro G, Bardini P, Marra L, Tabaton M, Danni O. Multiple signaling events in amyloid β-induced, oxidative stress-dependent neuronal apoptosis. Free Radic Biol Med 2003;35(1):45–58. [PubMed: 12826255]
29• . Ma QL, Yang F, Rosario ER, Ubeda OJ, Beech W, Gant DJ, Chen PP, Hudspeth B, Chen C, Zhao Y, Vinters HV, et al. β-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling: Suppression by omega-3 fatty acids and curcumin. J Neurosci 2009;29(28):9078–9089. Suggested an association between Aβ-induced oxidative stress, insulin signaling and the phosphorylation of tau by JNK. [PubMed: 19605645]
30. Ryan SD, Whitehead SN, Swayne LA, Moffat TC, Hou W, Ethier M, Bourgeois AJ, Rashidian J, Blanchard AP, Fraser PE, Park DS, et al. Amyloid-β_{42} signals tau hyperphosphorylation and compromises neuronal viability by disrupting alkylacylglycerophosphocholine metabolism. Proc Natl Acad Sci USA 2009;106(49):20936–20941. [PubMed: 19926863]
31. Alvarez AR, Sandoval PC, Leal NR, Castro PU, Kosik KS. Activation of the neuronal c-Abl tyrosine kinase by amyloid-β-peptide and reactive oxygen species. Neurobiol Dis 2004;17(2):326–336. [PubMed: 15474370]
32. Williamson R, Scales T, Clark BR, Gibb G, Reynolds CH, Kellie S, Bird IN, Varndell IM, Sheppard PW, Everall I, Anderton BH. Rapid tyrosine phosphorylation of neuronal proteins including tau and focal adhesion kinase in response to amyloid-β peptide exposure: Involvement of Src family protein kinases. J Neurosci 2002;22(1):10–20. [PubMed: 11756483]
33. Cancino GI, Perez de Arce K, Castro PU, Toledo EM, von Bernhardi R, Alvarez AR. c-Abl tyrosine kinase modulates tau pathology and Cdk5 phosphorylation in AD transgenic mice. Neurobiol Aging. 200910.1016/j.neurobiolaging.2009.07.007
34. Derkinderen P, Scales TM, Hanger DP, Leung KY, Byers HL, Ward MA, Lenz C, Price C, Bird IN, Perera T, Kellie S, et al. 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 2005;25(28):6584–6593. [PubMed: 16014719]
35. Tremblay MA, Acker CM, Davies P. Tau phosphorylated at tyrosine 394 is found in Alzheimer's disease tangles and can be a product of the Abl-related kinase, Arg. J Alzheimers Dis 2010;19(2): 721–733. [PubMed: 20110615]
36. Lee G, Newman ST, Gard DL, Band H, Panchamoorthy G. Tau interacts with Src-family non-receptor tyrosine kinases. J Cell Sci 1998;111(Pt 21):3167–3177. [PubMed: 9763511]
37. Sturchler-Pierrat C, Abramowski D, Duke M, Wiederhold KH, Mistl C, Rothacher S, Ledermann B, Burki K, Frey P, Paganetti PA, Waridel C, et al. Two amyloid precursor protein transgenic mouse models with Alzheimer disease-like pathology. Proc Natl Acad Sci USA 1997;94(24):13287–13292. [PubMed: 9371838]
38. Otth C, Concha, Arendt T, Stieler J, Schliebs R, Gonzalez-Billault C, Maccioni RB. AβPP induces Cdk5-dependent tau hyperphosphorylation in transgenic mice Tg2576. J Alzheimers Dis 2002;4(5): 417–430. [PubMed: 12446973]

39. Roberson ED, Scearce-Levie K, Palop JJ, Yan F, Cheng IH, Wu T, Gerstein H, Yu GQ, Mucke L. Reducing endogenous tau ameliorates amyloid β-induced deficits in an Alzheimer's disease mouse model. Science 2007;316(5825):750–754. [PubMed: 17478722]
40. Oakley H, Cole SL, Logan S, Maus E, Shao P, Craft J, Guillozet-Bongaarts A, Ohno M, Disterhoft J, Van Eldik L, Berry R, et al. Intraneuronal β-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: Potential factors in amyloid plaque formation. J Neurosci 2006;26(40):10129–10140. [PubMed: 17021169]
41. Ghosal K, Vogt DL, Liang M, Shen Y, Lamb BT, Pimplikar SW. Alzheimer's disease-like pathological features in transgenic mice expressing the APP intracellular domain. Proc Natl Acad Sci USA 2009;106(43):18367–18372. [PubMed: 19837693]
42. Tomiyama T, Matsuyama S, Iso H, Umeda T, Takuma H, Ohnishi K, Ishibashi K, Teraoka R, Sakama N, Yamashita T, Nishitsuji K, et al. A mouse model of amyloid β oligomers: Their contribution to synaptic alteration, abnormal tau phosphorylation, glial activation, and neuronal loss *in vivo*. J Neurosci 2010;30(14):4845–4856. [PubMed: 20371804]
43. Lewis J, Dickson DW, Lin WL, Chisholm L, Corral A, Jones G, Yen SH, Sahara N, Skipper L, Yager D, Eckman C, et al. Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. Science 2001;293(5534):1487–1491. [PubMed: 11520987]
44. Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, Metherate R, Mattson MP, Akbari Y, LaFerla FM. Triple-transgenic model of Alzheimer's disease with plaques and tangles: Intracellular Aβ and synaptic dysfunction. Neuron 2003;39(3):409–421. [PubMed: 12895417]
45. Lewis J, McGowan E, Rockwood J, Melrose H, Nacharaju P, Van Slegtenhorst M, Gwinn-Hardy K, Paul Murphy M, Baker M, Yu X, Duff K, et al. Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein. Nat Genet 2000;25(4):402–405. [PubMed: 10932182]
46. Allen B, Ingram E, Takao M, Smith MJ, Jakes R, Virdee K, Yoshida H, Holzer M, Craxton M, Emson PC, Atzori C, et al. Abundant tau filaments and nonapoptotic neurodegeneration in transgenic mice expressing human P301S tau protein. J Neurosci 2002;22(21):9340–9351. [PubMed: 12417659]
47. Nicolls MR. The clinical and biological relationship between type II diabetes mellitus and Alzheimer's disease. Curr Alzheimer Res 2004;1(1):47–54. [PubMed: 15975085]
48. Hong M, Lee VM. Insulin and insulin-like growth factor-1 regulate tau phosphorylation in cultured human neurons. J Biol Chem 1997;272(31):19547–19553. [PubMed: 9235959]
49. Nugent DA, Smith DM, Jones HB. A review of islet of Langerhans degeneration in rodent models of type 2 diabetes. Toxicol Pathol 2008;36(4):529–551. [PubMed: 18467681]
50• • . Clodfelder-Miller BJ, Zmijewska AA, Johnson GV, Jope RS. Tau is hyperphosphorylated at multiple sites in mouse brain *in vivo* after streptozotocin-induced insulin deficiency. Diabetes 2006;55(12):3320–3325. Demonstrated that in mice that have undergone hyperglycemia-induced tau hyperphosphorylation, GSK3β activity can be separated from increased levels of phosphorylated tau. Increased levels of tau phosphorylation in the brain were demonstrated to be the result of decreased phosphatase activity. [PubMed: 17130475]
51. Ke YD, Delerue F, Gladbach A, Gotz J, Ittner LM. Experimental diabetes mellitus exacerbates tau pathology in a transgenic mouse model of Alzheimer's disease. PLoS One 2009;4(11):e7917. [PubMed: 19936237]
52. Planel E, Tatebayashi Y, Miyasaka T, Liu L, Wang L, Herman M, Yu WH, Luchsinger JA, Wadzinski B, Duff KE, Takashima A. Insulin dysfunction induces *in vivo* tau hyperphosphorylation through distinct mechanisms. J Neurosci 2007;27(50):13635–13648. [PubMed: 18077675]
53. Planel E, Richter KE, Nolan CE, Finley JE, Liu L, Wen Y, Krishnamurthy P, Herman M, Wang L, Schachter JB, Nelson RB, et al. Anesthesia leads to tau hyperphosphorylation through inhibition of phosphatase activity by hypothermia. J Neurosci 2007;27(12):3090–3097. [PubMed: 17376970]
54. Salkovic-Petrisic M, Hoyer S. Central insulin resistance as a trigger for sporadic Alzheimer-like pathology: An experimental approach. J Neural Transm Suppl 2007;(72):217–233. [PubMed: 17982898]
55. Grunblatt E, Salkovic-Petrisic M, Osmanovic J, Riederer P, Hoyer S. Brain insulin system dysfunction in streptozotocin intracerebroventricularly treated rats generates hyperphosphorylated tau protein. J Neurochem 2007;101(3):757–770. [PubMed: 17448147]

56. Deng Y, Li B, Liu Y, Iqbal K, Grundke-Iqbal I, Gong CX. Dysregulation of insulin signaling, glucose transporters, *O*-GlcNAcylation, and phosphorylation of tau and neurofilaments in the brain: Implication for Alzheimer's disease. Am J Pathol 2009;175(5):2089–2098. [PubMed: 19815707]

57. Lefebvre T, Ferreira S, Dupont-Wallois L, Bussiere T, Dupire MJ, Delacourte A, Michalski JC, Caillet-Boudin ML. Evidence of a balance between phosphorylation and *O*-GlcNAc glycosylation of tau proteins – A role in nuclear localization. Biochim Biophys Acta 2003;1619(2):167–176. [PubMed: 12527113]

58• • . Yuzwa SA, Macauley MS, Heinonen JE, Shan X, Dennis RJ, He Y, Whitworth GE, Stubbs KA, McEachern EJ, Davies GJ, Vocadlo DJ. A potent mechanism-inspired *O*-GlcNAcase inhibitor that blocks phosphorylation of tau *in vivo*. Nat Chem Biol 2008;4(8):483–490. Describes the rational development of a small-molecule inhibitor of O-GlcNAcase that resulted in reduced AT180 and PHF1 tau phosphorylation. [PubMed: 18587388]

59. Trinczek B, Biernat J, Baumann K, Mandelkow EM, Mandelkow E. Domains of tau protein, differential phosphorylation, and dynamic instability of microtubules. Mol Biol Cell 1995;6(12): 1887–1902. [PubMed: 8590813]

60. Ferrer I, Gomez-Isla T, Puig B, Freixes M, Ribe E, Dalfo E, Avila J. Current advances on different kinases involved in tau phosphorylation, and implications in Alzheimer's disease and tauopathies. Curr Alzheimer Res 2005;2(1):3–18. [PubMed: 15977985]

61. Wagner U, Utton M, Gallo JM, Miller CC. Cellular phosphorylation of tau by GSK-3β influences tau binding to microtubules and microtubule organisation. J Cell Sci 1996;109(Pt 6):1537–1543. [PubMed: 8799840]

62. Schneider A, Biernat J, von Bergen M, Mandelkow E, Mandelkow EM. Phosphorylation that detaches tau protein from microtubules (Ser^{262}, Ser^{214}) also protects it against aggregation into Alzheimer paired helical filaments. Biochemistry 1999;38(12):3549–3558. [PubMed: 10090741]

63. Drewes G, Ebneth A, Preuss U, Mandelkow EM, Mandelkow E. MARK, a novel family of protein kinases that phosphorylate microtubule-associated proteins and trigger microtubule disruption. Cell 1997;89(2):297–308. [PubMed: 9108484]

64•. Fischer D, Mukrasch MD, Biernat J, Bibow S, Blackledge M, Griesinger C, Mandelkow E, Zweckstetter M. Conformational changes specific for pseudophosphorylation at serine 262 selectively impair binding of tau to microtubules. Biochemistry 2009;48(42):10047–10055. Describes the structural rearrangements, as determined by NMR, that occur in the microtubule-binding regions underlying tau-microtubule disassociation. [PubMed: 19769346]

65. Heston LL, White J. Pedigrees of 30 families with Alzheimer disease: Associations with defective organization of microfilaments and microtubules. Behav Genet 1978;8(4):315–331. [PubMed: 567976]

66. Iqbal K, Liu F, Gong CX, Alonso Adel C, Grundke-Iqbal I. Mechanisms of tau-induced neurodegeneration. Acta Neuropathol 2009;118(1):53–69. [PubMed: 19184068]

67. Bertrand J, Plouffe V, Senechal P, Leclerc N. The pattern of human tau phosphorylation is the result of priming and feedback events in primary hippocampal neurons. Neuroscience 2010;168(2):323–334. [PubMed: 20394726]

68. Sontag E, Nunbhakdi-Craig V, Lee G, Bloom GS, Mumby MC. Regulation of the phosphorylation state and microtubule-binding activity of tau by protein phosphatase 2A. Neuron 1996;17(6):1201–1207. [PubMed: 8982166]

69. Xu Y, Chen Y, Zhang P, Jeffrey PD, Shi Y. Structure of a protein phosphatase 2A holoenzyme: Insights into B55-mediated tau dephosphorylation. Mol Cell 2008;31(6):873–885. [PubMed: 18922469]

70• . Chatterjee S, Sang TK, Lawless GM, Jackson GR. Dissociation of tau toxicity and phosphorylation: Role of GSK-3β, MARK and Cdk5 in a *Drosophila* model. Hum Mol Genet 2009;18(1):164–177. Through the use of Drosophila tau mutants that could not be phosphorylated, this study outlined how resistance to phosphorylation drives toxicity, possibly through the suppression of tau-mediated microtubule dynamics. [PubMed: 18930955]

71. De Vos KJ, Grierson AJ, Ackerley S, Miller CC. Role of axonal transport in neurodegenerative diseases. Annu Rev Neurosci 2008;31:151–173. [PubMed: 18558852]

72. Kamal A, Stokin GB, Yang Z, Xia CH, Goldstein LS. Axonal transport of amyloid precursor protein is mediated by direct binding to the kinesin light chain subunit of kinesin-I. Neuron 2000;28(2):449–459. [PubMed: 11144355]
73. Stokin GB, Lillo C, Falzone TL, Brusch RG, Rockenstein E, Mount SL, Raman R, Davies P, Masliah E, Williams DS, Goldstein LS. Axonopathy and transport deficits early in the pathogenesis of Alzheimer's disease. Science 2005;307(5713):1282–1288. [PubMed: 15731448]
74. Utton MA, Noble WJ, Hill JE, Anderton BH, Hanger DP. Molecular motors implicated in the axonal transport of tau and α-synuclein. J Cell Sci 2005;118(Pt 20):4645–4654. [PubMed: 16176937]
75. Cuchillo-Ibanez I, Seereeram A, Byers HL, Leung KY, Ward MA, Anderton BH, Hanger DP. Phosphorylation of tau regulates its axonal transport by controlling its binding to kinesin. FASEB J 2008;22(9):3186–3195. [PubMed: 18511549]
76. Morel M, Authelet M, Dedecker R, Brion JP. Glycogen synthase kinase-3β and the p25 activator of cyclin dependent kinase 5 increase pausing of mitochondria in neurons. Neuroscience 2010;167(4):1044–1056. [PubMed: 20211702]
77. Thies E, Mandelkow EM. Missorting of tau in neurons causes degeneration of synapses that can be rescued by the kinase MARK2/Par-1. J Neurosci 2007;27(11):2896–2907. [PubMed: 17360912]
78. Morfini G, Pigino G, Mizuno N, Kikkawa M, Brady ST. Tau binding to microtubules does not directly affect microtubule-based vesicle motility. J Neurosci Res 2007;85(12):2620–2630. [PubMed: 17265463]
79• . LaPointe NE, Morfini G, Pigino G, Gaisina IN, Kozikowski AP, Binder LI, Brady ST. The amino terminus of tau inhibits kinesin-dependent axonal transport: Implications for filament toxicity. J Neurosci Res 2009;87(2):440–451. Suggested that specific AD tau conformations and tau filaments can selectively impair axonal transport, as measured in an in vitro transport model. [PubMed: 18798283]
80. Morfini G, Szebenyi G, Elluru R, Ratner N, Brady ST. Glycogen synthase kinase 3 phosphorylates kinesin light chains and negatively regulates kinesin-based motility. EMBO J 2002;21(3):281–293. [PubMed: 11823421]
81. Koushika SP. "JIP"ing along the axon: The complex roles of JIPs in axonal transport. Bioessays 2008;30(1):10–14. [PubMed: 18081006]
82. Helbecque N, Abderrahamani A, Meylan L, Riederer B, Mooser V, Miklossy J, Delplanque J, Boutin P, Nicod P, Haefliger JA, Cottel D, et al. Islet-brain1/c-Jun N-terminal kinase interacting protein-1 (IB1/JIP-1) promoter variant is associated with Alzheimer's disease. Mol Psychiatry 2003;8(4):413–422. 363. [PubMed: 12740599]
83•. Ittner LM, Ke YD, Gotz J. Phosphorylated tau interacts with c-Jun N-terminal kinase-interacting protein 1 (JIP1) in Alzheimer disease. J Biol Chem 2009;284(31):20909–20916. Describes the interaction of the axonal transport protein JIP1 with mutant or phosphorylated tau, and how this interaction disrupts the formation of the kinesin complex by interfering with KIF/KLC binding. [PubMed: 19491104]
84. Ittner LM, Fath T, Ke YD, Bi M, van Eersel J, Li KM, Gunning P, Gotz J. Parkinsonism and impaired axonal transport in a mouse model of frontotemporal dementia. Proc Natl Acad Sci USA 2008;105(41):15997–16002. [PubMed: 18832465]
85. Falzone TL, Stokin GB, Lillo C, Rodrigues EM, Westerman EL, Williams DS, Goldstein LS. Axonal stress kinase activation and tau misbehavior induced by kinesin-1 transport defects. J Neurosci 2009;29(18):5758–5767. [PubMed: 19420244]
86. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991;82(4):239–259. [PubMed: 1759558]
87. Lee VM, Balin BJ, Otvos L Jr, Trojanowski JQ. A68: A major subunit of paired helical filaments and derivatized forms of normal tau. Science 1991;251(4994):675–678. [PubMed: 1899488]
88. Sahara N, Maeda S, Takashima A. Tau oligomerization: A role for tau aggregation intermediates linked to neurodegeneration. Curr Alzheimer Res 2008;5(6):591–598. [PubMed: 19075586]
89. Santacruz K, Lewis J, Spires T, Paulson J, Kotilinek L, Ingelsson M, Guimaraes A, DeTure M, Ramsden M, McGowan E, Forster C, et al. Tau suppression in a neurodegenerative mouse model improves memory function. Science 2005;309(5733):476–481. [PubMed: 16020737]

90. Feuillette S, Miguel L, Frebourg T, Campion D, Lecourtois M. *Drosophila* models of human tauopathies indicate that tau protein toxicity *in vivo* is mediated by soluble cytosolic phosphorylated forms of the protein. J Neurochem 2010;113(4):895–903. [PubMed: 20193038]

91. Iqbal K, Alonso Adel C, Grundke-Iqbal I. Cytosolic abnormally hyperphosphorylated tau but not paired helical filaments sequester normal MAPs and inhibit microtubule assembly. J Alzheimers Dis 2008;14(4):365–370. [PubMed: 18688085]

92. Manning G, Whyte DB, Martinez R, Hunter T, Sudarsanam S. The protein kinase complement of the human genome. Science 2002;298(5600):1912–1934. [PubMed: 12471243]

93. Houlden H, Johnson J, Gardner-Thorpe C, Lashley T, Hernandez D, Worth P, Singleton AB, Hilton DA, Holton J, Revesz T, Davis MB, et al. Mutations in TTBK2, encoding a kinase implicated in tau phosphorylation, segregate with spinocerebellar ataxia type 11. Nat Genet 2007;39(12):1434–1436. [PubMed: 18037885]

94. Sato S, Xu J, Okuyama S, Martinez LB, Walsh SM, Jacobsen MT, Swan RJ, Schlautman JD, Ciborowski P, Ikezu T. Spatial learning impairment, enhanced Cdk5/p35 activity, and downregulation of NMDA receptor expression in transgenic mice expressing tau-tubulin kinase 1. J Neurosci 2008;28(53):14511–14521. [PubMed: 19118186]

95. Xu J, Sato S, Okuyama S, Swan RJ, Jacobsen MT, Strunk E, Ikezu T. Tau-tubulin kinase 1 enhances prefibrillar tau aggregation and motor neuron degeneration in P301L FTDP-17 tau-mutant mice. FASEB J 2010;24(8):2904–2915. [PubMed: 20354135]

96. Arrasate M, Mitra S, Schweitzer ES, Segal MR, Finkbeiner S. Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. Nature 2004;431(7010):805–810. [PubMed: 15483602]

97. Su Y, Ryder J, Li B, Wu X, Fox N, Solenberg P, Brune K, Paul S, Zhou Y, Liu F, Ni B. Lithium, a common drug for bipolar disorder treatment, regulates amyloid-β precursor protein processing. Biochemistry 2004;43(22):6899–6908. [PubMed: 15170327]

98. Manji HK, Moore GJ, Chen G. Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: Implications for the pathophysiology and treatment of manic-depressive illness. Biol Psychiatry 2000;48(8):740–754. [PubMed: 11063971]

99. Yuskaitis CJ, Jope RS. Glycogen synthase kinase-3 regulates microglial migration, inflammation, and inflammation-induced neurotoxicity. Cell Signal 2009;21(2):264–273. [PubMed: 19007880]

100. Sun KH, de Pablo Y, Vincent F, Johnson EO, Chavers AK, Shah K. Novel genetic tools reveal Cdk5's major role in golgi fragmentation in Alzheimer's disease. Mol Biol Cell 2008;19(7):3052–3069. [PubMed: 18480410]

101. Waetzig V, Czeloth K, Hidding U, Mielke K, Kanzow M, Brecht S, Goetz M, Lucius R, Herdegen T, Hanisch UK. c-Jun N-terminal kinases (JNKs) mediate pro-inflammatory actions of microglia. Glia 2005;50(3):235–246. [PubMed: 15739188]

102. Hundelt M, Fath T, Selle K, Oesterwind K, Jordan J, Schultz C, Gotz J, von Engelhardt J, Monyer H, Lewejohann L, Sachser N, et al. Altered phosphorylation but no neurodegeneration in a mouse model of tau hyperphosphorylation. Neurobiol Aging. 200910.1016/j.neurobiolaging.2009.06.007

103. Asuni AA, Boutajangout A, Quartermain D, Sigurdsson EM. Immunotherapy targeting pathological tau conformers in a tangle mouse model reduces brain pathology with associated functional improvements. J Neurosci 2007;27(34):9115–9129. [PubMed: 17715348]

104•• . de Calignon A, Fox LM, Pitstick R, Carlson GA, Bacskai BJ, Spires-Jones TL, Hyman BT. Caspase activation precedes and leads to tangles. Nature 2010;464(7292):1201–1204. Demonstrated that, in live neurons, caspase activation, which precedes the formation of NFTs, may be reversible, and does not necessarily lead to acute neuronal death. [PubMed: 20357768]

105. Biernat J, Mandelkow EM, Schroter C, Lichtenberg-Kraag B, Steiner B, Berling B, Meyer H, Mercken M, Vandermeeren A, Goedert M, Mandelkow E. The switch of tau protein to an Alzheimer-like state includes the phosphorylation of two serine-proline motifs upstream of the microtubule binding region. EMBO J 1992;11(4):1593–1597. [PubMed: 1563356]

106. Porzig R, Singer D, Hoffmann R. Epitope mapping of mAbs AT8 and Tau5 directed against hyperphosphorylated regions of the human tau protein. Biochem Biophys Res Commun 2007;358(2):644–649. [PubMed: 17499212]

107. Otvos L Jr, Feiner L, Lang E, Szendrei GI, Goedert M, Lee VM. Monoclonal antibody PHF-1 recognizes tau protein phosphorylated at serine residues 396 and 404. J Neurosci Res 1994;39(6): 669–673. [PubMed: 7534834]

108. Goedert M, Jakes R, Crowther RA, Cohen P, Vanmechelen E, Vandermeeren M, Cras P. Epitope mapping of monoclonal antibodies to the paired helical filaments of Alzheimer's disease: Identification of phosphorylation sites in tau protein. Biochem J 1994;301(Pt 3):871–877. [PubMed: 7519852]

109. Seubert P, Mawal-Dewan M, Barbour R, Jakes R, Goedert M, Johnson GV, Litersky JM, Schenk D, Lieberburg I, Trojanowski JQ, Lee VM. Detection of phosphorylated Ser^{262} in fetal tau, adult tau, and paired helical filament tau. J Biol Chem 1995;270(32):18917–18922. [PubMed: 7642549]