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Cytosolic Abnormally Hyperphosphorylated Tau But Not Paired Helical Filaments Sequester Normal MAPs and Inhibit Microtubule Assembly

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Abstract

Neurofibrillary degeneration of abnormally hyperphosphorylated tau, a hallmark of Alzheimer's disease (AD) and related tauopathies, occurs both as cytosolic aggregated/oligomeric protein (AD P-tau) and as neurofibrillary tangles. The abnormal hyperphosphorylation not only results in the loss of tau function of promoting assembly and stabilizing microtubules but, in the case of the cytosolic AD P-tau, also in a gain of a toxic function whereby the pathological tau sequesters not only normal tau, but also the other two neuronal microtubule associated proteins (MAPs), MAP1A / MAP1B and MAP2, and causes inhibition and disruption of microtubules. The sequestration of normal MAPs leads to a slow but progressive degeneration of the affected neurons. The affected neurons defend against the toxic tau by continually synthesizing new normal tau as well as by packaging the abnormally hyperphosphorylated tau into polymers, i.e., neurofibrillary tangles of paired helical filaments, twisted ribbons and straight filaments. The filamentous tau is inert; it neither interacts with tubulin and stimulates its assembly, nor binds to normal MAPs and causes disruption of microtubules. These findings suggest the inhibition of tau abnormal hyperphosphorylation and not the aggregation of tau as the preferred therapeutic target for AD and related tauopathies.

Keywords

Abnormal hyperphosphorylation of tau; Alzheimer disease; microtubule associated protein 2; microtubule associated protein tau; microtubules; neurofibrillary degeneration; protein phosphatase-2A; tauopathies

INTRODUCTION

In Alzheimer's disease (AD) and related disorders characterized by tau pathology, called tauopathies, tau is abnormally hyperphosphorylated and is accumulated as intraneuronal tangles of paired helical filaments (PHF), twisted ribbons and/or straight filaments (SF) [16, 17,19,20,27]. This hallmark brain lesion of these diseases directly correlates with dementia in these patients [1,11,37].

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A neuron, with its long axonal and dendritic arborization, is heavily dependent on its microtubule network which, among other functions, is critical for axonal transport. In the brain, the microtubule network of neurons is maintained by three microtubule associated proteins (MAPs), tau, MAP1 (A/B) and MAP2, which apparently perform similar functions, i.e., promote assembly and stabilize microtubules. Tau is the major, the smallest in size, and apparently the most dynamic of the three MAPs. It is also apparently most vulnerable in a disease situation. The biological activity of tau, a phosphoprotein, in promoting assembly and stability of microtubules is regulated by its degree of phosphorylation. Normal tau contains 2–3 moles of phosphate/mole of the protein [26], the level of phosphorylation for its optimal activity. Hyperphosphorylation of tau depresses its microtubule assembly activity and its binding to microtubules [2,29]. The etiopathogenesis of neurofibrillary degeneration and therapeutic strategies to inhibit this lesion have been the subject of several recent reviews [22,23]. In this article, whether abnormal hyperphosphorylation of tau or its aggregation causes neurodegeneration is discussed.

ABNORMAL HYPERPHOSPHORYLATION OF TAU CAUSES NEUROFIBRILLARY DEGENERATION

In AD brains, the levels of tau, but not the mRNA for this protein, are 4–8 fold increased as compared to age-matched control brains, and this increase is in the form of the abnormally hyperphosphorylated tau [24,25]. The abnormally hyperphosphorylated tau is found in AD brain in two subcellular pools, i.e., (i) as polymerized into neurofibrillary tangles of PHF mixed with SF; and (ii) as non-fibrillized form in the cytosol [13,19,26]. The tau polymerized into neurofibrillary tangles is apparently inert and only upon enzymatic dephosphorylation *in vitro*, when released from PHF/tangles, it behaves like normal tau in promoting microtubule assembly [21,39]. In contrast, the cytosolic abnormally hyperphosphorylated tau (AD P-tau), which can be as much as ~ 40% of the total abnormal tau in AD brain [26], does not interact with tubulin/microtubules but instead sequesters normal tau, MAP1A/ MAP1B and MAP2, causing inhibition and disassembly of microtubules *in vitro* [2–4] and in an extracted cell system [28]. Unlike AD P-tau, the PHF tau does not bind normal tau [8]. The association between AD P-tau and normal tau is not saturable and *in vitro* results in the formation of tangles of ~ 2.1 mm filaments [3]. These findings were replicated by Vandebroek and colleagues [38] in a less complex cellular model, the yeast. These authors found that the expression of the longest human brain four-repeat tau (τ 4L) and the three-repeat isoform (τ 3L) in yeast produced pathological phosphoepitopes, assumed a pathological conformation, and formed aggregates. These processes were modulated by yeast kinases Mds1 and Pho85, orthologues of GSK-3 β and cdk5. They observed that tau aggregated more when it was more phosphorylated, the mobility in SDS electrophoresis was slower with increased phosphorylation, isolated hyperphosphorylated tau was able to assemble into filaments, and the isolated hyperphosphorylated tau was able to nucleate the assembly of the normal, non-phosphorylated tau. The authors proposed that hyperphosphorylated tau was the biochemically stable form of tau and was the actual seed or nucleation factor that initiated and promoted the aggregation of tau. Our studies employing the hyperphosphorylated tau isolated from AD brain had led us to the same conclusion [3].

Recently Takashima's lab isolated a form of tau that they have named “granular tau” [30]. This form of tau is a precursor of PHF and appears in the neurons before PHF. This form of tau appears to be the same as the AD P-tau. Like the AD P-tau, the granular tau sediments at 200,000xg, is hyperphosphorylated, precedes tangle formation [12,26,30,31] and self assembles into filaments [6,31].

The association between AD P-tau and MAP1A/MAP1B or MAP2 is weaker than that between the AD P-tau and normal tau and does not result in the formation of filaments [4]. This toxic

property of the AD P-tau appears to be solely due to its abnormal hyperphosphorylation because dephosphorylation by alkaline phosphatase, protein phosphatase (PP)-2A, PP-2B and to a lesser degree by PP-1 converts the abnormal tau into a normal-like protein in promoting the micro-tubule assembly *in vitro* [2-4,21,39,40]. Furthermore, only the soluble form of AD P-tau binds MAPs and disrupts microtubules. When ADP-tau self-assembles into filaments, it becomes inert towards binding MAPs and disrupting microtubules [8]. The sequestration of functional tau by the abnormally hyperphosphorylated tau causes disruption of microtubule network and thereby leads to neurodegeneration.

Several missense mutations in tau co-segregate with the disease in FTDP-17 [18,34,36]. Four of these missense mutations, G272V, P301L, V337M and R406W, which have been studied to date, make tau a more favorable substrate than the wild-type human tau for abnormal hyperphosphorylation by brain protein kinases *in vitro* [7]. These mutated taus become hyperphosphorylated at a faster rate and self-aggregate into filaments more readily, i.e., at a phosphorylation stoichiometry of 4–6 as compared with 10 or more in the case of the wild-type protein. These faster kinetics of the hyperphosphorylation of the mutated tau might explain a relatively early onset, severity and autosomal dominance of the disease in the inherited FTDP-17 cases.

The six brain human tau isoforms, τ 4RL (4R, 2N), τ 4S (4R, 1N), τ 4 (4R, 0N), τ 3RL (3R, 2N), τ 3RS (3R, 1N), and τ 3 (3R, 0N, also called fetal tau), are differentially sequestered by AD P-tau, *in vitro* [5]. The association of AD P-tau to normal human brain recombinant taus is τ 4RL > τ 4RS > τ 4R and τ 3RL > τ 3RS > τ 3, and that of τ 4RL > τ 3RL. AD P-tau also inhibits the assembly and disrupts microtubules pre-assembled with each tau isoform with an efficiency which corresponds directly to the degree of interaction with these isoforms. *In vitro* hyperphosphorylation of recombinant tau converts it into an AD P-tau-like state in sequestering normal tau and inhibiting microtubule assembly. The preferential sequestration of 4R taus and taus with amino terminal inserts explains both (i) why fetal brain (fetal tau is with 3R and no N) is protected from Alzheimer neurofibrillary pathology and (ii) why intronic mutations seen in certain inherited cases of FTDP-17, which result in alternate splicing of tau mRNA, and consequently an increase in 4R:3R ratio, lead to neurofibrillary degeneration and the disease. *In vitro* at a phosphorylation stoichiometry of ~4 and above, the hyper-phosphorylated tau sequesters normal tau, whereas it requires a stoichiometry of 10 or more to self-aggregate into filaments [7,8,28]. On aggregation into filaments, tau loses its ability to sequester normal tau. Furthermore, AD P-tau, but not PHF, inhibits regeneration of microtubule network in detergent-extracted PC12 cells, indicating that the formation of filaments might be initiated as a self defense response by the affected neurons [6]. Eckermann et al. [15] generated two inducible transgenic mice lines: the “pro-aggregation” mutant DeltaK280, derived from one of the mutations observed in frontotemporal dementias, which aggregated avidly *in vitro*, and the “anti-aggregation” mutant DeltaK280/PP could not aggregate because two beta-breaking prolines were inserted. In the pro-aggregation line expression of mutant tau clearly showed pathological changes, increased tau phosphorylation and aggregation in comparison with the transgenic mouse line that was unable to aggregate [15]. The authors suggested that it was the aggregation of tau that induced the pathology, nevertheless phosphorylation levels in the pro-aggregation line were higher than in the anti-aggregation line tau expression, leaving open the possibility that tau conformation can alter its ability to be phosphorylated and that phospho-tau is the toxic entity.

The abnormal hyperphosphorylation of tau makes it resistant to proteolysis by the calcium activated neutral protease [39,40] and most likely it is because of this reason that the levels of tau are several-fold increased in AD [24,25]. Some increase in tau level in AD brain can also result from the activation of p70 S6 kinase which upregulates the translation of tau [9,33]. It is likely that to neutralize the ability of AD P-tau to sequester normal MAPs and cause

disassembly of microtubules, the affected neurons promote the self-assembly of the abnormal tau into tangles of PHF. The fact that the tangle-bearing neurons seem to survive many years [32] and that in AD brain the decrease in microtubule density was unrelated to PHFs accumulation [14] is consistent with such a self-defense role of the formation of tangles. Employing an inducible transgenic mouse model that expressed human four-repeat tau with the P301L mutation, SantaCruz and colleagues [35] found that the cognitive deficiencies correlate with the appearance of soluble hyperphosphorylated tau. In this model when tau expression was turned off, there was no clearance of the polymerized tau, soluble tau decreased, and there was improvement in cognition suggesting that the polymerized tau was not sufficient to cause cognitive decline or neuronal cell death. Andorfer et al. [10] showed that in human tau transgenic mice, while there was widespread neurodegeneration, the PHF-containing neurons, however, appeared “healthy” in terms of nuclear morphology, suggesting that the polymerized protein was probably neuroprotective [10].

The AD P-tau readily self-assembles into tangles of PHF/SF *in vitro* under physiological conditions of protein concentration, pH, ionic strength and reducing conditions [6]. Furthermore, dephosphorylation inhibits the self assembly of AD P-tau into PHF/SF, and the *in vitro* abnormal hyperphosphorylation of each of the six recombinant human brain tau isoforms promotes their assembly into tangles of PHF/SF. Thus, all these studies taken together demonstrate the pivotal involvement of abnormal hyperphosphorylation in neurofibrillary degeneration and the disruptive properties to the microtubule network of the cytosolic abnormal hyperphosphorylated tau, whereas AD P-tau polymer remains inert (Fig. 1).

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Fig. 1.

Molecular mechanism of neurofibrillary degeneration. Normal tau interacts with tubulin and stimulates its assembly and stabilizes microtubules. In AD brain, because of an imbalance in tau kinase and phosphatase activities and a change in its conformation induced by other post-translational changes or mutations as in inherited cases of FTDP-17, tau becomes abnormally hyperphosphorylated. The abnormally hyperphosphorylated tau resulting from any one of the above causes behaves as an inhibitory/toxic protein; it not only is unable to stimulate microtubule assembly and bind to microtubules, but also sequesters normal tau, MAP1A / MAP1B and MAP2, and leads to inhibition of assembly and disruption of microtubules. The breakdown of the microtubule network in the affected neurons compromises axonal transport, leading to retrograde degeneration which, in turn, results in dementia. The association between the AD P-tau and normal tau in the presence of glycosylation results in the formation of neurofibrillary tangles. The tangles are ubiquitinated for degradation by the non-lysosomal ubiquitin pathway, but apparently this degradation, if any, is minimal. Unlike the non-

polymerized abnormally hyperphosphorylated tau, the neurofibrillary tangles are inert but, with disease progression, these lesions grow in size and eventually might physically choke the affected cells to death.