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Review

Tau pathology in Alzheimer disease and other tauopathies

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Abstract

Just as neuronal activity is essential to normal brain function, microtubule-associated protein tau appears to be critical to normal neuronal activity in the mammalian brain, especially in the evolutionary most advanced species, the homo sapiens. While the loss of functional tau can be compensated by the other two neuronal microtubule-associated proteins, MAP1A/MAP1B and MAP2, it is the dysfunctional, i.e., the toxic tau, which forces an affected neuron in a long and losing battle resulting in a slow but progressive retrograde neurodegeneration. It is this pathology which is characteristic of Alzheimer disease (AD) and other tauopathies. To date, the most established and the most compelling cause of dysfunctional tau in AD and other tauopathies is the abnormal hyperphosphorylation of tau. The abnormal hyperphosphorylation not only results in the loss of tau function of promoting assembly and stabilizing microtubules but also in a gain of a toxic function whereby the pathological tau sequesters normal tau, MAP1A/MAP1B and MAP2, and causes inhibition and disruption of microtubules. This toxic gain of function of the pathological tau appears to be solely due to its abnormal hyperphosphorylation because dephosphorylation converts it functionally into a normal-like state. The affected neurons battle the toxic tau both by continually synthesizing new normal tau and as well as by packaging the abnormally hyperphosphorylated tau into inert polymers, i.e., neurofibrillary tangles of paired helical filaments, twisted ribbons and straight filaments. Slowly but progressively, the affected neurons undergo a retrograde degeneration. The hyperphosphorylation of tau results both from an imbalance between the activities of tau kinases and tau phosphatases and as well as changes in tau's conformation which affect its interaction with these enzymes. A decrease in the activity of protein phosphatase-2A (PP-2A) in AD brain and certain missense mutations seen in frontotemporal dementia promotes the abnormal hyperphosphorylation of tau. Inhibition of this tau abnormality is one of the most promising therapeutic approaches to AD and other tauopathies.

Keywords: Neurofibrillary degeneration; Microtubule-associated protein tau; Microtubule; Microtubule-associated protein 2; Neurofilament; Memantine; Abnormal hyperphosphorylation of tau; Protein phosphatase-2A

1. Introduction

Microtubule-associated protein (MAP) tau, MAP1 (A/B) and MAP2 are the major microtubule-associated proteins of a normal mature neuron. These three MAPs apparently perform similar functions, i.e., the promotion of assembly and stability of microtubules. This excessive redundancy in biology, i.e., having three different proteins to maintain the microtubule network in a neuron, is probably due to the essential requirement of microtubules for axoplasmic flow, which, in turn, is critical to neuronal activity. Thus, a neuron has a capacity to compensate the loss of function of one MAP with the other two MAPs. Both tau and MAP2 knockout transgenic mice show apparent normal development into adult life [1,2], whereas tau and MAP2 and as well as MAP2 and MAP1B double knockout transgenic mice show defects in axonal elongation and neuronal migration [2,3].

The biological activity of tau, primarily a neuronal protein, in promoting assembly and stability of microtubules is regulated by its degree of phosphorylation. Normal tau

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contains 2–3 mol phosphate/mol of the protein [4], the level of phosphorylation for its optimal activity. Hyperphosphorylation of tau depresses its microtubule assembly activity and its binding to microtubules [5,6].

Human brain tau is a family of six proteins derived from a single gene by alternative mRNA splicing [7,8]. These proteins differ in whether they contain three (τ3L, τ3S or τ3) or four (τ4L, τ4S or τ4) tubulin binding domains (repeats, R) of 31 or 32 amino acids each near the C-terminal and two (τ3L, τ4L), one (τ3S, τ4S), or no (τ3, τ4) inserts of 29 amino acids each in the N-terminal portion of the molecule; the two amino-terminal inserts, 1 and 2, are coded by exon 2 and exon 3, respectively.

In Alzheimer disease (AD) and related disorders called tauopathies, tau is abnormally hyperphosphorylated and is accumulated as intraneuronal tangles of paired helical filaments (PHF), twisted ribbons and or straight filaments [9–13]. This hallmark brain lesion of these diseases directly correlates with dementia in these patients [14–16]. The etiology and the pathogenesis of neurofibrillary degeneration and therapeutic strategies to inhibit this lesion have been the subject of several recent reviews (see Refs. [17–19]). In this article, the pathobiology of tau and the molecular mechanism by which the abnormal hyperphosphorylation of this protein might lead to AD and other tauopathies and the role of various protein kinases and phosphatases and modifications of tau are updated.

2. Tau pathology

2.1. Abnormal hyperphosphorylation of tau

Tau in AD brain is abnormally hyperphosphorylated and in this state is the major protein subunit of PHF/SF which forms neurofibrillary tangles, a hallmark lesion of this disease [9–13]. Tau pathology, which is seen only as accumulation of abnormally hyperphosphorylated protein, is also seen in several other human neurodegenerative disorders (see Table 1). In everyone of these disorders, called tauopathies, the accumulation of the abnormally hyperphosphorylated tau is associated with neurofibrillary degeneration and dementia. The discovery of mutations in tau gene and their cosegregation with the disease in the inherited frontotemporal dementia with Parkinsonism linked to chromosome-17 (FTDP-17) has established that abnormalities in tau protein as a primary event can lead to neurodegeneration and dementia [20–22].

Table 1
Tauopathies characterized by abnormal hyperphosphorylation of tau

• Alzheimer disease, including tangle-only form of the disease
• Down syndrome, adult cases
• Guam parkinsonism dementia complex
• Dementia pugilistica
• Pick disease
• Dementia with argyrophilic grains
• Fronto-temporal dementia
• Cortico-basal degeneration
• Pallido-ponto-nigral degeneration
• Progressive supranuclear palsy
• Gerstmann–Sträussler–Scheinker disease with tangles

Taus from brain biopsies obtained from tissue adjoining the epilepsy focus from young adults and from fetal brains are phosphorylated at some of the same sites as those known to occur in PHF-tau [23,24]. However, only a few of the sites seen in PHF-tau are phosphorylated in the fetal or adult brains and the level of phosphorylation at the sites phosphorylated is less than 5% of that in AD tau [25].

The abnormal hyperphosphorylation of tau appears to precede its accumulation in the affected neurons in AD. The abnormally hyperphosphorylated tau was discovered not only in neurofibrillary tangles [10] but also in cytosol from AD brains [11]. Quantitative immunocytochemical studies with mAb Tau-1 have revealed deposits of only abnormally phosphorylated tau, but not normal tau, in neurons without tangles (stage "0" tangles) both in Alzheimer and in normal aged hippocampi [26,27]. Tau in tangles, mostly ghost tangles, is known to be ubiquitinated [28–30], whereas the abnormally hyperphosphorylated tau isolated from AD brain cytosol was found to have no ubiquitin reactivity. All these studies suggest that the abnormal hyperphosphorylation of tau precedes its accumulation into neurofibrillary tangles [4]. Employing monoclonal antibodies to mitotic phosphoepitopes, Vincent et al. [31] also showed that phosphorylation of tau precedes the presence of PHF in AD brain.

One of the possibilities is that the abnormal hyperphosphorylation of tau might be due to a conformational change(s) in tau in the diseased brain, which might make it a better substrate for phosphorylation and or a worse substrate for dephosphorylation. Davies and his colleagues have developed a series of monoclonal antibodies to conformational alterations of tau and employing these antibodies, have shown that tau is conformationally altered in AD [32–34] and in transgenic mice overexpressing human tau [35]. While in inherited cases of FTDP-17, where the disease is caused by certain missense mutations in tau and these mutations make tau a more favorable substrate for hyperphosphorylation by brain protein kinases [36], such a scenario is less likely in AD because tau is not the only neuronal protein which is hyperphosphorylated in AD as a result of the protein phosphorylation/dephosphorylation imbalance. Biochemically, tubulin and neurofilaments [37,38] and immunocytochemically neurofilaments and MAP1B [39–41] have been found to be hyperphosphorylated in AD brain. Furthermore, both the cytosolic- and PHF-abnormally hyperphosphorylated taus are readily dephosphorylated by phosphatases in vitro [10,12,42–45].

The neurofibrillary degeneration of the Alzheimer type is seen only sparsely in aged animals and in experimentally induced conditions. None of the mutations in β-amyloid precursor protein (β-APP), presenilin-1 or presenilin-2,