Opinion

Mechanism of neurodegeneration through tau and therapy for Alzheimer’s disease

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1. Introduction

In Alzheimer’s disease (AD), β-amyloid deposition and neurofibrillary tangles (NFTs), composed of hyperphosphorylated tau fibrils, are considered to be major pathologic features. Evidence from the genetic studies of familial AD has given rise to the β-amyloid hypothesis in which β-amyloid is proposed as the cause of AD; thus, the reduction of β-amyloid has been viewed as a potential therapeutic target for AD. However, most studies targeting β-amyloid have failed in phase III clinical trial, as discussed extensively elsewhere. A major explanation for such failures may be that such therapies have been tested in patients with early- to mid-stage AD, when disease progression is already relatively advanced. In fact, when first AD symptoms are reported or detected, it seems that damage is irreversible and not amenable to slowing down or blockade. Accordingly, researchers are attempting to identify very early stages of disease, that may be therapeutically targetable; that is, they are now seeking an early window of therapeutic opportunity. Even so, this approach depends on differentiating between the trigger and the bullet in AD and their relationship to β-amyloid. At the same time, researchers are becoming aware that an alternative target for halting clinical progression, even in early to moderate AD, may be necessary.

2. Tau executes neuronal loss and brain dysfunction in AD

NFTs are the other pathologic hallmark of AD. Although β-amyloid deposition is seen only in AD, NFTs are associated with several neurodegenerative diseases, the so-called tauopathies. Because all tauopathies are accompanied by NFTs and neuronal dysfunction, NFTs are considered to be a common pathologic marker for a range of neurologic disorders. In these diseases, the rate of neuronal loss exceeds the occurrence of NFTs, suggesting that NFT formation and neuronal death share a common underlying mechanism. This hypothesis is strongly supported by the discovery of a tau gene mutation in patients with frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). The FTDP-17-associated tau gene mutation is the causal factor in FTDP-17, a dementing disease characterized by NFT formation and neuron loss. Analyses of mutated tau in FTDP-17 conclusively demonstrated that tau dysfunction or abnormality alone induces the neurodegeneration characterized by NFTs and neuronal death that ultimately leads to clinical dementia.

3. Neuronal loss occurs in a process of tau fibril formation

Mice that overexpress P301L mutant tau under the regulation of a tetracycline-inducible promoter display age-related NFTs, neuronal death, and behavioral deficits. Although inhibition of mutant tau in these mice blocks neuronal death and improves memory, NFTs continue to form. This suggests that NFTs are not themselves toxic, but rather that the mechanism of NFT formation is shared by the process underlying neuronal death and neuronal dysfunction. To understand a process of NFT formation that links with neuronal death, we first need to know how monomeric tau forms fibrillar tau. To track structural changes in tau in solution, and to understand the relationship between different tau aggregates, Maeda and colleagues investigated how tau assembly in vitro changes over time by measuring thioflavin T fluorescence using atomic force microscopy (AFM). As thioflavin T fluorescence increases, 2 forms of tau aggregates can be observed with AFM: a granular tau oligomer and a fibrillar tau aggregate. Before forming fibrillar aggregates, tau forms 2 different types of tau aggregate: oligomeric tau (sarkosyl-soluble, not detectable by AFM) and granular oligomeric tau (sarkosyl-insoluble, detectable under AFM). If NFTs represent tombstones of neurodegeneration, these 2 kinds of intermediate tau oligomer may play a role in synapse loss, neuron loss, and, ultimately, the neurodegeneration typically seen in tauopathies (Fig. 1).

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4. Tau aggregation inhibitor ameliorates neuronal loss in P301L tau mouse model

Analysis of our P301L tau transgenic mouse model revealed that neuronal loss and insoluble tau formation were detected without formation of pathologically relevant NFTs. Because P301L tau mice do not form tau fibrils but still exhibit neuronal loss, we suggest that toxicity of tau aggregates could be attributed to granular tau. For further testing of this notion, we aimed to reduce formation of granular tau oligomer by screening the chemical compound isoproterenol, which associates with tau to inhibit granular tau formation. Interestingly, oral administration of isoproterenol in our P301L tau mice resulted in reduced neuronal loss accompanied by inhibition of sarkosyl-insoluble tau level compared with vehicle control. Altogether, our studies offer novel insights about tau aggregation pathology, strongly suggesting that granular tau oligomer represents a toxic tau aggregate whereas isoproterenol seems to be a promising compound for blocking AD progression.

Competing interests

The author declares no competing financial interests.

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