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Review

Tau alteration and neuronal degeneration in tauopathies: mechanisms and models

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Abstract

Tau becomes characteristically altered both functionally and structurally in several neurodegenerative diseases now collectively called tauopathies. Although increasing evidence supports that alterations of tau may directly cause neuronal degeneration and cell death, the mechanisms, which render tau to become a toxic agent are still unclear. In addition, it is obscure, whether neurodegeneration in tauopathies occurs via a common mechanism or specific differences exist. The aim of this review is to provide an overview about the different experimental models that currently exist, how they are used to determine the role of tau during degeneration and what has been learnt from them concerning the mechanistic role of tau in the disease process.

The review begins with a discussion about similarities and differences in tau alteration in paradigmatic tauopathies such as frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) and Alzheimer's disease (AD).

The second part concentrates on major experimental models that have been used to address the mechanistic role of tau during degeneration. This will include a discussion of cell-free assays, culture models using cell lines or dissociated neurons, and animal models. How these models aid to understand (i) alterations in the function of tau as a microtubule-associated protein (MAP), (ii) direct cytotoxicity of altered tau protein, and (iii) the potential role of tau aggregation in neurodegenerative processes will be the central theme of this part.

The review ends with concluding remarks about a general mechanistic model of the role of tau alteration and neuronal degeneration in tauopathies and future perspectives.

Keywords: Alzheimer's disease; Tau; Microtubule-associated protein; Neurofibrillary tangle; Paired helical filament; Neurodegeneration; Cytoskeleton; Tauopathy

Tau proteins are microtubule-associated proteins (MAPs) that are abundant in the central nervous system (CNS), where they are expressed predominantly in axons [1]. Human tau proteins are encoded by a single gene on chromosome 17q21 that consists of 16 exons, and the CNS isoforms are generated by alternative splicing involving 11 of these exons [2,3]. In adult human brain, alternative mRNA splicing of exons 2, 3, and 10 generates six tau isoforms ranging from 352 to 441 amino acids in length (Fig. 1). The interaction between tau and microtubules are mediated by three or four C-terminal imperfect repeat domains (R1–R4, 31–32 amino acids each) encoded by exons 9–12 [3–5]. 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 (Fig. 1). These three- or four-repeat domain contains imperfect 18-amino acid repeats separated by 13- or 14-amino acid-long inter-repeat sequences [6]. In addition, alternative splicing of exons 2 and 3 results in 3R and 4R

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid β-protein; 3R, three-repeat tau; E, exon; 4R, four-repeat tau; FTDP-17, frontotemporal dementia and parkinsonism linked to chromosome 17; IR, inter-repeat; GSK-3β, glycogen synthase kinase-3β; MT, microtubule; MAP, microtubule-associated protein; NFTs, neurofibrillary tangles; NFL, neurofibrillary lesions; ND, not determined; PP2A, protein phosphatase 2A; PHF, paired helical filament; R, repeat; SF, straight filament; SP, senile plaques

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isoforms without (0N) or with either 29 (1N) or 58 (2N) amino acid inserts of unknown function. In adult human brain, the ratio of 3R tau to 4R tau isoforms is about one and the 1N, 0N, and 2N tau isoforms comprise about 54%, 37%, and 9%, respectively, of total tau [7]. 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 [8]. In the peripheral nervous system, inclusion of exon 4a in the amino-terminal half results in the expression of higher molecular weight proteins termed big tau [9–11]. Since its discovery more than 25 years ago, a number of well-defined functions of tau protein have been discovered and extensively characterized (for review, see Ref. [12]).

1. Tau in Alzheimer's disease and frontotemporal dementia and parkinsonism linked to chromosome 17

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 material: (i) extracellular amyloid protein in the shape of senile plaques (SP), and (ii) intracellular neurofibrillary lesions (NFL) made of abnormally and hyperphosphorylated tau protein. There are three main types of NFL according to their localizations in nerve cells: (i) neurofibrillary tangles (NFTs) in the cell body and apical dendrites of neurons, (ii) neuropil threads in distal dendrites, and (iii) abnormal (dystrophic) neuritis associated with some SPs (neuritic plaques) [13].

Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) refers to a group of autosomal-dominantly inherited neurodegenerative diseases characterized by early behavioral changes later followed by cognitive and motor disturbances (reviewed in Ref. [14]). FTDP-17 patients usually display predominant frontotemporal atrophy with neuronal loss, gliosis and cortical spongiform changes in layer 2. Neuropathologically, they all show the presence of abundant filamentous tau pathology in nerve cells, and for some in glial cells (reviewed in Refs. [15,16]). In 1998, the identification of exonic and intronic tau gene mutations associated with FTDP-17 established that tau dysfunction could cause neurodegeneration [17–19]. Recently a S352L tau gene mutation was described in a patient with a novel recessive tauopathy [20]. These findings and subsequent reports have so far identified 32 tau mutations in more than 80 families with FTDP-17.

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 (Fig. 2a). 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, S320F), exon 12 (V337M, E342V, S352L and K369I) and exon 13 (G389R and R406W) affect all six tau isoforms. By contrast, mutations in exon 10 (N279K, ΔK280, L284L, N296N ΔN296, 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 the regulation of exon 10 splicing and thus the ratio of 4R/3R tau protein.

Although the etiology, clinical symptoms, pathologic findings and the biochemical composition of tau inclusions

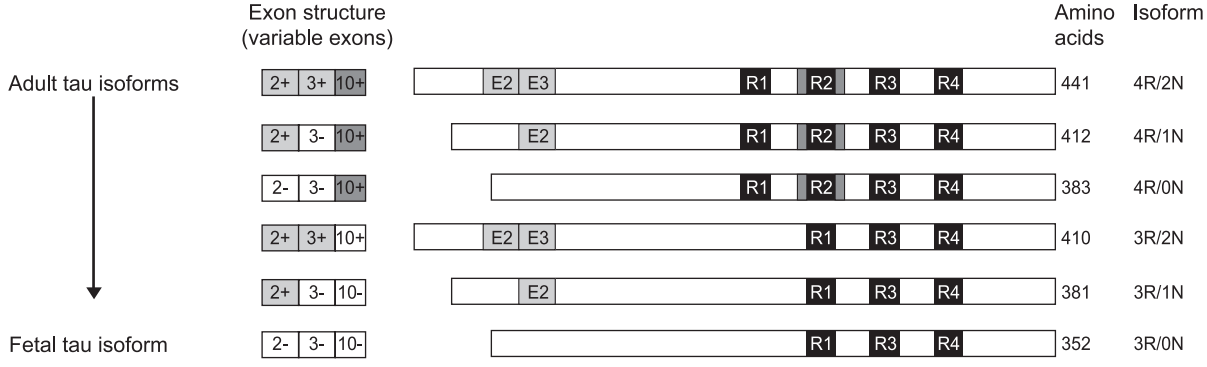

Fig. 1. Schematic representation of the six human CNS tau isoforms. These isoforms differ by the absence or presence of one or two 29-amino acid inserts encoded by exons 2 and 3 (E2, E3, light grey boxes) in the amino-terminal part, in combination with either three (R1, R3 and R4) or four (R1–R4) repeat regions (black boxes) in the carboxy-terminal part. The fourth microtubule-binding domain is encoded by exon 10 (E10, dark grey box). The adult tau isoforms include the longest 441-amino acids component (2+3+10+), the 412-amino acids component (2+3−10+), the 383-amino acids component (2−3−10+) the 410-amino acids component (2+3+10−), and the 381-amino acids component (2+3−10−). The shortest 352-amino acid isoform (2−3−10−) is found only in the fetal brain, and thus is referred as fetal tau isoform.