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Review Article

The ordered assembly of tau is the gain-of-toxic function that causes human tauopathies

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Q3 **Abstract** A pathological pathway leading from soluble to insoluble and filamentous Tau underlies human tauopathies. This ordered assembly causes disease and is the gain-of-toxic function. It involves the transition from an intrinsically disordered monomer to a highly structured filament. Based on recent findings, one can divide the ordered assembly into propagation of pathology and neurodegeneration. Short tau fibrils constitute the major species of seed-competent tau in the brains of mice transgenic for human P301S tau. The molecular species of aggregated tau that are essential for neurodegeneration remain to be identified.

Q4 *Keywords:* ■■■

1. Tau isoforms and their physiological functions

Tau is expressed predominantly in the central and peripheral nervous systems, where it is most abundant in the axons of nerve cells. It can be divided into four regions: an N-terminal projection domain, a proline-rich region, a repeat region, and a carboxy-terminal domain [1,2].

Six tau isoforms ranging from 352 to 441 amino acids are expressed in adult human brain. They are produced by alternative mRNA splicing of *MAPT*, the tau gene on chromosome 17q21.31 and differ from each other by the presence or absence of inserts of 29 or 58 amino acids in the amino-terminal half and the inclusion or not of the 31 amino acid repeat encoded by exon 10 of *MAPT* in the carboxy-terminal half of the protein (Fig. 1A) [3,4]. The inclusion of exon 10 results in the production of three isoforms with four repeats each (4R) and its exclusion in a further three isoforms with three repeats each (3R). The repeats (residues 252–376, in the numbering of the 441 amino acid isoform) and some adjoining sequences constitute the microtubule-binding domains. Tau is subject to post-translational modifications, including phosphorylation, acetylation, methylation, glycation, isomerization, O-GlcNAcylation, nitration, sumoylation, ubiquitination, and truncation [1]. The peripheral nervous system also expresses big tau, which carries a large alternatively spliced exon in the amino-terminal half [5,6].

Monomeric tau is natively unfolded and lacks defined secondary and tertiary structures. However, the absence of local order does not preclude the existence of global order in the form of long-range contacts. Single-molecule FRET confirmed the existence of long-range contacts between N-termini and C-termini, as well as between them and the repeats, giving rise to an S-shaped fold [7].

Relatively, little is known about the molecular mechanisms by which tau interacts with microtubules. When they were assembled using tubulin and tau in the presence of trimethylamine N-oxide and in the absence of paclitaxel, Tau repeats bound to a region on the inner surface of the microtubule that overlapped with the paclitaxel-binding site on β-tubulin [8]. Experiments in which tau was bound to preassembled, paclitaxel-stabilized microtubules gave rise to a different model in which tau was attached to the outer surface of the microtubule, where it localized to the ridges of protofilaments [9]. In more recent work, using a combination of NMR and mass spectrometry, tau was found to bind to a hydrophobic region between tubulin heterodimers, which overlapped with the binding pocket of vinblastine [10]. Cross-linking identified links between

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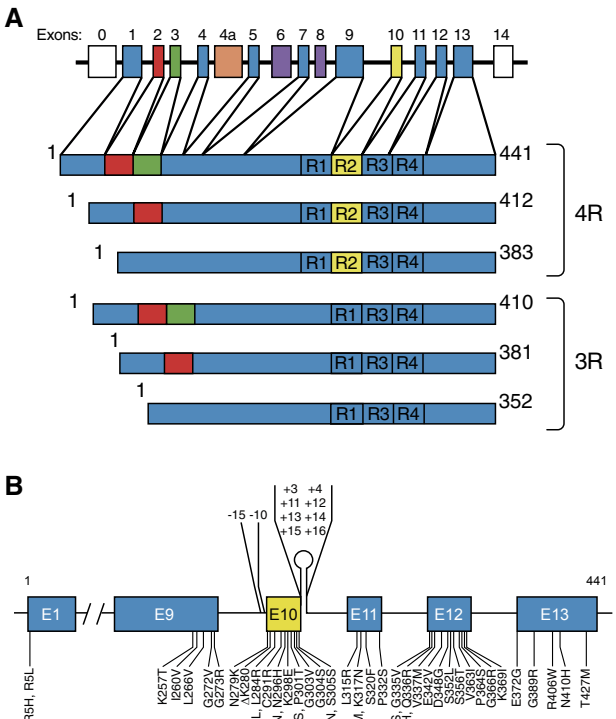

Fig. 1. Human brain tau isoforms and *MAPT* mutations. (A) *MAPT* and the six Tau isoforms expressed in adult human brain. *MAPT* consists of 16 exons (E). Alternative mRNA splicing of E2 (red), E3 (green), and E10 (yellow) gives rise to six tau isoforms (amino acids, 352–441). Constitutively spliced exons (E1, E4, E5, E7, E9, E11, E12, and E13) are shown in blue. E0, which is part of the promoter, and E14 are noncoding (white). E6 and E8 (violet) are not transcribed in human brain. E4a (orange) is only expressed in the peripheral nervous system. The repeats (R1–R4) are shown, with three isoforms having four repeats each (4R) and three isoforms having three repeats each (3R). Each repeat is 31 or 32 amino acids in length. Exons and introns are not drawn to scale. (B), Mutations in *MAPT* in cases of frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17T); 47 coding region mutations and 10 intronic mutations flanking E10 are shown.

residues K225, K240, K257, K311, and K383 in tau and the side chains of K336 and K338 in α-tubulin. Cross-links to β-tubulin were not detected.

Equal amounts of 3R and 4R Tau are found in the cerebral cortex of healthy adults [11]. The expression of Tau is roughly two times higher in gray matter of the neocortex than in white matter and cerebellum. Alternative mRNA splicing of *MAPT* is similar between brain regions. In developing human brain, only the shortest Tau isoform is found. Although Tau is expressed in many forms in vertebrates, the isoform ratios are not conserved. 3R, 4R, and 5R Tau isoforms are found in the brains of adult chickens [12], whereas most adult rodents only express 4R Tau isoforms. What appears to be conserved [13] is the expression of a single hyperphosphorylated 3R Tau isoform lacking N-terminal inserts during vertebrate development. Repeats similar to those in Tau are present in the high-molecular weight proteins MAP2 and MAP4 [14,15]. The genomes of *Caenorhabditis elegans* and *Drosophila melanogaster* each encode one protein with Tau-like repeats [16,17].

Heterozygous microdeletions of chromosome 17q21.31 give rise to a multisystem disorder (Koolen-de Vries syndrome), which is characterized by intellectual disability, hypotonia, and distinctive facial features [18–20]. Besides *MAPT*, three protein-coding genes (*CRHR1*, *SPPL2C*, and *KANSL1*) and two putative genes (*MGC57346* and *CRHR1-IT1*) are found in this region. The 17q21.31 microdeletion syndrome is caused by haploinsufficiency of *KANSL1*, which encodes a chromatin modifier, the KAT8-regulatory NSL complex 1, that influences gene expression through acetylation of lysine 16 of histone H4 [21–23]. A 50% reduction in tau levels does not appear to have a detrimental effect on the development of the human brain.

Four different *MAPT* knockout lines have been generated [24–27]. Mice from one line developed muscle weakness, motor deficits, hyperactivity, and learning difficulties. Mice from a second line [25] accumulated iron in the substantia nigra and had dopaminergic nerve cell loss, levodopa-responsive parkinsonism, and cognitive deficits [28]. However, this phenotype was not reported in a separate study [29]. Endogenous Tau may play a role in neuronal hyperexcitability. Thus, reducing Tau levels in adult mice protects against epileptiform activity [30]. Moreover, a reduction in endogenous Tau ameliorated synaptic deficits in mouse models of Aβ amyloidosis [31]. Tau may also have a physiological role in synaptic plasticity. Thus, at the CA1 synapse, Tau knockout mice displayed a deficit in long-term depression but not long-term potentiation [32]. By contrast, it has been reported that tau knockout mice exhibit a defect in long-term potentiation but not long-term depression [33]. Although the bulk of Tau protein is present in nerve cell axons, a microtubule-independent physiological function in dendritic spines has been postulated [34]. Tau binds to the SH3 domain of the nonreceptor kinase Fyn and transports it to dendritic spines, where Fyn phosphorylates NMDA-receptor subunit 2 at tyrosine 1472, thus stabilizing its interaction with the postsynaptic protein PSD95 and strengthening glutamate signaling.

2. Tau aggregation

Full-length tau assembles into filaments through its repeats, with the amino-terminal half and the carboxy-terminus forming the fuzzy coat of the filament [35–37]. Tau filaments from human brain have a cross-β structure characteristic of amyloid fibrils and their core consists of approximately 100 amino acids [38]. It thus appears that tau binding to microtubules and filament assembly are mutually exclusive (Fig. 2). In view of some of the findings described in the previous section, it appears unlikely that microtubules will disassemble in the absence of bound tau. Phosphorylation negatively regulates the ability of tau to interact with microtubules and filamentous tau is invariably abnormally