Review

Biological Psychiatry

Prion-like Spreading in Tauopathies

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ABSTRACT

Tau is a microtubule-associated protein that functions in regulating cytoskeleton dynamics, especially in neurons. Misfolded and aggregated forms of tau produce pathological structures in a number of neurodegenerative diseases, including Alzheimer's disease (AD) and tauopathy dementias. These disorders can present with a sporadic etiology, such as in AD, or a familial etiology, such as in some cases of frontotemporal dementia with parkinsonism. Notably, the pathological features of tau pathology in these diseases can be very distinct. For example, the tau pathology in corticobasal degeneration is distinct from that of an AD patient. A wealth of evidence has emerged within the last decade to suggest that the misfolded tau in tauopathies possesses prion-like features and that such features may explain the diverse characteristics of tauopathies. The prion-like concept for tauopathies arose initially from the observation that the progressive accumulation of tau pathology as the symptoms of AD progress seemed to follow anatomically linked pathways. Subsequent studies in cell and animal models revealed that misfolded tau can propagate from cell to cell and from region to region in the brain through direct neuroanatomical connections. Studies in these cell and mouse models have demonstrated that experimentally propagated forms of misfolded tau can exist as conformationally distinct "strains" with unique biochemical, morphological, and neuropathological characteristics. This review discusses the clinical, pathological, and genetic diversity of tauopathies and the discoveries underlying the emerging view that the unique features of clinically distinct tauopathies may be a reflection of the strain of misfolded tau that propagates in each disease.

Keywords: Alzheimer's disease, Animal models, Prion, Strains, Tau, Transmission

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Tauopathies are a spectrum of neurodegenerative diseases characterized by the brain accumulation of cellular proteinaceous inclusions predominantly comprising tau protein (1–3). The most common of these disorders is Alzheimer's disease (AD), in which tau predominantly aggregates and accumulates in neurons as somatodendritic neurofibrillary tangles and neuropil threads as well as in dystrophic neurites associated with extracellular deposits of amyloid-β peptides (Figure 1) (1–3). These tau aggregates (4–7) comprise structurally variable 8- to 20-nm twisted double-helical ribbons, referred to as paired helical filaments (8,9), and less abundant 15-nm-wide straight filaments (10,11). Population-based autopsy studies have suggested that tau pathological inclusions appear to spread in a predictable pattern that has been characterized by six Braak stages (I–VI) (12,13). More recent data indicate that aberrant changes in tau (i.e., phosphorylation at specific epitopes) can occur in the locus ceruleus in a significant percent of young adults in their 20s, and much earlier than the appearance of brain amyloid-β deposition (14). This early presentation of abnormal tau is reminiscent of the recently recognized occurrence of tau inclusions in the brains of cognitively normal individuals known as primary-aged tauopathy (15); however, it remains to be established if these accumulations of tau represent an early stage of AD or unrelated biological occurrences (16–18).

Tauopathies also include many other types of dementias, such as corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), tangle-only dementia, and Pick's disease, that occur without a necessity for amyloid-β deposition (3). In some of these diseases, the type and distribution of tau pathological inclusion can be a defining feature. In CBD, tau inclusions are observed in the form of neuronal cytoplasmic inclusions and neuropil threads as well as astrocytic plaques and oligodendrocytic coiled bodies (19–21). Tau pathology in PSP includes neuropil threads and classical flame-shaped neurofibrillary tangles or globose neurofibrillary tangles, but these structures are most prevalent in the basal ganglia, subthalamus, and brainstem, whereas in AD they are most abundant in the hippocampus and neocortex (19,20). Furthermore, tau inclusions in PSP are prominent in glial cells as tufted astrocytes, thorn-shaped astrocytes, and oligodendroglial coiled bodies (19–21). Collectively, these observations illustrate the diversity in tau pathology that occurs in human diseases.

TAU GENE, PROTEIN, AND FUNCTION

Tau refers to microtubule (MT)–associated proteins (22,23) expressed from the *MAPT* gene located on chromosome 17q21-22 (24,25). In human adult brain, six major tau isoforms ranging between 352 and 441 amino acids in length are produced as a result of alternative RNA splicing of exons 2, 3, and 10 (Figure 2) (26,27). The incorporation or exclusion of exon 2,

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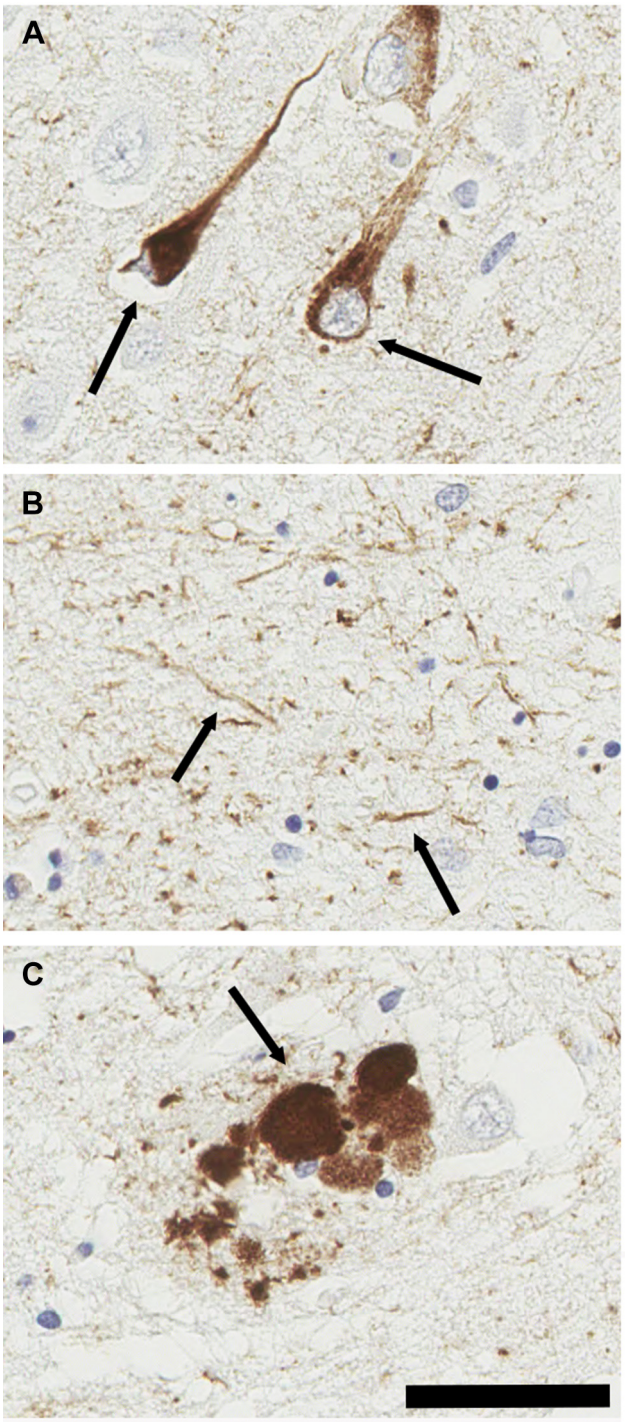

Figure 1. Representative images of **(A)** neurofibrillary tangles, **(B)** neuropil threads, and **(C)** dystrophic neurites within a senile plaque, as indicated by arrows, in the hippocampus of patients with Alzheimer's disease stained with anti-phospho tau antibody AT8. Scale bar = 50 μM.

or exons 2 and 3 (exon 3 is only ever included in tandem with exon 2), yields protein variants with 0 (0N), 29 (1N), or 58 (2N) amino acid inserts in the amino-terminal region. Similarly, exon 10 can be alternatively spliced to yield products containing either three (3R) or four (4R) tandem MT binding repeats of 31 or 32 amino acids. In the normal adult human brain, 3R and 4R tau isoforms are present at approximately equal amounts while 2N tau isoforms are significantly less abundant relative to the 0N or 1N isoforms (28,29). In the central nervous system, tau is preferentially found in neurons (30,31), but it can also be detected at lower levels in oligodendrocytes and astrocytes (31–33). Precisely how the diversity in tau isoforms and patterns of expression combine to produce the many clinical and pathological manifestations of tauopathy is an area of intense interest.

Although multiple functions have been attributed to tau (1), its function in binding and promoting MT assembly, nucleation, and bundling has been the most extensively studied (22,34–39). Consistent with its interaction with MTs, it can influence the function of other MT-interacting proteins such as dynein and kinesin to regulate trafficking of organelles and axonal cargo transport (40–42). Surprisingly, at least in mice, tau is not essential for MT function, as genetically engineered null mice are viable and do not present with an overt phenotype (43). The loss of tau in this model may be compensated or shadowed by the increased expression of other MT-binding proteins such as microtubule associated protein 1A (43,44).

Tau interacts with MT via the carboxyl-terminal region containing the three or four MT-binding repeats (3R, 4R) (45–47). Each individual repeat can bind to MTs, although with lower affinities than when combined in the full-length protein, as each repeat contributes to the overall MT affinity (48,49). Furthermore, MT binding is more complex than a simple linear array of binding sites (35,38,49), as tau also has a proline-rich region upstream of the repeat region that strongly influences MT binding and assembly (35,50). Nevertheless, 4R tau has a greater MT polymerization and binding capacity than 3R tau does (28,46). While the amino-terminal inserts do not significantly contribute to the MT binding affinity of tau, they can influence bundling (46). It is also well established that tau phosphorylation can reduce its ability to bind and modulate MT assembly (34,37,51–53). The prevailing view in the field is that the loss of MT binding by tau may contribute to the formation of pathologic features in tauopathies.

TAU AMYLOID AGGREGATION

Recent experimental data (discussed in detailed below) suggest that tau aggregation could propagate throughout the nervous system by a prion-like transmission mechanism (54,55), but the biological changes involved in the initial aggregation events (i.e., seed formation), elongation, and regulation of tau aggregation remain highly debated. Native tau is highly soluble and "natively unfolded" (56,57), but it has a tendency to form a global hairpin fold (58) that is not permissive for aggregation. Purified human tau is largely refractory to aggregation, although under some conditions it can self-aggregate into amyloid fibrils (59). In vitro tau filament assembly can be greatly facilitated by the presence of long polyanionic molecules such as sulfated glycosaminoglycans, polyglutamate, and nucleic acids (60–62) that likely suppress local intra- or intermolecular positive charge repulsion. Tau fibril polymerization also can be facilitated in vitro by fatty acids, such as arachidonic acid (63,64). The aggregation of tau