Alzheimer disease (AD) is characterized by 2 kinds of abundant abnormal filamentous lesions, neuritic plaques and neurofibrillary tangles, seen in the brain post mortem. The chief component of plaques is β-amyloid, a 40–42-amino acid proteolytic fragment of the amyloid precursor protein (APP). Rare mutations in the APP gene give rise to familial AD, but the vast majority of AD cases are sporadic, that is, without a dominant genetic cause. Cognitively normal people can show a large β-amyloid load, so simple accumulation of β-amyloid in the brain is not sufficient to lead to dementia, although APP mutations lead to a cascade of neuropathology, including tangles and eventually AD. There is a much clearer correlation between the number of neurofibrillary tangles found post mortem and the degree of dementia observed in life, so it is important to understand the molecular pathology involved.

Tangles form in the majority of nerve cells that degenerate in the course of the disease, where they are found in cell bodies and abnormal neurites associated with amyloid plaques. So-called paired helical filaments (PHFs) form the bulk of the filamentous material in tangles, with straight filaments as a minor component. Because tangles fill up the cytoplasmic space, normal cellular proteins can become trapped, confounding cytological attempts to identify the proteins that form the PHFs. Efforts in the mid-1980s led to partial purification of tangle fragments, isolation of a peptide fragment from PHFs, and the raising of an antibody, which both labeled the peptide fragment of an antibody, which both labeled the peptide fragment.

The sequence of the protein fragment was used to isolate cDNA clones which, by homology with the then-recently-sequenced mouse protein, proved to code for human microtubule-associated protein τ (2). This established unequivocally that τ formed an integral component of the PHFs.

Tau protein contains a tandem repeat of 31 or 32 amino acids in the C-terminal half, characterized by a PGGG motif. The repeat region was shown to have a microtubule binding function, and τ promotes assembly of tubulin and stabilizes microtubules. Subsequent cloning (3) showed that there were 2 kinds of τ, containing respectively 3 or 4 repeats (3R or 4R), produced from the τ gene by alternative mRNA splicing. The featured article discussed here extended this work to show that alternative splicing produces 6 isoforms of τ in adult human brain that differ by having 0, 1, or 2 inserts in the N-terminal half of the protein, combined with 3 or 4 repeats (thus 0N3R, 1N3R, 2N3R, 0N4R, 1N4R, and 2N4R), with sizes varying from 352 to 441 amino acids. There is also a much larger isoform found in the peripheral nervous system. Development of a sarcosyl extraction protocol gave a more tractable soluble preparation of PHFs, from which it was shown that PHFs comprise all 6 isoforms of τ in a hyperphosphorylated state (4).

In 1998, several groups showed that mutations in MAPT (microtubule-associated protein tau), the τ gene, gave rise to dominantly inherited dementing tauopathies, in which τ protein aggregates form in the brain in the absence of β-amyloid. Sporadic tauopathies also occur. Many τ mutations have now been found, some affecting coding and others affecting splicing, with the balance between 3R and 4R forms upset by the latter. Different classes of mutations give rise to clinically distinguishable diseases with pathologically characteristic τ deposits, which are associated with τ filaments having different structures. In some sporadic tauopathies, 3R isoforms predominate in the inclusions, whereas in others, 4R isoforms are found.

More recently, it has been shown that transgenic mice expressing P301S mutant human τ in nerve cells show essential features of tauopathies. Moreover, injection of brain extract from such P301S mice into the brains of transgenic mice expressing wild-type human τ induces assembly of wild-type human τ into filaments and spreading of pathology from the site of injection to neighboring brain regions (5). Coupled with the observation of the stereotypically staged development of tangles in AD, this suggests that a prion-like templating and spreading of aggregates of τ is central to disease progression.

This brief history of τ has focused on work from the authors’ own laboratories, but many researchers worldwide have contributed to our current understanding of τ in neurodegenerative diseases. It is hoped that further work will lead to treatments for these devastating diseases.
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References