
Alzheimer disease (AD)4 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 of PHFs, and the raising of an antibody, which both labeled the peptide fragment of PHFs, and the raising of an antibody, which both labeled the peptide fragment of PHFs, which was shown that PHFs comprise all 6 isoforms of tau in a hyperphosphorylated state (4).

In 1998, several groups showed that mutations in MAPT (microtubule-associated protein tau), the tau gene, gave rise to dominantly inherited dementing tauopathies, in which tau protein aggregates form in the brain in the absence of β-amyloid. Sporadic tauopathies also occur. Many tau 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 tau deposits, which are associated with tau 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 tau 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 tau induces assembly of wild-type human tau 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 tau is central to disease progression.
This brief history of tau has focused on work from the authors’ own laboratories, but many researchers worldwide have contributed to our current understanding of tau in neurodegenerative diseases. It is hoped that further work will lead to treatments for these devastating diseases.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

References