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Untangling the tauopathies: Current concepts of tau pathology and neurodegeneration

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ABSTRACT

Tau is the most common misfolded protein responsible for human neurodegenerative diseases. The identification of mutations in *MAPT*, the gene that encodes tau, causing dementia and parkinsonism established the notion that tau aggregation is responsible for the development of disease. An increased understanding of the pathway leading from conformational changes in tau protein and tau propagation to neuronal dysfunction, cell death and clinical manifestation will be the key for the development mechanism-based therapeutic strategies for tauopathies.

1. Introduction

Tau is the most common misfolded protein that forms intracellular inclusions in human neurodegenerative diseases. Tauopathies are a group of heterogeneous neurodegenerative conditions characterized by the deposition of abnormal tau protein in the brain (Table 1). Most tauopathies either cause dementia or parkinsonism, and in some conditions, a combination of both. Neuropathologically, these diseases are distinguished based on the pathological involvement of anatomical regions, cell types, morphology and type of tau isoforms in the inclusions [1]. Primary tauopathies, in which tau inclusions are the predominant pathology, can be summarised by the modern classification of frontotemporal lobar degeneration (FTLD-tau) which is categorized by the predominant type of tau isoforms in the inclusions [2](Fig. 1). Alzheimer's disease is referred as a secondary tauopathy as it is characterized by another predominant type of pathology, namely amyloid-β plaques. This review aims to provide a brief overview of the current understanding of tau pathology and neurodegeneration.

2. Historical perspectives

In 1907, Alois Alzheimer published the clinicopathological characteristics of a dementing illness and the histological findings of extracellular neuritic plaques and intracellular neurofibrillary tangles using silver stain in the cerebral cortex [3]. In 1963, using electron microscopy, Michael Kidd identified the paired helical filament (PHF) as the major structural component of the neurofibrillary tangle [4]. By the early 1990's, it was established that the PHF and straight filaments observed in Alzheimer's disease brain are composed of all six brain isoforms of the microtubule-associated protein tau (MAPT) in a hyperphosphorylated state [5]. In 1998, mutations in the tau gene, *MAPT*, were shown to cause a dominantly inherited form of frontotemporal dementia and parkinsonism, associated with high disease penetrance and hyperphosphorylated filamentous tau inclusions [6]. Since then, the causal relation between abnormal tau protein accumulation and neurodegenerative process has been firmly established.

3. Isoforms and biochemical composition of filaments

Tau is a microtubule-associated protein (MAP) that stabilizes microtubules and promotes microtubule assembly [7]. Tau is one of the most abundant MAPs with an important role in maintaining axonal transport and neuronal integrity. Tau is expressed at low levels in glial cells and has a physiological role in dendrites. In the

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Table 1
Diseases with tau inclusions.

1. Aging-related tau astrogliopathy
2. Alzheimer's disease
3. Anti-IgLON5-related tauopathy
4. Argyrophilic grain disease
5. Chronic traumatic encephalopathy
6. Corticobasal degeneration
7. Diffuse neurofibrillary tangles with calcification
8. Down's syndrome
9. Familial British dementia
10. Familial Danish dementia
11. Frontotemporal dementia and parkinsonism linked to chromosome 17 caused by *MAPT* mutations
12. Gerstmann-Straussler-Scheinker disease
13. Globular glial tauopathies
14. Guadeloupean parkinsonism
15. Myotonic dystrophy
16. Niemann-Pick disease type C
17. Non-Guamanian motor neuron disease with neurofibrillary tangles
18. Pantothenate kinase-associated neurodegeneration
19. Parkinsonism dementia complex of Guam
20. Primary age-related tauopathy
21. Pick's disease
22. Postenencephalitic parkinsonism
23. Prior protein cerebral amyloid angiopathy
24. Progressive subcortical gliosis
25. Progressive supranuclear palsy
26. SLC9A6-related mental retardation
27. Subacute sclerosing panencephalitis

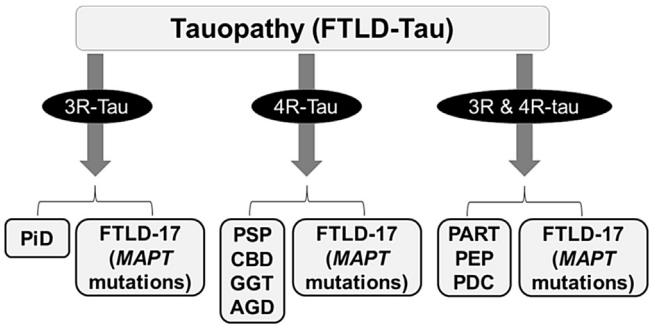

Fig. 1. Molecular classification of tauopathies (FTLD-Tau).
AGD: argyrophilic grain disease, CBD: corticobasal degeneration, FTLD: frontotemporal lobar degeneration, GGT: globular glial tauopathy, *MAPT*: microtubule-associated protein tau gene, PART: primary age-related tauopathy, PDC: parkinsonism dementia complex of Guam, PEP: post-encephalitic parkinsonism, PiD: Pick's disease, PSP: progressive supranuclear palsy.

adult human brain, six tau isoforms are expressed by alternative mRNA splicing of exons 2, 3 and 10 of the *MAPT* gene located on chromosome 17q21. The six tau isoforms, ranging from 352 to 441 amino acids, differ from each other by the presence or absence of 29- or 58-amino acid inserts located in the amino-terminal half and by the presence of either three (3R) or four (4R) tandem repeat sequences of 31 or 32 amino acids in the carboxy-terminal half (Fig. 2). Similar levels of 3R and 4R tau isoforms are expressed in normal human cortex. The expression of tau is two times higher in grey matter of the neocortex than in white matter and in the cerebellum. Regional variation in expression of tau could favour its assembly as tau assembly is concentration dependent.

The biochemical composition of tau filaments is not uniform, suggesting the presence of different tau 'strains' resembling those described in prions. Tau filaments in tauopathies are made up of either 3R- or 4R tau or both, which can be demonstrated by different electrophoretic migration patterns on tau immunoblotting (Fig. 1). Western blots of insoluble filamentous tau extracted from frozen brain samples of Alzheimer's disease, post-encephalitic parkinsonism and parkinsonism-dementia complex of Guam, all of which are mixed 3R and 4R-tauopathies, show three major bands of 60, 64, 68 kDa and a minor band of 74 kDa. In contrast, filamentous tau from brain tissue of progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), both of which are 4R-tauopathies, lacks the 60 kDa band, while filamentous tau from brain sample of Pick's disease, a 3R-tauopathy, demonstrates a major 60 KDa and 68 kDa band (Buee-Scherrer et al., 1997). Despite both being 4R-tauopathies, studies using immunoblotting of tau filaments from PSP and CBD brains have demonstrated distinct proteolytic fragments at low molecular weight below 40 kDa, suggesting that PSP and CBD are two distinct albeit closely related clinicopathological entities [8].

Recently, a study using cryo-electron microscopy facilitated a high resolution atomic characterization of the structures of the PHFs and straight filaments from the brain of an individual with Alzheimer's disease, establishing a basis for understanding the differences between molecular conformers of tau aggregates and showing how different isoforms are incorporated into the tau filaments [9].

4. Aggregation and hyperphosphorylation

The pathological transition of soluble to insoluble and highly structured filamentous tau underlies all human tauopathies. It is proposed that the ordered formation of filament assembly results in disease by causing gain-of-toxic function [10]. The insoluble tau filaments are most likely responsible for the propagation of tau pathology. Tau assembles into filaments through its tandem repeat with the amino-terminal half and the carboxy-terminus forming the fuzzy coat. A proportion of the assembled tau becomes truncated at the amino-terminus, a process required for its ubiquitination. In Alzheimer's disease, chronic traumatic encephalopathy (CTE) and post-encephalitic parkinsonism, when the tangle-bearing neurons die, the pathological material remains in the extracellular space, and they are commonly referred as the ghost tangles. All tau pathology implicated in human tauopathies is hyperphosphorylated, and as a result, becomes unable to interact

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