Untangling the Tauopathies:

Current concepts of tau pathology and neurodegeneration

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Abstract (74 words)

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.

Introduction

Tau is the most common misfolded protein that form 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](Figure 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.

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 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.

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 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 (Figure 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 (Figure 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 mixed 3R and 4R-tauopathies, show three major bands of 60, 64, 68kDa and a minor band of 74kDa. In contrast, filamentous tau from brain tissue of progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), both of which 4R-tauopathies, lacks the 60kDa band, while filamentous tau from brain sample of Pick's disease, a 3R-tauopathy, demonstrates a major 60KDa and 68kDa 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 40kDa, 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].

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 with microtubules. Tau hyperphosphorylation is likely to occur prior to filament assembly, although the exact role of tau hyperphosphorylation in the facilitation of filament assembly remains elusive.

Propagation and strains

Braak and Braak delineated the stereotypical progression of tau inclusions of Alzheimer's disease originating from a single site at the transentorhinal cortex[11]. Staging schemes depicting a stereotypical progression of abnormal protein inclusions from a single site have also been described for synucleinopathy, for instance, dorsal motor nucleus of the vagus nerve and olfactory bulb for the α-synuclein inclusions of Parkinson's disease[12].

Experimental studies have shown that the injection of tau inclusions into animal brains induces neurons to form intracellular inclusions at the injection sites, and their spreading to distant brain regions connected by neural network[13, 14]. The concept of different 'strains' of tau aggregates is consolidated by animal studies demonstrating that the intracerebral injection of brain homogenates from humans with pathologically confirmed PSP, CBD and AGD produced distinct lesions in mouse brains similar to those of the respective human tauopathies[13]. Tau aggregates from different tauopathies from human brain tissue exhibited

distinct confirmations or ‘strains’ and the proteopathic seeds can be transmitted into transgenic mouse brains and be re-introduced to naïve cells to replicate the same structural phenotype and manifest distinct pathological phenotypes[15]. These animal studies support the notion that a ‘prion-like’ templating mechanism is central to the disease progression in tauopathies[16, 17]. The term ‘prion-like’ refers to the release of protein aggregates from a small number of neurons and their uptake by neurons in other connected brain regions, followed by the initiation of a self-amplifying cascade[17].

Tau is an intracellular protein and propagation of tau requires aggregates to be released into the extracellular space, uptake by connected cells and seeded aggregation of soluble proteins. This proposed mechanism of propagation suggests that aggregation inhibitors and antibodies targeting extracellular tau aggregates are potential therapeutic targets to reduce tau-induced seeding and spreading.

Genetics

In 1998, the first mutations of the *MAPT* gene on chromosome 17q21-22 were reported in families with an autosomal dominantly inherited form of frontotemporal dementia with parkinsonism, which is now referred as FTDP-17T[6]. While the majority of tauopathies are sporadic, the finding of the *MAPT* gene confirms that tau dysfunction and tau aggregates are indeed directly linked with the pathogenesis of disease and clinical manifestation of cognitive and motor impairments. To date, more than 50 pathogenic mutations of the *MAPT* gene have been identified. Most of the mutations locate in exons 9-12 and the adjacent introns. Mutations of the *MAPT* gene reduce the ability of tau to interact with microtubules, which in turn promotes tau aggregation. Some mutations enable the hyperphosphorylation of tau and promote the assembly of tau into filaments. Others alter the ratio of 3R and 4R-tau isoforms, causing the overproduction of 4R-tau, a process that can lead to disease. FTDP-17 cases caused by different *MAPT* mutations can exhibit tau inclusions in nerve cells or in both nerve cells and glial cells[7]. Cases with *MAPT* mutations can have clinical phenotypes and pathological findings similar or identical to those of PSP, CBD, argyrophilic grain disease and Pick’s disease[7]. Different clinical phenotypic presentation may be observed in family members carrying the same mutations[18], indicating intrafamilial variability. Likewise, *MAPT* variants have been identified to increase the risk of developing tauopathies with heterogeneous clinical and neuropathological phenotypes[19].

MAPT gene in populations of European descent is characterised by two haplotypes caused by a 900-kb inversion (H1) and non-inversion (H2)[20]. The H2 lineage is found in 20% of the Europeans but is rare in Africans and almost absent in east Asians. The H2 haplotype is likely to be protective as it is associated with increased expression of exon 3 of MAPT in grey matter, which has an inhibitory role in tau aggregation, unlike exons 2 and 10 which promote aggregation[21]. The H1 haplotype and sub-haplotype H1c are risk factors for PSP and CBD[22].

Mechanistic and clinical implications of preclinical case study

There is a long prodromal phase between the formation of the initial intracellular tau aggregates and the onset of first clinical symptoms which requires extensive propagation of tau aggregates to have taken place. The prodromal phase opens a window of opportunity for early therapeutic interventions, making the quest for accurate and early diagnostic markers indispensable. While pathological staging schemes have been established for common neurodegenerative conditions such as Alzheimer's disease[11] and Parkinson's disease[12], the pattern of spatiotemporal progression of rarer conditions such as CBD remains elusive.

Recently, our group has characterised early CBD pathology in a quantitative study of three asymptomatic cases[23]. In these three cases, the pathognomonic 4R tau-positive astrocytic plaques are predominantly observed in the anterior frontal cortex and striatum. The astrogliopathy also shows an anterior-posterior gradient of tau pathology in the frontal lobe. The distribution of tau pathology observed in these asymptomatic cases leads us to propose the striatal afferent connection to the dorsolateral prefrontal cortex and basal ganglia circuitry as the earliest brain neural network affected in the early pathological process of CBD. Moreover, the overall tau burden in the asymptomatic cases is nine times less than the end-stage CBD cases. It is likely that a threshold of pathological burden will need to be reached in a strategic brain region before clinical symptoms begin to manifest.

Typically, moderate to severe neuronal loss in the substantia nigra is observed in post-mortem neuropathological assessment of end-stage CBD cases. In the three asymptomatic cases, the nigral cell population is found to be well preserved. This is consistent with reports of post-mortem confirmed cases in the literature which described normal dopamine transporter SPECT tracer uptake in patients at an early clinical stage and the subsequent

progressive declined in tracer uptake later in the disease course, corresponding to the progressive neurodegeneration of the nigrostriatal pathway[24].

The rarity of CBD, the lack of familial form, and the absence of reliable CSF and radiological biomarkers have made these rare preclinical cases extremely valuable for the understanding of the early pathology of CBD. The proposed early brain network affected by tau pathology may shed light on the use of *in vivo* tau imaging as a biomarker to identify preclinical or early CBD. Neuropathological series of clinical asymptomatic cases with early PSP pathology has also emerged in the literature[25], which contributes to improve our understanding of the early disease process of 4R-tauopathies.

Astroglial vs. neuronal tau pathology

In asymptomatic CBD cases, the brunt of tau pathology is observed in the astroglia in the form of astrocytic plaques rather than neuronal tau lesions such as neurofibrillary tangles, pretangles and threads[23]. This intriguing finding leads us to propose that CBD may be an astrogliopathy with secondary neuronal tauopathy, and as the disease progresses, neuronal tau inclusions become predominant in end-stage disease[23, 26].

The concept that tauopathies is possibly underpinned by astroglial pathology is supported by the entity of ageing-related tau astrogliopathy (ARTAG)[27]. Kovacs et al characterised the histological findings of a morphological spectrum of astroglial tau pathology commonly observed in the ageing brain without association with any co-existing neuropathological disorders or clinical symptoms such as dementia. Although the clinical significance of ARTAG is unclear, one may speculate that this entity may represent the prodromal phase of certain tauopathies, providing potential mechanistic insights.

Similarly, thorn-shaped astrocytes (TSAs), a characteristic feature of ARTAG, are frequently observed in post-mortem confirmed cases with CTE[28]. In both CTE and ARTAG, there is a predilection of TSAs in the perivascular, subpial and periventricular regions. Nevertheless, the accumulation of tau aggregates at the depths of the cortical sulci is a distinctive feature for CTE which differentiates CTE from ARTAG. The recent consensus diagnostic criteria require the observation of neuronal tau pathology in the cortical sulcal depths with a perivascular predilection to clinch the pathological diagnosis of CTE, while the ARTAG-like TSAs features are regarded by the recent diagnostic criteria as non-diagnostic and non-

supportive[29]. It remains to be established if the shared characteristic of the perivascular accentuation of astroglial tau pathology observed in both ARTAG and CTE represents a common down-stream mechanism of impaired blood-brain barrier; one that is caused by ageing-related process in ARTAG, and the other caused by chronic neuroinflammation triggered by repetitive head impacts in CTE[30].

Conclusion

Our understanding of tau inclusions and tauopathies has expanded in the past decades. The causal link of toxic-gain-of-function of tau and development of human neurodegenerative diseases is established in FTDP-17T and the same link probably applies to other sporadic tauopathies. More work is needed to understand the mechanistic pathway from tau aggregation and propagation to neuronal dysfunction, cell death and clinical manifestation. The answers to some of these questions will hold the key to the development of effective therapeutic strategies.

Figure legends

Figure 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

Figure 2: Human *MAPT* gene and the six tau isoforms expressed in the brain.

The six tau isoforms are expressed in the adult human brain by alternative pre-mRNA splicing of exons 2 (red), 3 (green) and 10 (yellow) of the *MAPT* gene. *MAPT* consists of 16 exons; exon 0 is part of the promoter, exon 14 is non-coding, exon 6 and 8 are not transcribed in human brain and exon 4a is only expressed in the peripheral nervous system. Blue bars indicate the microtubule-binding repeats of tau. (This diagram is kindly provided by Dr Rohan de Silva.)

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