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NEURODEGENERATIVE DISEASE IN 2015

Targeting tauopathies for therapeutic translation

Julio C. Rojas and Adam L. Boxer

Tau protein abnormalities are key pathogenic features of Alzheimer disease and other neurodegenerative diseases. In 2015, new studies of the less common tauopathies, including progressive supranuclear palsy, chronic traumatic encephalopathy and frontotemporal lobar degeneration, have identified *in vivo* biomarkers and mechanisms that initiate tau pathology.

The microtubule-associated protein tau (encoded by the *MAPT* gene) regulates microtubule structure and function in neurons[1]. In 2015, research rapidly advanced the prospect of tau-based therapeutics for neurodegenerative disorders (FIG. 1).

Tau-dependent cytotoxic mechanisms are pervasive in neurodegenerative disorders, occurring not only in Alzheimer disease (AD), but also in conditions such as chronic traumatic encephalopathy (CTE) and parkinsonian disorders[1]. These mechanisms involve post-translational modifications of tau, including hyperphosphorylation, cleavage and aggregation.

Tauopathies are diseases in which insoluble deposits of tau protein aggregate in neurons and glia, as shown by autopsy studies of human patients. When animal or cell culture models are inoculated with brain tissue from patients with tau pathology, tau can self-template and spread transcellularly in a prion-like fashion[2]. This finding suggests that the tau protein is an excellent target for therapeutic molecules that reduce its levels, alter its post-translational modification, or block its spread.

The mechanisms that initiate tau pathology are a major unresolved question. AD is the most common tauopathy, but translational studies designed to elucidate mechanisms of tau-dependent neurodegeneration are complicated by the presence of co-pathologies that influence the clinical phenotype. In 2015, Nag *et al.* highlighted this challenge by showing that the TAR DNA binding protein 43 (TDP-43) and hippocampal sclerosis make major contributions to the typical amnestic AD phenotype[3]. Autopsy specimens from 636 patients[3] showed that hippocampal sclerosis and TDP-43 were important contributors to cognitive impairment. A previous study from the same authors had demonstrated that comorbid synuclein and vascular pathologies are common in AD, and also contribute to the clinical phenotype[4]. Together, these comorbid pathologies could influence clinical assessments, making correlations with tau levels problematic. Initial translational efforts might, therefore, be more successful in disorders with more homogeneous underlying pathology, such as the primary tauopathies, progressive supranuclear palsy (PSP) or autosomal dominant frontotemporal lobar degeneration (FTLD) associated with *MAPT* mutations; in all of these disorders, abnormal tau is the main culprit.

Zhao *et al.*[5] demonstrated the advantages of focusing on PSP for understanding molecular mechanisms of tau-mediated neurodegeneration. Previous studies have identified strong genetic risk factors for PSP, particularly polymorphisms in *MAPT* itself[6], but the molecular mechanisms underlying these risk factors were poorly understood. Zhao and colleagues confirmed that a genetic variant that increases the risk of PSP is associated with upregulated appoptosin expression and subsequent high levels of cleaved tau[5]. In cell culture models, cleaved tau had a high tendency to dissociate from microtubules and aggregate[5]. Appoptosin also promoted tau cleavage via caspase-3 activation,[5] and its overexpression promoted synaptic abnormalities and prion-like transcellular spread of cleaved tau[5]. When mice received injections of an appoptosin-expressing virus into the globus pallidus, they developed bradykinesia and tau pathology similar to that seen in patients with PSP[5]. Overexpression of appoptosin was also observed in the brains of patients with AD or FTLD[5], providing support for links between the molecular mechanisms of tau-dependent neurodegeneration in PSP, AD and FTLD.

Another molecule that regulates tau structure and function is the peptidyl-prolyl *cis–trans* isomerase NIMA-interacting 1 (Pin1). *PIN1* mutations have previously been implicated as a genetic risk factor for AD. Pin1 exerts a neuroprotective effect by modulating the chirality of tau phosphorylated at residue 231 (p231 tau), maintaining it in a *trans*

Key advances

- Cistauosis is a conformational change in phosphorylated tau, observed in chronic traumatic encephalopathy and Alzheimer disease, that contributes to microtubule dysfunction, prion-like spread of abnormal tau and apoptosis[7]
- In cell culture and animal models, the neuropathological effects of cistauosis can be blocked by a therapeutic monoclonal antibody against the *cis*-phospho-tau epitope[7]
- Overexpression of the mitochondrial carrier protein appoptosin, associated with a strong genetic risk factor for progressive supranuclear palsy (PSP), promotes caspase-mediated tau cleavage, motor dysfunction and tau neuropathology[5]
- In asymptomatic carriers of mutations linked with frontotemporal dementia, cognitive and structural MRI changes are detected years before expected disease onset, suggesting the possibility of clinical prevention trials in *MAPT* mutation carriers[9]
- Elevated tau levels are measurable in the peripheral blood of individuals with a history of repetitive traumatic brain injury, and correlate with the severity of clinical symptoms[8]
- Pure tauopathies, such as PSP, constitute ideal human patient models for translational studies of tau, including clinical trials

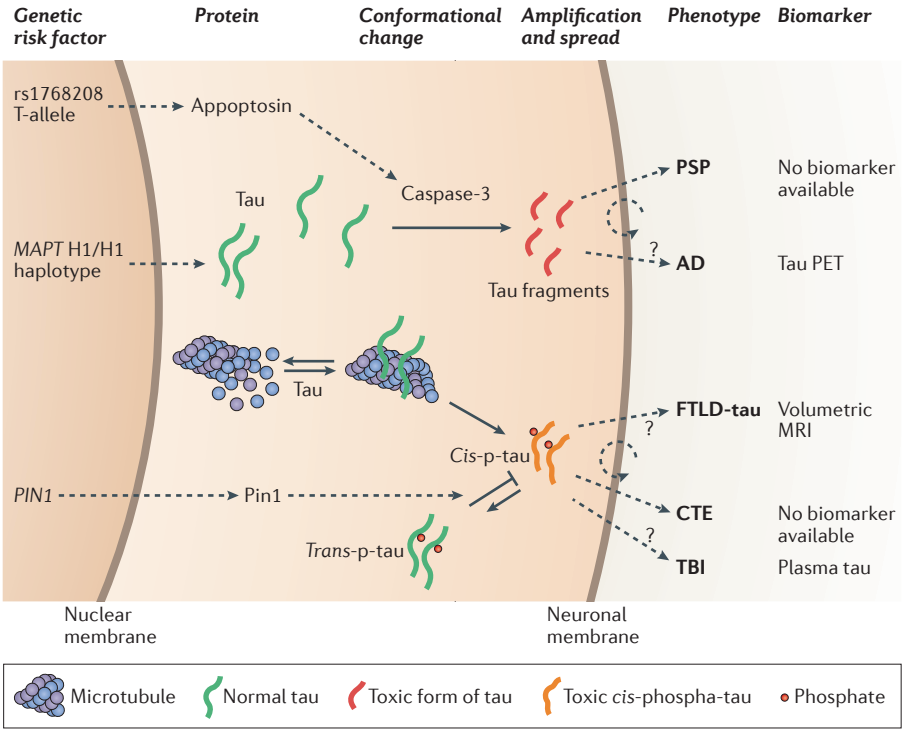

Figure 1 | **Advances in tau research in 2015.** The rs1768208 polymorphism, linked to progressive supranuclear palsy (PSP), elevates the level of appoptosin and promotes caspase-3-mediated tau cleavage. In PSP and Alzheimer disease (AD), the cleaved tau is thought to spread trans-synaptically, resulting in the disease[5]. In AD, tau-PET signal is elevated[10]. One of the functions of tau, encoded by the *MAPT* gene, is to stabilize microtubules. The *MAPT* H1/H1 haplotype is linked to PSP[6], and MRI can reveal brain atrophy in asymptomatic *MAPT* mutation carriers[9]. *PIN1* polymorphisms promote toxic *cis*-p-tau formation. In animal models, traumatic brain injury (TBI) induces *cis*-p-tau formation that leads to neuronal dysfunction. In human patients with TBI, tau pathology is reflected by elevated blood levels of tau [8]. CTE, chronic traumatic encephalopathy; FTLD, frontotemporal lobar degeneration.

conformation and preventing the formation of toxic *cis* p231 tau (*cis* p-tau), a process that Kondo *et al.* termed 'cistauosis' (REF. 7). Kondo and co-workers discovered that *cis* p-tau was prominent in autopsy specimens from humans with CTE[7], in line with the previous reports that have described fulminant tau pathology in CTE. The researchers were also able to induce cistauosis in mouse models of single or repetitive traumatic brain injury (TBI), and in cultured neurons by inducing neuronal stress[7]. In these models, cistauosis led to disruption of microtubule assembly, impaired axonal transport, and spread of *cis* p-tau to contiguous neurons via a prion-like mechanism with resulting induction of apoptosis. Remarkably, this pathogenic cascade was prevented by monoclonal antibodies to *cis* p-tau, which decreased cellular neurotoxicity, histopathological changes and behavioural deficits in rodent models of TBI[7]. Similar to appoptosin-induced tau cleavage, cistauosis occurred before insoluble tau deposition, and within days of the induction of of TBI[7]. The findings suggest that monoclonal antibodies that neutralize toxic forms of tau, such as *cis* p-tau, might be effective therapies.

An intriguing study by Olivera *et al.*[8] suggests that tau could spread into the periphery in individuals with TBI. In military personnel who reported having three or more TBIs, plasma tau concentrations were higher than in individuals with a single documented TBI, who in turn had higher plasma tau concentrations than controls without TBI. Plasma tau concentrations correlated with the severity of post-concussive symptoms. These findings complement the cistauosis model and suggest the possibility of monitoring tau-related neurodegeneration with a blood test.

If tau cleavage and cistauosis are initiating factors for tau-mediated neurodegeneration, intervention with anti-tau antibodies or other therapies early in the disease course (ideally before the onset of symptoms) is paramount. The Genetic FTD Initiative (GENFI) is a multicentre natural history study of carriers of autosomal dominant FTLD mutations, including asymptomatic individuals with *MAPT* mutations recruited in the UK, EU and Canada. In the first report of GENFI results[9], neuropsychological abnormalities could be detected up to 5 years and atrophy at least 10 years prior to the estimated time of symptom onset. A pattern of sequential atrophy was demonstrated, with insular and temporal cortices affected first, followed by frontal and subcortical areas and, around the time of symptom onset, parietal and cingulate cortices. These results suggest that clinical trials of interventions to prevent the onset of tau-related neurodegeneration in asymptomatic *MAPT* carriers are feasible. In North America, the ARTFL and LEFFTDS projects, which are similar to GENFI, will further enable such studies.

Advances in understanding the pathophysiology of tau-dependent neurodegeneration have sharpened the rationale for new therapies aimed at the tau protein itself. Insights from PSP and CTE have suggested mechanisms that initiate tau pathology, new targets for tau directed therapeutics and potential biomarkers to assess therapeutic effects in humans.

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