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Targeting tauopathies for therapeutic translation

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Abstract

Tau protein abnormalities are key pathogenic components of Alzheimer disease and other neurodegenerative diseases. New studies in the less common primary tauopathies, including progressive supranuclear palsy, chronic traumatic encephalopathy and frontotemporal lobar degeneration have identified novel mechanisms that initiate tau pathology and biomarkers to measure disease during life.

The microtubule-associated protein tau (encoded by the *MAPT* gene) regulates microtubule structure and function as well as other physiological processes in neurons.[1] In 2015, research rapidly advanced the prospects for tau-based therapeutics for neurodegenerative disease. 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. In tauopathies—diseases featuring insoluble deposits of aggregated tau protein in neurons and glia at autopsy—convergent evidence from animal and cell culture models both inoculated with human brain tissue show that pathogenic forms of 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 initiating tau pathology in the first place are a major unresolved question.

AD is the most common tauopathy, but translational studies hoping 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 have major contributions to the typical amnestic AD phenotype.[3] In 636 autopsy cases from the Religious Order Study, hippocampal sclerosis and TDP-43 were common, significant contributors to memory and global impairment. A previous study from the same authors had

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Competing interests statement

A.L.B. has received research support from Avid, Biogen, Bristol Myers Squibb, C2N Diagnostics, Cortice Biosciences, Eli Lilly, Forum Pharmaceuticals, Genentech and TauRx, He has served as a consultant for Asceneuron, Ipierian, Isis Pharmaceuticals, Janssen and Merck. He serves on a Data and Safety Monitoring Board for Neurogenetics Pharmaceuticals. He has stock and/or options in Alector and Delos. J.C.R. declares no competing interests.

demonstrated that synuclein and vascular co-pathologies are common in AD and also contribute to the clinical phenotype.[4] Together, these co-pathologies could influence clinical assessments such as memory tests and activity of daily living measurements, 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) and autosomal dominant frontotemporal lobar degeneration (FTLD) associated with *MAPT* mutations, in all of which tau is the major abnormal protein.

In one of the most important studies on tau in 2015, Zhao et al.[5] demonstrated the advantages of focusing on PSP for understanding molecular mechanisms of tau-mediated neurodegeneration. Genome-wide association 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. The authors confirmed that a SNP on chromosome 3, near the myelin basic protein gene, is a strong risk factor for PSP and is associated with the expression of appoptosin, a mitochondrial protein that supports the synthesis of heme. Appoptosin was upregulated in carriers of the risk allele, and its expression correlated with high levels of cleaved tau[5], which in cell culture models had a high tendency to dissociate from microtubules and aggregate. Appoptosin promotes tau cleavage via caspase-3 activation. Overexpression of appoptosin also promoted synaptic abnormalities and transcellular spread of cleaved tau in a prion-like manner[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]. The findings by Zhao and colleagues provide insight into the pathogenesis of PSP by demonstrating a direct link between a genetic risk factor and the molecular mechanisms mediating the development of its defining behavioral and pathological phenotype. Overexpression of appoptosin was also observed in brains 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), a phospho-Ser/Thr-Pro isomerase previously implicated as a genetic risk factor for AD. Pin1 exerts a neuroprotective effect by modulating the chirality of tau phosphorylated at residue 231, maintaining it in a *trans* conformation and preventing the formation of toxic *cis* p231 tau (*cis* p-tau), a process that Kondo et al. term ‘cistauosis’.[7] In their study, Kondo and co-workers discovered that *cis* p-tau was prominent in human CTE autopsy specimens[7], in line with the previous reports that have described CTE to be a tauopathy with particularly fulminant tau pathology. Kondo and colleagues were was also able to induce cistauosis in mouse models of single or repetitive traumatic brain injury (TBI), as well as by other forms of neuronal stress in cultured neurons[7]. In these models, cistauosis led to disrupted 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 was found to be a mechanism that occurs before insoluble tau

deposition and within days after the introduction of diverse forms of TBI[7]. This study provides additional evidence for common tau-dependent mechanisms of neurotoxicity and prion-like spread in CTE, TBI and AD. Moreover, 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. Using a highly sensitive immunoassay, the authors studied military personnel who reported having had TBI, and found that those with three or more TBIs had higher plasma tau concentrations than individuals with a single documented TBI, who in turn had higher plasma tau concentrations than controls. Plasma tau concentrations were correlated with 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, it will be necessary to intervene with new therapies such as anti-tau antibodies early in the course of disease, ideally before the onset of symptoms. The Genetic FTD Initiative (GENFI; http://genfi.org.uk/) is a multicentre natural history study of carriers of autosomal dominant FTLD mutation, 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 prior to the estimated time of symptom onset in 118 FTLD risk gene carriers, whereas atrophy was detectable on MRI scans at least 10 years before symptom onset. A pattern of sequential atrophy was demonstrated, with insular and temporal cortices affected first, followed by frontal and subcortical areas about 5 years before symptom onset, then parietal and cingulate cortices around the time of symptoms. These results suggest that it could be feasible to conduct clinical trials to prevent the onset of tau-related neurodegeneration in asymptomatic *MAPT* carriers. In North America, the ARTFL and LEFFTDS projects (https://www.rarediseasesnetwork.org/cms/ARTFL), 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. The recognition that typical late onset AD is a multi-component proteinopathy has extended the focus of tau translational research to other tauopathies such as PSP and CTE, which could have stronger pathophysiological links to tau. Insights from these disorders have identified potential mechanisms for initiation of tau pathology, new targets for tau directed therapeutics and potential new biomarkers needed to assess therapeutic effects in humans.

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Biographies

Julio C. Rojas received his MD from the Tecnológico de Monterrey School of Medicine in Mexico, and PhD in neuroscience from the University of Texas at Austin, Texas, USA. After

completing neurology residency at UT Southwestern Medical Center in Dallas, USA, he became a Behavioral Neurology Fellow at the Memory and Aging Center at the University of California, San Francisco, in California, USA, where he is part of the clinical trials team and provides care to patients with various neurodegenerative disorders. Rojas is interested in experimental neurotherapeutics, and his research focuses on biomarker development and cognitive enhancing interventions.

Adam L. Boxer, is an Associate Professor of Neurology at the University of California, San Francisco (UCSF) in California, USA, where he directs the Neurosciences Clinical Research Unit and the Alzheimer's Disease and Frontotemporal Lobar Degeneration (FTLD) Clinical Trials Program at the UCSF Memory and Aging Center. He is the Principal Investigator of the Advancing Research and Treatment for FTLD (ARTFL; https://www.rarediseasesnetwork.org/cms/ARTFL) Clinical Research Consortium, a collaborative project funded by the NIH to create a 15 center North American research network to support the development of new therapies for FTLD including PSP and CBD.

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Key advances

- **Cistauosis is a conformational change in phosphorylated tau relevant to chronic traumatic encephalopathy and Alzheimer disease that may contribute to microtubule dysfunction, prion-like spread of abnormal tau and apoptosis** [7]
- **Neuropathological effects of cistauosis can be blocked by a therapeutic monoclonal antibody to the *cis* phosphotau epitope in cell culture and animal models**[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]
- **Cognitive and structural MRI changes are present years before expected onset in asymptomatic carriers genes linked with frontotemporal dementia, suggesting that clinical prevention trials in tau *MAPT* mutation carriers will, eventually, be possible**[9]
- **Elevated tau levels are measurable in 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 clinical models for translational studies of tau including clinical trials**

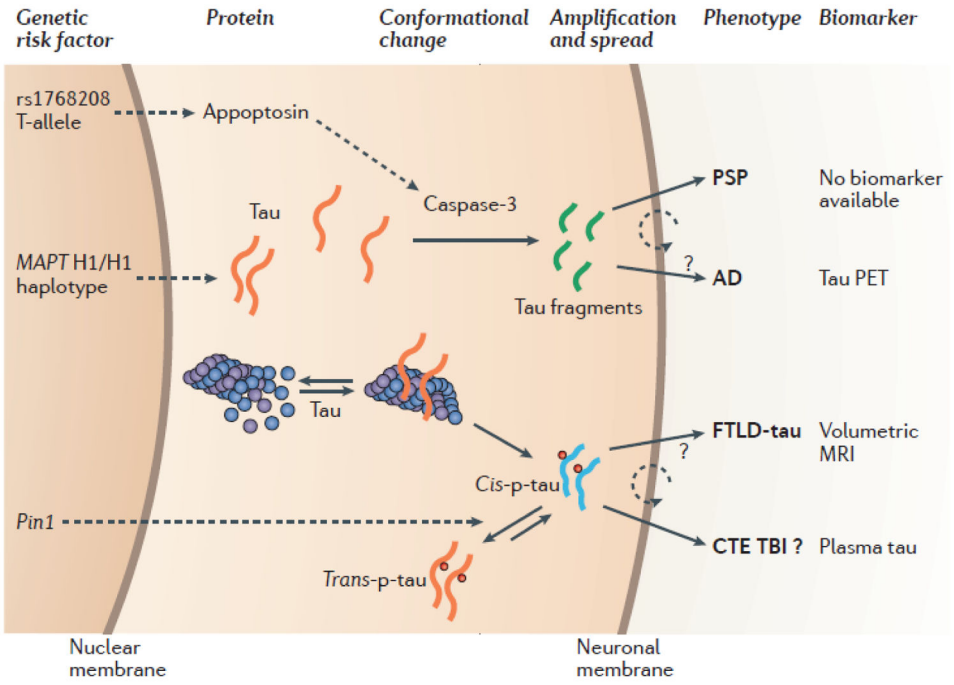

Figure 1. Advances in tau research in 2015

The rs1768208 polymorphism, linked with progressive supranuclear palsy (PSP), elevates the level of appoptosin, thereby promoting caspase-3-mediated tau cleavage. It is hypothesized that in both PSP and Alzheimer disease (AD), the cleaved tau spreads transsynaptically, causing disease.[5] The tau-associated neuropathology can be detected with tau-sensitive PET.[10] One of the main functions of tau protein, encoded by the *MAPT* gene, is to stabilize microtubules. *MAPT* H1/H1 haplotype is associated with PSP,[6] and MRI can reveal brain atrophy in asymptomatic *MAPT* mutation carriers.[9] *PIN1* polymorphisms promote formation of toxic *cis*-p-tau. Traumatic brain injury (TBI) induces *cis*-p-tau formation that leads to neuronal dysfunction in animal models. In patients with TBI, blood levels of tau are elevated.[8]