Preface

Is Tau a Prion-Like Protein?

Miguel Medina and Jesús Ávila

Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain
Centro de Biología Molecular “Severo Ochoa” CSIC-UAM, Madrid, Spain

It has been over a quarter century since the discovery in the mid-1980s that the paired helical filaments of neurofibrillary tangles were made up of abnormally hyperphosphorylated tau. A decade earlier tau had been first isolated from porcine brain as a heat stable protein essential for microtubule assembly. The following years clearly established tau as a microtubule-associated protein that under physiological conditions regulates microtubule assembly, dynamic behavior, and spatial organization, and has also been shown to regulate the axonal transport of organelles, including mitochondria. Further studies during the following couple of decades revealed the importance of post-translational modifications, mainly phosphorylation but also truncation, in tau function and dysfunction. Prominent tau pathology is present in a number of neurodegenerative disorders, predominantly within the neuronal compartment, but also within glial cells. Because of this shared histopathological feature, they are referred collectively as tauopathies, although they constitute a group of etiologically heterogeneous, clinically, and neuropathologically overlapping disease entities.

In tauopathies, the intracellular soluble tau forms filamentous structures of aggregated, hyperphosphorylated tau, which are associated with synaptic loss and neuronal death. The occurrence of fibrillar tau inclusions in tauopathies strongly supports a key role in the observed clinical symptoms and pathology but the key discovery directly involving tau protein in neurodegeneration and dementia came almost at the turn of the century from the finding that highly penetrant, dominant mutations in the MAPT gene encoding tau cause an inherited form of frontotemporal dementia and parkinsonism, confirming that tau dysfunction by itself can lead to neurodegeneration and dementia, in the absence of any amyloid pathology.

Recognition of the microtubule-associated protein tau as a key player in the pathobiology of human neurodegenerative diseases has since led to major efforts to understand its biological and pathological function(s). This has resulted in a better understanding of tau cellular functions beyond its classical role in the stabilization of microtubules to unveil novel physiological tau functions that may also play a role in pathogenesis. Such functions include neuronal polarization, axonogenesis, interactions with the plasma membrane and scaffold proteins, signal transduction, cell cycle, DNA protection, or determination of dendritic spine density. Furthermore, tau has been recently reported at the synapse in healthy brains, suggesting a potential role in the regulation of normal synaptic function.

Clinicopathological studies have shown that tau pathology is associated with progressive neuronal loss and cognitive decline. In the brains of AD patients, tau pathology propagates following an anatomically defined pattern described by the commonly used neuropathological Braak sequential staging. Mounting evidence strongly suggests that accumulation of abnormal tau might be mediated through spreading of seeds of the protein from cell to cell, and point to the involvement of extracellular tau species as the main agent in
the interneuronal propagation of neurofibrillary lesions and spreading of tau toxicity throughout different brain regions in these disorders. That would support the concept that pathology initiates in a very small part of the brain many years before becoming symptomatic, spreading progressively to the whole brain within 10–20 years, reminiscent of some features of the prion protein propagation mechanism.

Precisely, this prion-like behavior of tau prompted us together with Karen Duff and Ken Kosik to organize a workshop entitled “Is tau a protein-like protein? Implications for physiology and pathology”, held in Madrid on October 28–30, 2013 as part of the Cantoblanco Workshops in Biology. This workshop brought together world class experts to discuss up-and-coming areas in the tau field that may reveal novel mechanisms and targets for therapeutic intervention, inspiring new insights and approaches in the battle against neurodegenerative diseases. Session topics included biochemistry and processing of tau in physiological and pathological conditions; cell-to-cell tau propagation and in vivo spreading; novel therapeutic approaches including tau immunization. The list of invited speakers for this workshop included Khalid Iqbal, Eickhard Mandelkow, Susanne Wegmann, Akhioko Takashima, Alejandra Alonso, Illana Khalid Iqbal, Eckhard Mandelkow, Susanne Wegmann, Ikiboro Takashima, and collaborators.

During the workshop, tribute was paid to some colleagues that had made fundamental contributions to the tau field throughout the years and that regrettably are no longer with us (Inge Grundke-Iqbal, Irith Ginzburg, Pierre Brion, Naruhiko Sahara, George Bloom, Jurgens Gotz, Einar Sigurdsson, Norbert Zilka, Rakez Kayed, and Marc Diamond. Some of the speakers kindly agreed to submit their contributions related to the meeting topic that made up this special issue.

In this issue, Sayas reports on the significance of the interplay between tau and microtubule plus-end tracking proteins (+TIPs) in modulating microtubule dynamics during neurite and axon extension, whereas Gozes et al. give an account on the in vivo effect of two new neuroprotective peptides derived from davunetide/NAP, a microtubule-stabilizing peptide in clinical trials for PSP and other tauopathies, on animal models of tauopathies. Hanger and colleagues review novel tau functions both at the intracellular as well as extracellular level, paying special attention to its potential role at the synapse. Avila et al. address different ways by which tau gets into the extracellular space and its potential role in signaling through muscarinic receptors and eventually in the spreading of pathology. On the other hand, Saman and coworkers follow a system biology approach to identify exosomal proteins specifically linked to tau secretion and aggregation. The interaction between extracellular tau and muscarinic receptor has been further investigated in vivo by Martinez-Aguilar et al. by using tear secretion in rabbits as a model. De Cristobal et al. reports on the use of FDG-PET imaging to characterize a transgenic mouse model of tauopathy that overexpresses human tau with a triple mutation. A different model (P301L) is used by Sahara and colleagues to investigate the role of tau oligomers in neurodegeneration by using a newly generated oligomer-specific tau antibody (TOC1). A different anti-tau oligomer-specific mouse monoclonal antibody (TOMA) is used by Castillo-Carranza et al. to investigate the potential of anti-tau oligomer passive immunization in preventing the seeding and propagation of tau pathology in human tau transgenic mice. The use of anti-tau antibodies as passive immunotherapy for AD and other tauopathies is reviewed by Gordon et al., together with recent developments of small molecules tau ligands and antibody-derived probes for clinical PET detection of tau lesions. Active immunization with tau phospho-peptides is the approach followed by Ando et al. in a pilot study carried out in another mouse model of tauopathy (THY-Tau22). Finally, Ribano and colleagues report on the neuropathological evaluation of brains from argyrophilic grain disease, a sporadic 4R tauopathy that they propose as an optimal natural disease model for testing hypotheses related to tau propagation in human tissue.

In summary, this special issue intends to highlight some recent developments in tau biology relevant to AD and tauopathies. It has become increasingly clear that, apart from the well-established intracellular functions of tau in microtubule stabilization and axonal transport, intracellular and extracellular tau...
most likely have important signaling roles that could contribute to the neurodegenerative process in AD and related tauopathies. In addition, recent studies have suggested that misfolding of tau in diseased brain leads to abnormal conformations of tau that can be taken up by surrounding neurons. Thus, pathological progression could indeed involve transmission of tau protein through a prion-like mechanism resulting in neurodegeneration in susceptible brain regions. Key questions still remain open, such as the neuronal population selectivity, the nature of the tau species involved, or the precise seeding/templating mechanisms, among many others. More research is needed to identify disease mechanisms driving release and propagation of tau pathology and to determine the impact of extracellular tau on cognitive decline during neurodegeneration.

Despite the fact that the presence of extensive tau pathology is central to the disease, tau-based therapeutic strategies have received little attention until recently. The observation that misfolded tau can be secreted and taken up by adjacent neurons calls for the development of novel strategies to block the propagation of tau pathology in the brain, such as some immunotherapy approaches discussed here. These are exciting times in the tau field as the next few years will certainly bring new insights into the precise molecular mechanisms underlying propagation of tau pathology, likely identifying novel therapeutic approaches intended to interfere early on in the devastating neurodegenerative process.

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