The Biology of Tau and its Role in Tauopathies


Two days of tau: a meeting focused on its biology and pathology

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Abstract

Tauopathies are a clinically diverse group of neurodegenerative dementias involving perturbations of the level or phosphorylation state of the microtubule-binding axonal protein tau. Despite intense effort in recent years, the precise role of tau in the pathology of the various behaviourally and neuropathologically distinct tauopathies, the mechanisms of tau toxicity and the potential functional interaction of tau and amyloid in Alzheimer’s disease remain elusive. Nevertheless, novel observations regarding the various aspects of tau-misregulation-dependent pathogenesis are emerging from various cellular, vertebrate and invertebrate animal models and are supported by new clinical data. This Focused Meeting brought together scientists working on tau and tauopathies from different disciplines and various experimental models. The aim was to enhance our understanding of the protein itself and disorders associated with its misregulation through synergy.

Although scientific meetings regarding the pathogenesis and potential treatments of a single disease are not uncommon, a meeting focused on a single protein implicated in a number of devastating human disorders known as tauopathies, seems more of a rarity. In fact, the January 2010 meeting in Cambridge on the biology and pathology of the neuronal protein tau was the second in 10 years! But what is it about tau that commands multiple presentations and discussions ranging from biophysics to behavioural biology and human pathology over two full days?

Tau as its name (tubulin-associated unit) implies, is a neuronal microtubule-binding protein distributed preferentially in axons. The microtubule-binding domain of the protein comprises three to five repeated sequence motifs that are highly conserved in metazoans from nematode worms to humans, but the number of protein isoforms is not the same in all. Whereas one protein appears to be present in the nervous system of Caenorhabditis elegans and Drosophila, four are present in mice and six are present in humans. The multiple isoforms in these vertebrate species arise by alternative splicing of a single transcript, thus differing in the number of microtubule-binding repeats (Rs) and repeat sequences at the N-terminus (Ns). The functional significance of multiple isoforms is unclear at the moment, but proteins with four Rs are thought to bind more tightly to microtubules and one 3R isoform appears specific to the human fetal nervous system. Another characteristic of tau isoforms is their extensive constitutive phosphorylation, which is of functional importance as hyperphosphorylation reduces microtubule binding.

Mutations in the single gene that encodes the six human tau isoforms result in heritable FTDP-17 (frontotemporal dementia with parkinsonism linked to chromosome 17). Most known mutations linked with FTDP-17 map on to the microtubule-binding repeats and the mutant protein is also hyperphosphorylated. However, tau mutations have not been detected in all other tauopathies that range from AD (Alzheimer’s disease) to Pick’s disease, progressive supranuclear palsy and corticobasal degeneration, among others. Nevertheless, all tauopathies are characterized by more or less morphologically distinct intraneuronal cytoplasmic aggregates known as neurofibrillary tangles (NFTs) which consist of hyperphosphorylated tau. It is not difficult then to imagine how mutations leading to tau hyperphosphorylation result in an excess of non-microtubule-bound tau, its consequent aggregation and the resultant pathologies including neuronal death. However, how and why non-mutant tau that

Key words: Alzheimer’s disease, frontotemporal dementia with parkinsonism linked to chromosome 17, microtubule, neurofibrillary tangle, tau, tauopathy.

Abbreviations used: AD, Alzheimer’s disease; FTDP-17, frontotemporal dementia with parkinsonism linked to chromosome 17; NFT, neurofibrillary tangle.
characterizes all tauopathies, except for FTDP-17, becomes hyperphosphorylated, aggregation-prone and pathogenic is less apparent. Why such events appear to affect particular neuronal populations and brain areas, as suggested by the names and symptoms of each tauopathy, is even less well known. Then there is the question of how these sporadic aberrations in tau metabolism or phosphorylation, which presumably originate in a single or a small number of neurons, expand through the brain. Why is there an age-dependence in the appearance of disease symptoms and cellular pathology including NFTs? This is observed even for FTDP-17, where mutant protein must be accumulating for a long time before signs of dementia become apparent. Finally, is the hyperphosphorylated aggregated protein toxic for neurons, or does the reduction in molecules competent to bind microtubules mimic functional loss of tau? These questions, along with the hypothesis and ideas stemming from this meeting. Such findings are detailed in the papers that follow. However, it was the representation of multiple experimental models to study tau and tauopathies ranging from in vitro to whole-animal invertebrate and vertebrate systems that were the highlight of the meeting.

Various animal models of tauopathies have been generated to investigate the relationship of mutant and normal tau accumulation, hyperphosphorylation and misregulation with neuronal dysfunction. Although most models focused primarily on emulating neurodegeneration and NFT formation, a number of investigations aimed at elucidating the causes of the cognitive decline and dementia and the locomotor defects often used in clinical differentiation among tauopathies. The contributions of the genetically facile invertebrate models of C. elegans and Drosophila in the discovery of novel molecules involved in tau pathogenesis was apparent from the oral and poster presentations. Importantly, human orthologues and homologues of these molecules appear to be involved in tauopathies when examined, further underlining the importance of these models for ‘gene discovery’. Vertebrate cultured neuron models and whole-animal models provided essential windows into the pathogenesis of tau hyperphosphorylation, NFT formation, disease progression and cognitive effects of perturbing tau function in the vertebrate brain, often providing ‘validation’ of discoveries via the invertebrate models.

These studies also brought to light important differences in the results and potential interpretation among the multiple models. These differences are easily explained away upon consideration of the experimental particulars of each study. A lot of the work in Drosophila, as in other models, focused on the pathogenicity of tau with emphasis on neurodegeneration. Genetic screens in the Drosophila eye have provided a wealth of tau-interacting proteins facilitated by the ease of detecting the effects of cytotoxicity on the orderly structure of the ommatidia comprising the retina. Inter-laboratory differences appear to result from the choice of wild-type or tau carrying FTDP-17-linked mutations in these screens. Another variable contributing to such differences became apparent as the choice of tau isoform used in each model. Both the number of Rs (microtubule-binding repeats) and N-terminal sequences (GN–2N) often yielded distinct results in Drosophila retina and central nervous system, but also in the mouse brain. These distinctions probably reflect the largely unexplored functional differences among the human tau isoforms which may also manifest themselves in a tissue-specific manner. This hypothesis can be addressed in a systematic and co-ordinated fashion in the expedient invertebrate models and validated in the mouse.

Similarly, results from various mouse models varied regarding NFT formation, cognitive deficits when tested and neurodegeneration. Again, a parsimonious explanation for such differences could be the particular human isoform utilized and whether it carries FTDP-17-linked mutations as well as the particular mouse neurons expressing it. A detailed systematic study of these differences and an investigation of the potential contribution of the endogenous mouse tau isoforms in these phenotypes will probably advance our understanding of tauopathies and the associated cognitive symptoms, including memory loss and neurodegeneration.

It appears, then, that inter-model synergy and coordination will be the driving force for future rigorous tests of the hypotheses and ideas stemming from this meeting. Such studies will be essential to uncover and validate molecular hallmarks that differentiate dysfunction-causing from toxic hyperphosphorylated tau. This is an essential distinction because managing tauopathies, including AD, is to pharmacologically ameliorate the associated cognitive symptoms, aiming to delay or block progression to neurodegeneration. It is hoped that such reports will be presented in the next meeting on the biology and pathology of tau.

Funding

This conference was jointly funded by the Alzheimer’s Society, the Alzheimer’s Research Trust and the Biochemical Society.

Received 25 May 2010
doi:10.1042/BST0380953