



The complex enigma of tau

It is perhaps the hottest molecule in the field of neurodegenerative diseases, possibly in all neurology. Widely found in neurons, tau seems to attract attention like no other protein in the brain. Interest in it crosses disease boundaries and specialties. Different forms of tau have now been implicated in Alzheimer's disease, several types of frontotemporal dementia, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), chronic traumatic encephalopathy and even epilepsy.¹ But precisely how tau causes brain dysfunction remains a real puzzle.

Although it has been known for some time that tau is normally associated with microtubules within neurons, the hypothesis that it is crucial for the stability of cellular processes that depend on microtubules, such as axonal transport, has become less attractive. As Chang *et al.*² recently conclude, there is very little compelling evidence to show that reductions in tau lead to derangements of microtubule structure or function. So what does tau normally do?

Intriguingly, several lines of evidence suggest that tau actually might play a key role in many different functions.^{2,3} These include actions within signalling pathways, a role in synaptic physiology and plasticity, and even in neural and brain network oscillations. Further, the concept that intraneuronal aggregation of misfolded tau—the hallmark under the microscope—is the key driver of neural dysfunction is also under challenge. Whereas this perspective considers tau to produce its pathological effects through some loss of function (e.g. loss of microtubule stability) there is increasing evidence that, to the contrary, it might actually lead to a gain of function. Alternatively, tau might normally enable cellular processes which no longer occur effectively in the presence of pathological tau species.²

This issue of *Brain* contains another twist. The results of a new study suggest that mitochondrial deficits at presynaptic terminals might be an early pathological feature in tauopathy.⁴ In Alzheimer's disease, accumulation of intracellular neurofibrillary tangles consisting of hyperphosphorylated tau has been considered to be a major marker of disease. Soluble forms of this species of tau are known to cause mitochondrial dysfunction. In this new report, the authors show that tauopathy is associated with activation of Parkin-mediated mitophagy—a lysosomal mechanism that is crucial for the normal elimination of mitochondria.


The significance of these findings in the context of other potential pathological roles of tau remain to be determined, but a second paper in this month's *Brain* provides evidence *in vivo* of the complex relationship between tau pathology and loss of synapses, indexed using the PET ligand ¹¹C-UCB-J.⁵ The investigators studied PSP and CBD cases (defined as individuals who were negative on amyloid PET imaging) using a combination of tau PET and the ¹¹C-UCB-J marker of synaptic density. The results are consistent

with tau-induced synaptic toxicity. Although interpretation is complex, this is an exciting advance in attempting to examine the impact of tau pathology on synapses in humans.

Recent findings have also demonstrated that tau fibrils can exist in previously unknown configurations. By extracting tau fibrils purified from the brains of patients with a variety of different neurodegenerative conditions, it was possible to show that they are very heterogeneous.⁶ Although it still remains to be established how some of these might exert their toxic effects, it is clear that there are many forms of tau and considering 'tauopathy' as a homogeneous entity is likely to be a mistake. The protein might have many different effects, depending on its soluble forms or the configurations in which it aggregates.

One key concept that has gained a lot of traction in recent years is the possibility that pathological tau might act as a seed which somehow recruits and promotes soluble tau into further aggregation, followed by its abnormal spread throughout the brain.⁷ A wide-ranging investigation now suggests we should exercise caution when considering such a mechanism.⁸ The authors used five different methods to quantify tau, including from post-mortem seed amplification assays to tau PET studies in patients. Their results for Alzheimer's disease, suggest that local replication within a brain region, rather than spread between regions, might be the major determinant of overall rate of accumulation of tau. Thus, they argue that targeting local replication of tau would be the most promising strategy to control its accumulation, at least in Alzheimer's disease.

The bewildering complexity of tau is on full display in this plethora of recent findings. Although the pace of research in this area has been breathtaking to witness, one thing remains clear: tau firmly remains an enigma. We are far from understanding the neurobiology of tau in either normal or abnormal brains. Despite a lack of comprehensive understanding, we do seem to be catching some important glimpses into its diverse functions.

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