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Letter to the Editor

Tangled tau: Active pathology or footprint of disease?

Alzheimer's disease (AD) research is approaching crisis point. While disease prevalence relentlessly increases as the population ages, treatments are still limited in number and effect. There is little hope on the horizon as clinical trials for new AD drugs have a dishearteningly high failure rate–greater than any other field at 99.6% [1]. Most of the work on AD has focussed on beta-amyloid, with the importance of the microtubule-associated protein tau only being elucidated relatively recently. Tau-targeting treatments currently being tested, in clinical and preclinical settings, are geared toward preventing tau hyperphosphorylation and aggregation into neurofibrillary tangles (NFTs) [2]. However, there is a lack of consensus from animal models on whether these processes are worth targeting. Tau tangles may well correlate with disease severity and stage, but there is compelling evidence indicating that tangles represent a footprint of pathology, and soluble tau is the unseen culprit.

Neurodegeneration and memory decline in mice expressing human P301L-tau was halted by the reduction of tau's expression [3]. However, NFT accumulation continued unchanged, indicating that these aggregates are not sufficient to cause the observed phenotype. A further study demonstrated that memory impairment correlated with the presence of oligomeric soluble tau [4]. What is more, *Drosophila* engineered to express human tau exhibit similar cognitive defects and neurodegeneration but lack entirely the presence of NFTs [5].

Tau hyperphosphorylation by several kinases reduces its affinity for the microtubules and promotes aggregation, resulting in defective axonal transport and neuronal function which probably underpins certain aspects of the disease. Levels of hyperphosphorylated tau in human cerebrospinal fluid correlate well with disease severity and trajectory [6]. Yet, *Drosophila* displays an AD phenotype with minimal tau phosphorylation, although pathology was worsened by enhancing phosphorylation [7]. Furthermore, numerous phosphodeficient tau mutants retain their toxicity [8]. Hyperphosphorylation likely results in both gain-of-toxicity and loss-of-function of tau, but it does not appear to be a prerequisite for toxicity. As such, hyperphosphorylation and consequent aggregation could be the attempted, and somewhat botched, clear-up and disposal of soluble tau, perhaps by immune cells [9,10]. Aggregates may well be biologically inert, hence why human NFT-containing neurons can survive for many years [11,12].

Post-mortem human studies revealed a change in the relative abundance of tau isoforms in brains from those with AD. Isoforms containing exon 10 were upregulated, with a concomitant downregulation of exon 10-lacking isoforms [13]. This suggests that alterations of tau biology occur well before hyperphosphorylation and aggregation—alterations which could play a key role in AD pathophysiology.

While evidence regarding the underpinnings of AD, and other tauopathies, remains unclear, it is vital to investigate all possible avenues in the search for new drug targets. Soluble tau appears to be toxic, and there is conflicting evidence regarding the role of hyperphosphorylation and aggregation. More work is here needed to resolve the part played by soluble tau in AD pathophysiology. With which cellular components does soluble tau interact and what are the consequences? *Drosophila* may be a powerful tool. Their unrivaled molecular tractability and a wealth of well-characterized assays, from behavior to imaging, make them ideal for studying the cellular and molecular determinants of disease. These animals also represent a relatively high-throughput system and observations made in *Drosophila* can be validated in rodent models and beyond to permit rational treatment design.

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