A Tale of Two Taus

Reviewer: Dr Ed Needham, Neurology Registrar, Norfolk and Norwich University Hospital.

It is always exciting when a breakthrough in fundamental science leads to a concept that may be applicable to a wide number of diseases, and such is the case in the paper by Kondo et al., which primarily investigates the role of phosphorylated tau proteins (P-tau) in neurodegeneration following traumatic brain injury (TBI).

It has long been recognised that victims of TBI can develop a tauopathy known as Chronic Traumatic Encephalopathy (CTE), which bears a pathological semblance to Alzheimer's disease (AD). Furthermore, TBI is a risk factor for the development of AD in its own right. Despite clear clinical association, however, the pathophysiological bridge from TBI to CTE to AD remains elusive.

Previous work in AD has suggested that *trans* P-tau is a beneficial, physiological protein, whereas *cis* P-tau plays a pathogenic role in tauopathy (Nakamura et al., 2012). The authors of the current study developed monoclonal antibodies to both the *cis* and *trans* isomers of P-tau, and utilised them firstly to delineate the role of tau following TBI, hypoxia and metabolic stress, and secondly as therapeutic agents.

The paper starts with the identification of *cis* P-tau in the axons of all post-mortem brains from 16 patients with Chronic Traumatic Encephalopathy (CTE) compared with no patients in a control cohort of 8; the presence and distribution of trans P-tau was identical in both groups.

Murine models were then adopted to explore the temporal and spatial progression of tauopathy, and its subsequent effect on neurons. At 48 hours post-TBI, *cis* P-tau was detectable in a severity-dependent manner, and remained raised in those with both repetitive minor and single severe TBI. At this early time point the *cis* P-tau was restricted mainly to the cortex, but by six months the pathogenic tau isomer was detectable in other regions, including the hippocampi.

Identical production of *cis* P-tau was also demonstrated in two other models of brain injury: hypoxia and serum starvation.

To assess the pathogenic effect of *cis* P-tau on healthy neurons, the authors exposed cultured neurons to the brain lysate of TBI and healthy mice, and showed that *cis* (but not *trans*) P-tau was subsequently detectable in the neurons treated with TBI lysate, and was associated with accelerated apoptosis.

Having successfully utilised the mAbs to delineate the relative roles of tau in the above situations, attention is turned to their potential therapeutic value. Importantly, the *cis* P-tau mAb is highly specific in its binding, thereby avoiding unintended effects on the beneficial *trans* P-Tau, and universally beneficial effects of its application were seen in the various murine experiments. Immunodepletion of *cis* P-tau: prevented apoptosis in cultured neurons following the addition of brain lysate from TBI, hypoxia and serum starvation mice; stopped the spread of *cis* P-Tau from the cortex to other structures; potently inhibited the destructive processes affecting axonal microtubules and mitochondria; halted the development of tau oligomers, aggregation and tangle epitopes, as well as cortical and white matter atrophy; and protected against risk-taking behaviour (a putative consequence of medial prefrontal cortex damage) which was widespread in untreated TBI mice.

This study provides new insights into a therapeutically modifiable pathway which may have clinically significant implications in a spectrum of neurological disease states including primary neurodegenerative disorders, cerebrovascular disease, traumatic brain injury and hypoxic-ischaemic encephalopathy.

Nakamura K, Greenwood A, Binder L, Bigio EH, Denial S, Nicholson L, Zhou XZ,Lu KP. Proline isomer-specific antibodies reveal the early pathogenic tau conformation in Alzheimer's disease. Cell. 2012 Mar 30;149(1):232-44.

Kondo A, Shahpasand K, Mannix R, Qiu J, Moncaster J, Chen CH, Yao Y, Lin YM,Driver JA, Sun Y, Wei S, Luo ML, Albayram O, Huang P, Rotenberg A, Ryo A,Goldstein LE, Pascual-Leone A, McKee AC, Meehan W, Zhou XZ, Lu KP. Antibody against early driver of neurodegeneration cis P-tau blocks brain injury and tauopathy. Nature. 2015 Jul 23;523(7561):431-6.