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## Cis P-tau is induced in clinical and preclinical brain injury and contributes to post-injury sequelae

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Traumatic brain injury (TBI) is characterized by acute neurological dysfunction and associated with the development of chronic traumatic encephalopathy (CTE) and Alzheimer's disease. We previously showed that cis phosphorylated tau (cis P-tau), but not the trans form, contributes to tau pathology and functional impairment in an animal model of severe TBI. Here we found that in human samples obtained post TBI due to a variety of causes, cis P-tau is induced in cortical axons and cerebrospinal fluid and positively correlates with axonal injury and clinical outcome. Using mouse models of severe or repetitive TBI, we showed that cis P-tau elimination with a specific neutralizing antibody administered immediately or at delayed time points after injury, attenuates the development of neuropathology and brain dysfunction during acute and chronic phases including CTE-like pathology and dysfunction after repetitive TBI. Thus, cis P-tau contributes to short-term and long-term sequelae after TBI, but is effectively neutralized by cis antibody treatment. Our results state showed that axonal injury and cis P-tau induction in clinical severe TBI; CSF cis P-tau correlates well with outcome in TBI patients; cis P-tau found in deeper brain regions in CTE patients; cis mAb improves acute phase outcomes after ssTBI; cis mAb improves chronic phase outcomes after ssTBI; delayed cis mAb administration improves outcomes after ssTBI; - cis mAb prevents CTE pathology and dysfunction after rmTBI and also the efficacy of cis mAb in improving outcomes across studies.

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