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Antibody against early driver of neurodegeneration cis P-tau blocks brain injury and tauopathy

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Traumatic brain injury (TBI), characterized by acute neurological dysfunction, is one of the best known environmental risk factors for chronic traumatic encephalopathy and Alzheimer's disease, the defining pathologic features of which include tauopathy made of phosphorylated tau protein (P-tau). However, tauopathy has not been detected in the early stages after TBI, and how TBI leads to tauopathy is unknown. Here we find robust cis P-tau pathology after TBI in humans and mice. After TBI in mice and stress in vitro, neurons acutely produce cis P-tau, which disrupts axonal microtubule networks and mitochondrial transport, spreads to other neurons, and leads to apoptosis. This process, which we term 'cistauosis', appears long before other tauopathy. Treating TBI mice with cis antibody blocks cistauosis, prevents tauopathy development and spread, and restores many TBI-related structural and functional sequelae. Thus, cis P-tau is a major early driver of disease after TBI and leads to tauopathy in chronic traumatic encephalopathy and Alzheimer's disease. The cis antibody may be further developed to detect and treat TBI, and prevent progressive neurodegeneration after injury.

Results

Here we used cis P-tau mAbs to demonstrate the presence of, and specifically eliminate, pathogenic cis P-tau in clinically relevant in vitro and in vivo models of sport- and military-related TBI. We detected robust cis P-tau signals after sport- and military-related TBI in humans and mice, and in stressed neurons. Following TBI or neuronal stress, cis P-tau induces cistauosis well before previously identified tauopathy is apparent. Treating TBI mice with cis mAb ablates cis P-tau and eliminates cistauosis, prevents the development of widespread tauopathy and restores histopathological and many functional outcomes of TBI. Cistausosis is an early precursor of previously described tauopathy and an early marker of neurodegeneration that can be blocked by cis mAb. We previously showed that cis P-tau has an early pathological role in Alzheimer's disease27–34,42. Our current data provide a direct link from TBI to CTE and Alzheimer's disease, and suggest that cistauosis is a common early disease mechanism in TBI, CTE and Alzheimer's disease, and that cis P-tau and its mAb may be useful for early diagnosis, prevention and therapy for these devastating diseases. Atlanta (GA): Centers for Disease Control and Prevention.

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