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Xiao Cis P-tau as an early and druggable driver of neurodegeneration in brain injury and Alzheimer's disease

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Alzheimer's disease (AD) and its related neurodegenerative disorder called chronic traumatic encephalopathy (CTE) share a common environmental risk factor, traumatic brain injury (TBI) and a common neuropathological signature, neurofibrillary tangles made of phosphorylated tau. However, the underlying disease mechanisms are still not clear and there is no effective therapy. We have previously shown that Pin1-catalyzed cis-trans isomerization of proteins after specific proline-directed phosphorylation is a unique signaling mechanism and its deregulation plays a major role in the development of certain diseases notably AD and cancer. In the AD, Pin1 protects against age-dependent neurodegeneration in an AD by preventing age-dependent accumulation of the phosphorylated Thr231-Pro motif in tau (P-tau) in the pathogenic cis conformation by converting it to the physiologic trans. However, unlike phosphorylation or dephosphorylation, nothing is gained or lost during Pin1-catalyzed post-phosphorylation cis-trans isomerization and there was no tool available to detect these two conformations in the cell. To address this major problem, we developed novel peptide chemistry to generate the cis and trans-P-tau antibodies, leading to the discovery that is cis, but not trans, P-tau is a previously unrecognized early conformation leading to tau pathology and neurodegeneration in the AD but is converted to the physiological trans by Pin1. We have further demonstrated that diverse causes of severe TBI in humans (motor vehicle accidents, assaults or falls) acutely and robustly induces toxic cis P-tau in cortical axons and cerebrospinal fluid, correlating with axonal injury and patient's clinical outcome. In mouse models of severe or repetitive TBI, treatment with cis P-tau antibody in immediate or delayed regimen not only effectively eliminates early cis P-tau induction and spread, but also potently prevents the development and progression of a range of pathologic and functional outcomes during acute and chronic phases. These results indicate that cis P-tau is a common early disease driver in the AD, TBI and CTE and suggest that cis P-tau antibody may be useful for early diagnosis, prevention and/or therapy for these devastating diseases.

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