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A Major Early Driver of Tauopathy and Neurodegeneration that is Blocked by Antibody

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Traumatic brain injury (TBI) is the best-known environmental risk factor for Alzheimer's disease (AD), whose defining pathologic features include tauopathy made of hyperphosphorylated tau (PHF-tau) and is characterized by acute neurological dysfunction. However, tauopathy is undetectable acutely after TBI and how TBI leads to tauopathy which in turn would increase risk of AD is unknown. Here we identify a neurotoxic cis conformation of phosphorylated tau at Thr231 as a major early driver of TBI and neurodegeneration that is effectively blocked by the conformation specific monoclonal antibody. We found robust cis p-tau after sport- and military-related TBI in humans and mice. Acutely after TBI in mice and stress *in vitro*, neurons prominently produce cis p-tau, which disrupts axonal microtubule network and transport, spreads to other neurons, and leads to apoptosis, a pathogenic process, which we nominated "cistauosis" that appears long before known tauopathy. Treating TBI mice with cis antibody not only blocks early cistauosis, but also prevents tauopathy development and spread, and restores brain histopathological and functional outcomes. These results uncover cistausosis as an early precursor of tauopathy and an early marker of neurodegeneration after sport and military TBI. We anticipate that cis p-tau will be a new early biomarker and that cis p-tau antibody or vaccines may be used to treat or even prevent TBI, chronic traumatic encephalopathy and AD.

Biography

Koorosh Shahpasand has completed his PhD from Tokyo Metropolitan University in 2012, and did his postdoctoral training at Harvard Medical School on the elucitation of cis/trans p-tau conformations during Neurodegeneration; the results of which have been published in Nature. He is now freshly employed assistant professor at Royan Institute and supervising several research projects related to tauopathies. Notably, he has been recently awarded by a prestigous grant from Alzheimer's Association at Chicago.

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