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Central Role of PP2A in Sporadic Alzheimer Disease and Tauopathies

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Alzheimer's disease (AD) is a multifactorial disease which involves more than one mechanism. The density of tau pathology in the neocortex, as in AD, adults with Down syndrome, and a number of tauopathies, directly correlates with cognitive impairment. Protein phosphatase-2A (PP2A) is the major regulator of tau phosphorylation. PP2A activity is known to be regulated negatively by phosphorylation of its catalytic subunit PP2Ac at Tyr307, demethylation of PP2Ac at Leu309, and by two heat- and acid-stable proteins, inhibitor-1 (I_1^{PP2A}) and inhibitor-2 (I_2^{PP2A}). PP2A activity is compromised in the brains of AD and Guam Parkinsonism-amyotrophic lateral sclerosis (PD ALS) cases as well as in the spinal cords of ALS cases. In the AD brain and the ALS spinal cord the decrease in PP2A activity involves cleavage and translocation of I_2^{PP2A} from the neuronal nucleus to the cytoplasm, most likely as a consequence of acidosis and excitotoxicity due to ischemic changes. In Guam PD ALS the inhibition of PP2A activity involves an increase in phosphorylation of PP2Ac at Tyr307 due to activation of mGluR5, followed by dissociation of PP2Ac from the receptor and its phosphorylation by Src kinase. Expression of I_{2NTF} and or I_{2CTF}, both of which can inhibit PP2Ac, produces tau hyperphosphorylation in the brain, phosphorylation and proliferation of neurofilaments in the spinal cord, and corresponding behavioral impairments in rats. Rescue of the PP2A activity deficit could rescue tau hyperphosphorylation and cognitive impairment. PP2A appears to be critically involved in modulating tau pathology and serve as a switch to turn off and on AD type pathology and consequent behavioral changes.