

THE ROLE OF CYCLIN-DEPENDENT KINASE 5 IN BRAIN DEVELOPMENT AND DEGENERATION

LI-HUEI TSAI

Howard Hughes Medical Institute, Harvard Medical School, Department of Pathology, 200 Longwood Ave, Boston, MA 02115

Cyclin-dependent kinase 5 (Cdk5) is a proline-directed protein kinase that phosphorylates serine and threonine residues. As monomeric Cdk5 displays no enzymatic activity, an interaction with either p35 or p39, two proteins abundantly expressed in post-mitotic neurons, is necessary for Cdk5. Cdk5 is a pleiotropic kinase that plays numerous functions in the mammalian central nervous system. The most well characterized role of Cdk5 is its involvement in the developmental regulation of cortical development. Cdk5-deficient mice display widespread neuronal positioning defects in the cortex, hippocampus and the cerebellum. In particular, the normal lamination pattern of neurons in the cortex is inverted in both the p35 and Cdk5 deficient mice. On top of the neuronal positioning defects, Cdk5 and p35 deficient mice display defects in fasciculation of several axon tracks. Recent evidence suggests that Cdk5 may be downstream of the GDNF and the *Sema3A* signaling pathways in regulation of neurite extension and axon guidance. To date, more than two dozens of substrates have been identified for Cdk5. Phosphorylation of these substrates by Cdk5 is implicated in cytoskeleton dynamics, dopamine signaling, and synaptic plasticity.

Increased Cdk5 activity has been observed in several neurodegenerative diseases, including Alzheimer's Disease (AD) and animal models of amyotrophic lateral sclerosis (ALS) and Niemann Pick type C (NPC) disease. In all of these cases, the increase in Cdk5 activity is accompanied by the accumulation of a truncated form of p35, p25. p25 is fully capable of activating Cdk5; however, p25 is more stable and displays a different subcellular localization than p35. Cdk5 was originally identified as a major kinase that phosphorylates the microtubule associated protein tau on several residues. Cdk5 has also been shown to be associated with early stages of neurofibrillary tangles suggesting that aberrant Cdk5 activation may be involved in the development of neurofibrillary pathology.

To test the hypothesis that the generation and accumulation of p25 causes neurodegeneration *in vivo*, we created inducible mouse lines overexpressing p25 in the postnatal forebrain. Using this mouse model, we provide direct evidence for a role of p25 in neurodegeneration. We show that p25 overexpression results in substantial brain atrophy, progressive neuronal loss, and hyperphosphorylation/aggregation of tau. Interestingly, while the phosphorylation of tau and other pathological Cdk5 substrates is upregulated, the phosphorylation of known physiological Cdk5 substrates is not increased in p25 Tg mice. Our results indicate that p25 may redirect Cdk5 to alternative

substrates and activate other kinases that are involved in neurodegeneration. These findings support the concept that neurodegeneration and tau pathology are a consequence of pathogenic p25/Cdk5 activation and highlight the significance of protein phosphorylation in the progression of neurodegenerative diseases.