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My laboratory is interested in elucidating the pathogenic mechanisms underlying neurological disorders affecting learning and memory. The major research areas include neuropsychiatric disorders, autism, and Alzheimer ' s disease.

Schizophrenia is a severe and disabling brain illness. While the etiology is poorly understood, accumulating evidence suggests that neurodevelopmental defects are involved. The loss of function of the Disrupted in Schizophrenia 1 (DISC1) gene is implicated in schizophrenia, bipolar disorder, and major depression. DISC1 encodes a large scaffolding protein that interacts with several distinct signaling pathways. We recently showed that DISC1 is indispensable for the production of new neurons during brain development and adult neurogenesis. Moreover, we found that DISC1 regulates neurogenesis via the Wnt signaling pathway. Biochemically, DISC1 inhibits GSK3β, thereby increasing β-catenin protein levels. Thus, the action of DISC1 is reminiscent to that of lithium, a mood stabilizer used in the treatment of bipolar disorder.

Together, these results establish an essential role for DISC1 in neurogenesis and underscore a potential involvement of the Wnt signaling pathway in the pathophysiology of psychiatric disorders. We are currently assessing the biology and signaling components of several other genes implicated in schizophrenia and bipolar disorder.

Autism spectrum disorder is a developmental disorder characterized by impaired social interaction, dysfunctional verbal and nonverbal communication, and repetitive behaviors. While the cause for autism is largely unknown, mutations in genes implicated in synapse development have been identified in autism and autism spectrum disorders. Cdk5 is a small protein serine/threonine kinase with important functions in the nervous system. While best understood for its role in regulating the cytoarchitecture of the developing brain, emerging evidence supports an important role for Cdk5 in dendritic spine development and synaptogenesis. As a protein kinase, Cdk5 phosphorylates a wide range of protein substrates, many of them localized at the synapse. We recently reported

that the MAGUK family member CASK is an *in vivo* substrate of Cdk5. Phosphorylation of CASK by Cdk5 regulates the membrane localization of CASK, which in turn facilitates neurexin/neuroligin-mediated synaptogenesis. In addition, Cdk5 phosphorylation of CASK positively impacts Ca++ influx mediated by voltage-gated N-type calcium channels. We recently found that Cdk5 phosphorylates another synaptic scaffolding protein, Shank3. Mutations in the Shank3 gene have been identified in autism and autism spectrum disorder patients. We are currently investigating whether Shank3 phosphorylation by Cdk5 play a role in spine/synapse development.

Alzheimer ' s disease is a devastating and irreversible brain disorder that eventually leads to dementia. Accumulating evidence indicates that the hyperactivation of Cdk5 plays a role in Alzheimer ' s-like neurodegeneration. Hyperactivation of Cdk5 is caused by the production and accumulation of p25, a calpain cleavage product of p35, which is, in turn, a brain-specific regulatory activator of Cdk5. Transgenic mice overexpressing p25 develop rapid and severe neurodegeneration that includes DNA double strand break damage, cell cycle re-entry, tau and β-amyloid pathology, and learning impairments. We recently showed that learning impairments and memory loss could be markedly attenuated when the p25 transgenic mice were treated with non-selective inhibitors of histone deacetylases (HDAC), drugs which induce dynamic chromatin remodeling. Recently, we further identified HDAC2 as the potential target for the HDAC inhibitors that exert beneficial effects on learning and memory. In contrast, HDAC1 plays a key role in protecting neurons from p25 and other neurotoxic insults. Interestingly, we found that class III HDACs, such as SIRT1, also play a protective role and enhance learning and memory.

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Additional Publications

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