Missing protein may be key to autism

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A missing brain protein may be one of the culprits behind autism and other brain disorders, according to researchers at MIT's Picower Institute for Learning and Memory.

The protein, called CASK, helps in the development of synapses, which neurons use to communicate with one another and which underlie our ability to learn and remember. Improperly formed synapses could lead to mental retardation, and mutations in genes encoding certain synaptic proteins are associated with autism.

In work published in the Dec. 6 issue of *Neuron*, Li-Huei Tsai, Picower Professor of Neuroscience at MIT, reported that she has uncovered an enzyme that is key to the activity of CASK.

Tsai studies a kinase (kinases are enzymes that change proteins) called Cdk5. While Cdk5's best-known role is to help new neurons form and migrate to their correct positions during brain development, "emerging evidence supports an important role for Cdk5 at the synapse," she said.

To gain a better understanding of how Cdk5 promotes synapse formation, Tsai's lab looked into how Cdk5 interacts with synapse-inducing proteins like CASK. A key scaffolding protein, CASK is one of the first proteins on the scene of a developing synapse.

Scaffolding proteins such as CASK are like site managers, supporting protein-to-protein interactions to ensure that the resulting architecture is sound. Mutations in the genes responsible for Cdk5 and CASK have

been found in mental retardation patients.

"We found that Cdk5 is critical for recruiting CASK to do its job for developing synapses," Tsai said. "Without Cdk5, CASK was not in the right place at the right time, and failed to interact with essential presynaptic components. This, in turn, led to problems with calcium influx." The flow of calcium in and out of neurons affects processes central to nervous system development and plasticity--its ability to change in response to experience.

Gene mutations and/or deletions in synaptic cell surface proteins and molecules called neurexins and neuroligins have been associated with autism. The problem with CASK recruitment investigated by the Tsai laboratory creates the same result as these genetic changes.

The Picower study also provides the first molecular explanation of how Cdk5, which also may go awry in neurodegenerative diseases such as Alzheimer's, promotes synapse development.

"There are still a lot of unknowns," said Tsai, who is also a Howard Hughes Medical Institute investigator. "Causes for psychiatric disorders are still very unclear, but accumulating evidence strongly suggests that alterations in the synaptogenesis program can lead to these serious diseases."

In addition to Tsai and Picower researcher Benjamin A. Samuels, co-authors are associated with Harvard Medical School; Johns Hopkins University School of Medicine; McLean Hospital in Belmont, Mass.; and Academia Sinica in Taiwan.

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Source: MIT