Misfolded Neural Proteins Linked to Autism Disorders

September 10, 2010

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An international team of scientists, led by researchers at the University of California, San Diego, has identified misfolding and other molecular anomalies in a key brain protein associated with autism spectrum disorders.

Palmer Taylor, associate vice chancellor for Health Sciences at UC San Diego and dean of the Skaggs School of Pharmacy and Pharmaceutical Sciences, and colleagues report in the September 10 issue of the *Journal of Biological Chemistry* that misfolding of a protein called neuroligin-3, due to gene mutations, results in trafficking deficiencies that may lead to abnormal communications between neurons.

Genetic misfolding of neuroligins is thought to prevent normal formation and function of neuronal synapses. The gene mutation has been documented in patients with autism.

"It makes sense that there's a connection," said Taylor. "The neuroligins are involved in maintaining neuronal synapses and their malfunction is likely to affect a neurodevelopmental disease."

Neuroligins are post-synaptic proteins that help glue together neurons at synapses by connecting with pre-synaptic protein partners called neurexins. They are part of a larger family of alpha-beta-hydrolase fold proteins that includes many molecules with diverse catalytic, adhesion and secretory functions.

Using live neurons in culture, the researchers found that different mutations caused different degrees of misfolding of the protein structure, which translated into trafficking deficiencies of varying severity regardless of alpha-beta-hydrolase protein type, yet resulted in distinctly different congenital disorders in the endocrine or nervous systems.

Both neuroligins and the autism mutations are relatively new to science. The former were characterized 15 years ago, the latter discovered just seven years ago. Taylor said identifying and describing the misfolded protein link advances understanding of the complex causes of certain autisms, including the influences of genes versus environment, and perhaps offers a new target for potential drug therapies.

"If the mutation is identified early, it might be possible to rescue affected neurons before abnormal synaptic connections are established" said co-author Davide Comoletti, a research scientist at the Skaggs School of Pharmacy. "But much work remains. We may be able to find a treatment to fix a cell in culture, but to rescue function *in vivo* may not be feasible with the same strategy."

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