Researchers connect APC protein to autism and mental retardation

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A clue to the causes of autism and mental retardation lies in the synapse, the tiny intercellular junction that rapidly transfers information from one neuron to the next. According to neuroscientists at Tufts University School of Medicine, with students from the Sackler School of Graduate Biomedical Sciences at Tufts, a protein called APC (adenomatous polyposis coli) plays a key role in synapse maturation, and APC dysfunction prevents the synapse function required for typical learning and memory. The findings are published in the August 18 issue of *The Journal of Neuroscience*.

"Both sides of the synapse are finely tuned for efficient transmission; an imbalance on either side can negatively impact function, resulting in cognitive deficits. Our study reveals that APC forms a key protein complex in the postsynaptic neuron that also provides signals to direct synapse maturation in the presynaptic neuron, ensuring that the two sides of the synapse mature in concert to provide optimal function," said senior author Michele H. Jacob, PhD, professor in the department of neuroscience at Tufts University School of Medicine. Jacob is also a member of the cell, molecular and developmental biology; cellular and molecular physiology; and neuroscience program faculties at the Sackler School of Graduate Biomedical Sciences at Tufts.

In the in vivo study, the team blocked APC function and found that synaptic levels of the cell adhesion proteins neuroligin and neurexin dropped considerably. Without normal levels of these proteins, synapses were less mature both structurally and functionally. Mutations in the

genes for neuroligin and neurexin are associated with autism in humans, but until now, little was known about the mechanisms responsible for localizing these proteins at the synapse.

"Our laboratory study is the first to show that APC is needed to recruit neuroligin and neurexin to the synapse. This finding provides new insights into the mechanisms required for proper synapse function as well as molecular changes at the synapse that likely contribute to autistic behaviors and learning deficits in people with APC loss of function gene mutations," said Jacob.

"Our study also sheds light on a poorly-understood but essential process, the cross-talk that occurs between presynaptic and postsynaptic neurons. When we perturbed APC function on the postsynaptic side, we saw changes on both sides of the synapse, indicating that APC organizes a protein complex that communicates against the normal flow of traffic," said first author Madelaine Rosenberg, PhD, an affiliate of the department of neuroscience at TUSM.

The research team's next step is to examine the behavioral and cognitive changes that occur when APC is deleted in neurons of the mammalian brain. They have developed a new mouse model that will allow them to investigate how the loss of APC function leads to synaptic changes and impaired learning and memory.

More information: Rosenberg MM, Yang F, Mohn JL, Storer EK, Jacob MH. The Journal of Neuroscience. 2010. (August 18); 30(33): 11073-11085. "The Postsynaptic Adenomatous Polyposis Coli (APC) Multiprotein Complex Is Required for Localizing Neuroligin and Neurexin to Neuronal Nicotinic Synapses in Vivo." Published online August 18, 2010, doi:10.1523/JNEUROSCI.0983-10.2010