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Researchers develop better way to see molecules at work in living brain cells

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By creating a better way to see molecules at work in living brain cells, researchers affiliated with MIT's Picower Institute for Learning and Memory and the MIT Department of Chemistry are helping elucidate molecular mechanisms of synapse formation. These studies could also help further understanding of how synapses go awry in developmental diseases such as autism and Fragile X syndrome. The study will appear in the Oct. 7 issue of *Cell*.

Using the new technique, which is more accurate and sensitive than existing methods, the researchers found that certain protein-protein interactions can affect early phases of synapse maturation. Their work will help scientists understand exactly how two adjacent neurons form a synapse—the meeting point where information transfer among brain cells occurs. This method provides information on the dynamics of proteins in synapses on a minute-by-minute time scale, the researchers said.

"How nascent contacts mature into excitatory or inhibitory synapses is an area of intense interest," said Amar Thyagarajan, Autism Speaks Postdoctoral Fellow in the laboratory of Alice Y. Ting, associate professor of chemistry. "Trans-synaptic signaling complexes seem like a good place to start looking for clues to this process since they mediate signaling into the pre- and post-synaptic cells during this process."

Study co-authors Thyagarajan and Ting are Picower Institute affiliates.

The researchers studied the interaction of the proteins neurexin and neuroligin on the surface of neurons. These adhesion molecules--two of many in the brain that regulate synapse formation, maturation, function and plasticity--not only function as the "glue" that hold neurons together but also mediate signaling so that the appropriate molecular components are recruited for the pre- and postsynaptic cells.

Neurexins and neuroligins can be thought of as a chemical bridge and communication network that spans the synaptic cleft.

Called BLINC (Biotin Labeling of Intercellular Contacts), the new technique creates a fluorescent signal only when neurexin and neuroligin interact. "The only way for a BLINC signal to occur is when two neurons contact each other," Thyagarajan said.

For a long time, it had been known that neurexins and neuroligins are important for synapse maturation. However, their exact function was unclear since most previous studies used indirect methods such as manipulating gene expression to infer function.

"Our motivation was that if we could come up with a way to directly observe this complex, then maybe we could better understand its function in synapse maturation," Thyagarajan said.

"We developed BLINC to visualize this complex in live synapses in culture. We then used BLINC in different modalities to discover that synaptic activity causes the neurexin-neuroligin complex to grow in size," he said. "This growth is necessary for the recruitment of AMPA receptors to young synapses.

"AMPA receptor recruitment is a hallmark of excitatory synapse maturation, so our study demonstrated how a trans-synaptic complex can affect early phases of synapse maturation," Thyagarajan said.

More information: "Imaging Activity-Dependent Regulation of Neurexin-Neuroligin Interactions Using trans-Synaptic Enzymatic Biotinylation," by Amar Thyagarajan and Alice Y. Ting. *Cell*, 7 October, 2010. www.cell.com/abstract/S0092-8674%2810%2901073-1

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