NEWS

Neurexin found to have diverse partners at synapse

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27 JULY 2010

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Complex cluster: Neurexin's interaction with neuroligin and LRRTM2 spurs protein assembly on both ends of the synapse. Above, green indicates all dendrites, blue indicates a dendrite expressing both LRRTM2 and neuroligin-1, and red indicates presynaptic inputs.

Scientists have discovered that neurexins — proteins linked to autism — bind to a wide variety of molecules at the junction between neurons.

This array of binding partners, some of which have themselves been implicated in autism and schizophrenia, suggests that neurexin's interactions at the junction, or synapse, are even more complicated than previously thought.

The breakdown of any one of the players could lead to improper cell signaling, ultimately giving rise to disease, researchers say.

Located at the tip of the neuron sending a signal, neurexins have long been known to bind another family of proteins, called neuroligins, on the receiving neuron. Together, these proteins somehow trigger the assembly of crucial parts of the synapse, including the machinery that sends and receives signals between neurons.

This partnership has received much attention because mutations in the genes for neurexin and **neuroligin** crop up in some people with autism and other brain disorders[1].

Several studies in recent months have revealed that neurexin has several other partners.

Three independent studies have shown that neurexin interacts with a family of proteins called leucine-rich repeat transmembrane neuronal proteins (LRRTMs)[2,3,4]. These proteins help link cells together, and have also been **linked to autism** and schizophrenia[5].One of the teams, led by **Ann Marie Craig** at the University of British Columbia, showed that the interaction of neurexin and LRRTM2, like the partnership with neuroligin, spurs the clustering of proteins on both ends of the synapse[2].

Neurexin can also directly bind to receptors for the neurotransmitter gamma-aminobutyric acid (GABA), which dampens brain signals[6]. Finally, neurexin participates in a three-part bridge between neurons by binding cerebellin 1 precursor protein, or CBLN1, found exclusively in the cerebellum, which in turn binds a receptor on the receiving cell[7].

Adding to this complexity, the three genes encoding neurexin can be cut and combined in different ways to create more than 1,000 versions of the protein[8].

The resulting redundancy safeguards synapse development, suggests **Nils Brose**, director of the Max Planck Institute for Experimental Medicine in Göttingen, Germany. "It looks as though this system has lots of safety latches, so that it still works if one molecule is gone."

Cell culture experiments support his theory, showing that defects in these interactions compromise how well a synapse works, rather than its initial formation.

That's encouraging for future autism therapies, Brose says, because it is easier to design drugs to repair correctly positioned synapses than to create synapses in just the right spots. "If I were a clinician, I'd rather deal with a synaptic defect than with a wiring defect," he says.

Synaptic teamwork

Some interactions with neurexin could be unique to specific types of synapses, such as those that produce excitatory signals, the researchers say. Some synapses might depend on several different neurexin partners acting in parallel.

"Neurons have a lot of machinery that drives them toward making synapses," notes Craig, professor of psychiatry at the University of British Columbia.

For example, Craig reported last year that LRRTMs induce excitatory synapses that use glutamate as a chemical messenger[9]. Her new study, published 2 June in the *Journal of*

Neuroscience, suggests that they work alongside neuroligins at the same synapse.

Binding to a different partner, neurexin can also influence inhibitory synapses that use the chemical messenger GABA, according to a study published 13 May in *Neuron*[6]. Thomas Südhof's team at Stanford University reported that neurexins on the transmitting end of the synapse can bind directly to a type of GABA receptor on the receiving end, which suppresses signals flowing through these receptors.

Genes encoding **GABA receptors** have been associated with autism[10]. To identify the interactions most relevant to autism, it will be important to catalog the full range of binding partners for each kind of neurexin. For example, Craig and her team find that not all neurexins are alike: Some bind LRRTMs only, others bind neuroligins only, some others bind both, and still others bind neither.

Taken together, these findings emphasize the importance of considering the whole complex of interactions with neurexin when thinking about disorders like autism, notes **Ramzi Nasir**, a developmental behavioral pediatrician at Children's Hospital Boston.

In April, Nasir described the clinical features of 12 individuals, including some with autism, who have deletions within the neurexin 1 gene[11].

"Putting neurexin at the center of the picture may not be appropriate," he adds. "Maybe we should think of the neurexin complex at the center of the picture instead."

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