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New information revealed about a protein implicated in autism and similar disorders; could lead to better drug design

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(Medical Xpress) -- University of Michigan researcher Gabrielle Rudenko and her Life Sciences Institute lab have solved the structure of a protein that is implicated in a number of neuropsychiatric disorders including autism spectrum disorder, schizophrenia and mental retardation.

This information allows scientists to better understand the molecular workings of these disorders, which will someday lead to the design of more effective drugs.

The protein structure in question is neurexin 1 alpha, which is a very large and complex protein. Neurexins are cell-surface proteins that are found exclusively in the brain and play a role in mediating the organization and adhesion of synapses. Synapses are the physical contact and communication points between neurons, and are made up of the presynaptic membrane, the postsynaptic membrane and the space between them called the synaptic cleft. Alpha-neurexins are found predominantly bound to the pre-synaptic membrane. Their very large extracellular regions, which contain more than 1,400 residues and nine domains, protrude into the synaptic cleft and bind to a number of different important synaptic proteins.

Neurexins undergo a process called alternative splicing where the messenger RNA gets modified and the result is that the encoded protein

has extra amino acids at a number of very specific sites in the extracellular region of the protein. There are thousands of different splice forms and it is known that the presence or absence of different splice inserts at these sites changes the protein partner recognition profile of neurexins and the protein partners with which they can interact with in the synaptic cleft.

"When we solved the structure, which was just a monster because of its size and the crystallographic system the protein crystals happened to grow in, what became immediately clear was that the extracellular domain of neurexin 1 alpha has many characteristic structural properties that make it a good molecule to be a synaptic organizer," Rudenko said. "This means that we think that this protein may work as a scaffold molecule in the synaptic cleft to organize the different proteins that are bound to it, into large multi-protein complexes which may give these proteins and thus the synapse an added characteristic."

"Furthermore, the overall size and shape, as well as the organization of the domains within the extracellular domain of neurexin 1 alpha all give us very definitive ideas as to how this molecule is oriented in the synaptic cleft and can recruit its different protein partners, influenced by alternative splice inserts."

Their findings were published recently in *Structure* (Cell Press), and the lab work was carried out by Rudenko and lab members Fang Chen, Vandavasi Venugopal and Bev Murray.

"What's so striking is that the neurexins as well as many of their protein partners have recently been implicated in a number of neuropsychiatric disorders. Many genetic studies are coming from different angles yet pull up these same proteins repeatedly, proteins, which we know from the studies by many labs interact with each other in biochemical and cell-based assays, and form a protein interaction network in the synaptic cleft

that somehow must contribute to a common biological pathway touched in these diseases." said Rudenko, who in addition to her position with the U-M Life Sciences Institute is also assistant professor in the Department of Pharmacology.

It is known that neurexins interact with many important molecules in the synaptic cleft, but it is not yet known why lesions in alpha neurexins increase the risk for neuropsychiatric disorders.

Having solved the structure of neurexin 1 alpha, next steps for Rudenko's lab include investigating the proteins that neurexin 1 alpha organizes and gaining further understanding how neurexins and their protein partners can contribute to the molecular basis of neuropsychiatric disorders when they are defective.

For Rudenko, solving the structure of neurexin 1 alpha extracellular domain opened an important door that she's eager to step through, "The fact that by solving its three-dimensional structure, you can actually see a protein that takes part in a biological pathway that somehow is involved in neuropsychiatric disease is tremendously exciting for me, as someone who is trying to understand the molecular basis of these diseases."

More information: www.cell.com/structure/abstrac … 0969-2126(11)00136-5

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