New insights in pathological mechanism that causes dysfunctional synapses

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Genetic analysis of human patients has shown that mutations in genes involved in synaptic communication can drive neuropsychiatric and neurological diseases such as autism spectrum disorder and Alzheimer's disease. Through a global analysis of the synaptic machinery Jeffrey Savas (Northwestern University Feinberg School of Medicine) and Joris de Wit (VIB/KU Leuven) together with their colleagues revealed for the first time a new pathway that governs the proper sorting of many essential synaptic proteins in neurons. Disruption of this sorting pathway in neuropsychiatric and neurological diseases severely hampers the efficient communication between neurons.

Joris de Wit (VIB/KU Leuven): "Our results suggest that therapeutic targeting of this pathway may prove efficacious in treating multiple neurological diseases. Jeff and I started this work in the US, when Jeff was a postdoc with John R. Yates III at The Scripps Research Institute and I was a postdoc with Anirvan Ghosh at the University of California San Diego. We continued this work after we both established our own labs, with the help of Luís Ribeiro here at VIB/KU Leuven. This intense international collaboration has enabled us to use cutting-edge proteomic technology to study the entire synaptic machinery rather than individual elements. Our work identifies a master regulator of sorting of synaptic proteins and shows that experimental disruption of this pathway impedes efficient communication between neurons. Mutations in this sorting pathway have been found in several synaptic diseases, including Alzheimer's disease. Our work highlights the importance of proper synaptic protein sorting for efficient neuronal communication and

suggests that therapeutic targeting of this pathway could prove beneficial to improve synaptic function in brain disorders."

Key findings of the paper

Synapses are specialized, protein-rich cell junctions that are essential for normal brain function and are dysfunctional in many diseases and disorders of the nervous system. Synapses are made up of many different proteins that link neurons together and regulate communication between these cells. Our results now show that perturbed sorting of these synaptic proteins hampers neuron-neuron communication and culminates in an increased level of silent synapses.

These results highlight the importance of proper synaptic protein sorting, which was a previously under-appreciated aspect of synapse development, function, and disease. Novel high-content protein analysis technologies enabled us to study synapses on a global level, which has led to a new level of understanding of the pathological mechanism that causes dysfunctional synapses in several neurological diseases, including autism spectrum disorder and Alzheimer's disease.

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