Researchers identify brain protein for synapse development

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A new study from UC Davis Health System identifies for the first time a brain protein called SynDIG1 that plays a critical role in creating and sustaining synapses, the complex chemical signaling system responsible for communication between neurons. The research, published in the Jan.14 issue of the journal *Neuron,* fills a major gap in understanding the molecular foundations of higher cognitive abilities as well as some brain disorders.

"We know that synapses are essential for learning, memory and perception and suspect that imbalances in synapse formation impact disorders of the brain such as autism and schizophrenia," said Elva Diaz, assistant professor of pharmacology and senior author of the study. "Our study is the first to identify SynDIG1 as a critical regulator of these important brain connections."

The majority of synapses in the brain use glutamate as a neurotransmitter. While past research revealed that regulation of a certain class of glutamate receptor -- AMPA receptors -- are critical to communication between neurons, Diaz set out to discover novel molecular mechanisms of AMPA receptors that could support the formation and vitality of synapses.

She began by evaluating a gene (tmem90b) predicted to encode a novel transmembrane protein that is expressed exclusively in the central nervous system and highly similar across vertebrates, but otherwise not well-described. Microarray analyses revealed that this gene was

expressed during synapse formation.

"I've always been interested in the discovery of new molecules, especially those with unique paths and intracellular influences," said Diaz, whose work focuses on the molecular mechanisms of brain development. "This is where answers to many disease processes can be found."

Diaz named the protein SynDIG1 -- or the synapse differentiation induced gene product -- and set out to define its role in synapse development. She and a team of molecular neurobiologists and electrophysiologists isolated cells from rat hippocampal neurons for a number of tests to understand the protein's functions.

One of the most important of those tests showed that SynDIG1 co-exists with AMPA receptors at the site of synapse formation, suggesting that it is essential to synapses in their earliest stages. Additional experiments revealed that manipulating SynDIG1 expression levels in the neurons changed both the number and quality of synapses, proving it had key roles in synapse formation as well in their lifespan and viability.

"Reducing SynDIG1 expression led to much fewer and smaller synapses, while increasing expression created more mature, stable synapses," said Diaz. "We think it is a key driver of the entire synaptic process, but we need to test this in an in vivo model before we can confidently say this is true."

Next, Diaz and her research team will test the role of SynDIG1 in live mice where the gene that encodes the protein is knocked out to determine the molecular and behavioral outcomes. She will also test the role of SynDIG1 in both early and established brain cells.

"We predict that SynDIG1 will be equally important in both new and

older neurons, meaning that it has importance in both neurodevelopmental and later-onset diseases," said Diaz. "We could be on the path to redefining many brain diseases as synapse diseases instead."

Provided by University of California - Davis