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Farp1 gives both sides of the story

Postsynaptic signaling protein helps organize both pre- and postsynapses.

During brain development, neuronal axons and dendrites explore their environment by extending actin-rich filopodia. If protrusions from different neurons contact each other, it's thought that they can develop into stable excitatory synapses by rearranging their membranes and cytoskeletons to form axonal boutons and dendritic spines. Cheadle and Biederer identify a signaling protein that not only regulates dendritic filopodia and spine morphology but also signals across the synaptic cleft to organize presynaptic membranes (1).

Synapse formation and organization relies on a variety of cell surface adhesion molecules that connect the pre- and postsynaptic membranes. SynCAM 1, for example, promotes the formation and maintenance of excitatory synapses (2, 3). "We've learned about many membrane proteins that drive synapse formation," says Thomas Biederer from Yale University in New Haven, Connecticut. "But, in most cases, we don't really know the signaling pathways that they operate."

To identify regulatory molecules that might act downstream of SynCAM 1, Biederer and his graduate student Lucas Cheadle looked for proteins whose expression was altered in the brains of SynCAM 1 knockout mice (1). Using quantitative mass spectrometry to analyze the composition of isolated synaptic membranes, Cheadle and Biederer found that the level of a postsynaptic protein called Farp1 was strongly reduced in the absence of SynCAM 1. In addition to a FERM domain that could interact with SynCAM 1, Farp1 contains a lipid-binding PH domain and a DH region typically found in guanine nucleotide exchange factors that activate Rho GTPases. "It had all the hallmarks we were looking for, which immediately made it something that we wanted to focus on," Biederer explains.

Farp1 promotes dendritic growth in chick motor neurons (4), but nothing is known about its function in mammals. After confirming that Farp1 interacts with SynCAM 1, Cheadle and Biederer investigated the protein's function in cultured rat hippocampal neurons. Knocking down Farp1 reduced the motility of dendritic filopodia early in synaptogenesis and inhibited the formation of dendritic spines. "And when we overexpress Farp1, we obtain more motile filopodia and, later on, more synapses," Biederer says. "So this supports the idea that mechanisms that control the frequency of axodendritic contacts also affect synapse development."

> "When we look at synapses, we should think of them as a structural and functional unit."

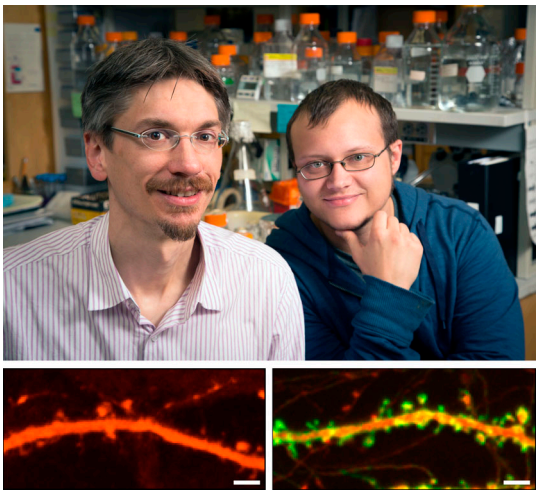
Farp1 controls synaptogenesis downstream of SynCAM 1, the researchers found. Overexpressing SynCAM 1 promoted the assembly of dendritic spines in control neurons but had no effect on cells lacking Farp1. Overexpressing Farp1, on the other hand, restored spine formation in SynCAM 1-deficient neurons.

Despite its strict localization to dendrites, however, Farp1 also signals across the synaptic cleft to regulate presynaptic terminals. "That was unexpected," Biederer recalls. "The organization of presynaptic active zones is altered when we manipulate postsynaptic Farp1 levels." Knocking down Farp1 decreased the intensity of the active zone marker bassoon, whereas overexpressing Farp1 increased bassoon intensity, an effect dependent on SynCAM 1-mediated adhesion between the pre- and postsynaptic membranes. "It's taught us that, when we look at synapses, we should think of them as a structural and functional unit," Biederer says. "Changes on one side of the synapse affect the other."

Though SynCAM 1 relays Farp1's signal across the synapse, what happens inside presynaptic terminals remains unclear. On the postsynaptic side, however, Farp1 appears to organize dendritic spines by activating the Rac1 GTPase to stimulate actin polymerization. Rac1 and other Rho proteins act downstream of several postsynaptic signaling pathways, suggesting that the activation of Rho family GTPases could be a convergence point that coordinates synapse formation. "This could help us understand how different upstream signaling proteins cooperate," Biederer says.

Farp1 itself may also act downstream of multiple membrane receptors to regulate different aspects of neuronal development and synaptogenesis. "We'd also like to investigate the dynamics of mature synapses and determine whether synaptic plasticity is regulated by Farp1," Biederer adds.

Focal Point



Thomas Biederer (left) and Lucas Cheadle (right) identify a postsynaptic signaling protein called Farp1 that works with the synaptic adhesion molecule SynCAM 1 to promote the assembly of postsynaptic dendritic spines and organize presynaptic active zones. Neurons (red) lacking SynCAM 1 form few protrusive spines along their dendrites (bottom, left), but spine formation is rescued by the overexpression of Farp1 (green, right). How Farp1 signaling affects presynaptic terminals is unclear, but the protein controls postsynaptic spine morphology by activating the Rac1 GTPase to stimulate actin filament assembly.

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