# This Week in The Journal

## p140Cap Targets GluN2A to Lipid Rafts

Costanza Angelini, Alessandro Morellato, Annalisa Alfieri, Lisa Pavinato, Tiziana Cravero, et al.

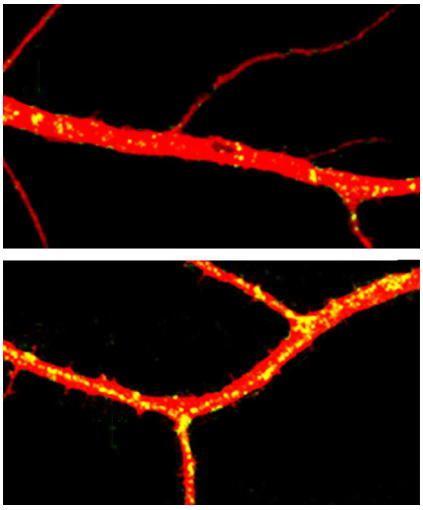
(see pages 7183–7200)

The postsynaptic density (PSD) of excitatory synapses contains an extraordinary number of proteins, including AMPA and NMDA receptors, accessory proteins that regulate receptor properties, and signaling proteins activated downstream of receptor activation. These proteins are held in a large complex by scaffolding proteins, which facilitate and regulate protein interactions. One such scaffolding protein is p140Cap. Loss of p140Cap impairs spine maturation and interferes with long-term potentiation (LTP). Work by Angelini, Morellato, et al. suggests that these impairments result from decreased targeting of NMDA receptor (NMDAR) GluN2A subunits to lipid rafts.

Co-immunoprecipitation and pull-down assays indicated that p140Cap binds directly to the cytoplasmic tail of GluN2A. In addition, p140Cap interacted with the scaffolding protein PSD95, the lipid-raft protein flotilin-1, and the small GTPase Rac1. Consistent with its interaction with flotilin-1, some—but not all—p140Cap was associated with lipid rafts. Importantly, knocking out p140Cap reduced associations between GluN2A and PSD95, flotilin-1, lipid rafts, and Rac1. It also reduced Rac1 activity.

Although p140Cap and GluN2A were detected in cultured hippocampal neurons within 5 d of plating, they did not colocalize until synaptogenesis was underway, more than a week later. Moreover, treating cultures with drugs that induce LTP increased colocalization of p140Cap with GluN2A, as well as with the presynaptic protein Bassoon. Finally, knocking out p140Cap decreased the unitary current of NMDARs and impaired the recruitment of GluN2A to synapses after chemical induction of LTP.

These data suggest that p140Cap helps tether GluN2A and Rac1 to PSD95 and target this complex to lipid rafts in dendritic spines. This targeting is promoted by synaptic activity and appears to be essential for Rac1 activation, consistent with the documented role of lipid rafts as signaling platforms. Notably, Rac1 has been shown to regulate the actin cytoskeleton of spines. Thus, failure to target GluN2A to lipid rafts may impair its ability to activate Rac1, and this might explain the loss of LTP and reduced spine maturation found in p140Cap-deficient mice



Syntaphilin (yellow) is largely excluded from dendrites (red) in cultured hippocampal neurons (top). Treating cultures with IL-1$\beta$ greatly increases the amount of syntaphilin in dendrites (bottom). See Joshi, Zhang, et al. for details.

## Dendritic Displacement of a Mitochondrial Anchor Is Toxic

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(see pages 7318–7329)

Inflammation and mitochondrial dysfunction are key contributors to neurodegeneration in many diseases, as well as after brain injury. Multiple sclerosis (MS), for example, is characterized by repeated cycles of inflammation driven by antibodies targeting myelin proteins. Although MS is considered a demyelinating disease, neurons also degenerate. Recently, Joshi, Zhang, et al. discovered that syntaphilin, a mitochondrial anchor that is normally expressed predominantly in axons, enters dendrites in a genetic mouse model of MS, and such mislocalization sensitizes neurons to excitotoxicity. The authors now report that the inflammatory cytokine IL-1$\beta$, in conjunction with activation of NMDA receptors (NMDARs), drives dendritic intrusion of syntaphilin.

Treating cultured hippocampal neurons for 24 h with IL-1$\beta$ significantly increased the amount of syntaphilin in dendrites, and this was accompanied by increases in dendritic fragmentation and neuronal death. Treating cultures with glutamate or NMDA similarly drove syntaphilin into dendrites, even at concentrations that did not increase neuronal death. Importantly, neither IL-1$\beta$ nor NMDA (at concentrations that increased neuron death in wild-type cultures) induced significant cell death in cultures from syntaphilin-deficient mice. Moreover, an NMDAR antagonist reduced both dendritic intrusion of syntaphilin and neuronal death in cultures treated with either IL-1$\beta$ or NMDA. Finally, a tyrosine kinase inhibitor that disrupts interactions between IL-1$\beta$ and NMDA prevented dendritic intrusion of syntaphilin in cultures treated with either of these molecules.

These results suggest that excitotoxicity driven by excessive activation of NMDARs is associated with the displacement of syntaphilin into dendrites, which leads to dendritic fragmentation. The results further suggest that excessive activation of NMDARs can be promoted by IL-1$\beta$, a master regulator of inflammation. Therefore, dendritic intrusion of syntaphilin, likely affecting mitochondrial function, may be a pathological event common to many neurodegenerative conditions.

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