This Week in The Journal

● Cellular/Molecular

Complexin Influences Ca^{2+} Dependence of Vesicle Release

Ramon A. Jorquera, Sarah Huntwork-Rodriguez, Yulia Akbergenova, Richard W. Cho, and J. Troy Littleton

(see pages 18234–18245)

Fusion of vesicles to the plasma membrane is driven by formation of SNARE complexes composed of proteins residing in vesicular and target membranes. Formation of this complex brings the membranes together and delivers energy sufficient to drive fusion. Fusion can occur spontaneously, but at synapses, complexin clamps vesicles when the SNARE complex is partially formed; then, when calcium enters the terminal, synaptotagmin drives synchronous fusion of multiple vesicles. Experiments by Jorquera et al. demonstrate how complexin and synaptotagmin cooperate to regulate spontaneous (spike-independent) and evoked vesicle release in *Drosophila* larvae. Knocking out complexin increased the frequency of spontaneous vesicle release at neuromuscular junctions, thus reducing the size of the readily releasable pool and the proportion of vesicles released synchronously during spikes. Surprisingly, complexin knockout also reduced the calcium dependence of release. Furthermore, knocking out synaptotagmin rescued spontaneous release rates in complexin-null larvae. Altogether, the results suggest that synaptotagmin can facilitate vesicle fusion independently of calcium, but complexin makes synaptotagmin–SNARE interactions calcium dependent.

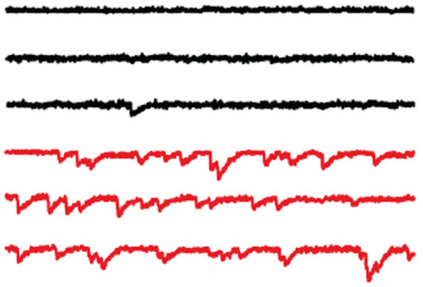
▲ Development/Plasticity/Repair

miR-21 Increases Tissue Damage after Injury

Oneil G. Bhalala, Liuliu Pan, Vibhu Sahni, Tammy L. McGuire, Katherine Gruner, et al.

(see pages 17935–17947)

Astrocytes react to CNS injury by growing larger, with thicker processes. Reactive astrocytes form a barrier around injured areas, limiting the spread of inflammation and tissue damage. But the scar formed by reactive astrocytes ultimately impedes recovery by inhibiting axonal regeneration. Enhancing the protective effects of reactive astrocytes while limiting their damaging effects might therefore increase functional recovery. Possible targets for such efforts include microRNAs whose expression levels change after tissue damage and which regulate translation of many other transcripts. Bhalala et al. discovered that levels of microRNA miR-21 greatly increased in astrocytes surrounding sites of spinal cord injury (SCI) in mice. SCI-induced astrocytic hypertrophy was reduced in mice overexpressing miR-21, and the lesion area expanded. In contrast, overexpressing an "miRNA sponge"—which contained multiple sequences complementary to miR-21 and thus competed with endogenous targets—increased astrocyte reactivity after SCI. Astrocytes in these mice remained reactive for weeks after injury, and axonal labeling increased within the lesion area, suggesting that inhibiting miR-21 promotes axonal regeneration.



The frequency of miniature EPSCs, representing spontaneous vesicle release, is greatly increased at neuromuscular junctions of fly larvae lacking complexin (red) compared with wild-type larvae (black). See the article by Jorquera et al. for details.

■ Behavioral/Systems/Cognitive

Gravin Anchoring of PKA Allows Learning

Robbert Havekes, David A. Canton, Alan J. Park, Ted Huang, Ting Nie, et al.

(see pages 18137–18149)

Protein kinase A (PKA) is activated by many transmembrane receptors, and it initiates signaling cascades that have diverse effects. Specificity of PKA action is achieved partly by A-kinase-anchoring proteins (AKAPs), which compartmentalize PKA with different sets of receptors and downstream effectors. PKA is involved in several forms of synaptic plasticity, and preventing PKA from binding to AKAPs impairs hippocampal-dependent learning. But which AKAPs are required for PKA-dependent learning is unresolved. A likely candidate is gravin. According to Havekes et al., gravin is expressed throughout mouse hippocampus, and mice lacking gravin had deficits in PKA-dependent forms of hippocampal long-term potentiation and hippocampal-dependent learning tasks such as spatial learning and contextual fear conditioning. In several learning paradigms, PKA phosphorylates β2-adrenergic receptors (β2-ARs), which then activate a signaling cascade involving ERK1/2. But phosphorylation of β-AR and ERK1/2 after fear conditioning was lower in gravin-deficient mice than in wild-type. The data suggest that gravin is the requisite PKA anchor for β-AR- and hippocampus-dependent learning.

♦ Neurobiology of Disease

Peripheral Cytokines Can Trigger Neuropathology

Jill Bouchard, Jennifer Truong, Kristofer Bouchard, Diana Dunkelberger, Sandrine Desrayaud, et al.

(see pages 18259–18268)

Evidence that inflammatory agents promote neurodegeneration is rapidly accumulating. These agents, which include various cytokines, can cross the blood–brain barrier, and those released by peripheral immune cells affect the brain—triggering behaviors associated with sickness, for example. Although plasma levels of cytokines increase years before the onset of neurological symptoms in Huntington's disease (HD), activated astrocytes and microglia have been thought to release the cytokines involved in this and other neurodegenerative diseases. But Bouchard et al. demonstrate that peripherally produced cytokines speed disease onset and progression in mouse models of HD, and that activation of cannabinoid CB2 receptors greatly reduces HD pathology. CB2 activation inhibits cytokine release from immune cells, and accordingly, CB2 agonist reduced blood levels of interleukin-6 (IL-6), which are normally elevated in HD mice. Antibodies against IL-6 also improved motor function in HD mice. Importantly, the effects of CB2 agonist were blocked by coadministration of a brain-impermeable CB2 receptor antagonist, indicating that the effects resulted from peripheral actions.