In This Issue

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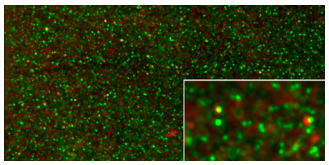
Building memories with actin



Activated PAK (red) gathers at synapses (green) and might help consolidate fresh memories.

Memories aren't made of actin filaments. But their assembly is crucial for long-term potentiation (LTP), an increase in synapse sensitivity that researchers think helps to lay down memories. Rex et al. reveal that LTP's actin reorganization occurs in two stages that are controlled by different pathways, a discovery that helps explain why it is easy to encode new memories but hard to hold onto them.

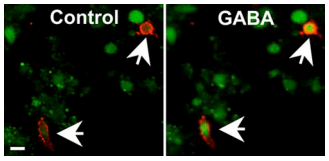
If you can't seem to forget those ABBA lyrics you heard in seventh grade but can't remember Lincoln's Gettysburg address, the vagaries of LTP might be to blame. Neuroscientists think that the process, in which a brain synapse becomes more potent after repeated stimulation, underlies the formation and stabilization of new memories. LTP involves changes in the anatomy of synapses and dendritic spines, a process that depends on reorganization of the supporting actin cytoskeleton. However, researchers didn't know what controlled these changes.

Rex et al. tackled the question by dosing slices of rat hippocampus with adenosine, a naturally occurring signal that squelches LTP. Adenosine prevents phosphorylation and inactivation of cofilin, an inhibitor of actin filament assembly, the team found. Cofilin's involvement, in turn, implicates signaling cascades headed by GTPases, such as the RhoA-ROCK and Rac-PAK pathways. The researchers showed that a ROCK inhibitor stalled actin polymerization and resulted in a short-lived LTP. A Rac-blocking compound had no effect.

That doesn't mean the Rac-PAK pathway isn't involved in LTP, however. The team discovered that the Rac inhibitor prolonged cells' vulnerability to a molecule that prevents the stabilization of new actin filaments. That result led Rex et al. to conclude that the two pathways exert their effects at different points. The Rho-ROCK pathway initiates the cytoskeletal changes of LTP, and the Rac-PAK pathway solidifies them so that heightened synapse sensitivity can persist. The researchers hypothesize that one pathway encodes memories, while the other makes sure they stick around.

Rex, C.S., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200901084.

Brain-repairing cells follow trail of GABA



Two NG2 cells (arrows) soak up calcium after a dose of GABA.

Like paramedics waiting for an emergency, cells that help heal injuries are stationed around the brain. Tong et al. have intercepted the signal that dispatches these cells to their posts.

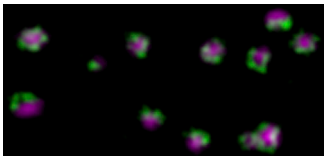
NG2 cells spawn the oligodendrocytes that produce insulating myelin for the central nervous system. During development, NG2 cells arise in the brain's ventricular zone and then fan out to other parts of the organ. They remain in position, presumably providing a reserve that can replace lost and damaged oligodendrocytes after an injury. The unanswered question is what triggers their move.

Tong et al. connected the cells' migration to their electrophysiology. Like neurons, NG2 cells depolarize after stimulation, allowing in a flood of sodium ions—although they can't muster a full-fledged action potential. After this surge of sodium ions, a calcium influx follows as sodium–calcium exchanger proteins kick into gear. The researchers found that the neurotransmitter GABA, released from neighboring neurons, spurs the sodium and calcium inflow into NG2 cells. Reducing the levels of sodium channels or exchanger proteins with RNAi stymied GABA's effect on calcium.

The team also gauged NG2 cell movement in culture and in brain slices from newborn rats. The cells traveled toward sources of GABA. By inducing sodium and calcium inflow, the findings suggest, GABA prods NG2 cells to disperse through the brain. This pathway differs from the pathway that spurs neuron migration, which involves calcium channels.

Tong, X., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200811071.

Calcium channel roundup



The N-terminal (magenta) and C-terminal (green) of Bruchpilot color the active zones of a synaptic terminal.

Thanks to a protein that helps fruit flies remain airborne, researchers have deciphered a key step in synapse maturation. Fouquet et al. show that the protein forms part of a synaptic structure that clusters the calcium channels necessary for neurotransmitter release.

The active zone of the presynaptic terminal lives up to its name. Vesicles crowd in to discharge their loads of neurotransmitter into the synaptic cleft. Bunches of calcium channels swing open when an action potential arrives and then shut. Also located at the active zone are filaments that extend into the cytoplasm. At the neuromuscular junction of fruit flies, these structures, known as T-bars disappear when the active zone protein Bruchpilot is missing. Calcium channels also disperse. Researchers thought that Bruchpilot, German for "crash pilot," a reference to the aerial ineptitude of insects lacking the protein, helps corral calcium channels and thus boosts synaptic efficiency. But whether Bruchpilot was a signaling protein or a structural component of T-bars was unclear.

By studying the effects of different Bruchpilot mutants on synapse development, Fouquet et al. showed that the protein is a building block for T-bars. Bruchpilot seems to stretch out along the T-bar, with its N-terminal close to the calcium channels of the active zone membrane. The team found that Bruchpilot moves into the active zone fairly late in development of an individual synapse, slightly after one component of the calcium channels. Although Bruchpilot can latch onto this component, the asynchrony suggests that the protein doesn't help tow the channels to the active zone. Instead, Bruchpilot's job might be to help them remain gathered there. The next question to answer, the researchers say, is how T-bars affect the movement of vesicles to the active zone membrane.

Fouquet, W., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200812150.