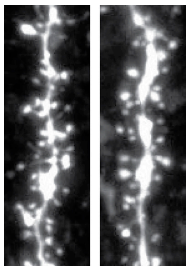
In This Issue

Text by Ben Short
bshort@rockefeller.edu

TRIMming γ-actin levels improves the memory



Compared with a wild-type control (left), spine density is increased in the hippocampal neurons of TRIM3-deficient mice (right).

Schreiber et al. reveal that a ubiquitin ligase regulates synaptic plasticity and memory formation by targeting γ-actin for degradation.

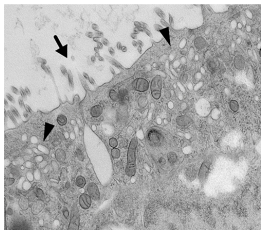
The ubiquitin ligase TRIM3 localizes to the dendrites and synapses of hippocampal neurons, but its function in the brain remains unclear. Schreiber et al. found that mice lacking TRIM3 learned to anticipate electric shocks quicker than wild-type animals. Accordingly, TRIM3-deficient hippocampal neurons had a higher density of dendritic spines and showed increased long-term potentiation, a type of synaptic plasticity associated with learning and memory.

TRIM3 has been proposed to target several synaptic proteins for degradation, but the levels of these candidate substrates were unaltered in TRIM3-knockout mice. Schreiber et al. therefore looked for alternative TRIM3 targets and found that the enzyme can polyubiquitylate γ-actin (probably cotranslationally, because TRIM3 localizes to synaptic ribonucleoprotein particles containing γ-actin–encoding mRNAs). Synaptic γ-actin levels were consequently increased in the absence of TRIM3, the researchers discovered. Although this was associated with enhanced memory consolidation over shorter time periods, depleting γ-actin from hippocampal neurons enhanced mice's long-term memory of electric shocks, suggesting that the temporal regulation of γ-actin levels by TRIM3 is critical for the appropriate timing of synaptic plasticity.

γ-Actin is almost identical to β-actin, but its incorporation into actin filaments increases their stability in vitro. Author Ronald van Kesteren says that it will be important to investigate how γ-actin levels influence actin stability and synapse morphology in vivo.

Schreiber, J., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201506048

Special delivery to the apical membrane



Intestinal cells expressing a mutant form of *MYO5B* lack apical microvilli (arrow) and accumulate secretory vesicles in their subapical region (arrowheads).

Vogel et al. describe a selective exocytic pathway that goes awry in the rare genetic disorder microvillus inclusion disease (MVID).

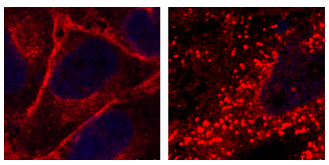
MVID patients suffer a life-threatening loss of intestinal function shortly after birth. Their intestinal cells lose their apical microvilli, which instead accumulate in intracellular inclusions, while numerous secretory vesicles pile up beneath the apical plasma membrane. Many cases of MVID are caused by mutations in the gene encoding the unconventional myosin motor Myo5B, which is recruited to apical secretory vesicles by the GTPases Rab8 and Rab11.

Vogel et al. found that Myo5B's interaction with the two Rab proteins promoted its association with other proteins involved in apical transport, including components of the exocyst tethering complex, the vesicle SNARE-like protein Slp4a, and the apical membrane SNARE syntaxin3, whose gene has also been linked to MVID.

The researchers then used genome editing to generate a human intestinal epithelial cell line carrying a *MYO5B* mutation found in MVID patients. These cells recapitulated the defects seen in patient-derived samples, including the accumulation of vesicles beneath the apical plasma membrane. In these cells, syntaxin3 didn't associate with its cognate vesicle SNAREs, indicating that Myo5B is required to bring secretory vesicles close enough to the apical membrane for them to undergo SNARE-dependent fusion. Several key proteins, including the sodium/hydrogen exchanger NHE3 and the glucose transporter GLUT5, were not delivered to the apical membrane in *MYO5B* mutant cells. Several other apical proteins still localized correctly, however, indicating that the Myo5B pathway selectively transports specific apical cargoes. The authors now want to identify ways to restore this pathway when Myo5B's function is compromised.

Vogel, G.F., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201506112

Notch commandeers COMMD9 for endosomal sorting



Notch2 (red) accumulates at the surface of control cells (left) but is retained in intracellular endosomes in the absence of COMMD9 (right).

An endosomal protein complex regulates Notch signaling by promoting Notch receptor recycling to the cell surface, Li et al. reveal.

The 10 members of the COMMD protein family are conserved from protozoans to humans. COMMD1 assembles with several endosomal proteins to form a "CCC" complex that promotes delivery of the copper transporter ATP7A to the plasma membrane. Whether other COMMD proteins act similarly to regulate the endosomal sorting of other membrane proteins remains unclear.

Li et al. found that COMMD9—whose gene is deleted in patients with WAGR syndrome—interacts with CCC subunits and with members of the Notch receptor family. Notch surface levels were reduced in cells lacking COMMD9; the receptors were instead retained in endosomes and delivered to lysosomes for degradation, resulting in decreased activation of the Notch signaling pathway. Accordingly, mice lacking *Commd9* developed cardiovascular defects similar to Notch-deficient animals and died during embryogenesis.

CCC complexes appear to incorporate multiple COMMD proteins and link them to key components of the endosomal sorting machinery. COMMD9 preferentially interacted with COMMD5 and COMMD10, and depleting COMMD5 also impaired Notch receptor trafficking to the plasma membrane. Senior author Ezra Burstein thinks that different combinations of COMMD proteins may act as sorting receptors for specific endosomal cargoes. Alternatively, the various family members could operate at distinct stages of the endocytic and secretory pathways.

Li, H., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201505108