In This Issue

Sticking to the nuclear envelope

A mutation in torsinA, an AAA ATPase protein, causes DYT1 dystonia in humans. On page 855, Goodchild and Dauer identify two protein binding partners of torsinA, one that localizes to the ER membrane and one that spans the inner membrane of the nuclear envelope. The team hypothesizes that DYT1 is a nuclear envelope disease, and that identification of such protein complexes will provide a mechanistic probe into a poorly characterized region of the cell.

In wild-type cells, the majority of torsinA protein localizes to the lumen of the ER, while a small proportion associates with the nuclear envelope. In cells carrying the disease-associated mutation, the proportion of torsinA at the envelope increases. Furthermore, a torsinA mutant that cannot hydrolyze ATP, and therefore becomes trapped on its target protein, selectively localizes to the nuclear periphery.

To find out what torsinA binds at the nuclear envelope, the team screened a series of nuclear envelope proteins in cells expressing GFP-labeled torsinA. Overexpression of LAP1, a lamin-associated protein, increased the proportion of perinuclear torsinA, and further analysis demonstrates an association between torsinA and the lumenal domain of LAP1. Based on sequence comparisons, Goodchild and Dauer identified a second torsinA binding protein, LULL1, an ER protein that has a single transmembrane domain and a long lumenal domain similar to that of LAP1. The torsinA-LULL1 association is also dependent on the luminal region of LULL1.

The association between lamins, LAP1, and torsinA suggests that torsinA dysfunction may cause problems typical of laminopathies, including improper chromatin organization, transcriptional problems, or overall changes in nuclear architecture. Because the function of AAA ATPase proteins is known—they typically use the energy of ATP hydrolysis to disassemble multiprotein complexes or unfold individual proteins—the researchers think they can use the complex as a launching point to learn about the function of the nuclear envelope.

Exocytosis in small steps

Neuroendocrine cells have two modes of exocytosis. In one mode, the vesicle fuses to the target membrane, and in the other—referred to as kiss-and-run—the vesicle touches the membrane and creates a small temporary pore. On page 929, Richards et al. show that the small synaptic vesicles in hippocampal neurons also use both mechanisms. The two modes of exocytosis differ in their kinetics and amplitude of the release, and may generate different postsynaptic responses.

To determine whether neurons have two pathways for exocytosis, the team loaded only a fraction of the synaptic vesicles with a fluorescent dye, a trick that allows them to resolve the activity of individual vesicles. They saw two types of exocytic events occurring: fast large releases of dye and slow small ones. The researchers conclude that the fast release events occur when a vesicle fuses with the plasma membrane, dumping its total dye content at a rate limited only by diffusion. On the other hand, the small release events appear to occur when a vesicle forms only a small pore in the plasma membrane. The speed of dye release in these small events is the same as that which occurs if the researchers use a toxin to poke a 1–2-nm hole in the membrane of a synthetic vesicle.

Richards et al. hypothesize that these different types of synaptic release may have a functional role in neural signaling. For example, it is known that when the vesicles of these hippocampal neurons fuse with the membrane and dump their whole load of neurotransmitter into the synaptic cleft, they excite the postsynaptic neuron. It could be that the dribbling release of neurotransmitter that occurs in the slow small exocytic events instead desensitizes the postsynaptic neuron. The data to confirm this are lacking, but several groups are now trying to figure out how to combine the electrophysiology and fluorescence experiments to find out.

![LULL1 (red) draws torsinA (green) away from the nuclear envelope.][1]

![Synaptic vesicle release comes in two sizes: large and small.][2]