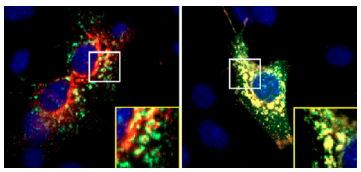
In This Issue

Text by Mitch Leslie
mitchleslie@comcast.net

VPS35 leaves endosomes lost in transition



Relative to control cells (left), cells short on VPS35 (right) accumulate more BACE1 (red) in endosomes (green).

Sluggish recycling of a protein-slicing enzyme could promote Alzheimer's disease (AD), Wen et al. show.

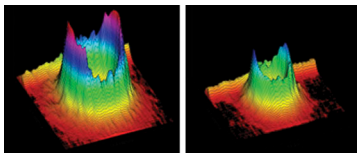
Aβ, the protein that accumulates in the brains of AD patients, is formed when enzymes cut up its parental protein, known as amyloid precursor protein. One of those enzymes is β-secretase or BACE1. BACE1 cycles between the Golgi apparatus and the plasma membrane, traveling through endosomes on the way. A protein complex called the retromer helps transport proteins from endosomes to the Golgi. Previous studies have found reduced levels of two retromer components, including the protein VPS35, in the brains of AD patients.

To find out whether VPS35 affects AD, the team crossed two mouse lines to create animals that are prone to many AD symptoms and generate half the normal amount of VPS35. The mice displayed AD-like abnormalities earlier than their parental strains, and their brains accumulated more Aβ.

Cells lacking VPS35 carried extra BACE1 in their endosomes. BACE1 is more active in the acidic interior of endosomes than in the more basic surroundings of the Golgi apparatus. Thus, by leaving more BACE1 trapped in endosomes, the decline in VPS35 levels could spur the formation of more Aβ. Although no VPS35 mutations have so far turned up in AD patients, the protein's level in the brain dwindles with age in mice. The researchers suspect that certain AD risk factors, such as oxidative stress, also diminish VPS35 levels in the brain.

Wen, L., et al. 2011. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201105109.

The actomyosin ring bulks up



Purple in this heat map indicates that there is more myosin II in a larger contractile ring (left) than in a smaller one (right).

Calvert et al. reveal that large fungal cells have more myosin II associated with their contractile rings than do smaller cells, which allows them to constrict the ring faster during cytokinesis.

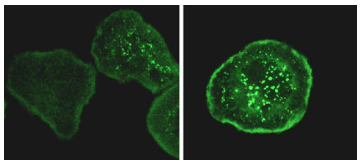
A recent study of *C. elegans* embryos showed that the time required for the contractile ring to close during cytokinesis was about the same no matter the size of the cell, which means the ring must tighten faster in larger cells. Scientists have been keen to test whether girth affects constriction rate in other species. The obstacle has been finding organisms whose dividing cells differ enough in size.

Calvert et al. recognized a candidate for such a study—the fungus *Neurospora crassa*. Its filaments, or hyphae, can vary up to fourfold in diameter and undergo a process called septation that's somewhat akin to mitosis.

As in nematodes, the ring closed faster in larger hyphae. But *N. crassa* differed from nematodes in a couple of ways. In *N. crassa*, the contractile rings of larger cells started out with more myosin II than the rings of smaller cells, which could drive faster constriction. Indeed, reducing the amount of ring-associated myosin II slowed the rate of constriction. In addition, the amount of myosin II in the ring remained constant as the ring tightened, instead of declining as in nematodes. Therefore, in *N. crassa*, the design and mechanics of the contractile ring vary with size. Future studies will investigate whether the same relationship holds in other species.

Calvert, M.E.K., et al. 2011. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201101055.

HPK1 tones down the T cell receptor



Cells with a normal version of HPK1 (left) carry fewer microclusters (green spots) than does a cell with a faulty version of HPK1 (right).

Like a fire alarm that keeps ringing after the blaze is out, the T cell receptor (TCR) can cause problems if it continues transmitting signals. Lasserre et al. clarify the intricate mechanism that turns off the receptor.

The TCR detects pathogens and enlists the adaptive immune system to combat the invaders. On the surface of a T cell, TCR molecules huddle with several other kinds of proteins to form signaling microclusters. However, prolonged signaling can prompt autoimmune attacks, so cells need a way to disperse the microclusters. Previous work suggested that the protein kinase HPK1 inhibits T cell signaling by phosphorylating a key microcluster adaptor called SLP76, spurring it to bind to members of the 14-3-3 protein family. But how HPK1's actions turned down TCR signaling remained unclear.

Lasserre et al. showed that HPK1 slips into microclusters and breaks them up. To join a microcluster, SLP76 first hooks up with the protein GADS, which connects to another protein, LAT, that admits the pair to the microcluster. HPK1 phosphorylated not only SLP76 but also GADS, prompting both molecules to link up with 14-3-3 proteins. In turn, the 14-3-3 proteins force SLP76 and GADS to separate from LAT, breaking up the microcluster and curbing signaling. In the future, researchers will need to work out the mechanism that adjusts HPK1 activity under normal and pathological conditions. Mice and humans lacking the protein are prone to autoimmune diseases, suggesting that it may be a promising target for drugs to treat these illnesses.

Lasserre, R., et al. 2011. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201103105.