SNAREs drum up calcium

On page 195, Merz and Wickner show that when two intracellular vesicles fuse, the interaction of their SNARE proteins triggers a short-lived calcium release. The work provides the first clear connection between calcium release and the fusion cycle, and supports a model in which the pairing of SNAREs in trans coordinates the downstream signals that lead to vesicle fusion.

Previous work had hinted at a requirement for calcium signaling during vesicle fusion, but it was unclear what triggered the calcium release. In the new work, the authors isolated vacuoles from mutant yeast strains and analyzed their fusion in vitro. For calcium release to occur in this system, four different vacuolar SNARE proteins from two different membranes must interact after the priming step of the fusion cycle. Staging experiments suggest that each of these trans-SNARE interaction events triggers a short-lived calcium release.

Merz and Wickner propose that, after priming, the formation of SNARE complexes between apposed membranes during the docking step could serve as a checkpoint in the fusion cycle. Once the trans-SNARE complexes form, the resulting calcium release signifies that the priming step is over, inducing downstream calcium-dependent signals that ultimately bring about fusion.

Conjunction of junctions goes beyond function

The growth of a network of branching tubes during organogenesis and the formation of a watertight epithelial barrier may seem like very different processes, but on page 313, Wu et al. uncover a surprising connection between the two. The work also reveals a common molecular basis for the formation of invertebrate septate junctions and vertebrate tight junctions.

In the new work, the authors cloned the *sinuous* gene of *Drosophila*, which was previously found in a screen for mutations that affected tracheal tube formation. The product of *sinuous* shares homology with claudins, the family of proteins responsible for forming the seals of vertebrate tight junctions. *Sinuous* localizes to the fly septate junction, and is essential for the formation of normal barriers.

The molecular and functional similarities between tight junctions and septate junctions—structures that were previously considered analogous rather than homologous—suggest that different types of barrier junctions arose from a single, claudin-containing ancestral structure. The nonbarrier functions of junction components could have driven their divergence. For example, the activity of *sinuous* in tracheal development seems to be distinct from its function in septate junction barrier formation. The authors are now trying to determine how this novel claudin works in both processes.

How insulin signals globally and acts locally

Insulin stimulation in adipocytes sends signals through two pathways, one dependent on phosphatidylinositol-3-kinase (PI3K) and the other acting through the small membrane-associated GTPase TC10. On page 279, Kanzaki et al. reveal an unexpected convergence of the two pathways, and show that the localization of atypical protein kinase C (PKCζ) to specific lipid raft microdomains confers specificity on the system.

Previous work had suggested that PI3K could activate PKCζ or protein kinase B, but the relative importance of these downstream effectors was controversial. In the new study, the authors found that both the PI3K and TC10 pathways can activate PKCζ in adipocytes, but only the TC10 pathway recruits PKCζ to TC10-containing lipid raft microdomains. The localization is directed by Par6 and Par3, proteins that are known to link GTPases to PKCs in the worm *C. elegans*. PI3K activation is a common result of many signaling pathways and thus has many readouts, some of them inappropriate for insulin signaling. Kanzaki et al. believe that insulin stimulates PI3K to levels that are by themselves insufficient to generate all downstream events, either desirable or undesirable. But the convergence of the TC10 stimulation on raft-localized PKCζ pushes the stimulation to a level sufficient to turn on only the few desirable downstream events, such as the recruitment of glucose transporters, that function in raft microdomains.