GLUT4 ready to go

Vesicles containing the glucose transporter GLUT4 travel rapidly on a microtubule network that lies just under the plasma membrane in resting cells, according to results from Lizunov et al. (page 481). The vesicles occasionally touch the plasma membrane and, when stimulated by insulin, quickly fuse with it.

GLUT4 is sequestered in vesicles in resting cells. Insulin exposure induces the vesicles to fuse to the plasma membrane. But how these vesicles are stored in the resting cell was unclear.

To find out, the team used total internal reflection fluorescence (TIRF) microscopy on freshly isolated adipose cells transfected with GLUT4-GFP. Whereas confocal microscopy illuminated vesicles scattered throughout the cytoplasm, TIRF movies showed the vesicles just under the plasma membrane. These sub-membrane vesicles were moving on microtubules in unstimulated cells. Within ten minutes of insulin exposure, 50% of the GLUT4 had reached the surface—and most of the vesicles on the microtubule network were clustered at sites on the membrane.

The authors aim to find out what the vesicles are doing as they move around the resting cell, sampling the plasma membrane. They speculate that the moving vesicles might allow the cell to rapidly respond to a narrow area of insulin exposure. JCB

Evidence for AMPAR association

Characterization of AMPA receptors (AMPARs) purified from wild-type mice and from a mouse strain carrying an epitope-tagged version of the GluR2 subunit shows that AMPARs interact with only a subset of proteins previously thought to associate with the receptors, report Fukata et al. (page 399).

Changes in the number of AMPARs alter how well synapses conduct currents in the brain and are thought to control memory storage. A large number of proteins have been found to associate with AMPARs by in vitro assays, such as two-hybrid screens or coexpression in cell lines, but evidence for functional interaction is limited.

When Fukata et al. purified AMPAR components from brain extracts of transgenic mice expressing the epitope-tagged GluR2, only BiP, a common ER chaperone, and transmembrane AMPAR regulatory proteins (TARPs) came down in a quantitative manner. Because BiP and TARPs were in distinct AMPAR complexes, the researchers hypothesized that BiP–GluR2 may be an immature transitory complex.

Why didn’t the other known AMPAR proteins come down? The authors think that only a few of the previously identified proteins associate with the majority of AMPARs in brain cells. The other proteins might interact with the receptors in a small subset of cells or under specific conditions. And the new work is consistent with emerging genetic data showing that, when these other proteins are removed, there are limited effects as compared with the phenotype of the stargazer mouse, a TARP mutant that lacks functional AMPARs in a common neural cell type in the brain. JCB

Junctions tighten myelin sheaths

ight junction-like structures run along myelin sheaths in both the central and peripheral nervous systems (CNS and PNS), but have only been functionally characterized in the CNS. Miyamoto et al. (page 527) find evidence that these structures work as true tight junctions to seal off the myelin sheath and are required for proper neural conductance in the Schwann cells of the PNS.

Claudin proteins are major cell adhesion molecules in tight junctions. Mutations in claudin-11 compromise the CNS, but leave the PNS untouched, begging the question as to whether the morphologically similar structures in the PNS act as tight junctions and if so whether a claudin family member is involved.

Miyamoto et al. went looking for a claudin family member expressed in the PNS. Claudin-19 fit the bill. Mice lacking functional claudin-19 showed behavioral and morphological abnormalities suggestive of peripheral nerve damage and disruption of the tight junction-like structures. Recordings of compound action potentials showed two currents, one fast and one slow. This change in conductance properties indicated that, without claudin-19, the myelin sheath of Schwann cell appeared to be inadequately sealed from the environment. Thus the mutation may have interfered with normal saltatory travel of neural currents.

The dependence on tight junctions may be greater in thinner myelinated axons than in thicker ones because the thinner axons lack the bulk that would compensate for improperly sealed wrappings. The team is continuing to follow the now two-year-old mice to see if a lack of proper tight junctions induces demyelination later in life. JCB