Myo6 gets choosy

Stimulated neurons that lack myosin VI (Myo6) fail to endocytose a subtype of glutamate receptors called AMPARs, report Osterweil et al. on page 329. However, the neurons do not have a general endocytosis defect, suggesting a role for Myo6 in specific endocytic events.

Unlike other myosins, Myo6 moves toward the minus ends of actin filaments. Thus, in polarized cells or cell regions, such as the dendritic spines of neurons, Myo6 moves toward the inside of the cell. Dominant-negative mutants of Myo6 have a generalized defect in endocytosis, but this may be explained by Myo6’s interaction with AP2, a clathrin adaptor protein, rather than Myo6’s normal function.

Osterweil et al. turned instead to Myo6 mutant mice (sv/sv animals). Neurons in the hippocampi of these mice made fewer synaptic connections and had shorter dendritic spines than normal. Additionally, when the researchers stimulated sv/sv neurons in culture with either AMPA or insulin, both of which cause endocytosis of AMPARs, the cells showed less AMPAR internalization than control cells. The sv/sv cells were normal for transferrin endocytosis, suggesting that only specific endocytic targets are affected.

In ongoing work the group finds that only some endocytic events are blocked in other organs of sv/sv animals, suggesting Myo6 may regulate specific endocytosis in a variety of cell types.

A GTP signal to the nucleolus

Nucleolar size and cell growth rate are positively correlated, perhaps based on ribosome biogenesis being localized to the nucleolus, but little is known about how nucleolar size is controlled. One possible mechanism is reversible localization of key regulators. On page 179, Tsai and McKay identify the mechanism controlling one such localization system. They find that nucleostemin, a nucleolar protein found preferentially in stem cell and cancer cells and required for them to remain in the cell cycle, localizes to the nucleolus when it is GTP bound.

Based on mutants, three regions of nucleostemin affected nucleolar localization. An NH2-terminal basic region conferred short-lived nucleolar binding, whereas an internal domain appeared to inhibit entry into the nucleolus. However, this inhibitory function was turned off when GTP was bound to the third region, a GTP-binding domain. Furthermore, mutations that blocked GTP binding reduced nucleolar localization, as did the addition of an inhibitor of GTP biosynthesis.

Together, the data suggest that the inhibitory domain and the GTP-binding domain work together as a gating mechanism to control nucleostemin’s entry into the nucleolus, and that GTP is the switch that opens the gate. The use of GTP to control nucleolar localization enables the cell to transmit information regarding the surrounding environment to the nucleolus via cell-signaling pathways, and may provide a mechanism to link growth signals with the size and activity of the nucleolus.

Growth and trafficking

The lipid phosphatase Sac1p inhibits transport out of the Golgi and, based on its expected target, should increase transport out of the ER. Now, Faulhammer et al. find that Sac1p switches from its ER role to the Golgi role in response to lower nutrient levels, thus reducing trafficking and providing an initial link between growth and secretion (page 185).

Faulhammer et al. found that Sac1p localized to the ER during exponential growth and was retained there by a direct interaction with an integral ER membrane protein called dolichol phosphate mannose synthase, or Dpm1p. When the researchers transferred these fast growing cells to nutrient-poor media, Sac1p moved to the Golgi within minutes.

Sac1p was physiologically active in both compartments, a point that has previously been missed by researchers focusing on fast-growing cells. In the ER, the protein stimulated trafficking, but in the Golgi, it reduced the amount of phosphatidylinositol-4-phosphate and slowed vesicle traffic.

It is not yet clear what alteration in Dpm1p or Sac1p facilitates relocation of Sac1p to the Golgi during nutrient deprivation, but the rapid response suggests that it is likely to be some sort of protein modification event. Two major signaling pathways, TOR and RAS, are already known to sense nutrient availability, making them likely candidates for upstream regulators of Sac1p shuttling.