How big is your organelle?

Simple questions in cell biology seldom have simple answers, but on page 405, Marshall and Rosenbaum provide evidence for a strikingly straightforward mechanism for controlling the sizes of organelles. Determination of flagellar length in Chlamydomonas provides a tractable experimental system for studying organelle size regulation, and Marshall and Rosenbaum found that an equilibrium between assembly and disassembly of tubulin at the flagellar tip can explain most aspects of flagellar length control.

Using a new assay to visualize tubulin turnover, the authors demonstrate that flagella are dynamic structures in which tubulin continuously assembles and disassembles at the distal end. Movement of tubulin by intrflagellar transport (IFT) is required for microtubule assembly at the flagellar tip, but IFT is not required for microtubule disassembly; when IFT is blocked, the flagella shorten and disappear, whereas inhibiting disassembly causes flagella to lengthen. Computer simulations using a steady-state model show that flagellar length could be determined by a simple balance of tubulin assembly and disassembly rates. More complex three-dimensional organelles may require additional size control mechanisms, but the new results demonstrate that a complicated “size sensor” may not be necessary.

The growth cone gets a grip

Like a rock climber, a neuronal growth cone senses its substrate to identify the route that will provide the best grip. For the growth cone, this involves probing with adhesion molecules that direct cytoskeletal reorganization and movement, but how does the cell determine that a particular spot will withstand tension? On page 427, Suter and Forscher report that slight initial tension on the adhesion molecule apparently induces tyrosine kinase activity, which then stiffens the growth cone’s grip through a positive-feedback mechanism.

When the Aplysia growth cone adhesion molecule apCAM interacts with physically restrained beads coated with apCAM ligand, the growth cone steers across the surface of the beads. Tyrosine phosphorylation increases at sites where the cells bind to restrained beads, but not at sites with unrestrained beads. Inhibitors of myosin or Src family tyrosine kinases reduce growth cone traction on restrained beads.

The authors propose that the tension from apCAM binding to restrained beads leads to Src family tyrosine kinase activation, which then promotes the strengthening of apCAM–actin linkages. The stronger linkages further increase tension, until the apCAM–actin linkage is strong enough to guide growth cone extension. Similar to the mechanisms proposed for integrin-mediated substrate interactions, this would drive growth cone migration along the path providing the best molecular grip.

Death by unligated integrin

Integrins have traditionally been considered relatively indirect inducers of apoptosis, since integrin-mediated adhesion promotes cell survival, whereas inhibiting normal integrin signaling triggers cell death. Now on page 459, Stupack et al. describe an active integrin-mediated death pathway, a finding that helps explain seemingly contradictory earlier results from inhibitor studies and targeted gene disruptions.

The authors studied adherent cells in an artificial three-dimensional extracellular matrix, and found that expression of unligated integrins or integrin β subunit cytoplasmic domains in these cells induces apoptosis. The cells remained attached to the matrix while initiating cell death, distinguishing this integrin-mediated apoptotic pathway from anoikis, in which cells die after losing adherence. Instead, the unligated integrins recruit caspase 8 to the membrane and activate an apoptotic pathway that is independent of death receptors and distinct from stress-associated apoptosis.

Stupack et al. propose that integrins can act as biosensors, initiating apoptosis when a cell enters a microenvironment that lacks one or more ligands for its integrins. Integrin-mediated death may also explain why specific integrin antagonists cause apoptosis and inhibit angiogenesis, but humans or animals lacking the same integrins exhibit apparently normal angiogenesis. An antagonist that blocks integrin ligation would induce the active integrin-mediated death pathway, whereas disrupting expression of the integrin would only remove one of several possible triggers for apoptosis.