Gerhart et al. report that stably committed muscle stem cells may wait in a quiescent state in mature non-muscle tissues like brain and liver, retaining the ability to differentiate into skeletal muscle if the opportunity arises (page 381). This discovery may provide both an important tool for developing regenerative therapies, and a challenge to the characterization of some stem cells as multipotential, an idea based on reported conversions of one cell type to another. Some of the conversion experiments were performed with non-clonal cell populations. The current work suggests that the varied phenotypes observed in the earlier experiments may have arisen from a heterogeneous population of mature stem cells committed to different lineages. The authors found scattered cells expressing MyoD, a marker for skeletal muscle precursors, in a wide variety of fully differentiated organs in chicken fetuses. When cultured in vitro, some cells from the fetal organs gave rise to skeletal muscle, and when the MyoD-positive cells were isolated by fluorescence activated cell sorting, almost all were able to form skeletal muscle. The cells resemble skeletal myoblasts, and appear to be stem cells stably committed to forming muscle. Previous work suggests that some cells in the neuronal tissues of mice also express muscle-specific transcription factors, and Gerhart et al. believe that stably committed precursors of other lineages may also be distributed in mature organs.

Although the evolutionary utility of having muscle stem cells in nonmuscle tissues is not immediately obvious, one possibility is that they could be recruited to help the embryo recover from a loss of somite tissue. Medically, the presence of these cells may explain the origins of rhabdomyosarcomas, malignant tumors that express skeletal muscle proteins but often arise in non-muscle tissue. Because these cells are stably committed to a specific lineage, they might also be useful for regenerative therapies, particularly if they are able to induce multipotential stem cells to differentiate in damaged tissue.

When proteins become misfolded in the ER, a quality control system targets them to the cytoplasm for degradation. On page 355, Vashist et al. have uncovered two separate sorting systems involved in ER quality control, and have identified a novel gene required for one of the two pathways. The findings indicate that ER quality control is more complex than previously believed.

By tracking the fates of several mutant proteins in *Saccharomyces cerevisiae*, the authors identified a sorting step in the ER in which misfolded proteins are targeted to one of two pathways. Some proteins are packaged into COPII transport vesicles, while others are excluded from vesicles and retained in the ER. Proteins packaged into vesicles are transported to the Golgi apparatus, then returned to the ER by retrograde transport, at which point the two pathways converge and both the retained and retrieved proteins are degraded.

Each mutant protein only follows one pathway, suggesting that the sorting system is highly selective. Although the results are consistent with a model in which membrane proteins are retained while soluble proteins follow the retrieval pathway, the authors stress that more extensive analysis will be required to identify the preferences of the sorting system.

A genetic screen uncovered a mutant allele of the *BST1* gene that blocks the transport of misfolded proteins from the ER to the Golgi without affecting most normal protein transport. Although the retrieval pathway is blocked in these cells, proteins targeted to the retention pathway by the ER are still degraded normally.

Vashist et al. are now identifying additional genes specifically involved in the retention and retrieval pathways.
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 intratubular 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.

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.

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.