Neurons die one way or another

On page 987, Yu et al. identify a novel cell death pathway that bypasses mitochondria. The results indicate that various strategies exist to kill off neurons. A lot of the killing of sympathetic neurons occurs in the first week after birth. During that paring period, ~50% of sympathetic neurons die due to a lack of nerve growth factor (NGF). Neurons deprived of NGF in vitro die through the classical cell death pathway, which includes the release of cytochrome c from mitochondria and the resulting activation of caspases. Other factors can also promote neuronal survival, but it now seems that the method used to kill cells after withdrawal of these factors is not the same.

Yu et al. find that depriving sympathetic neurons in vitro of GDNF kills cells without mitochondrial involvement. Different caspases were activated than in NGF-dependent neurons, cytochrome c was not released, and mitochondrial structure was maintained in GDNF-deprived neurons.

Initiation of this pathway probably involves the GDNF receptor Ret, which may activate caspase-2 when GDNF is absent. Whether certain neurons depend solely on GDNF for survival in vivo remains to be seen. Perhaps the mitochondria-independent pathway is only a back-up in case the main system fails. But if death pathways are factor- and cell type–specific, some neuronal death might be blocked selectively by interfering with one but not another death pathway.

Fusion fuels killing

On page 1123, Hernandez et al. demonstrate that a human bacterial pathogen makes host defense cells self-destruct by engulfing their own organelles. This engulfment, known as autophagy, is commonly used by eukaryotic cells to remove damaged organelles by enveloping them in membranes (probably derived from the ER) that later fuse with lysosomes. High levels of autophagy is also a form of programmed cell death—a process that the bacterium Salmonella is now shown to hijack.

The authors show that the Salmonella protein SipB is all the bacteria need to get autophagy rolling. SipB is a translocase that sends pathogenic effector proteins into host cells. The authors show that SipB also functions within the infected cell, where it finds its way to mitochondria. There, SipB’s demonstrated fusion activity may explain the appearance of damaged and bloated mitochondria, which then become a target for the autophagic apparatus. The end results, visualized by the group, were multilamellar closed vesicles that resemble autophagic vesicles, contain mitochondrial and ER proteins, and occasionally surround entire mitochondria.

Salmonella can also kill macrophages through a faster necrosis-like pathway that, unlike autophagy, depends on caspase-1 activity. The two killing methods may result in different immunological responses from the host, but as yet it is not even clear whether macrophage death is a benefit for the host (by halting bacterial replication) or the pathogen (by impairing defense responses).

Tearing down actin

Proteins that take apart actin filaments are hardly creative, according to Galkin et al. (page 1057), who show that destabilizing proteins induce structural states that are normally seen at the depolymerizing end of actin.

That end—the so-called pointed end—normally depolymerizes in the cell even as actin monomers are added at the other “barbed” end. This treadmilling is disturbed by ADF/cofilin (AC) proteins, which tear down actin filaments near the leading edge of migrating cells. The authors used electron microscopy and three-dimensional reconstructions to investigate how AC proteins promote instability and dismantle filaments.

AC-bound filaments looked like the pointed ends of naked actin filaments. Both were missing a contact between subdomain (SD) 2 of one actin monomer and SD1 of the monomer just above it in the filament. In contrast, strong SD1–SD2 interactions were found throughout the rest of the naked actin filaments. These contacts must be weakened for actin strands to adopt a tilted conformation that favors destabilization. AC proteins thus induce this naturally unstable state wherever they bind and cause either depolymerization (if subunits fall off the ends) or severing (if a filament segment is broken off).