In Brief

Bacterial Cell Death

Streptomyces cell death, which occurs as the bacteria develop fruiting bodies and form spores, has been dismissed as nonspecific autolysis caused by cell wall degradation. Now Miguélez et al. (page 515) show that the cell death is complex: it occurs at two different times in two different locations and as a series of defined steps that leave the cell wall intact.

Streptomyces grow first along and through their growth medium, as multinucleoid hyphae. This substrate mycelium subsequently forms stalks that rise above the growth medium. Parts of the aerial hyphae septate to form spores.

Cell death occurs in two major waves. As aerial hyphae are growing, nucleoids at the level of the growth medium begin degenerating. Sporulation then starts, by which time the substrate mycelium is dead and a second death process is starting in the aerial hyphae, from the bottom up. Two days later all cells are either dead or spores.

The first sign of degeneration is a loosening of the fibrillar DNA structure. The nucleoid and then cytoplasm become less electron-dense, ending with a nucleoid that is electron-translucent and has fibrillar structure. Only at the end of this process does the plasma membrane retract from the cell wall and form vesicles. The cell wall is left intact, probably as both a mechanical support and nutrient conductor for the aerial hyphae.

A genetic dissection of the death process would seem to be the next logical step. This may uncover a link to programmed cell death in other organisms, as the *Streptomyces* genome contains distant relatives of some mammalian apoptosis genes (Aravind, L., V.M. Dixit, and E.V. Koonin. 1999. *Trends Biochem. Sci.* 24:47–53).

Myogenin Controls Muscle Metabolism

Fast muscle fibers rely on glycolysis for the intense but short-lived bursts of activity needed for throwing a ball or regaining balance. But muscles that are used for activities such as standing need greater endurance. These slow muscle fibers use oxidative metabolism for a less intense, longer-lived supply of energy. Endurance training may cause muscle fibers to change from a glycolytic to oxidative pattern of energy usage, and now Hughes et al. report that overexpression of the muscle differentiation factor myogenin can induce just such a switch (page 633).

"This makes myogenin one of the prime candidates for the pathway connecting electrical activity and phenotype," says senior author Kristian Gundersen. The other links in this pathway are not known, although a number of the genes for mitochondrial metabolic enzymes have sequences that could be used for direct binding and regulation by myogenin.

Catenin as an Inhibitor

Catenins are known primarily as linkers from cadherins to actin, a pro-adhesive role, but now Aono et al. report that $p120^{ctn}$ acts as an inhibitor of cadherin-based adhesion (page 551).

Aono et al. start with colon carcinoma cells that have all the components for E-cadherin–dependent adhesion, but somehow remain dispersed. Treatment of the cells with the protein kinase inhibitor staurosporine, or with small amounts of trypsin, induce E-cadherin–dependent adhesion and a coincident shift in the mobility of $p120^{ctn}$. The mobility shift is consistent with a dephosphorylation of $p120^{ctn}$.

The binding site for $p120^{ctn}$ is a juxtamembrane portion of cadherin that has previously been implicated in adhesion inhibition. Consistent with that theory, a truncated $p120^{ctn}$ that still binds cadherin (and presumably displaces the full-length $p120^{ctn}$) can restore cell adhesion to the carcinoma cells. Furthermore, once the $p120^{ctn}$-binding site is removed from an N-cadherin construct, the construct can induce N-cadherin–dependent adhesion of the carcinoma cells.

A loss of cell adhesion may aid carcinoma cells in metastasis and the avoidance of regulatory signals from nearby cells. Normal cells may use $p120^{ctn}$ as a reversible adhesion switch for processes such as cell movement during development. The proteins cleaved by trypsin are yet to be identified, but they may be cell surface receptors involved in such pathways.

Intermediate Filaments and Scar Formation

Astrocytes become reactive after an injury to the brain or spinal cord, increasing their production of cytokines and the intermediate filament proteins vimentin, nestin, and glial fibrillary acidic protein (GFAP). Scar formation by the reactive astrocytes is intact in mice that lack either vimentin or GFAP, but is defective in mice that lack both (Pekny et al., page 503).

The scar in the spinal cord of the double mutant is less dense than normal, and includes fissures and blood. Defects in cortical scar formation are presumably the cause of extensive bleeding and delayed healing in many of the double mutant animals, which in some cases leads to death.

Inhibition of IF production has been suggested as a therapeutic approach to brain injury, as astrocytic scars may be a barrier to neuron regrowth, but this study shows that the scars may be important for protection. Intermediate filaments may provide tensile strength to keep the scar together.

A Differentiation Factor Increases Bone Resorption

Human bone is continuously being resorbed and replaced. Control over this process of remodeling is exquisite; imbalances often lead to excess bone resorption, the basis of osteoporosis. On page 527, Burgess et al. report that a fac-

tor required for differentiation of precursor cells to form the bone-resorbing cells, or osteoclasts, also directly increases the resorbing activity of mature osteoclasts.

Burgess et al. suspected that the differentiation factor, osteoprotegerin ligand (OPGL; also known as TRANCE, ODF, and RANK ligand), was involved in osteoclast activation in addition to differentiation based on in vivo studies. In these studies, an OPGL antagonist caused remodeling changes that were too rapid to be explained by differentiation effects alone, and OPGL treatment induced bone resorption in animals without any apparent increase in osteoclast number. These observations led Burgess et al. to test the in vitro effects of OPGL on newly isolated, mature osteoclasts. OPGL-treated osteoclasts resorbed up to seven times more bone surface area than untreated osteoclasts, with no increase in osteoclast cell number.

OPGL acts, at least in part, by increasing the number of resorption cycles per active osteoclast. This conclusion is based on the observation of individual resorption events by scanning electron microscopy. Many of these events are clustered in groups in the sample treated with OPGL, which suggests that single stimulated cells undergo multiple resorption cycles. There are also more single resorption events, however, so OPGL may also activate previously inactive osteoclasts.

OPGL increases the number of cells with actin rings, the structures that define a sealed zone at the bone surface, within which bone-degrading protons and proteases can be safely released. However, it is not clear whether the extra resorption events are primarily sequential (a small osteoclast performing multiple cycles) or simultaneous (a large osteoclast with multiple actin rings).

The search for OPGL started with the discovery of OPG, a soluble decoy receptor for OPGL that inhibits osteoclast differentiation. OPG is currently in clinical trials for osteoporosis, and a small molecule antagonist of OPGL may make another excellent clinical candidate.

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