Stress stunts organ growth

Organ size is controlled by a combination of morphogens and mechanical stress, propose Lars Hufnagel, Boris Shraiman (University of California, Santa Barbara, CA), and colleagues. Morphogen gradients, they show, are not sufficient to prevent overgrowth.

The popular gradient model proposes that differences in morphogen concentration across an organ are sensed by individual cells, which respond by proliferating. As a tissue grows, this gradient flattens until it no longer prods division. But Shraiman and colleagues now show that a morphogen’s gradient does not change with organ size.

In the developing fly wing, the Dpp morphogen is made in a central stripe, and its concentration decays outward in both directions. By comparing fly larvae at various developmental stages, the group shows that this concentration pattern depends mainly on its diffusion and decay rates and is the same in wings of all sizes.

The authors instead propose that cells near the edge stop dividing when they get too far away and thus receive insufficient morphogen. They then needed to explain how the central cells know to stop proliferating at the same time as the outer cells. “I’m a physicist,” says Shraiman. “And to a physicist, mechanical stress is a very natural thought.”

The supposed stress comes from differences in growth rates. As neighboring cells are tightly joined by adherens junctions and thus cannot change position, proliferating cells in the center are getting crushed, while the outer quiescent cells are being stretched.

Computational modeling suggests that mechanical stress negatively feeding back on morphogen-induced growth can account for size control. Now the group needs to test their model and find the stress detectors. Molecules such as β-catenin that link the cytoskeleton to adherens junctions and also induce gene expression are some of their favored candidates.

Reference: Hufnagel, L., et al. 2007. Proc. Natl. Acad. Sci. USA. doi:10.1073/pnas.0607134104.

Death by default

Our cells have a death wish, say Simon Willis, Jerry Adams, David Huang, and colleagues (Walter and Eliza Hall Institute, Melbourne, Australia). The apoptotic executioners are Bax and Bak, which seem to bring about death by poking holes in mitochondria. But even thriving cells have plenty of Bax and Bak, suggesting these proteins are either inhibited in healthy cells or must be activated for apoptosis.

The balance between cellular life and death is shifted by proapoptotic BH3-only proteins and pro-survival Bcl-2 proteins. When certain BH3-only proteins were shown to bind to Bax, many researchers concluded that this interaction activated Bax. Liposome experiments supported this idea: the liposomes survived Bax but leaked when BH3 peptides were also added. But genetic evidence for the model was lacking, especially since BH3-only proteins were originally found to neutralize a Bcl-2 protein.

Having created the necessary knockout mice, Willis et al. now show that Bax and Bak do not require prior activation by the proposed BH3-only proteins. Instead, Bax and Bak seem to provoke apoptosis spontaneously when BH3-only proteins have soaked up protective Bcl-2 proteins.

A direct physiological interaction between Bcl-2 and Bax proteins has yet to be demonstrated convincingly, leaving Huang to wonder just how the executioners are regulated. “Bax and Bak,” he speculates, “might be intrinsically unstable proteins with a capacity to change [to an active, deadly] conformation. With lots of Bcl-2, the cell can block it.” But once BH3-only proteins occupy the Bcl-2, Bax and Bak might self-activate, resulting in suicide.

Death as a default pathway has precedents. “Developmental biologists would agree,” says Huang. They propose that “in developing tissues, cells die unless actively provided with a survival signal.” Huang thinks it might be “easier to communicate which cells should stay alive rather than which are to die.” JCB

Reference: Willis, S.N., et al. 2007. Science. 315:856–859.