Research Roundup

Spitz on growth control

Self reliance is not enough. Some organs rely on the kindness of others to control their size, according to Joseph Parker (Columbia University, New York, NY).

Correct organ size is measured in mass, not cell numbers—forcing or blocking cell division generally does not change an organ's overall dimensions. Parker found the same is true in the fly embryonic P compartment, which forms part of the larval epidermis. Increases in P compartment cell numbers were countered by more apoptosis and smaller cells. With fewer numbers, on the other hand, each cell grew larger to accommodate for their missing comrades.

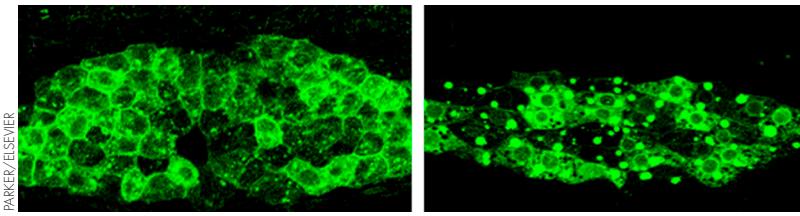
In looking for a molecular explanation, Parker figured it would make sense to "have size information encoded right there in the patterning system" that also controls cell fate and positioning. For the P compartment, these patterning molecules are extracellular ligands called Spitz and Wingless. The new results show that more or less Spitz signaling creates larger and smaller P compartments, respectively.

At the individual cell level, Spitz suppressed apoptosis and encouraged cell growth by activating the EGF receptor and downstream MAP kinase pathways. To explain how overgrowth is prevented, Parker reasoned that "the simplest model is that the level of Spitz is fixed in the compartment. More proliferation means less Spitz per cell." Those cells thus grow less and are more susceptible to apoptosis.

Organs were previously thought to have autonomous control over their size. But the new model only works if Spitz is provided by an external source—otherwise, a bigger P compartment would make more Spitz and grow even larger. Although Spitz is expressed everywhere, it is activated solely in the neighboring A compartment, from where it apparently diffuses into the P compartment.

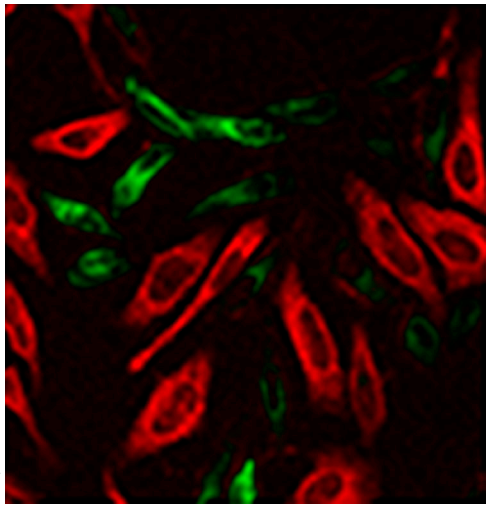
Because ligands such as Spitz are short-range diffusers, the model probably only applies to small or embryonic structures in the range of tens to hundreds of cells. "For larger organs like the liver," Parker says, "diffusion is a rickety thing" that might require backup size control mechanisms. JCB

Reference: Parker, J. 2006. *Curr. Biol.* 16:2058–2065.



PARKER/ELSEVIER

Too much EGF receptor signaling increases P compartment size (left). Too little reduces it (right).



AHN/ELSEVIER

Viral US3 (green) degrades PDI (red) to thwart antigen presentation.

Fight infection with oxidation

Redox regulation and immunology collide in a new report by Boyoun Park, Kwangseog Ahn (Seoul National University, South Korea), and colleagues.

When scientists think of the immune system's antigen selection procedure, oxidation/reduction is just about the last thing to come to mind. Yet the group now shows that an oxidation step by protein disulfide isomerase (PDI) helps load antigenic peptides into MHC class I molecules, which then present the antigen on the cell surface.

PDI is best known as a chaperone, but the authors found it associated with ER proteins that pull antigens into the ER from the cytosol. Its chaperone activity seems to be intact here: it binds strongly to antigens and probably protects them from the abundant ER proteases. But PDI's role goes beyond chaperone duties.

PDI also regulates a disulfide bond in the peptide-binding sites of MHC class I molecules. Only in its oxidized form, the authors find, does an MHC class I molecule accept antigenic peptides. This oxidation is performed by PDI when optimal, high-affinity antigens are abundant. In their absence, however, PDI instead reduces MHC (cells contain an equilibrium of oxidized and reduced forms of PDI). The big mystery that remains is whether and how PDI distinguishes between optimal and suboptimal peptides, particularly since each type of MHC class I molecule has its own antigen preferences.

This selective sampling is important because cells may have only about four hours to present antigens before certain virus replicate and escape. In this time, MHC molecules have to sample lots of possible antigens before finding the right one. According to Ahn, "the PDI delivery function is what might help MHC find a substrate quickly enough to mount an immune response." In the absence of PDI's peptide-binding activity, most surface MHC class I molecules were empty, probably because they left the ER with low-affinity peptides that quickly fell off.

If the authors reduced PDI levels, virus-infected cells were unable to activate T cell responses. Cytomegalovirus brings about this defenseless state on its own by using its US3 protein to degrade PDI. JCB

Reference: Park, B., et al. 2006. *Cell.* 127:369–382.