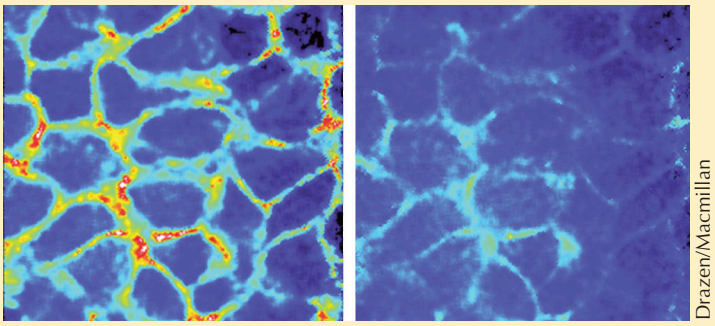
Research Roundup

Intimacy is a cellular turn-on

The simple act of coming closer together ignites signaling pathways in epithelial cells, as shown by Daniel Tschumperlin, Jeffrey Drazen (Harvard School of Public Health, Boston, MA), and colleagues. The results describe how cells might activate cellular responses to mechanical stress.

Cells are pushed closer together by physical forces. In the lung, for instance, epithelial cells feel the pressure from underlying muscle tissue, particularly in asthmatic patients. The authors see that these forces do not change cellular volume. Rather, they squeeze out fluids from between neighboring cells.



Drazen/Macmillan

The space (red) between cells gets cramped when pressure is applied (right).

The resulting close cellular proximity means that ligands that get secreted between cells are more concentrated and therefore more likely to activate signaling pathways. "Now there's less space for these things to bounce around in before they find a receptor," says Tschumperlin.

Lung cells under mechanical stress phosphorylate ERK as a result of EGFR activation. The authors find that this phosphorylation is due to the HB-EGF ligand. Assuming that ligand secretion and diffusion rates are uniform, they calculate that ligand concentration is inversely proportional to the width of the space between cells. Putting their equation to the test, they found that stress, or an increase in ligand equivalent to that predicted from that stress, both activated ERK phosphorylation to the same extent.

"When we put our results together, it seemed so obvious that we had to go back to the literature to see why no one had suggested it before," says Tschumperlin. "No proteins or molecules or channels sensitive to stress are needed. Cells just use the existing machinery, not directly changing any proteins, in a changing extracellular volume."

This simple system may extend to any cell type that releases ligands into a restricted space. Proliferating cells that get more tightly packed during development, for example, might activate differentiation pathways at the right place and time. ■

Reference: Tschumperlin, D., et al. 2004. *Nature*. 10.1038/nature02543.

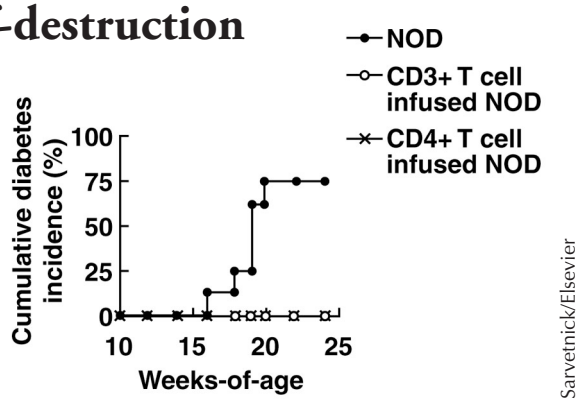
Fighting foreigners prevents self-destruction

Children everywhere rejoice—there may be such a thing as being too clean. According to Cecile King, Nora Sarvetnick (Scripps Research Institute, La Jolla, CA), and colleagues, overprotection from exposure to germs might cause autoimmune diseases.

Autoimmune diseases, including rheumatoid arthritis and lupus, are generally thought to result from an overstimulated immune system. This assumption does not, however, explain why these diseases are more prevalent in sterile western societies or why they often correlate with depleted numbers of T cells. Sarvetnick and colleagues now show that the combination of a depleted and understimulated immune system leads to autoimmunity.

The authors find that a mouse model of autoimmune diabetes has just this combination. These mice make too much of the IL-21 cytokine, which promotes proliferation (like other cytokines) but not survival (unlike other cytokines). Thus, their T cells continually multiply but never fill up the immune system.

These rapidly multiplying T cells (which likely respond to self-antigens from nearby organs) caused autoimmune diabetes. But diabetes was prevented if the mice were injected either with enough T cells to fill the immune system or with bacterial proteins so that multiplying T cells expanded robustly to these non–self-antigens.



Sarvetnick/Elsevier

Autoimmunity (filled circles) is prevented if mice are given doses of T cells to fill their immune systems.

"Most people do not want to think of autoimmunity as a form of immunodeficiency," says Sarvetnick. But T cells in sanitized western children might be faced with a problem: without enough stimulation by foreign antigens to prompt T cell expansion, the T cells that do fill the immune system may have more than the normal share of autoreactive clones. So a bit of play time in the dirt might serve kids well. ■

Reference: King, C., et al. 2004. *Cell.* 117:265–277.