Fibronectin for branching

Branched organs are shaped when epithelia make their own paths, according to a study by Takayoshi Sakai, Melinda Larsen, and Kenneth Yamada (National Institutes of Health, Bethesda, MD). The pathmaker in this process is fibronectin (FN), which tells cells to let go of their neighbors and instead grab hold of the underlying matrix.

Organs such as the lung and kidney gain surface area by forming numerous branches, which are generated by cycles of budding and cleft formation in epithelial cells. Branching is known to involve growth factor–regulated interactions between the epithelium and mesenchyme, but the authors wanted to know how individual cells respond during branching. Using the developing mouse salivary gland as a model, the group now reports that epithelia change their architecture by secreting FN fibrils in newly forming clefts.

Although cleft-initiating signals are not yet known, cleft formation was induced by FN expression in cells bordering the cleft. Inhibition of FN mRNA expression in the epithelium or antibody inhibition of FN or its integrin receptor inhibited branching and cleft formation. In contrast, exogenous expression of FN induced excess branching in cultured salivary glands. FN fibrils suppressed local levels of the cell–cell adhesion molecule cadherin in nearby epithelial cells. Cadherin loss, which occurs via both local redistribution and mRNA suppression, probably releases the epithelial cells from each other as they attach to the matrix FN.

Lung and kidney epithelia also have cleft FN pools that function as in salivary glands, suggesting that FN is widely used for branching. “We wonder whether this kind of local developmentally regulated appearance of fibronectin is possibly a general strategy in tissue remodeling,” says Yamada.


Spare the Mbl, spoil the rod?

New results from Richard Daniel and Jeff Errington (University of Oxford, Oxford, UK) indicate that bacteria have different strategies to control cell shape through cell wall deposition, depending on the presence of an actin-like protein.

Distant homologues of eukaryotic actin were only recently identified in bacteria. In the rod-shaped Bacillus subtilis, these proteins, members of the MreB family, form helical cables along the cell axis and are required for the maintenance of proper cell shape. Daniel and Errington now show that MreB proteins direct the deposition of cell wall material.

The authors probed for new cell wall material in Bacillus by labeling precursors inserted into peptidoglycan (PG), the major component of the cell wall. New PG was inserted in a helical pattern matching that of an MreB family member, called Mbl. Mutation of Mbl led to loss of the helical pattern in the cell cylinder. It is not clear how Mbl controls PG synthesis, but the authors believe that the MreC and MreD membrane proteins may connect the cytoplasmic cables to the external cell wall machinery.

Additional transient PG synthesis was found at sites where cell division occurred. Cells lacking Mbl survived by acquiring mutations that allowed them to maintain growth from finished division sites. They continued to grow as long as cell division was not inhibited.

Round bacteria such as Streptococcus lacked MreB proteins and inserted new wall material only at sites of division. Two groups of rod-shaped bacteria also lacked MreB-type proteins. The group found that one of these bacteria, Corynebacterium, relied entirely on continuous growth from cell division sites, just like the B. subtilis mbl mutants. MreB-directed wall synthesis allows cells to grow more rapidly, since new material can be added throughout the growing cell. But polar-growing cells may have the advantage of a static wall that can be reinforced by additional modifications to increase its strength.

Remodeling the nucleus

**Daniel Colón-Ramos, Mariano A. García-Blanco (Duke University, Durham, NC), and colleagues demonstrate in a recent article that Chlamydomonas nuclear architecture changes to accommodate cytoplasmic needs.**

Chlamydomonas is a highly polarized cell that offers a unique system to study changes in nuclear shape. Loss of this algae’s flagella (after certain chemical or mechanical stresses) causes the nucleus to adopt a pear-like shape and take an anterior position in the cell, nearer where the flagella once sat. García-Blanco wondered whether sites of transcription of the β tubulin gene, which is strongly up-regulated upon deflagellation, move closer to the flagella to expedite their rebuilding. Immunochemistry and electron microscopy revealed that the β tubulin gene did not move from its posterior nuclear position. But the experiments did uncover an unexpected asymmetry of nuclear pore complex distribution.

Even in flagellated cells, the complexes were preferentially located at the posterior side of the nucleus, near a polysome-rich portion of the cytoplasm. Deflagellation further exaggerated the asymmetry. The changes correlated with accumulation of β tubulin transcripts near the concentrated translation machinery. Says García-Blanco, “what we don’t know yet is what causes what.” He hopes to find mutants that uncouple events following deflagellation to determine whether nuclear architecture directly targets mRNA cytoplasmic localization.


Glutamate in unusual places

Glutamate has a critical physiological function unrelated to its job as a neurotransmitter, according to results from M.M. Reddy and Paul Quinton (University of California, San Diego, CA). The duo find that glutamate activates an epithelial ion channel that is mutated in patients with cystic fibrosis.

Cystic fibrosis is caused by mutations in the CFTR anion channel, which is found in various epithelial tissues, including the lungs. A long-standing assumption that CFTR is activated by phosphorylation and ATP has recently been challenged by observations that the channel is open regardless of kinase activity in sweat glands. Activated CFTR, CFTR is activated by glutamate only from the cytoplasmic side, however, and thus is distinguished from standard glutamate receptors, which respond to extracellular glutamate. Reddy does not yet know whether glutamate binds to CFTR directly or activates it indirectly.

Cl⁻ may not be the only CFTR-conducted ion important for normal gland function. Reddy found that bicarbonate ions also passed through the CFTR channel in the presence of both glutamate and ATP. Mutant versions of CFTR found in patients with severe forms of cystic fibrosis were deficient in both Cl⁻ and bicarbonate transport. Milder CFTR mutations spared bicarbonate transport. The findings suggest that defects in bicarbonate transport should not be ignored in the search for treatments for cystic fibrosis.


Dying cells say come-hither

Apoptotic cells are swallowed whole by phagocytes before they can release intracellular molecules that might produce inflammatory responses. Phagocytes get their instructions from cell surface markers on the dying cells. But in an entire organism the chances that the scavengers will encounter a dying cell in time are low. In a recent report, Kirsten Lauber, Sebastian Wesselborg (University of Tübingen, Tübingen, Germany), and colleagues show that apoptotic cells ensure their discovery by sending a long-distance chemotactic message to phagocytes. The new discovery reveals an additional signaling pathway that may be impaired in patients with autoimmune diseases.

The attractive signal for phagocytes was identified as lysophosphatidylcholine (LPC), a hydrolysis product of a plasma membrane phospholipid. LPC was released from apoptotic cells of various types via caspase–3–mediated activation of the calcium-independent form of phospholipase A₂ (iPLA₂). Inhibition of either caspase–3 or iPLA₂ blocked chemotaxis of macrophages in vitro. The group also showed that culture supernatants of apoptotic cells injected under the skin of mice caused macrophages to invade the injected area.

The phagocyte side of the story has yet to be worked out. For instance, it is not clear which receptors recognize LPC. Possibilities include G-protein–coupled receptors such as G2A, which binds to LPC and stimulates migration of blood cells.