Virtual adherens junctions

The textbook model of adherens junctions has been exploded, or severed, by Bill Weis, Soichiro Yamada, Frauke Drees, Sabine Pokutta, and W. James Nelson (Stanford University School of Medicine, Stanford, CA). There is no direct link, they say, between cadherin, via $\beta$- and $\alpha$-catenin, to actin.

Weis’s original goal was ambitious—a structural understanding of adherens junctions. First came biochemistry. “It was only when we attempted to reconstitute [the junctions],” he says, “that we found that nobody had actually done it before.” The textbook model was all based on binary interactions.

The group now reports that $\alpha$-catenin can either bind as a monomer to $\beta$-catenin and thus cadherin, or bind as a homodimer to actin. But the binding events are mutually exclusive so there is no direct link from cadherin to actin. Consistent with this, cadherins and actin have very different dynamics.

Weis stresses that their two model systems—clustered soluble fragments of $\text{T}^\text{cadherin}$ and membrane patches—are something less than a full-blown adherens junctions. But such imprecision may be reasonable. In cells, says Weis, although “there is certainly local [cadherin] clustering, I don’t think there’s precise geometry.”

In the dimeric state $\alpha$-catenin inhibits actin polymerization by Arp2/3, perhaps favoring formin’s ability to create stable actin cables over Arp2/3’s ability to promote protrusive actin branching. The membrane patches did not, however, reconstitute assembly of actin filaments, suggesting that other proteins are missing. These other proteins may link actin to other membrane proteins, or they may reinforce the actin-modifying behavior of $\alpha$-catenin.

“People are very intrigued and excited” by the new results, says Weis. But the new textbook is clearly a work in progress. One of the biggest mysteries is how a system with no direct linkages generates force during morphogenesis. “Maybe all you need to do is to organize the gel state of actin correctly, and that organization will support the mechanical function of the junction,” says Weis. But “with constriction, you clearly need to be linked to something.”

References: Yamada, S., et al. 2005. Cell. 123:889–901.
Drees, F., et al. 2005. Cell. 123:903–915.

Sending the advance party for metastases

Tumor cells induce other cells to act as trailblazers, say Rosandra Kaplan, Rebecca Riba, Shahin Rafii, David Lyden (Weill-Cornell, New York, NY), and colleagues. Those cells set up remote sites to which the tumor cells can subsequently metastasize.

The trailblazers are bone marrow–derived cells (BMDCs) that were earlier implicated in building blood vessels in established tumors. When Kaplan saw the cells in metastases she thought it was the same story. “For a long time we thought the tumor cells got there and then brought the bone marrow cells afterwards,” she says. But careful examination showed that, both in mice and humans, the BMDCs showed up several days before the first tumor cells. Interfering with the trailblazing BMDCs prevented metastasis.

The group now thinks that growth factors from the tumors have two distinct activities. They coax BMDCs out of the bone marrow and into the circulation. And they induce fibroblasts in other tissues to proliferate and make fibronectin. These fibroblast actions in turn attract the fibronectin-binding BMDCs, which settle into their niche and start producing other factors that attract the tumor cells.

This rather complex dance “is very logical,” says Lyden. “Tissue regeneration is happening all the time: you need to make new blood vessels all the time; you need to heal wounds all the time.” The tumor, he thinks, is inducing remote sites to act as if they are wounded or inflamed, thus recruiting the BMDCs as healers. The BMDCs need to recruit yet other cells to complete the healing, yet in the process they pull the tumor cells into the mix.

The molecular details thus far consist of a specific receptor [VEGFR1] and integrin (the fibronectin ligand VLA-4) on the BMDCs. Kaplan and Lyden are now defining the profile of factors made by different tumors in the hopes that this will be predictive of future metastatic sites.

Reference: Kaplan, R.N., et al. 2005. Nature. 438:820–827.

BMDCs (green) arrive early (left), preparing the way for tumor cells (red).