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 β- and α-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 α-catenin can either bind as a monomer to β-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 T-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 α-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 α-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.
Group effort from poliovirus

The pathogenesis of poliovirus relies on virus diversity per se, not the selection of any particular adaptive mutation, say Marco Vignuzzi, Raul Andino (UCSF, San Francisco, CA), and colleagues. Different variants may achieve different tasks in a group effort to navigate the host environment. This is how a quasispecies, or group of variants, is meant to behave, based on theory and mathematical modeling. “But really this is the first study that provides experimental evidence,” says Andino.

Andino had previously used a mutagen to push viruses into evolutionary oblivion; he now uses a mutant that survives this treatment because of a less error-prone polymerase.

These G64S viruses generated far fewer chemical-resistant variants and responded poorly to a challenge with this antiviral drug. But G64S was also far less potent in mice: it had to be given in a 300-fold higher dose to cause 50% lethality, and was unable to establish infection in the spinal cord and brain.

Treating G64S with a chemical mutagen before inoculation restored its sequence diversity and in vivo potency. Virus reisolated from the brain did not, however, show signs of a particular variant being selected for competency to enter the spinal cord. Indeed, this isolated virus was less diverse than the original, mutagen-treated stock, and was by itself unable to reinfect the central nervous system of mice.

Cooperation also occurs during coinfections, where one virus species can infect only in the presence of another. For now, Andino has few clues about how the quasispecies might be dividing up tasks in the body, but he is devising a microarray-based method to map the diversity that polio needs to conquer a host.

Reference: Vignuzzi, M., et al. 2005. Nature. doi:10.1038/nature04388.

Remodeling replication

Cloned nuclei are plucked from a comfortable, differentiated cell and thrust into an egg primed for embryonic development. For a frog nucleus, part of that switch is a conversion into embryonic DNA replication mode, says Jean-Marc Lemaître, Marcel Méchali, and colleagues (CNRS, Montpellier, France). The absence of this switch may partially explain the woeful, 2–3% success rate of nuclear transfer cloning.

Most researchers trying to improve cloning efficiency have concentrated on epigenetics—how to change modified chromatin proteins from a differentiated to an embryonic activity pattern.

But a frog’s embryonic divisions differ from mature divisions in another sense: they take only 30 minutes each, in part because they use many more replication origins. In the new experiments, cloned nuclei replicated slowly and with fewer replication origins. Putting the nuclei first into a frog mitotic extract, however, boosted the number of origins and the speed and efficiency of replication in the subsequent cell cycle.

The switch was associated with closer spacing between origins, a randomization of attachment sites to the nuclear matrix, and shorter loops of DNA between nuclear matrix attachment sites. In each cycle the attachment sites were converted to a more dispersed, mature form during DNA replication, but were rerandomized during mitosis.

Many mammals lack rapid early cell divisions but, says Méchali, “origins may be fixed in different places in different cell types.” For efficient cloning, “it may be important to fix them into a pattern appropriate for embryogenesis.”

Reference: Lemaître, J.-M., et al. 2005. Cell. 123:787–801.

Golgi directs dendritic traffic

Neuronal Golgi is polarized toward and into the longest and most complex dendrites, say April Horton, Michael Ehlers (Duke University, Durham, NC), and colleagues. Thus it may help determine the stereotyped shape of dendritic arbors.

The mammalian Golgi is most often seen as a single copy perinuclear organelle, but Golgi “outposts” have been sighted in dendrites before. The Ehlers group found that these outposts were usually only found in the neuron’s longest and most complex dendrite and were often positioned at branch points in the dendritic arbor, as if to direct traffic. Additionally, the main Golgi apparatus in the cell body polarized toward what would become the longest dendrite, and there was fourfold greater secretory flux into these favored dendrites. Disruption of Golgi structure left dendritic growth intact, but equalized growth rates between different dendrites.

Dendrites can assert individual identities if their localized ribosomes and mRNAs make soluble proteins. The nonrandom Golgi organization may extend this ability to membrane and secreted proteins.

What controls dendritic Golgi organization is uncertain, but it may well be related to systems that fragment the Golgi during mitosis or reorient it during cell migration.

Reference: Horton, A.C., et al. 2005. Neuron. 48:757–771.