Research Roundup

Rafting across polarized cells

For raft proteins, direct delivery is not the travel route of choice, according to Roman Polishchuk, Jennifer Lippincott-Schwartz (NIH, Bethesda, MD), and colleagues. They find that, contrary to earlier evidence, glycosyl phosphatidylinositol (GPI)–anchored raft proteins make a detour to the basolateral membrane of polarized MDCK cells before crossing the cell to their final destination in the apical membrane.

Direct delivery had been plausible, as sorting of GPI-anchored proteins into rafts, and thus away from basolateral proteins, occurs in the trans-Golgi network (TGN) before either departs for plasma membranes. Few or no apical proteins were ever seen in the basolateral membrane. And finally, transport across the cell seemed unlikely: the main method of departure, clathrin-mediated endocytosis, did not transport rafts.

Lippincott-Schwartz recently found that rafts are continually endocytosed by a nonclathrin pathway, overcoming the clathrin objection. And at the basolateral surface, she says, “all of these biochemical experiments would have potentially missed a transient appearance.”

The NIH team found that GPI-YFP and basolateral proteins were segregated as they left the TGN, but nevertheless shared the same tube-shaped carriers. (Others have claimed one cargo type per carrier, but did not prebleach to reduce background.) Those carriers must be paying a visit to the basolateral membrane, as both proteins got stuck intracellularly when fusion to the basolateral membrane was prevented with tannic acid, a cell-impermeable fixative. When tannic acid was applied to the apical side, only the apical cargo was intracellular, presumably after making its transient basolateral stop. Evidence for this trip across the cell came from a tracer and antibody, which were applied to the basolateral side but travelled with GPI-YFP apically.

A nonraft apical protein went straight to the apical side of the cell. Why should the cell bother with the more circuitous route taken by GPI-YFP?

Myc conquers all

More Myc makes you stronger, according to Eduardo Moreno and Konrad Basler (Universität Zürich, Switzerland) and Claire de la Cova, Laura Johnston (Columbia University, New York, NY), and colleagues. They find that cell clones producing more dMyc overproliferate and outcompete their neighbors, with the neighbors dying off by apoptosis.

The concept of cell competition is not a new one. Fly cells mutant for various ribosomal proteins are known to suffer from competition-related elimination by wild-type cells. But now the two groups show that competition occurs in response to varying levels of the growth promoter dMyc, even when the “weaker” of the two cell groups are expressing wild-type levels of dMyc.

The Swiss group found that weaker cells could be rescued by either stimulating their rate of endocytosis (with an activated Rab5) or turning on genes downstream of the survival factor Dpp: outcompeted cells also had reduced expression of Dpp targets. Basler suggests weaker cells lose out because their lower metabolism is not driving a sufficiently robust endocytic cycle, leaving them with insufficient endocytosed survival factors.

But when it comes to Dpp, says Johnston, “we haven’t been able to find any evidence.” This colors her thinking of what the more competitive cells are doing. “We think they are not just sopping up nutritional and growth factors,” she says. “We think there’s a signal being sent” between cells of different metabolic capabilities.

The genesis and identity of such a signal remain unknown, but Johnston thinks it will connect competition to regulation of organ size. Her team found that fly wing discs repressed for apoptosis showed much greater variability in size than normal. They are currently testing whether this effect is based on competition or some other apoptosis-related phenomenon.

Basler remains skeptical of a connection to organ size. “We look at competition only as an artificial phenotype—at best it is an elimination phenomenon—at best it is an elimination plan for weak cells,” he says. “It’s more like a policeman—present but normally not needed.”

Where it might be important, he says, is in a stem cell niche where every cell must be a high performer. Incipient cancers may take advantage of this biology by expanding their domain at the expense of outcompeted normal cells.

References: de la Cova, C., et al. 2004. Cell. 117:107–116.
Moreno, E., and K. Basler. 2004. Cell. 117:117–129.