Research Roundup

**Lipid-driven sorting and fission**

Changes in membrane shape during trafficking require proteins, and those proteins are thought to operate mechanically to extrude or squeeze membranes. But biological membranes are also thought to be poised near a phase transition between liquid-ordered (L\text{d}) and liquid-disordered (L\text{o}) states. Aurélien Roux, Patricia Bassereau, Bruno Goud (Institut Curie, Paris, France), and colleagues now report that in vitro tube formation is favored from L\text{d} domains, and phase separation induces fission. Proteins that affect lipid distributions in vivo may thus favor or disfavor tubulation and fission events during protein trafficking.

The preferential tubulation from L\text{d} domains makes sense, as reduced interactions between lipid head groups make these domains more easily deformable. The French team used biotinylated lipids and kinesin-laden beads to pull tubes out of lipid vesicles in vitro. More easily deformable domains make sense, as reduced interactions between lipid head groups make these domains more easily deformable. The French team used biotinylated lipids and kinesin-laden beads to pull tubes out of lipid vesicles in vitro. More tubes were pulled from L\text{d} domains. But even in vesicles lacking visible segregation between L\text{d} and L\text{o} domains, the pulled tubes were enriched in lipids from the L\text{d} phase because the other lipids sort out of the tubes.

For some lipid compositions such a sorting event promotes phase separation in tubes. In vitro, the induction of phase separation (via photooxidation of cholesterol) induced fission; in many cases this clearly occurred at an L\text{d}/L\text{o} boundary. If this holds up in vivo, those interested in trafficking may have to think about lipid dynamics as much as protein mechanics. Membrane fission proteins have been thought of as motors driving a constriction event, but “the main function of these proteins,” says Goud, “might be to help promote this phase transition.”

Reference: Roux, A., et al. 2005. EMBO J. doi: 10.1038/sj.emboj.7600631.

**Kept alive by a bacterial pull**

*N. gonorrhoeae* use their type IV pili (Tfp) to pull on the epithelial cells they are infecting, say Heather Howie, Magdalene So (Oregon Health and Science University, Portland, OR), and colleagues. This pull, perhaps mimicking normal cell attachment signals, activates gene expression that enhances cell survival.

The Tfp had already shown their talents: their retraction pulls the bacteria along on a surface. The Oregon group now show that infection with Tfp-containing bacteria further activates a subset of genes, mostly MAP kinase targets, that are normally activated by *Neisseria* infection.

A similar set of genes was induced by pulling on magnetic beads that had been coated with pili proteins and stuck to the epithelial cells. This treatment also reduced apoptotic markers.

At 100 pN of force per retraction event, 10 pili per bacteria, and 10–100 bacteria per microcolony, the force at each site on an epithelial cell may reach 10^{-5}–10^{-2} pN. This is in the same range as the force applied to an integrin complex in a ligament. In many cells such forces are needed to generate survival signals, as they indicate to the cell that it is firmly attached to a substrate. *Neisseria* may be co-opting this signal to boost the survival of its host cells in the face of immune reactions that would tend to eliminate the infected cell.

Reference: Howie, H., et al. 2005. PLoS Biol. 3.e100.

**Time encoding by ERKs**

Time encoding by ERKs here are many more biological processes than there are signaling pathways. How, then, do multiple signals converge on one pathway and yet elicit diverse responses? Satoru Sasagawa, Shinya Kuroda (University of Tokyo, Japan), and colleagues find that rapid increases in epidermal and nerve growth factors (EGF and NGF) trigger transient ERK activation, whereas it is the final concentration of NGF that determines whether a sustained ERK activation occurs. The differences probably explain why EGF prompts PC12 cell proliferation whereas NGF makes the same cells differentiate.

The Tokyo group used in vivo measurement and in silico simulations to show that changes in growth factor concentration prompted fast SOS recruitment and thus Ras activation. Slower Ras-GAP recruitment was effective in turning off the Ras and thus made the response transient.

By contrast, the sustained response was dominated by the levels of Rap1 activation. Rap1-GAP activity was constitutive rather than inducible, so the overall response depended only on how much activator was supplied by the growth factor receptor. High constant levels of NGF (and a lack of the degradation seen with the EGF receptor) gave sustained ERK activation necessary for PC12 differentiation.

Thus, Ras and Rap1 capture transient and sustained receptor activation, respectively. This is translated into either transient or sustained ERK activation. Kuroda and colleagues are now looking at how this difference in the persistence of ERK activity is converted into distinct cellular behaviors.

Reference: Sasagawa, S., et al. 2005. Nat. Cell Biol. doi:10.1038/ncb1233.