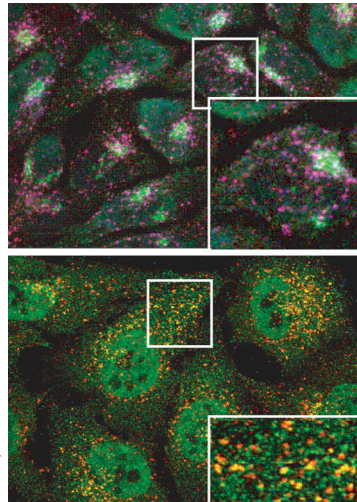# SNX1 hugs the curves

A sorting protein uses the coincidence of a lipid signal and membrane curving to direct its tubulation activity to the correct compartment, as shown by Jez Carlton, Peter Cullen (University of Bristol, UK), and colleagues. Relatives of this sorting nexin, SNX1, may control trafficking to and from a number of intracellular compartments.

TGN localization (top) of a receptor (green) is lost when SNX1 (blue) is missing (bottom).

SNX1 chooses its home via two membrane-binding domains. One targeting domain is the PX domain, which is known to bind to the endosomal phosphoinositide, PI3P. The second is a BAR domain, which was shown to target a fly protein to highly curved membranes and tubulate them.

Cullen's group shows that these domains combine to put mammalian SNX1 on the tubular portion of early endosomes (which also have less curved vesicular domains). This placement was needed to recycle a mannose-6-phosphate receptor from endosomes to the TGN. The cargo is probably selected by the retromer complex, which associates with SNX1.

The pinching off of endosomal tubules may be SNX1-driven, but Cullen is not yet convinced, as he needed a lot of SNX1 to get tubulation in vitro. Nine SNX1 relatives have both BAR-like and PX domains. As mammalian PX domains have different PIP binding partners, the nine might direct various trafficking pathways. JCB

Reference: Carlton, J., et al. 2004. *Curr. Biol.* 14:1791–1800.

GTPase modes modeled

A new computational model from Scott Bornheimer, Shankar Subramaniam, and colleagues (University of California, San Diego, CA) predicts how the GTPase cycle operates in one of several modes. Several GTPase cycle models exist, but many include only the G protein, its activator (often a receptor), GTP, GDP, and phosphate. Subramaniam's group added a GAP, the G protein deactivator, to the equations, and used experimental data from the GTPase cycle of a mouse G protein stimulated by a acetylcholine receptor (largely from Mukhopadhyay and Ross. *PNAS.* 96:9539–9544) to build their model.

"Variability in the concentration of the players in vivo is common," says Subramaniam. "How will the cell achieve maximum or moderate turnover? What happens when it's starved of GAP? How can the cell compensate to accomplish the same end point?" The model can now predict answers to these questions.

Four modes were found in which G protein activity is unaltered by changes in receptor or GAP concentrations. Between these extremes are infinite variations. In some modes, particularly when G protein levels are low, the cycle operates while the G protein and receptor are not physically clustered. In this mode, GAPs are able to shut down G protein signaling entirely.

In other situations, clustering is required for G protein activity, and GAPs can change the signaling amplitude but cannot eliminate it. The authors are now using FRET to determine how local clustering changes with altered component concentrations. JCB

Reference: Bornheimer, S.J., et al. 2004. *Proc. Natl. Acad. Sci. USA.* doi:10.1073/pnas.040700910.
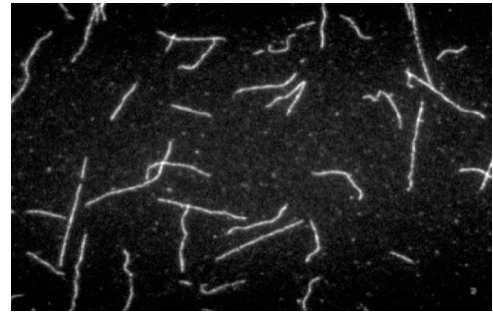
Profilin helps formin to steer actin monomers into the barbed ends of actin filaments.

Profilin for processivity

Profilin helps formin to speed actin assembly and enhance ATP hydrolysis, according to Stéphane Romero, Marie-France Carlier (CNRS, Gif-sur-Yvette, France), and colleagues.

Formins initiate actin filaments at various places such as filopodia, focal adhesions, and the cytokinetic ring. The authors show that when formin is alone on barbed ends, it slows filament dynamics by binding to and falling off the barbed ends. But when another actin-binding protein, profilin, is added, formin becomes a processive motor for rapid actin elongation.

The profilin/formin combination speeds polymerization two ways. First, it increases by 15-fold the on-rate of actin to barbed ends. "Electrostatic or hydrodynamic properties of formin," suggests Carlier, "may allow profilin–actin to associate much faster at short distances than is [possible when] limited by diffusion." This is a much faster rate than that of Arp2/3. The disparate on-rate constants thus allow for different actin velocities at the same actin monomer concentration.

Formin's second ability is to hasten ATP hydrolysis by actin, which is the rate-limiting step of filament growth at high actin–profilin levels. Enhanced hydrolysis may result from structural changes to the ATP-binding site, which should be revealed by structural studies of actin–formin–profilin. JCB

Reference: Romero, S., et al. 2004. *Cell.* 119:419–429.