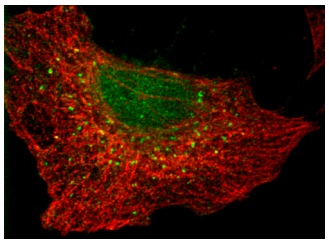
In This Issue

Text by Mitch Leslie
mitchleslie@comcast.net

The downside of microtubule stability



In a cell lacking dynamin 2, the pre-Golgi vesicles (green spheres) remain dispersed.

Stalled microtubules might be responsible for some cases of the neurological disorder Charcot-Marie-Tooth (CMT) disease, Tanabe and Takei report. A mutant protein makes the microtubules too stable to perform their jobs, the researchers find.

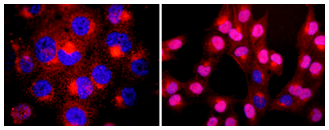
The mutations behind CMT disease slow nerve impulses, reduce their strength, or both. One of these mutations leads to production of faulty dynamin 2, a protein that is crucial for endocytosis but also latches onto microtubules. Tanabe and Takei investigated how defective dynamin 2 hampers cells.

Normal microtubules are continually extending and shrinking. But microtubules from cells that made the faulty version of dynamin 2 were abnormally stable, as measured by how many acetyl groups were attached to them. The researchers also found that blocking normal dynamin 2 with RNAi had the same effect as the mutation, confirming that one of dynamin 2's functions is to promote microtubule turnover.

Removing dynamin 2 shattered the Golgi complex, Tanabe and Takei discovered. Dynamic microtubules help construct the Golgi complex in two ways: they capture the vesicles that combine to form a mature Golgi complex; and they provide a track along which these vesicles can travel to their rendezvous point near the nucleus. By breaking up the Golgi apparatus and then watching the fragments reunite, the researchers found that dynamin 2 was essential for the capture step, not for transportation. Dynamin 2 also clings to microtubules of the mitotic spindle, and the team next wants to determine whether the protein regulates microtubule dynamics during the cell cycle.

Tanabe, K., and K. Takei. 2009. *J. Cell Biol.* doi:10.1083/jcb.200803153.

CD44's nuclear road trip



STAT3 (red) waits in the cytosol (left) but hitches a ride into the nucleus with CD44 (right).

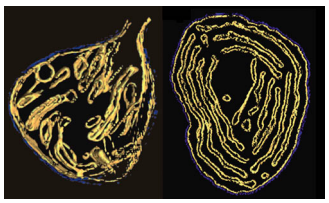
Lee et al. reveal how a characteristic surface marker for cancer stem cells triggers abnormal growth. The protein makes a dash for the nucleus, picking up a couple of accomplices, including the transcription activator STAT3, along the way.

The surface receptor CD44 is overexpressed in many tumor types, including stomach cancer. Responding to neighboring cells and the extracellular matrix, the protein helps control everything from differentiation to survival. At the membrane, CD44 promotes signaling through the integrin proteins by corralling lipid rafts. Other scientists had previously shown that a snippet of CD44 could turn on genes in the nucleus. But whether the full-length protein could get there and what functions it might perform once it arrived were uncertain.

Lee et al. found that after stimulation, CD44 molecules evacuate the membrane of stomach cancer cells via the endocytic pathway. The proteins wend through the cytosol and eventually slip into the nucleus through a nuclear pore. A mutant protein lacking the nuclear localization sequence was locked out of the nucleus. But CD44 doesn't travel solo. On the way, it links up with STAT3 and another protein, p300. This meeting leads to STAT3's acetylation and activation. Once the combo reaches the nucleus, it latches onto the promoter for the *cyclin D1* gene, which nudges the cell from the G1 phase into the S phase, thus speeding cell division. Other cancer-related surface receptors such as EGFR migrate into the nucleus. But they exert their effects through their enzymatic activity, whereas CD44 serves as a scaffold for other proteins, the researchers say. Still a mystery is how CD44's mobility relates to its role as a cancer stem cell marker.

Lee, J.-L., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200812060.

How a membrane gets the bends



Crista junctions are prevalent in a normal mitochondrion (left) but disappear when Fcj1 is absent (right).

Two dueling proteins help crimp the inner mitochondrial membrane into its familiar, accordion-like shape, Rabl et al. show.

The inner membrane of a mitochondrion is split into two parts. The peripheral portion, the inner boundary membrane, rests against a second membrane that encapsulates the organelle. Meanwhile the innermost portion, or cristae membrane, doubles back on itself again and again to form pleats, or cristae. A section of cristae membrane bends at two points—its tip and its base, where it connects to the inner boundary membrane. The tube-like structure that links the cristae and inner boundary membranes at this point is called a crista junction. How these connections form is a mystery.

To find out, Rabl et al. screened slow-growing yeast mutants, which often harbor malformed mitochondria. They pinpointed a strain that sported a faulty version of a protein they dubbed Fcj1. The protein embeds in the inner membrane and is particularly common at crista junctions, making it the first component of the junctions to be identified. Cranking up Fcj1's expression boosted the number of these junctions. When the team deleted Fcj1, by contrast, crista junctions vanished, and the cristae membrane distorted into parallel stacks of vesicles rather than a series of folds.

The researchers found that the ATP-making protein complex F_1F_O shows the opposite distribution to Fcj1—it amasses at cristae tips but is scarce at crista junctions. The two proteins appear to have an opposing function as well. Fcj1 prevents dimers of the synthase from zipping together. The researchers hypothesize that the curvature of the membrane at any point depends on the balance of Fcj1 and the ATP synthase. F_1F_O bends the membrane in one direction, whereas Fcj1 bends it the opposite way.

Rabl, R., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200811099.