In This Issue

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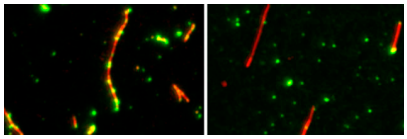
Bringing stability to microtubules



MCAK (green) binds less efficiently to microtubules (red) when α-tubulin is detyrosinated (right), increasing their stability.

The removal of a single tyrosine residue from the C terminus of α-tubulin dramatically affects microtubules and their depolymerizing motors, say Peris et al.

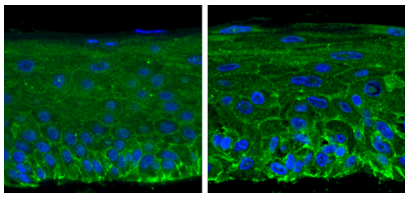
α-tubulin undergoes a cycle of tyrosine removal and readdition, catalyzed by a carboxypeptidase and tubulin tyrosine ligase (TTL). Microtubules containing detyrosinated α-tubulin are more stable, and this modification is often used as a marker to distinguish different populations of microtubules within cells. But removing tyrosine was thought to be a consequence rather than a cause of microtubule stability.

Peris et al. examined the cytoskeletal dynamics of cells whose α-tubulin is largely detyrosinated because they lack TTL. Microtubules disassembled more slowly in these cells, suggesting that detyrosination actually causes microtubule stability. Detyrosinated microtubules are poor substrates for depolymerizing motor proteins, the team discovered. Kinesin motors such as MCAK take longer to move along the filament and disassemble the tubulin subunits.

Overexpressing MCAK in cells lacking TTL restored normal microtubule dynamics, whereas removing MCAK from wild-type cells caused microtubules to stabilize as if they were detyrosinated. By showing that the absence of tyrosine reduces the activity of depolymerizing motors, the researchers have answered the conundrum of why stable microtubules are detyrosinated. Senior author Annie Andrieux now wants to solve another long-term mystery by identifying the tubulin caroboxypeptidase responsible for removing tyrosine in the first place.

Peris, L., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200902142.

Desmoglein directs differentiation



Activated EGFR (green) is only found in the bottom undifferentiated layer of wild-type skin cultures (left) but spreads throughout the skin in the absence of Dsg1 (right).

The cell adhesion protein desmoglein 1 (Dsg1) has an extra function in suppressing EGF receptor (EGFR) signaling, helping skin cells differentiate into the different layers of the epidermis, report Getsios, Simpson, et al.

Desmogleins are transmembrane components of desmosomes, which hold epithelial cells together and help them resist mechanical stress by connecting with the intermediate filament cytoskeleton. In a multi-layered epithelium such as the epidermis, different desmogleins are expressed in distinct patterns, and may therefore direct the process by which the different layers are specified.

Getsios and colleagues were particularly interested in Dsg1 because its expression in the skin matches the time and place that undifferentiated skin cells stop dividing and develop into all the other layers of the epidermis. Organotypic cultures made from skin cells lacking Dsg1 failed to differentiate in the more mature layers. Surprisingly, Dsg1 didn't need its adhesive activity to support proper differentiation; nor did it rely on two of its desmosomal partners, plakoglobin and desmocollin 1, to exert its effect.

Dsg1 did, however, need to be at the cell membrane where it promotes skin morphogenesis by inhibiting EGFR signaling. EGFR keeps skin cells in their undifferentiated state, and the team found that this receptor was active throughout Dsg1-deficient organotypic cultures. Blocking EGFR or its downstream kinases Erk1/2 restored normal differentiation to skin cells lacking Dsg1. Author Kathleen Green says this is an important demonstration that transmembrane desmosomal proteins like Dsg1 can have signaling functions distinct from their role in cell adhesion. The next challenge is to determine how the protein interferes with EGFR.

Getsios, S., C.L. Simpson, et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200809044.

Fibronectin is a good catch for integrin

Kong et al. find a touch of romance in the engagement between integrin adhesion receptors and their extracellular matrix ligands. The more life tries to pull them apart, the more they want to stay together.

As a cell crawls along, integrin heterodimers bind extracellular matrix molecules such as fibronectin and help the cell gain traction. You might expect that the harder the integrin–fibronectin bond is pulled, the more likely it is to break. But some types of molecular bond—called catch bonds—actually grow stronger as more force is applied to them.

Researchers have long speculated that integrins might display this unusual behavior, but experiments measuring the forces that disrupt integrin–ligand interactions failed to find any evidence of catch bonds. Kong et al. took a slightly different approach. They used atomic force microscopy to measure how long individual bonds between $\alpha_5\beta_1$ integrin and fibronectin lasted when pulled apart with constant forces. As the pulling force increased, the $\alpha_5\beta_1$–fibronectin association lasted longer, indicating that the molecules do form catch bonds.

The increased force might induce a conformational change in the proteins that locks the bond tighter. Kong et al. provide evidence that this switch occurs in the extracellular head domain of $\alpha_5\beta_1$. Senior author Cheng Zhu, however, speculates that such a conformational change could be propagated across the plasma membrane to the integrin's tail, altering its association with the cytoskeleton and downstream signaling molecules. Force-induced changes in adhesion strength and signaling may help cells migrate and respond to their local environment.

Kong, F., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200810002.