In This Issue

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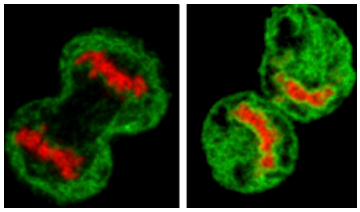
Preventing the nuclear envelope from getting on a roll



In dividing cells, removing one inner membrane protein slows the final stage of nuclear envelope construction.

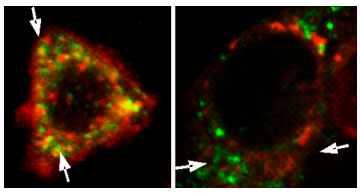
A cadre of chromatin-binding proteins helps rebuild the nuclear envelope after mitosis, Anderson et al. show. The proteins anchor the nascent envelope to the chromosomes and allow it to expand.

The nuclear envelope is an obstacle to chromosome separation. So before mitosis, the membrane dissolves and the lipids and some of the proteins it contained take refuge in the endoplasmic reticulum (ER). After segregation, ER membranes coalesce and surround the chromosomes, restoring the envelope. The researchers previously showed that reticulons, proteins that curl ER sheets into tubes, hamper envelope reconstruction. That suggests that other proteins must counteract this rolling tendency so that the reforming nuclear envelope bends just the right amount. Anderson et al.'s suspicions fell on a group of proteins from the inner nuclear membrane, including LBR and MAN1, that fasten the developing envelope to chromatin.

Cells work fast, rebuilding the nuclear envelope in about 10 minutes. The team demonstrated that trimming the levels of these inner membrane proteins one at a time slowed the reconstruction but didn't stop it. Restoration of the nuclear envelope occurs in two steps—first the ER membranes home in on the chromatin, and then they reshape into nuclear envelope sheets. Reducing levels of three of the inner membrane proteins hindered the second step, not the first. Two components of nuclear pores also took part in the rebuilding. The researchers suggest that by tacking sections of ER membrane to the chromosomes, the inner membrane proteins prevent ER membranes from rolling up and enable them to eventually enclose the chromosomes.

Anderson, D.J., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200901106.

Calcium's route to freedom



TPC1 (green) shows up in the lysosomes (red, left) but not the ER (red, right).

Researchers had already identified a molecular key that opens some intracellular calcium storehouses. Brailoiu et al. now reveal the door, the channel that actually lets calcium exit.

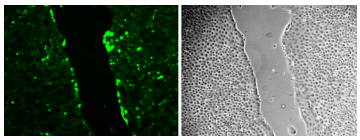
Cells stow calcium within certain organelles, releasing it into the cytosol in response to myriad cues. Researchers have pinpointed the messengers that spur the endoplasmic reticulum (ER) to unload its calcium. Another signal, NAADP, triggers so-called acidic stores—the endosomes and lysosomes—to do the same, but which calcium channel NAADP activates was uncertain. A recent study revealed that in plants, the two-pore channels release calcium from the vacuole, another acidic environment. Brailoiu et al. wondered whether NAADP might target one of these little-known channels in animals.

The channels are in the right place; in cells engineered to produce human two-pore channels, the molecules were expressed in the endosomes and lysosomes, but not the ER. The channels' abundance dictates responsiveness to NAADP. When human cells fashioned extra amounts of the channel TPC1, they were hypersensitive to NAADP. But when the researchers reduced TPC1 levels by RNAi, the cells discharged little calcium after stimulation. What's more, mutation of a single, conserved amino acid in the putative pore region of TPC1 prevented NAADP-induced calcium release.

The work suggests that TPC1 is a target of NAADP, complementing a *Nature* paper published in May that showed NAADP spurs calcium release via TPC2. Researchers now need to work out whether NAADP acts directly on the channels or through intermediaries.

Brailoiu, E., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200904073.

Killing the β-catenin messenger



β-catenin signaling (green) fires up along a scratch in a cell layer.

When cells cozy up to each other, they tune out Wnt signals, Maher et al. show. The cells dial down their sensitivity by speeding the destruction of β-catenin (β-cat), a key component of the Wnt pathway.

β-cat hooks up with transcription factors to switch on genes in response to Wnt. A phosphodestruction complex, which phosphorylates and then chops up β-cat, provides one control mechanism for dampening the Wnt pathway. Cadherin can also diminish Wnt signaling by capturing β-cat at adherens junctions, suggesting adhesion between cells might alter signal transmission via β-cat.

Maher et al. discovered that the heavily phosphorylated form of β-cat amassed at cell junctions. However, forcing cells apart by altering extracellular calcium levels boosted amounts of a lightly phosphorylated, transcriptionally competent β-cat version. β-cat signaling was also higher when cells lacked neighbors, such as at the edge of a colony or along a scratch in a cell layer.

Driving changes in β-cat levels is the phosphodestruction complex, the researchers suggest. Its components build up at cell junctions. And when cells stick together, the complex's breakdown of β-cat in the cytosol accelerates.

What draws the phosphodestruction complex to cell contacts and controls its activity remains uncertain. But the results suggest that when cells touch, cadherin diminishes their sensitivity to Wnt signals by firing up the phosphodestruction complex, and boosting the demolition of β-cat. If intercellular contacts break, such as during migration, the phosphodestruction complex slows, priming the cell to respond to Wnt signals.

Maher, M.T., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200811108.