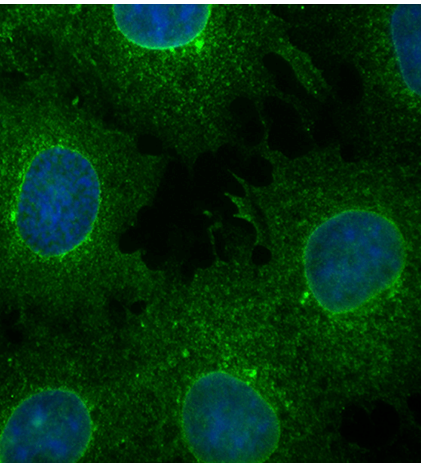
In This Issue



Lis1 (green) accumulates at the nuclear envelope and helps control its breakdown.

Timing the breakdown

Before chromosomes can go their separate ways during mitosis, the nuclear envelope has to dissolve. As Hebbar et al. reveal, breakdown of the membrane might influence the fate of cells in the developing brain by controlling when they divide.

The ventricular zone is the developing brain's maternity ward, where stem cells give birth to neurons and other cell types. Within these stem cells, nuclei continually move up and down, and their position when division occurs helps settle the fate of the progeny. One daughter cell will always become a replacement stem cell, but the second daughter will typically become a neuron if cell division occurs when the nucleus is at the top of the cell, or will likely become another type of precursor if the nucleus is at the bottom. Changing the timing of division could alter the progeny's fate because the nucleus might be at a different position.

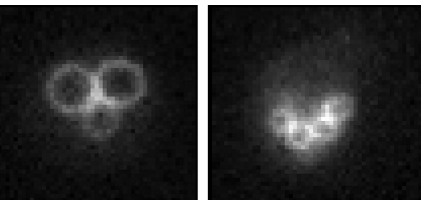
Hebbar et al. discovered that the breakdown of the nuclear envelope helps determine division's onset. The researchers were studying two proteins essential for normal brain development, Lis1 and Ndel1, which latch onto each other and then grab dynein, a motor protein. Several years ago, scientists revealed that dynein spurs formation of pockets on one side of the nucleus, stressing the nuclear envelope and causing it to tear and eventually disintegrate. Hebbar et al. showed that the amount of Lis1 and Ndel1 in the cell can accelerate or slow formation of these pockets.

The team also discovered that phosphorylation of Ndel1 flips the switch for pocket formation, dislodging Lis1 and Ndel1 from dynein. That might unleash the motor protein to dent the nuclear envelope.

When they examined embryonic mice that carry half the normal amount of Lis1, the scientists found that stem cells from the animals' ventricular zone showed fewer pockets and delayed nuclear envelope disintegration. Such a slowdown could be disastrous for the developing brain. It could cause the cells to divide at the wrong point in their oscillations, triggering an overproduction of neurons and eventual depletion of stem cells. In fact, previous work has shown that this mouse strain produces neurons at the expense of precursors.

Previous studies indicated the orientation of the mitotic spindle determines cell fate, but the work suggests nuclear envelope breakdown, which occurs before the spindle gets into position, contributes to the decision.

Hebbar, S., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200803071.



When yeast cells overproduce the Rab blocker Gyp7, their vacuoles fragment (right).

Rab(ble) rouser

It takes more than one inhibitor to keep a Rab down, Brett et al. report. The team determined that yeast cells use two switches to turn off this vesicle management protein.

The Rab proteins regulate the transport and fusion of vesicles. Researchers have teased out the Rab control pathways in vitro, discovering that GTPase-activating proteins (GAPs) turn off Rabs. But scientists know little about what happens in living cells.

So Brett et al. followed the dynamics of yeast vacuoles, which split or fuse depending on the cell's situation. To nail down what inactivates a fusion-promoting Rab called Ypt7, the scientists cranked up the levels of different Gyp proteins—the yeast versions of GAPs. Confirming results of in vitro studies, the researchers showed that Gyp7 inhibits Ypt7.

But Gyp7 can't do the job alone, the team found. It needs help from another protein called Yck3, which phosphorylates two targets of Ypt7: a protein complex that tethers vacuoles to each other and a second complex that promotes vacuole fusion. Ypt7 doesn't take this interference lying down, however. The researchers determined that active Ypt7 blocks phosphate addition.

The study helps fill in the complex control circuit for Ypt7. The team proposes that the network includes a "feed forward" loop, in which Ypt7 maintains its own activation by pre-empting Yck3. The end result might be a signaling circuit that is particularly sensitive to changes in Ypt7 activity.

Brett, C.L., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200801001.

Rules of gene attraction

Active genes can be sociable, snuggling up to one another. Brown et al. offer a new explanation for this clustering, suggesting that genes gather for the services of RNA splicing enzymes

A gene's location in the nucleus often reflects its activity. Hard-working genes tend to congregate in the interior of the nucleus, whereas their lazier counterparts hang out at the edge. Moreover, active genes on different chromosomes sometimes bunch up. How often active genes come together is uncertain. Whether the associations serve a purpose is also unclear, although some researchers propose that genes converge at so-called transcription factories that contain RNA polymerase.

To address these issues, Brown et al. pinpointed five genes that crank up during the differentiation