

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.

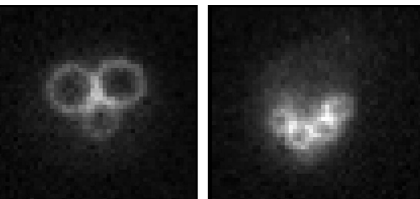
Hebbar et al. discovered that the breakdown of the nuclear envelope helps determine division's onset. The researchers were studying two proteins essential for normal brain development, Lis1 and Ndel1, which latch onto each other and then grab dynein, a motor protein. Several years ago, scientists revealed 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

of human red blood cells. Some of the genes were friendlier than others. For example, two α -globin genes were about five times more likely to be near each other than were two β -globin genes.

Next, the researchers tested whether a gene's chromatin environment affects its tendency to cluster. In human cells, β -globin sits in a tightly packaged chromatin region, whereas α -globin's neighborhood is looser. But in mouse cells, α -globin resides in a condensed region. The team replaced the mouse α -globin gene with the human version, so that the ordinarily loose human gene was now in a condensed chromatin environment. Like the β -globin gene in human cells, the inserted α -globin gene in mouse cells was aloof, suggesting that a gene's surroundings do influence its position relative to other genes. However, the team found that the inserted gene worked normally, showing that associations aren't essential for normal transcription.

The results also indicate that genes aren't sharing transcription factories. The average distance between associating active genes, the researchers determined, was about 10 times the diameter of a factory. Instead, the genes were congregating at nuclear speckles, much larger structures than factories that harbor enzymes for splicing RNA after transcription. The team concludes that genes associate because they sometimes happen to be drawn to the same speckle.

Brown, J.M., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200803174.

Laminin reaches across the synapse

Like a plug and a socket, a nerve and a muscle fiber mesh at the neuromuscular junction. The extracellular matrix protein laminin shapes both sides of the junction to ensure they fit together, Nishimune et al. report.

A neuromuscular junction in a newborn mouse is functional but simple, with a globular nerve terminal meeting a flat, oval structure on the muscle fiber. As the animal matures, the nerve terminal branches into a claw shape, and the muscle side contorts into a matching conformation. But what coordinates these changes so the two sides mirror each other? The researchers think that one molecule in the synapse sculpts both sides.

Their chief suspect was the synapse-spanning protein laminin. Made by the muscle, laminin sports α , β , and γ chains and is part of a sheath that covers the muscle fiber. Previous work had shown that the $\beta 2$ chain of laminin spurs differentiation of the nerve terminal. The team has now found evidence that the α chains of laminin influence post-synaptic patterning. For example, maturation of the post-synaptic side slowed in mice lacking the $\alpha 5$ chain of laminin in their muscles. Moreover, post-synaptic development faltered in myotubes, or muscle fiber precursors, from these mice.

The researchers discovered that laminin corrals molecules of its receptor, dystroglycan, on the post-synaptic surface. Dystroglycan, in turn, gathers receptors that respond to acetylcholine released by the nerve, though how dystroglycan rounds up these receptors is uncertain. Overall, the work suggests that laminin influences pre-synaptic and post-synaptic development, thus providing a way to coordinate maturation of the sending and receiving sides of the synapse.

Nishimune, H., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200805095.

Pumping up caveolae

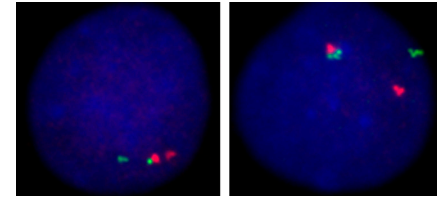
The sodium pump is branching out. As Cai et al. show, the pump not only moves ions, it controls trafficking of a membrane protein that is crucial for intercellular communication and other functions.

The Na/K-ATPase, or sodium pump, ejects sodium ions from the cell and brings in potassium. Besides swapping ions, the pump helps structure the cell membrane. Pump molecules are prevalent in caveolae, pockets in the plasma membrane involved in cell-cell signaling and endocytosis. Instead of assembling these structures at the membrane, cells build pre-fab caveolae in the Golgi apparatus and then ship them for installation. Because pump molecules can bind to caveolin-1 (Cav1), the main structural protein of caveolae, Cai et al. wondered whether the pump helped govern dispersal and positioning of Cav1.

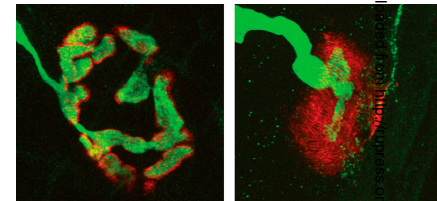
To find out, the researchers used RNA interference to trim the amount of non-pumping Na/K-ATPase. The treatment reduced the amount of Cav1 in the membrane and the number of caveolae. Adding a non-pumping version of Na/K-ATPase restored the normal distribution of Cav1, but a version that couldn't attach to Cav1 had no effect.

The researchers found that in the treated cells, Cav1 emerged from the Golgi apparatus, suggesting that the pump's disappearance doesn't impair caveolin construction. However, Cav1 in the plasma membrane was prone to return to the cytoplasm. A protein called Src promotes this endocytosis of Cav1, but the pump inactivates Src. Overall, the study suggests that by blocking Src and by latching onto Cav1, the sodium pump helps direct Cav1 to the membrane and keep it there.

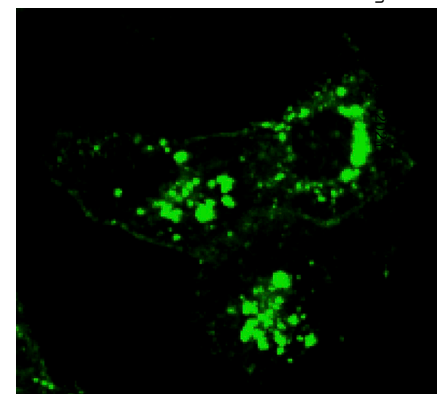
Cai, T., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200712022.



Genes that are activated during red blood cell differentiation (green and red) cozy up in a human erythroblast.



The two sides of the neuromuscular junction normally interlock (left), but not when certain laminin α chains are absent (right).



When the sodium pump is scarce, Cav1 (green) loiters near the nucleus instead of infiltrating the cell membrane.

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