In This Issue

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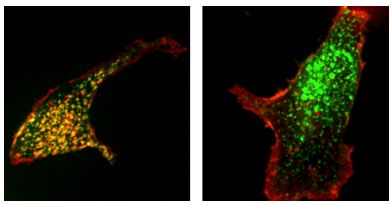
Splicing reverses protein's function



STIM2α (green, left) binds to Orai1 channels (red), but STIM2β (green, right) doesn't.

Alternative splicing transforms a protein that stimulates calcium uptake into one that inhibits it, Rana et al. discover.

The proteins STIM1 and STIM2 sense when the endoplasmic reticulum is running low on calcium. They then prod Orai channels in the plasma membrane to open and allow more calcium into the cell through a process called store-operated calcium entry.

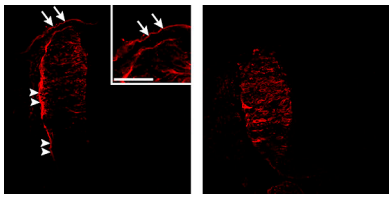
Rana et al. identified a second isoform of STIM2 that arises by alternative splicing. This version, STIM2β, carried an eight-amino-acid insert that was absent from the previously identified isoform, STIM2α. The exon encoding this segment was well conserved in mammals, and its splicing was regulated during tissue development, suggesting that it has an important function.

Surprisingly, Rana et al. found that STIM2β blocks calcium influx through the Orai1 channel. Unlike STIM1 and STIM2α, STIM2β can't bind to Orai1. It reaches the channel by hitching a ride with STIM1 or STIM2α.

How it blocks the channel once it gets there remains unclear. The inhibition appears to involve a specific interaction between STIM2β and Orai1, because mutations in the eight-amino-acid insert of STIM2β strongly reduce the inhibition. The authors think that having the option of producing STIM2β might enable cells to tune the strength or dynamics of their calcium signals.

Rana, A., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201412060

A Hedgehog inhibitor gets around



HHIP1 (red) normally amasses in the neural tube's basement membrane (arrowheads, left), but a version of the protein that can't bind to heparan sulfate doesn't accumulate there (right).

Cells secrete an inhibitor that controls the distribution and activity of Hedgehog proteins, Holtz et al. show.

The Hedgehog pathway shapes the developing brain, lungs, digestive system, and many other parts of the body. Secreted activators of the pathway can have far-flung effects. However, Hedgehog inhibitors, such as PTCH1 and PTCH2, appear to act locally. They accumulate on the surface of cells that produce them, binding to any Hedgehog proteins that arrive. Researchers thought that the Hedgehog inhibitor HHIP1 was also a homebody.

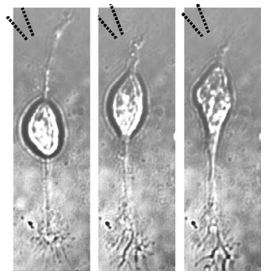
Holtz et al. found otherwise when they investigated the effects of Hedgehog inhibitors on the developing neural tube of chicken embryos. During spinal cord development, the Hedgehog pathway spurs neural progenitors to divide and stimulates cell fate specification. Inducing progenitor cells to produce versions of PTCH1 or PTCH2 hampered Hedgehog signaling only in those cells. But if the team induced cells to produce HHIP1, the inhibitory effect spread to other cells in the neural tube, suggesting that HHIP1 was secreted. Holtz et al. confirmed that cultured fibroblasts also released the inhibitor.

Secreted HHIP1 was captured by heparan sulfate molecules, which decorate the cell surface and the extracellular matrix. In chicken embryos, HHIP1 accumulated in the basement membrane that surrounds the neural tube and is rich in heparan sulfate. A version of HHIP1 unable to bind heparan sulfate lost much of its ability to block the Hedgehog pathway.

Holtz et al. also detected HHIP1 in the basement membrane of the lungs, where the Hedgehog pathway orchestrates branching of the airways. HHIP1 occurred together with Hedgehog pathway activators in the basement membrane, and its loss altered their distribution. The study indicates that HHIP1's interaction with heparan sulfate controls its location and thus its influence on the Hedgehog pathway.

Holtz, A.M., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201411024

Neurons join forces to push ahead



A granule cell crawls toward a source of brain-derived neurotrophic factor.

Three sites on a crawling neuron produce the force that pushes it along, Jiang et al. reveal.

Traction force propels a cell forward or backward. One study of fibroblasts found that a single location called the contraction center was responsible for the cell's traction force, but where a migrating neuron, with its small cell body and long projections, generates traction remains unclear.

The researchers used traction force microscopy to map the forces generated by cerebellar granule cells. They found that a granule cell has three contraction centers: just behind the tip of its forward projection, at the base of this projection, and in its tail. Myosin II activity and F-actin polymerization produced the force at each contraction center. However, the researchers found that microtubules dampened force generation, perhaps because they stiffen the cell.

All three contraction centers can operate at the same time, so Jiang et al. investigated how cells coordinate their activity. Granule cells crawl toward brain-derived neurotrophic factor (BDNF) and recoil from the protein Slit2. When Jiang et al. placed BDNF at the front of a neuron's cell body, the location of the strongest contraction center shifted forward and the neuron moved ahead. But when they placed Slit1 at the front of the cell body, the location of the strongest center shifted toward the rear and the cell went into reverse. The researchers conclude that, depending on its course, the cell adjusts the forces produced by each contraction center.

Jiang, J., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201410068