In This Issue

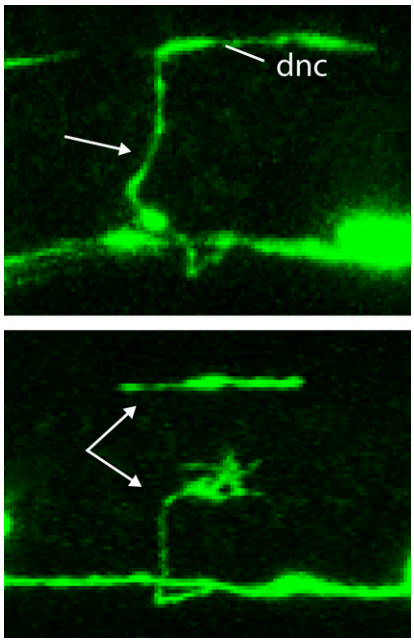
Nervous breakdown

Like the waistband of your pants after Thanksgiving dinner, neurons have to be able to stretch and then return to shape. On page 269 Hammarlund et al. pinpoint the protein that confers this springiness, showing that neurons lacking the molecule fracture.

Movements such as bending your elbow put strain on neurons, but the source of the cells' elasticity has been a mystery. Hammarlund et al. suspected that the protein β-spectrin was involved. In red blood cells, the protein weaves into a mesh that supports the cell membrane, enabling erythrocytes to rebound after being crushed and dented during their travels through the circulatory system.

The researchers tested spectrin's function in neurons by observing nematodes that lack the protein. In embryonic worms, neurons grew normally between the animals' two nerve cords, indicating that spectrin isn't necessary for development. But after the worms hatched, their neurons began to display defects such as abnormal branching, frequent breaks, and signs of new growth, which doesn't normally occur after the embryonic stage. By tracking individual neurons, the scientists demonstrated that the breaks came first; the aberrant growth and misguided branches followed as worms attempted to repair the severed cells.

To determine whether movement snaps the neurons, the researchers scrutinized paralyzed animals. Few of their neurons broke. Hammarlund et al. conclude that the fragility of spectrin-lacking neurons might explain some kinds of neurodegenerative diseases. For example, patients with spinocerebellar ataxia type 5—an inherited form of paralysis that ran in Abraham Lincoln's family—carry a faulty β-spectrin gene. Neurons might deteriorate in these patients because they break first, the researchers suggest. JCB



An axon (arrow) snaps (top to bottom) in a worm lacking β-spectrin.

Caught in the middle

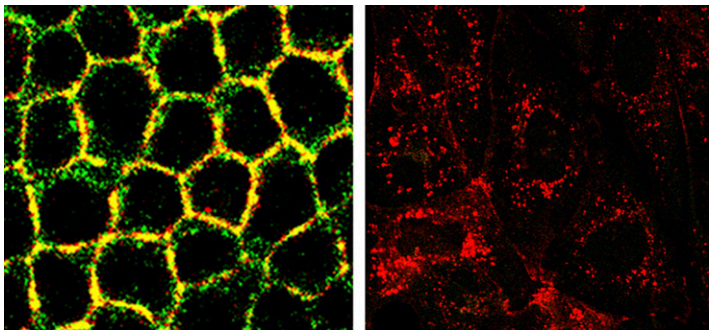
The protein E-cadherin puts a leash on cancer cells, and on page 343 Ling et al. clarify how cells deliver the molecule to the membrane. A connector protein fastens E-cadherin to a transporter that hauls it to the cell surface. The findings might improve researchers' understanding of metastasis in epithelial cancers and reveal how cells direct E-cadherin to the basolateral portion of the membrane.

Epithelial cells hold tight to their neighbors through connections called adherens junctions. The structures form when E-cadherin proteins protruding from adjoining cells clasp, and the cells snuggle up. To control these liaisons, cells add E-cadherin to the membrane or withdraw it into the cytoplasm. Because E-cadherin blocks cancer cells from spreading, researchers want to determine how cells direct the protein to the membrane.

Ling et al. observed that the protein PIPKIγ concentrates at adherens junctions, so they investigated whether the molecule takes part in transporting E-cadherin. They first determined that PIPKIγ latches onto E-cadherin. In cells depleted of PIPKIγ by RNAi, E-cadherin no longer made it to the cell membrane and accumulated in the cytoplasm.

Its partners in E-cadherin transport, the researchers discovered, include the clathrin adaptor protein complexes, which cart proteins to and from the membrane. If cells manufacture a faulty version of one adaptor protein that lacks the PIPKIγ binding site, little E-cadherin makes it to the membrane, the scientists found. They conclude that proteins can reach the cell membrane either by binding to clathrin adaptors directly, as shown before, or by binding PIPKIγ, which in turn links to the adaptors.

The results could clarify the defect behind a type of inherited stomach cancer. Patients carry a mutation that alters the site where E-cadherin couples to PIPKIγ. The two molecules bind weakly, and E-cadherin stays in the cytoplasm. The findings also indicate that PIPKIγ helps target E-cadherin to the basolateral membrane, but the possible mechanism or involvement of signaling pathways is not yet clear. JCB



When PIPKIγ (green, left) is no longer present (right), E-cadherin (red) is stuck in the cytoplasm.

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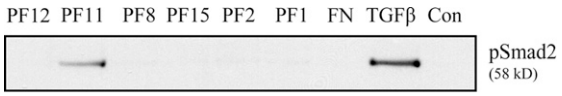


Only particular fibrillin-1 fragments activate TGFβ signaling.

Liberating TGFβ

Overactive TGFβ spurs Marfan's syndrome, which might have been responsible for Abraham Lincoln's rangy physique. But how the molecule gets released from storage and switched on is uncertain. On page 355 Chaudhry et al. fill in a key step, showing that a piece of an extracellular matrix (ECM) protein frees inert TGFβ.

TGFβ helps control whether cells move, divide, specialize, and survive. Cells often lock up the potent cytokine by fastening a complex containing its inactive form to fibrillin-1 fibers in the ECM. Discovering how this sequestered TGFβ breaks loose might clarify the mechanism of Marfan's syndrome, in which fibrillin-1 mutations lead to symptoms such as a weakened aorta and leaky heart valves.

Chaudhry et al. demonstrated that fibrillin-1 itself helps release the TGFβ complex. The researchers narrowed this ability to a small fragment of the protein. The segment doesn't bind to TGFβ. Instead, it attaches tightly to the end of fibrillin-1 that carries the cytokine complex. The researchers hypothesize that this interaction alters the shape of full-length fibrillin-1 and dislodges the inert TGFβ. Other enzymes could then activate it.

Fibrillin fragments wouldn't normally be loose in the extracellular matrix, but some fibrillin mutations distort the protein so that it is more likely to be sliced up by ECM enzymes. That might unleash the TGFβ-releasing segment, the researchers speculate. JCB

How kinases dodge trouble

Newly synthesized kinases have one thing in common with teenagers: they can go astray without supervision. As Mandal et al. reveal on page 319, cells keep the regulatory proteins in line by assigning them a bodyguard. The molecular guardian helps kinases avoid premature destruction.

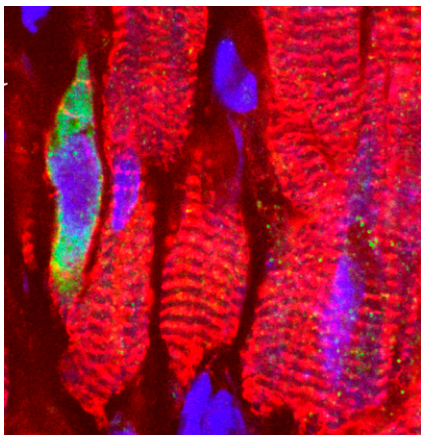
Researchers already knew that the protective protein, Cdc37, teams with the chaperone Hsp90 to help freshly synthesized kinase chains fold into shape. But evidence indicates that Cdc37 also works independently of Hsp90. To pin down Cdc37's other job, the researchers measured the amounts of 65 kinases in yeast cells that produce a defective version of the Cdc37 protein. Levels of 80% of the kinases were lower than in control cells. However, faulty Cdc37 didn't alter gene expression, and translation appeared to run normally, suggesting that the decline occurred after cells fashioned the kinases.

They found that, in cells with defective Cdc37, newly synthesized kinases broke down swiftly. But the kinases escaped destruction if the researchers first added a drug that stalls the proteasome, the cellular garbage disposal that chops up misshapen proteins. Without protection from Cdc37, newly formed kinases appear to get shunted into the proteasome for recycling. Cdc37 latches onto its targets at their active site during or shortly after translation. The researchers suspect that the protein can somehow sense its charges' shape and prevent them from misfolding, which would trigger their demolition. JCB

Stem cell side show

Before scientists can harness heart stem cells to repair damage to the organ, they have to pin down the elusive cells. On page 329, Oyama et al. bolster the case for a group of cells known as side population cells, showing for the first time that they home in on injured heart muscle and differentiate into all the types of cardiac cells in vivo.

Previous research has turned up several candidates for cardiac stem cells, including the side population cells. In the bone marrow, side population cells function as stem cells. The situation in the heart wasn't clear, however. If they are grown with heart muscle cells in vitro, cardiac side population (CSP) cells can specialize into heart muscle. However, researchers didn't know what stimulates the cells to differentiate or what they're capable of in vivo.



A CSP-derived cell (green) settles into injured heart tissue.

Oyama et al. offered cultured CSP cells a variety of growth factors, but found that only two—including the hormone oxytocin—coaxed the cells to differentiate. Whether these molecules control differentiation in vivo isn't clear, the scientists say, but their discovery might help researchers devise a recipe for nurturing the cells.

To study CSP cell behavior in vivo, the researchers injected tagged cells into rats. CSP cells ended up in several organs, but mainly in the heart. More of them found their way to the organ if it was damaged, indicating that they respond to signals from injured cardiac tissue. These new arrivals specialized into heart muscle cells, but also into blood vessel and connective tissue cells. That finding demonstrates that CSP cells can spawn all cell types in the heart, the researchers note. They conclude that CSP cells are serving as stem cells in the heart. JCB