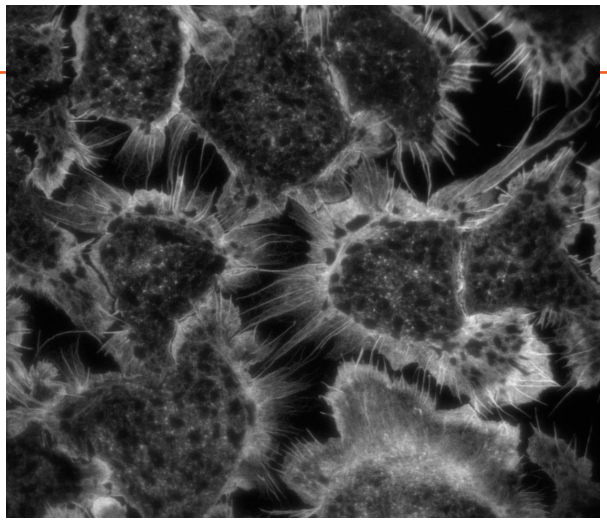
In This Issue



uPAR only needs to bind to vitronectin in the matrix to prompt cells to extend lamellipodia and filopodia.

uPAR's signaling two step

The uPA receptor (uPAR) is a loner. Jutting from the plasma membrane, it has no apparent connection to the cell interior. But, as Madsen et al. demonstrate on page 927, uPAR induces cells to cling tightly to a surface. The behavior might recruit other receptors and explain how the seemingly isolated uPAR exerts its influence.

Stimulating uPAR galvanizes cells—they attach to a surface, flatten, move, and divide. Cancer cells exploit the receptor's power by cranking up its expression. But based on its structure, uPAR seems like a signaling dead end, and researchers had assumed that uPAR handed off its messages by binding to integrins.

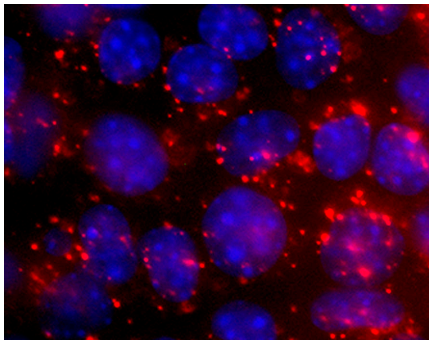
Madsen et al. tested that idea by replacing every amino acid in the receptor one at a time with alanine. They found that cells showed the typical response to uPAR stimulation unless the alanine swap meddled with the receptor segments that bind to vitronectin, a protein in the extracellular matrix. Tampering with uPAR's integrin-binding sites had no impact.

To show that attachment to vitronectin was sufficient for message transmission, the researchers modified cells to make a composite protein. One end sported the membrane-anchoring portion of uPAR, and the other end carried the vitronectin-recognizing stretch of an unrelated matrix-binding protein. The hybrid protein sparked the same effects as uPAR. Together, the results show that lateral interactions between integrins and uPAR aren't essential for relaying signals to the inside of the cell.

Integrins still take part in communication, however. Cells grown on a form of vitronectin that lacked an integrin-binding site ignored uPAR stimulation. Madsen et al. conclude that uPAR signaling occurs in two steps. The receptor first latches onto vitronectin, spurring the cell to snuggle up to the surface. This close contact then promotes liaisons between vitronectin and integrins, which send the messages on their way. JCB

Merlin casts spell on proliferation protein

The tactic that the protein Merlin uses to prevent tumors isn't magical, but it is unique, as Curto et al. report on page 893. The protein locks up a growth-inducing receptor in the membrane so that it can't broadcast its signals. The results suggest a possible way to combat some hard-to-treat cancers.



Even when crowded, cells lacking Merlin continue to take in vesicles holding EGFR (red).

Like its mythological namesake, Merlin is powerful and mysterious. Its gene, *NF2*, goes awry in several cancers. But researchers didn't know how Merlin checks cell proliferation. Some evidence pointed to an interaction with the epidermal growth factor receptor (EGFR), which spurs cells to divide. In fruit flies, for example, the Merlin and EGFR pathways intersect.

To determine whether Merlin targets EGFR, the researchers compared the receptor's activity in normal cells and cells lacking Merlin. As the culture dish became crowded, the normal cells shut down EGFR signaling and stopped dividing. But in the Merlin-deficient group, EGFR remained active even as cells piled up.

Stimulated EGFR exits the surface of the membrane and enters the cell; many researchers think this step is crucial for signal transmission. In cells missing Merlin, Curto et al. found, EGFR intake continued even as culture density increased. But internalization stopped in cells that made Merlin, and EGFR was shunted into the most insoluble part of the membrane. That discovery indicates that, when cells feel crowded, Merlin incarcerates EGFR so that it can't transmit further growth-promoting messages.

As contact between cells is known to spur Merlin expression, the results also help clear up the long-standing mystery of how cells stop dividing when they touch each other, a phenomenon called contact inhibition.

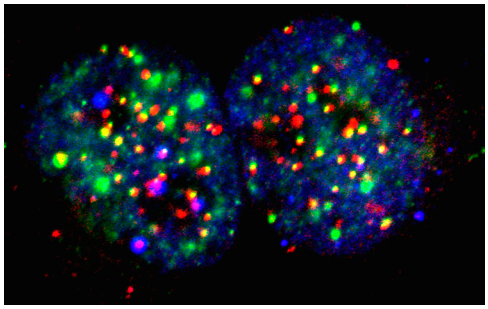
Tumors that arise because of *NF2* defects often sprout in the spinal cord or brain and can be hard to remove. The work suggests that EGFR blockers, some of which are already on the market, might attack these growths. JCB

Text by Mitch Leslie
mitchleslie@comcast.net

Coilin to the centromere's rescue

Before they advance through mitosis, cells carefully check for damage to their DNA and to the spindle that helps divvy up the chromosomes. During interphase, cells also monitor the centromeres that will be necessary for chromosomes to separate, as Morency et al. show on page 757. The researchers identify a crew of proteins that hurries to marred centromeres.

Centromeres provide anchorage for kinetochores, which latch onto the spindle fibers that pull the chromosomes apart. Cells halt mitosis if kinetochores are defective. But scientists didn't know whether cells also kept track of centromere integrity.



Coilin (green) gloms onto damaged centromeres (red).

Morency et al. had previously observed that centromeres are subject to attack by the herpes simplex virus, which spurs cells to demolish the centromere proteins CENP-A, CENP-B, and CENP-C. The researchers have now identified a novel cell response to this destruction during interphase. Three proteins—coilin, fibrillarin, and SMN—clustered at the battered centromeres. Depleting any of the three CENP proteins with siRNA lured coilin to the centromeres. But fibrillarin and SMN remained aloof. That difference suggests that these two proteins respond to more severe damage than does coilin.

Coilin, fibrillarin, and SMN don't appear to replace the missing CENPs, and their function at the centromeres remains a mystery. The proteins are also found in bodies where small RNAs mature, so perhaps they deliver these RNAs to centrosomes to trigger repair. Whether centromere damage naturally occurs often enough to hamper cells is uncertain, but it could result from any stress that injures the DNA or chromatin. JCB

Closing the connexin connection

Unlike preschoolers, cells are good about sharing. They swap ions, nutrients, and other molecules via membrane channels called gap junctions. But on page 881, van Zeijl et al. show that local loss of a phospholipid permits cells to become selfish and shut the channels.

Open gap junctions are crucial for heart contraction, wound repair, and other functions. But cells can temporarily shut the channels—when injured, for instance—and cancer cells can shut them permanently. G protein–coupled receptors close these portals, which are often made from the protein connexin43. But how that closure happens was unclear.

G protein–coupled receptors latch onto the enzyme PLCβ, which in turn slices up the membrane phospholipid PIP_2. The researchers found that blocking PLCβ or cranking up PIP_2 production kept the channels open, suggesting that PIP_2's digestion helped close them. To confirm the conclusion, van Zeijl et al. used a two-part, PIP_2-cutting enzyme that assembles on the membrane only after a dose of the drug rapamycin. Adding the compound shut gap junctions.

How PIP_2 influences channels was initially mysterious, as it did not attach to connexin43. But the group discovered that PLCβ hooked onto the protein ZO-1, which does link to connexin43. The results suggest a mechanism in which ZO-1 positions PLCβ so that it can chop up PIP_2 near connexin43. The next step remains unclear. Presumably, PIP_2 breakdown stimulates a protein that nudges the junction closed, but its identity is unknown. JCB

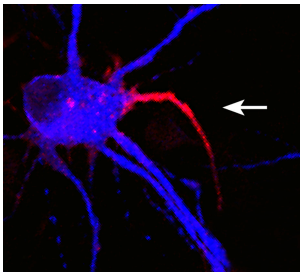
To build a node

Neurons rely on different structures to ignite nerve impulses and to propel them along the axon. Dzhashiashvili et al. show on page 857 that these structures develop in distinct ways. One structure depends on internal signals, whereas the other receives guidance from glial cells that wrap the axon in a myelin sheath.

The two types of structures, axon initial segments (AISs) and nodes of Ranvier, are molecularly similar, carrying current-producing sodium channels, the adhesion molecule neurofascin186 (NF186), and the actin–membrane linker ankyrin G. AISs touch off an action potential, whereas the nodes relay it along the axon. Evidence suggested that the two structures formed differently, but researchers didn't know the details.

To determine how NF186 gets into place, the researchers created composites that contained part of this protein and part of ICAM1, an immune molecule that neurons don't make. The composite accumulated in AISs only if it contained the intracellular part of NF186. The results for nodes were the opposite—the hybrid proteins built up only if they sported the extracellular part of NF186. That finding suggests that the neighboring Schwann cells direct NF186 into nodes.

The researchers also showed that Ankyrin G is essential for both structures but congregates differently. It concentrates in AISs before drawing in NF186. However, NF186 is essential before nodes can attract ankyrin G. The results indicate that AISs are built from inside out, and nodes from outside in. JCB



Ankyrin G (red) clusters at the axon initial segment of a neuron.