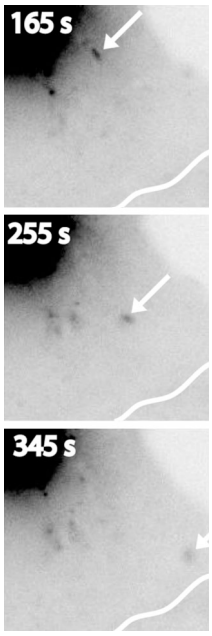
In This Issue



A vesicle of aquaporin-3 (arrow) heads (top to bottom) for the initial contact site between two cells.

Polarizing power of touch

When one epithelial cell meets another, it immediately begins to polarize its membrane, as Nejsum and Nelson report on page 323. The researchers describe the mechanism that helps create distinct membrane domains by delivering characteristic proteins.

As an epithelial cell polarizes, the basolateral portion of the cell membrane—the sides and bottom—accumulates one set of proteins, whereas another set takes up residence in the apical, or upper, surface. Researchers know more about how cells keep these two regions unique than about how the difference arises. Studies suggest that, as fresh proteins emerge from the Golgi apparatus, they carry an address that directs them toward a specialized patch on the membrane. Nejsum and Nelson wanted to determine how and when this patch assembles and when cell polarity appears.

The researchers followed the travels of two membrane proteins as they left the Golgi apparatus: the basolateral aquaporin-3 and the apical aquaporin-5. Nejsum and Nelson found that vesicles packed with aquaporin-3 homed in on sites where cells had just made contact. The protein congregated with E-cadherin, which builds up at these intersections and helps lash neighboring cells together. Aquaporin-5, by contrast, spread around the cell membrane.

Previous work suggested that, in polarized cells, three components spirit proteins from the Golgi apparatus to the membrane. Vesicles ride microtubules to the edge of the cell. There, a protein complex called Exocyst ties the containers to the membrane until the SNARE complex can help plug in the proteins. Nejsum and Nelson wanted to find out when this mechanism was set up and started working. Aquaporin-3 showed a haphazard distribution if the scientists disrupted either complex, or if they broke up microtubules. The findings indicate that, immediately after cells touch, Exocyst, the SNARE complex, and microtubules team up to guide basolateral proteins to the contacting membrane, thus establishing cell polarity. The next question is how Exocyst and SNARE get into position at the sites of cell contact. JCB

Kinetochores take alternative transportation

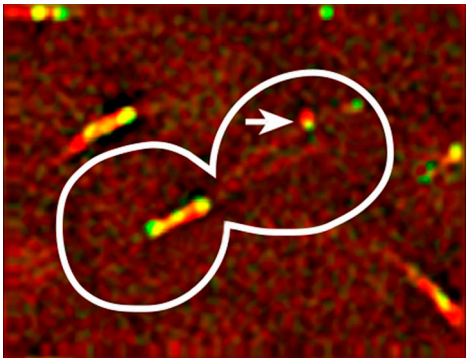
Kinetochores heading for the spindle poles early in mitosis have two travel options, as Tanaka et al. show on page 269. They can slide on microtubules or get tugged along as the fibers shrink.

Before it can parcel out its chromosomes, a mitotic cell has to position them between the spindle poles. The process starts when microtubules from one pole attach to the kinetochore on the centromere of a chromosome. The kinetochore then moves toward that pole. Two years ago, the researchers showed that, during this early stage, kinetochores attach to the side of the microtubules and slide along. The protein Kar3 was essential for the motion. But that wasn't the whole story.

Tanaka et al. probed the initial kinetochore–microtubule interaction by temporarily inactivating one yeast centromere, forcing the microtubules to disengage. Reactivating the centromere allowed the scientists to follow what happens after one microtubule catches on. They discovered that cells with Kar3 rely on sliding to transport chromosomes nearly 70% of the time. Further work demonstrated that Kar3 is the main power source for this form of transportation.

But what happens the other 30% of the time? The researchers found that kinetochores link to the ends of microtubules, traveling toward the poles as the structures shorten. They determined that this end-on pulling requires a protein complex called Dam1, which previous studies indicated encircles the microtubule like a ring. Collapse of microtubules might drive end-on pulling through Dam1. As the structures depolymerize, they fray and bend backward, pushing the Dam1 ring along.

End-on pulling capitalizes on energy from microtubule relaxation, whereas sliding requires ATP. Cells rely on sliding because it delivers kinetochores to their destination sooner, the researchers speculate. Although end-on pulling produces higher speeds, it also wastes time because it only works after the microtubule plus end grabs a kinetochore. The researchers suspect that Dam1 drives the end-on pulling that separates the chromosomes later in mitosis. JCB



Kar3 (green) and kinetochores (red dot at tip of arrow) slide along a microtubule together.

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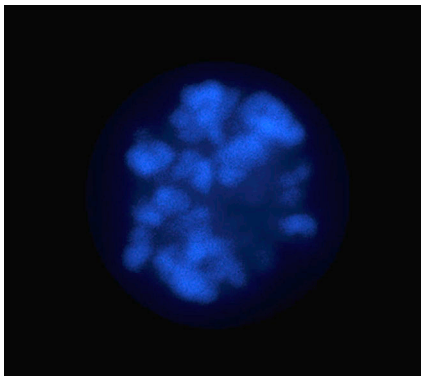


DNA (blue) breaks up as a cell with a faulty spindle checkpoint prepares to kill itself.

Caspase-free mitotic death

On page 283, Niikura et al. document a new way for abnormal cells to kill themselves. The mechanism might weed out potentially cancerous cells in which the spindle checkpoint has malfunctioned.

Before progressing through mitosis, cells verify that the microtubules of the spindle apparatus are properly attached to the chromosomes. If they aren't, the spindle checkpoint kicks in, halting mitosis to permit repairs. If the spindle checkpoint goes awry, cells can amass extra chromosomes and become cancerous. Apoptosis disposes of many of these aneuploid cells during the next G1 phase. Niikura et al. wanted to find out whether spindle checkpoint defects can also trigger cells to die during mitosis.

The researchers used RNAi to cut cells' output of the checkpoint protein BUB1. Three drugs that disrupt the kinetochore–microtubule connection spurred these cells to expire during mitosis. Like victims of apoptosis, BUB1-deficient cells harbored fractured DNA. However, their demise didn't involve caspase enyzymes, suggesting that this type of cell suicide—which the researchers dubbed caspase-independent mitotic death (CIMD)—is distinct from apoptosis. CIMD doesn't depend on p53, which prompts cells with DNA damage to take their own lives, but does require its cousin p73. The results indicate that cells have a mitotic self-elimination mechanism in case the spindle checkpoint falters. Some details of CIMD remain mysterious, however. For example, the researchers are now investigating why CIMD can occur if BUB1 levels are low, but not if the protein is altogether absent. JCB

Putting Dia1 in its place

When a cell crawls or extends pseudopods to snare a bacterium, the front edge of its membrane seethes with activity. On page 193, Brandt et al. show that a key protein that incites cell movement depends on a partner to maneuver it into the center of the action.

Polymerization of actin molecules provides the driving force for cell movement and phagocytosis. One protein that sparks this elongation is Dia1, which RhoA switches on. Previous studies have shown that, during phagocytosis, Dia1 accumulates at the advancing portion of the membrane. But researchers didn't know how it ends up there.

To find out, Brandt et al. went fishing for proteins that latch onto Dia1. They hooked one called IQGAP1 that clusters with Dia1 at the front edge of crawling cells. Depleting IQGAP1 with RNAi prevented Dia1 from homing in on these sites. IQGAP1 and Dia1 also colocalized at the phagocytic cup, the indentation created when pseudopods reach out. Blocking the interaction between the two proteins curtailed phagocytosis. The researchers also showed that IQGAP1 had no direct effect on actin extension, which suggests its job is to ferry Dia1 to active parts of the membrane. The researchers hypothesize that IQGAP1 might stabilize active Dia1, thereby increasing local actin polymerization. They now want to work out the timing of the process, such as when Dia1 arrives at an extension and how long it remains there. JCB

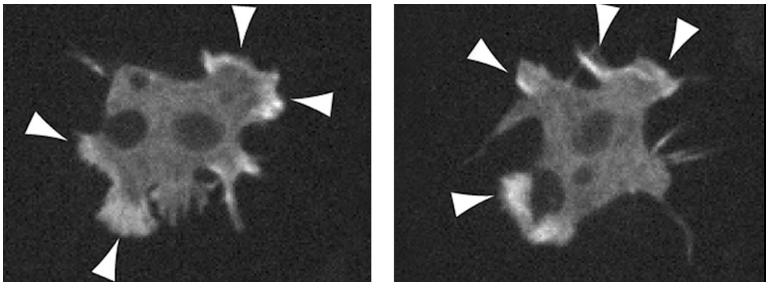
Self-starting slime mold

Hungry cells often wander around, hunting for something tasty. On page 185, Sasaki et al. tease out a molecular circuit that activates spontaneously and initiates these random movements.

Slime mold cells make a beeline for their bacterial food, and researchers have dissected the pathway that controls this directional travel. Bacterial molecules prod G-protein–coupled receptors on the cell surface, leading to activation of the proteins Ras and PI3K. In turn, PI3K cranks out PIP_3, which spurs actin molecules to polymerize and push the cell membrane forward. But scientists didn't know what governs cells' random crawling in search of food.

Many of the same molecules participate, Sasaki et al. learned when they studied slime mold cells that lack G-protein–coupled receptor signaling. Ras and PI3K switched on, PIP_3 formed, and cell extensions elongated as the result of actin polymerization.

The team also found that Ras and PI3K turn on at the same sites on the cell membrane where new extensions sprout. PI3K can't switch on without Ras, and vice versa, suggesting that the two molecules are locked into a positive feedback loop. The findings indicate that aimless crawling is under control of a molecular circuit that fires without external stimulation. The randomness occurs, the scientists speculate, because components of the loop such as Ras show a low but fluctuating level of activity. Any increase in activity at a particular location on the membrane gets amplified by positive feedback, triggering the cell to move in that direction. JCB



PI3K (arrows) accumulates in the stretching pseudopods of a slithering cell.