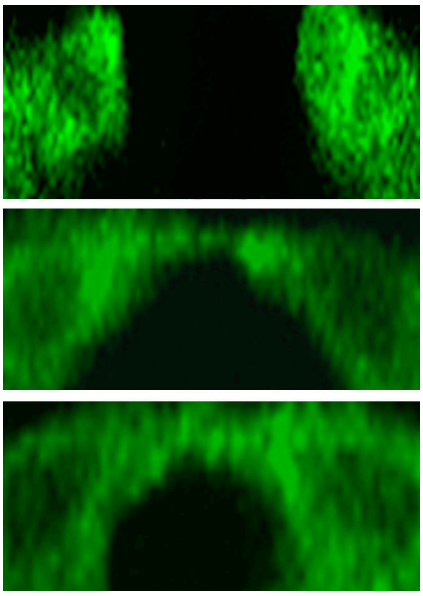
In This Issue



***Drosophila* cardioblasts meet and bend into a tube.**

UNTYING TUBE FORMATION

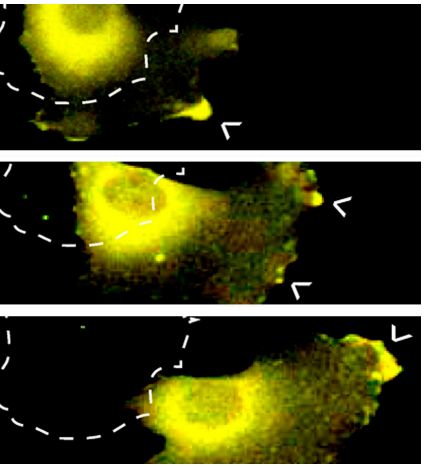
From the trachea to the capillaries of the retina, the body teems with tubes. Even the heart is a glorified tube. Two papers have identified a pathway that helps tube cells create an opening.

Building a tube from solid tissue involves making space between adjacent cells to form a lumen. The two groups recorded similar results about the process, but they started with different goals. Medioni et al. wanted to determine the changes in cell shape and polarity, whereas Santiago-Martínez et al. wanted to know how cells modify their stickiness so they can separate.

Both teams took a close look at the embryonic *Drosophila* heart, which forms when two rows of cardioblasts converge and flex to produce a hollow cylinder. Medioni et al. performed live imaging with confocal microscopy to follow this cellular choreography, and Santiago-Martínez et al. captured three stages of the process with EM. The groups observed the same changes. Cardioblasts in opposite rows first attach at the top. They then bow outward into a sickle shape and connect at the bottom, leaving a doughnut hole in the middle. The two studies also reached similar conclusions about a pathway that involves the extracellular matrix protein Slit and its receptor, Robo. In effect, the pathway creates a non-stick surface on the lumen side of heart cells.

Santiago-Martínez et al. think that the Slit/Robo pathway works by exiling the protein E-cadherin, which hooks neighboring cells together, from the cells' future lumen surface. Medioni et al. found that cardioblasts with mutant Slit remain round and display an expanded cell-to-cell adhesion domain that holds the lumen closed.

Medioni, C., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200801100.
Santiago-Martínez, E., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200804120.



Gαi3 (yellow) clusters at the leading edge (arrows) of a crawling cell.

DRIVEN TO THE BRINK BY A G PROTEIN

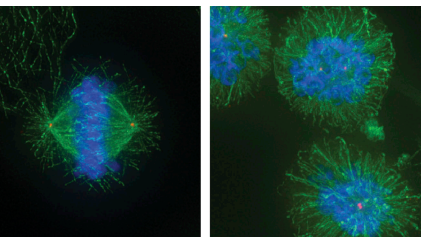
Missing links aren't just for paleontologists. Ghosh et al. report what might be the long-sought connection between cell surface receptors and the direction in which cells crawl.

Nearby food and growth factors galvanize a cell. At the section of the membrane nearest the stimulus, activity of the signaling molecule Akt cranks up and actin elongates into stress fibers essential for crawling. The cell then pushes forward this part of its membrane, the leading edge. Surface receptors first detect the stimulus, and then trigger G proteins, which pass the signal on. What scientists don't know is how cells confine the molecular action to the leading edge. The team suspected it might involve an intermediary, the protein GIV, which can latch onto G proteins and stimulate Akt.

To find out, Ghosh et al. investigated the interaction between GIV and a G protein component known as Gαi3. If Gαi3 is absent, the team found, actin doesn't extend, Akt activity doesn't rev up, and cells are stuck. Gαi3 homes in on the leading edge, and it appears to drag GIV along with it. In cells lacking Gαi3, GIV collects near the Golgi apparatus instead of dispersing to the edge of the cell. Gαi3 might even instigate a positive feedback loop because it presents GIV to Akt to be switched on; GIV can then further amplify Akt activity.

GIV and Gαi3 also help macrophages and tumor cells migrate, the team found. By ferrying GIV to the leading edge, Gαi3 might ensure that only one portion of the membrane undergoes the changes required for movement.

Ghosh, P., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200712066.



A normal spindle (left) contrasts with frizzy ones from cells lacking TPX2 (right).

NEW SPIN ON SPINDLE SIZE

Like bridges and extension cords, the spindle that helps separate chromosomes during mitosis has to be the right length. Bird and Hyman show that two interacting proteins help set the spindle's dimensions.

When a cell builds a spindle, microtubules extend from several locations, including the chromosomes and the centrosomes. One mystery about the process is how cells dictate spindle length. A protein that might be involved is Aurora A, which promotes microtubule growth and is necessary for spindle formation. Another protein, TPX2, switches on Aurora A and helps position it on the spindle. By preventing TPX2 from activating Aurora A, Bird and Hyman tested whether this pair helps determine spindle length in human cells.

The standard way to address the question would be to add the gene for a defective version of TPX2, along with a viral promoter that controls its activity. However, previous work has shown that this method impairs mitosis. Instead, the researchers incorporated the mutant gene into a bacterial

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artificial chromosome that also harbored the gene's normal regulatory sequences. Inserted into a cell, this combination produces a more realistic pattern of gene activity, the scientists say.

When the scientists blocked Aurora A activation in this way, a squat spindle resulted. Although the cells could divide, mitosis often went awry, and they sometimes split into three daughter cells. With TPX2 unable to switch on Aurora A, microtubules that sprouted early in mitosis were unstable, the researchers found. Moreover, although microtubules extended from the centrosomes without Aurora A, they didn't grow from chromosomes. That result raises the possibility that Aurora A determines spindle size by spurring elongation of microtubules from the chromosomes. The researchers now want to determine what proteins Aurora A turns on to exert its effect.

Bird, A.W., and A.A. Hyman. 2008. *J. Cell Biol.* doi:10.1083/jcb.200802005.

HELPING CELLS LOSE THEIR INHIBITIONS

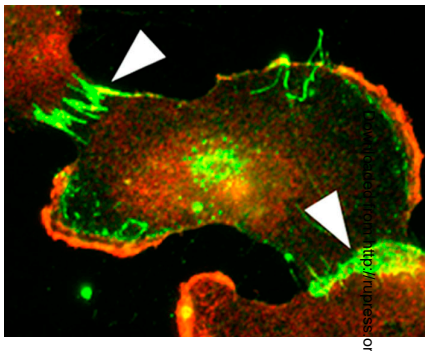
Cells are usually polite and stop crawling when they run into a neighbor. But cells sometimes need to get pushy, and a membrane protein allows them to remain mobile after making contact, Nakao et al. show. The protein works by relocating a migration-promoting complex.

Cancer cells are anti-social and lose contact inhibition, the reluctance to crawl after touching other cells. However, normal cells also have to shed this restraint during wound healing and development. Nakao et al. found a possible trigger for the behavior while studying OL-protocadherin (OL-pc), a member of the cadherin family of membrane proteins that typically fasten cells together. The team found that neurons from mice missing OL-pc couldn't extend their axons. The researchers wondered whether the protein also affects cell movement.

Nakao et al. inserted the gene for OL-pc into nervous system tumor cells that normally can't make the protein. Isolated cells moseyed along, the researchers found, but they sped up in crowded cultures in which cells frequently make contact. A protein complex containing Nap1 and WAVE1 promotes migration, and Nakao et al. discovered that OL-pc delivers it to sites of cell–cell contact.

To simulate wound healing, the researchers scratched the surface of a cell culture. Cells without OL-pc slithered slowly into the scrape, maintaining contact with each other. Cells that manufactured the protein, by contrast, rushed in haphazardly, often leaving their neighbors behind. That result suggests that instead of building contacts between cells like other cadherins do, OL-pc breaks the connections that help coordinate cell behavior. Whether OL-pc contributes to cancer cells' lack of contact inhibition remains to be seen.

Nakao, S., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200802069.



OL-protocadherin ushers the migration-stimulating protein Nap1 to cell junctions (arrowheads).

BAD BREAKS DON'T DOOM MEIOTIC CELLS

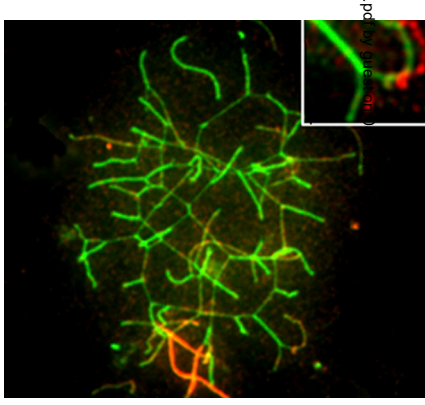
Mahadevaiah et al. challenge a popular explanation for why would-be sperm cells die during meiosis, revealing that the main cause isn't too much broken DNA.

Meiotic cells fracture their DNA to allow crossing over. Repair of these double-stranded breaks (DSBs) occurs when homologous chromosomes pair up. Some researchers postulate a so-called pachytene checkpoint that triggers apoptosis of spermatocytes during meiosis if chromosomes fail to pair up (known as asynapsis) and too many unfixed DSBs remain. However, Mahadevaiah et al. hypothesized that spermatocyte mortality resulted from the failure to shut down the genes on the X and Y chromosomes, which can also be lethal for the cells. This silencing normally occurs during male meiosis.

To test the idea, the researchers first examined meiotic cells from male mice that lack a DSB instigator called Spo11. Asynapsis is prevalent in the cells but, despite the lack of DSBs, most of the cells perished. The team found that the majority of the spermatocytes didn't shutter the X and Y chromosomes. The researchers then checked three other types of mutant cells with widespread asynapsis, plenty of unrepaired DSBs, and high mortality. All three failed to silence the sex chromosomes.

However, evidence suggested a complication: the large number of DSBs in these cells hampered X and Y shutdown. To determine what happens in cells capable of sex chromosome silencing, Mahadevaiah et al. studied mouse spermatocytes that harbor a copy of the human 21st chromosome in addition to their normal chromosome complement. This loner has no chromosome to pair with and thus carries unrepaired DSBs. These cells managed to shut down their sex chromosomes and keep apoptosis levels low. Overall, the researchers say, the results point to a breakdown of sex chromosome silencing as the main cause of death for meiotic spermatocytes.

Mahadevaiah, S.K., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200710195.



Red highlights unsynapsed chromosomes in a spermatocyte, while paired ones show up as green.