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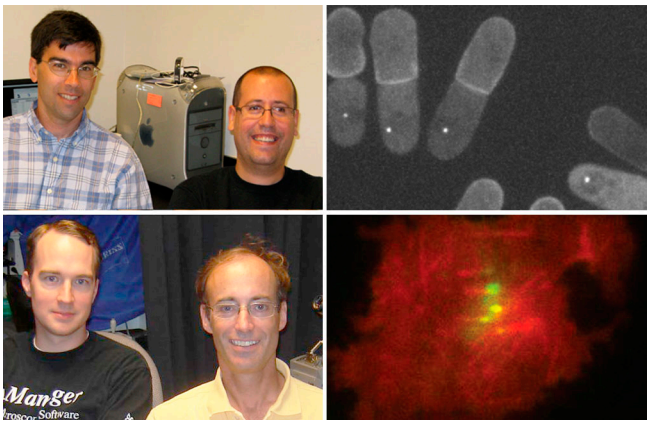
Managing the breakup

How cells set the where and when of cytokinesis

Compared with the complex choreography required to sort chromosomes during mitosis, cytokinesis might seem fairly simple. But ensuring that the contractile ring of actin and myosin pinches off daughter cells also takes some fancy footwork. Two independent groups (1, 2) offer fresh details about how cells cue cytokinesis at the right time and place.



Focal Point

Top: Asymmetry might set the cytokinesis clock, Dannel McCollum (left) and Juan Carlos García-Cortés (right) determined. The cytokinesis-triggering septum initiation network (indicated by a bright dot on the spindle pole body) turns on only in one side of these yeast cells. Bottom: Eric Griffis (left) and Ron Vale (right), together with James Spudich, reveal that microtubules and the motor protein Kinesin-6 help dictate where cytokinesis occurs. Here, Kinesin-6 (green) has migrated to the equator of a mitotic cell.

Cytokinesis can't begin until the chromosomes have separated, and to forestall multiple divisions it has to end when the daughter cell is independent. García-Cortés and McCollum (1) show that mitotic cells stay on this schedule thanks to a team of proteins that sparks cytokinesis but also initiates its own shutdown.

In the fission yeast *Schizosaccharomyces pombe*, the septum initiation network, or SIN, instigates cytokinesis. The mystery was how cells commit SIN at the right time. The SIN activator Spg1 rides on the spindle pole bodies that anchor the mitotic spindle. Previous work (3) showed that the protein Etd1, which turns on Spg1, amasses at the ends of the cell. García-Cortés and McCollum wondered whether the lengthening of the spindle as chromosomes pull apart might bring Spg1 and Etd1 together, thereby activating SIN. To test that idea, the researchers followed Spg1 activation in cells dosed with a drug that halts spindle elongation. In cells where drug exposure came after the spindle had stretched out, Spg1 turned on as normal. But if the cells entered mitosis after addition of the drug—and thus could not lengthen their spindles—Spg1 remained inactive. The researchers also found that tethering Spg1 to Etd1 prompted cells to divide again and again, further evidence that the rendezvous between the two proteins spurs cytokinesis when chromosome separation is complete.

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A complication to the story—Spg1 and SIN only flip on in half of the cell—might explain how cells determine when to curtail cytokinesis. After the contractile ring has tightened, SIN triggers the elimination of Etd1 in the cell half where Spg1 was turned on. In turn, that leads to the shutdown of Spg1 and then SIN. According to the researchers, asymmetry of SIN signaling might serve as an indicator that the cytoplasm has been divided. "It provides a mechanism for how cells can know when they've finished cytokinesis," says senior author Dannel McCollum. What researchers don't understand is how the cell chooses which end will activate Spg1 and SIN.

Even if a cell's timing is impeccable, cytokinesis will go awry if the contractile ring assembles at the wrong location. The findings from Vale, Spudich, and Griffis (2) suggest that the molecular motor Kinesin-6 helps designate where the cell will split.

Previous studies have shown that the GTPase RhoA (4) is the master regulator of cytokinesis and switches on in the cleavage furrow. Why it activates there isn't clear. Other studies indicate that certain microtubules dictate the site of the contractile ring (5). Kinesin-6, which hauls RhoA effectors, might connect these two mechanisms.

The team used total internal reflection fluorescence microscopy to follow Kinesin-6 and myosin in *Drosophila* cells that were just entering anaphase. They observed that myosin filaments disappeared from the poles of the fly cells and appeared again at the equator—both changes require Kinesin-6. Contrary to some other studies, the researchers didn't observe the molecules traveling en masse from one location to the other. Instead, the researchers think that myosin filaments at the poles dissolve and then reform at the equator.

Kinesin-6 itself has to concentrate at the cleavage furrow. The researchers found that the molecules first hop on the tips of growing microtubules. Microtubules that reach the cell center stabilize and form bundles. Eventually, all of a cell's Kinesin-6 accumulates on microtubule tips or in a broad swath around the cell's midsection. The work suggests that Kinesin-6 helps demarcate the cleavage furrow by delivering RhoA activators that spur the formation of myosin filaments at the cell equator. "Our data suggest that the process of building the contractile ring is largely due to the concentration of positive factors, rather than a directed delivery of negative factors," says co-author Eric Griffis. What triggers myosin disassembly at the poles and reassembly at the cleavage furrow remains unclear.

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