Emi1 ensures timely mitosis

Talk about a career change. Di Fiore and Pines report on page 425 that a protein long thought to inhibit mitotic progression actually promotes mitosis and prevents cells from making too many copies of their DNA.

The cell cycle is driven by destruction. To advance to the next stage, a cell demolishes the roadblocks that keep progress in check. Flagging these obstacles for destruction is the job of the anaphase promoting complex/cyclosome (APC/C). Its targets include cyclin B1 and securin, which block mitotic progression and anaphase. It was thought that APC/C itself was kept in check by a protein called Emi1. Emi1’s breakdown early in mitosis allowed APC/C activation, the argument went.

Emi1’s disappearance, however, begins too soon, Di Fiore and Pines now find. By tracking fluorescent Emi1, the authors found that it was degraded at prophase. When the researchers injected cells with indestructible Emi1, the APC/C still fired up. Together, the experiments reveal that demolition of Emi1 isn’t what frees the APC/C to start mitosis.

To find out what Emi1 was really doing, the scientists blocked it using RNAi. Cells stalled before reaching mitosis and destroyed their cyclin A and cyclin B1 prematurely. Since these proteins are targets of APC/C, the authors conclude that Emi1 works by suppressing the APC/C during interphase, not mitosis, and helps to protect cyclins A and B1, which are necessary for progress into mitosis.

The Emi1-deficient cells also displayed bulging nuclei, packed with excess DNA. One of Emi1’s jobs, the researchers conclude, is to prevent cells from replicating their chromosomes more than once. The results indicate that Emi1 ensures that every round of DNA replication is followed by a round of cell division. But, the findings also reopen the question of what keeps the APC/C in line during mitosis.

Hungry cells forget which way is up

A cell modifies its polarity depending on how much energy is available, as Mirouse et al. demonstrate on page 387. The findings suggest a link between energy status and tumor suppression.

How the tumor suppressor LKB1 keeps cancer in check is not certain. The protein fires up PAR-1, which helps establish cell polarity, and the energy-sensor AMPK. When ATP is scarce, AMPK shuts down division and other energy-draining activities. A leading hypothesis is that LKB1 controls cell polarity through PAR-1 and growth through AMPK. But pinning down AMPK’s functions has been difficult because vertebrates harbor multiple genes. Drosophila, however, has only one AMPK gene, and Mirouse et al. netted some mutants.

Epithelial cells from the mutant flies seemed normal when food was abundant. But energy-starved cells began to lose their polarity. Actin distribution was altered, for example, and a protein usually confined to the basal portion of the cell crept up the sides. Famished cells also became disorganized, forming clumps that resembled tumors. To rule out the possibility that the abnormalities stemmed from ATP scarcity, the researchers tested cells with faulty mitochondria due to a mutated tenured gene. Like their academic namesakes, the cells have little energy and don’t do much. But their polarity didn’t change.

The results suggest that AMPK allows cells to couple their polarity and growth to food availability. LKB1 might also exert its tumor suppressing effects in part through AMPK.
The up side of a gas shortage

The key to building strong bones and healthy joints is oxygen scarcity in the developing embryo. As Provot et al. show on page 451, a protein activated by low oxygen levels orchestrates the formation of limb bones and joints. The work demonstrates that one function of the protein is spurring differentiation of cartilage-constructing chondrocytes.

An embryo acquires all of its oxygen via diffusion, and some parts of the body can run short. But instead of suffocating tender young cells, an oxygen shortage galvanizes them to differentiate. Low oxygen levels switch on a transcription factor called hypoxia-inducible-factor-1 (Hif-1). The researchers had previously shown that Hif-1 promotes growth and survival of chondrocytes, which sculpt a cartilage template that later fills with bone. Provot et al. wanted to determine whether the transcription factor spurs cells to specialize into chondrocytes.

The team knocked out one subunit of the protein, Hif-1α, only in limb bud mesenchyme of mice. This tissue, which spawns chondrocytes and other cell types, normally pumps out Hif-1α and is oxygen-starved. The modified mice were born with stumpy, malformed legs. As embryos, their limbs were slow to fashion cartilage, and differentiation of mesenchymal cells into chondrocytes was tardy. Moreover, large numbers of cells perished in the center of the animals’ forming bones.

Limb joints are also hypoxic, and the Hif-1α-deficient mice displayed defects such as abnormally fused bones in the paws and delayed joint formation. The flaws were more severe in the wrists and ankles, which have the lowest oxygen concentrations. The findings establish that Hif-1 promotes chondrocyte differentiation and joint formation in response to hypoxia. The next step, the researchers say, is to pin down which pathways Hif-1 activates to produce these effects. JCB

Breaking actin to rebuild it

To keep moving, a crawling cell requires a continuous supply of actin molecules. As Kiuchi et al. show on page 465, cofilin meets this need mainly by snipping apart actin fibers.

As a cell slithers, addition of new actin molecules to the actin fibers at its leading edge nudges the membrane forward. Cofilin boosts the amount of available actin monomers in the cell. It depolymerizes actin fibers, removing individual molecules. It can also sever fibers, leaving barbed ends for actin nucleation. Scientists weren’t sure which action was more important for actin polymerization and how much cofilin contributed to the actin pool.

By tracking fluorescent actin, Kiuchi et al. determined that cofilin is responsible for more than half of the available monomers. Experiments with a cofilin mutant that couldn’t depolymerize actin and another that couldn’t clip it revealed that most of the free actin comes from severed fibers.

Cofilin spurs fibers at the cell’s margin to add monomers. That effect might occur either because cofilin hikes the amount of free actin or because it increases the number of barbed ends, which are sticky to the monomers. But actin injected into cells hooks onto the fibers even if cofilin is blocked, ruling out the second explanation. The results indicate that cofilin keeps the actin pool well-stocked mainly by dismembering existing fibers. JCB

When VEGF strays

Unlike many signaling molecules that remain true to one receptor, vascular endothelial growth factor (VEGF) is a two-timer. As Ball et al. show on page 489, VEGF also activates the receptor for the related platelet-derived growth factor (PDGF). VEGF is involved in everything from wound repair to cancer, and the study is the first to catch it being unfaithful.

By prodding vascular cells to travel and divide, VEGF sparks formation and growth of blood vessels. PDGF is similar structurally and functionally. But although the growth factors are evolutionarily related—and so are their receptors—nobody had previously shown any cross-reactions.

Ball et al. chanced on the discovery when they noticed that VEGF stimulated mesenchymal stem cells (MSCs) to migrate and proliferate. No surprise, except that MSCs lack VEGF receptors. The cells kept moving when dosed with antibodies that block the VEGF receptor. But they halted after treatment with antibodies against PDGF receptors. The researchers also found that VEGF promoted receptor phosphorylation, a sign of activation.

The researchers don’t yet know whether PDGF can latch onto VEGF receptors. Another mystery is under what conditions stimulating the PDGF receptor with VEGF, rather than its normal ligand, is advantageous. The growth factors might convey slightly different messages. To find out, scientists could determine whether the receptor’s responses to the two growth factors occur at the same speed and activate similar downstream pathways. JCB