In This Issue

**Catastrophe gradient drives anaphase B**

It takes a polar catastrophe—oodles of them, actually—to get through anaphase, suggest Cheerambathur et al. on page 995. Their modeling reveals that concentrating microtubule catastrophes near the spindle poles might drive the second half of anaphase.

Anaphase in fly cells is a two-step process: first the chromosomes migrate to the poles (anaphase A), then the spindle lengthens, pushing the DNA further apart (anaphase B). To understand the microtubule changes that lead to anaphase B, the authors combined modeling studies with in vivo observations of microtubule dynamics.

The experimental studies revealed that microtubule plus ends became concentrated in the central spindle at the onset of anaphase B. The changes were driven by cell cycle–regulated signaling pathways, not by any intrinsic properties of microtubules.

Determining which spindle proteins are targeted by these pathways is tricky, however. Most candidates have a host of different mitotic functions, making specific effects difficult to pick out. The group thus turned to computational modeling.

Only one of their envisioned scenarios accounted for both the plus-end redistribution and the rapid microtubule turnover dynamics in the spindle. In this model, microtubule plus ends near the poles were threefold more likely switch from growth to depolymerization—an event known as a catastrophe—than were plus ends at the midzone.

The authors imagine that losses at the poles concentrate plus ends in the midzone and thus make it more likely that a microtubule from one pole will capture a partner from the other pole. This bias should expand the microtubule overlap at the midzone, where the pushing forces that elongate the spindle are generated. The remaining short microtubules near the pole, meanwhile, probably keep hold of the chromosomes.

To test their model experimentally, the group will have to screen for factors that affect this catastrophe gradient. It is not yet clear how the gradient is generated. Perhaps it reflects a gradient of a depolymerase activity, such as kinesin-13, which is known to hover near the poles. JCB

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**Scarred by a death receptor**

Even when it’s not killing, a death receptor still finds ways to inflict damage. On page 1119, Sachs et al. show that a TNF receptor helps build scars that can get in the way of healing.

Tissue scars are formed from build-ups of extracellular matrix proteins. In particular, a blood-clotting factor called fibrin escapes from damaged vessels and is deposited as a temporary matrix in the tissue. The deposits can block nerve regeneration and cause lung and vascular diseases.

Fibrin’s degradation by plasmin allows healing to proceed more efficiently. Sachs and colleagues thus went looking for factors that either block or help this degradation. They had noticed that fibrin deposits were often found in areas with high levels of the TNF receptor family member, p75NTR. Although usually associated with the nervous system, where it mainly activates apoptosis, p75NTR is also expressed in the liver and lung upon injury.

Mice lacking p75NTR now reveal that this death receptor prevents fibrin degradation. The mutant mice had less fibrin deposition upon nerve injury than did injured normal mice. Revved up plasmin activity accounted for the better degradation in the mutants. Plasmin can be turned on by two activators, tPA and uPA, but only tPA levels were higher in the mutants.

The gene for tPA is induced by cAMP signaling, which the authors found is dampened by p75NTR. They identified a binding site in the receptor for a specific phosphodiesterase that targets cAMP degradation to the membrane. Although p75NTR also binds to neurotrophins, these extracellular ligands were not necessary for cAMP degradation. Receptor expression and recruitment of the phosphodiesterase seem to be enough.

tPA is the drug used immediately following strokes to prevent lasting brain damage. The drug Rolipram also reduces fibrosis, via its broad-scale inhibition of phosphodiesterases. Both have unwanted side effects, however. A better, more specific strategy to boost cAMP levels and fibrinolysis might be to interfere with the interaction of p75NTR and its particular phosphodiesterase partner. JCB
The UPR for cytokinesis

A stress-coping strategy of the ER is needed in every cell cycle, show Bicknell et al. (page 1017). The ER’s unfolded protein response (UPR), previously associated only with unusual or stressful conditions, is needed for the routine event of cytokinesis.

While a normal cell (left) has finished cytokinesis, a UPR mutant (right) is still stuck.

Hypoxic reaction to reactive oxygen

When oxygen is scarce, mitochondria pump out reactive oxygen species (ROS) that alert the cell to the shortage, say Bell et al. (page 1029).

Mitochondria are needed to activate hypoxia-responsive pathways, which help restore O₂ levels and are jump-started by the stabilization of hypoxia-inducible factor (HIF)-1α. But mitochondria do many things—they consume O₂, churn out ATP, and produce ROS. So just how cells sense hypoxia is hotly debated.

By uncoupling mitochondrial O₂ consumption from ROS production, Bell et al. now prove that the ROS are the key. Using genetic manipulations—particularly tricky in mitochondrial studies, which often rely instead on chemical inhibitors—the group created cells that have a loss of cytochrome b activity. These cells could not respire or make ATP, but they did still produce ROS and respond to hypoxia by stabilizing HIF-1α.

The additional loss of ROS production blocked HIF-1α stabilization. Although ROS are formed at mitochondrial complexes I, II, and III, only those leaking from III seemed to be essential for hypoxia signaling, according to RNAi and inhibitor studies. The authors would now like to track down the machinery within complex III that senses the low O₂ and then dials up ROS formation.

HIF-1α is stabilized when it is no longer hydroxylated by prolyl hydroxylase enzymes (PHDs), but it is currently unclear how ROS block these enzymes. As PHDs require O₂ for their action, they were once thought to be the main hypoxia sensor. But even extremely low O₂ levels are enough for hydroxylation. The ROS pathway instead gives cells a chance to start building new O₂-supplying blood vessels before conditions become so severe. JCB

Dynein’s spindly trip

Dynein has finally found a partner with direction. On page 1005, Griffis et al. identify a cofactor for the motor that seems to bring it to kinetochores and only kinetochores.

With everything it has to do in the cell, dynein has many places to be. During mitosis, dynein is needed at kinetochores, where it eventually drags spindle assembly checkpoint proteins off attached chromosomes so that anaphase can begin.

Plenty of cofactors that target the motor to its various locales have been identified, including dynactin and Lis1. But, like the motor, these partners have more destinations in mind for dynein than just kinetochores.

Not so for Spindly, a fly protein that Griffis et al. found in a high-throughput RNAi screen. This protein, and its human counterpart, was required to target dynein to kinetochores at the onset of mitosis. Without Spindly, cells were stuck in metaphase with dynein-free, checkpoint protein–laden kinetochores. All other assayed dynein functions, however, were left intact.

During interphase, Spindly was found at microtubule plus ends, where it somehow helped control cell shape, apparently without dynein’s help. The authors are now tracking down how the loss of this protein in interphase creates the spindly cell shape that inspired its name. JCB