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.

The UPR is activated when the ER is overloaded with misfolded proteins. It increases ER capacity and helps reduce the load. But the authors wondered whether everyday ER fluctuations might also tweak the UPR.

One particularly taxing process, the cytokinesis, is cell division. Sure enough, cytokinesis was slowed in budding yeast cells that lacked the UPR. The stalls required no additional stress; division was enough. No other mitotic stages were affected.

The ER supports cytokinesis by making new phospholipids for the pinching process and as the first stage of the secretory pathway, which provides necessary vesicles to the bud neck. Either of these cytokinetic duties might put enough strain on the ER to activate the UPR slightly.

Artificially induced ER stress prevented yeast cells from completing cytokinesis. This blockade might stem from the absence of the required secretory vesicles or phospholipids. Or it might be activated as a checkpoint, stalling division until the ER is in better shape.

Unlike yeast, the mammalian UPR dampens translation, which stalls cells in G1 by limiting cyclin D1 levels. If pushed through this blockade, however, the cells might reveal a need for the UPR in breaking apart mammalian daughter cells.

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 respirate 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.

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.