Neural progenitors play favorites

Programmed cell death is essential for preventing hyperproliferation during normal embryonic brain development and is also critical to the pathogenesis of several neurodegenerative diseases. Using mouse embryonic stem cells to model neuronal differentiation, Bieberich et al. (page 469) now show that when neural progenitor cells divide, only one progeny cell survives due to asymmetric distribution of pro- and anti-apoptotic factors between daughter cells.

In the developing mouse brain, apoptosis often correlates with the presence of the lipid ceramide and the protein PAR-4, and current models predict that neuronal apoptosis follows soon after cell division. The authors found that, in neuronal progenitors derived from embryonic stem cells, PAR-4 and the intermediate filament protein nestin (a marker of neural progenitors) are asymmetrically distributed after mitosis. One daughter cell inherits high PAR-4 and low nestin levels, and undergoes apoptosis. The other daughter inherits low PAR-4 and high nestin levels, and survives. Ceramide apparently induces apoptosis in the PAR-4–positive cell but not in the nestin-positive cell, possibly through active destruction of ceramide in the surviving daughter. The authors are now trying to determine how ceramide and PAR-4 interact to induce cell death and also hope to identify the mechanism that ensures asymmetric inheritance of PAR-4 and nestin.

A simple way to get cleavage

To partition cellular components into dividing daughter cells, the spindle apparatus induces the formation of a cleavage furrow, but results conflict about which specific components are required for this process. By physically dissecting the spindle apparatus in grasshopper spermatocytes, Alsop and Zhang now show on page 383 that bundled microtubules are the only structural constituent of the spindle apparatus required for inducing cleavage.

Previous work has pointed indirectly to asters, the central spindle, and chromosomal passenger proteins as essential inducers of the cleavage furrow. In the new study, the authors used micromanipulation to create pockets of cell membrane containing specific components of the spindle apparatus. As long as functional microtubules are present in these artificial cells, cleavage furrows are induced and ingress while the microtubules undergo reorganizations characteristic of metaphase, anaphase, and telophase. Alsop and Zhang stress that other components of the spindle apparatus undoubtedly influence furrow formation when they are present, but only microtubules are essential.

The authors are now introducing various degrees of asymmetry in microtubule distribution in the artificial cells. The results suggest that shifting the zone where the plus-ends of spindle microtubules overlap redefines the location of the cleavage furrow.

Watching kinetochores sweat

Even after decades of study, it is still unclear whether kinetochores or microtubules provide the motive force to pull chromosomes toward opposite poles during cell division. On page 377, Maddox et al. propose that each makes its own contribution. They find that a combination of kinetochore-generated force and poleward flux of the microtubules moves the chromosomes in Xenopus egg extracts.

The authors are the first to distinguish kinetochore microtubules from other microtubules, using high-resolution fluorescent speckle microscopy and labeled kinetochore proteins. Their high-resolution view of kinetochore–microtubule interactions shows that kinetochores exist in either microtubule-polymerizing or -depolymerizing states. Their data help to explain why metaphase chromosomes oscillate in some types of cells but not others. Like a boat rowing against a current, polymerizing kinetochores resist microtubule flux. But if flux is fast enough, they are still pulled poleward, thus generating tension between sister chromatids. In cells with low flux rates, such as yeast and cultured mammalian cells, the switching of kinetochores between polymerizing and depolymerizing states would cause chromosomes to oscillate.

In cells with high flux rates, including Xenopus eggs, the resistive tension from microtubules pulling continuously out of kinetochores promotes polymerization and prevents oscillations. The authors found that, in anaphase, kinetochores switch to depolymerization—rowing with the current—and thus pull chromatids apart faster than the rate of flux.