In This Issue

**Spill and kill**

Lysosomes spill their guts and kill their host cells, as revealed on page 231. Artal-Sanz et al. show that cells are more likely to escape a necrotic death sentence if they contain less acidic lysosomes.

Necrosis—considered the unprogrammed counterpart to apoptotic death—is the deadly result of a severe and abrupt loss of energy, nutrients, or oxygen. These stimuli create sudden alterations in intracellular pH or ion levels that ultimately turn on destructive proteases within the cell.

Some of these proteases, such as cathepsins, work best at very low pH. Acidification of the cell occurs during necrosis. Further, a pump that acidifies lysosomes, where cathepsins are normally sequestered, is required for necrosis in worms.

The new study shows that lysosomes are themselves needed during necrosis. By interfering with lysosomal biogenesis, the authors hindered neuronal necrosis in worms. Mutations that created abnormally large lysosomes, by contrast, aggravated necrosis.

Lysosomes have to be acidified to be necrosis inducing. The authors found that alkalinization of the organelles using weak bases suppressed necrosis. It also further reduced death in mutant neurons with unusually low amounts of cathepsins.

The authors suspect that lysosomes start leaking their contents at early stages of necrosis. Their idea is supported by past evidence that the protease calpain—which is activated by high Ca\(^{2+}\) levels during necrosis—damages lysosomal membranes. The damage might open the door for a slow escape of cathepsin and H\(^+\)—thus both freeing proteases that dismantle the cell and creating the acidic environment in which they thrive. At later stages of death, the authors saw, lysosomes ruptured completely.

Necrosis dominates the neuronal death caused by ischemia during a stroke. Perhaps the damage can be minimized if therapies are devised to prevent lysosomal acidification locally. The drugs would probably only be beneficial, however, if administered very shortly after the stroke. JCB

**Flux without sliding**

On page 173, Cameron et al. find that kidney cells do not depend on sliding forces to generate flux in their mitotic spindles.

Flux is the poleward translocation of spindle microtubules relative to the poles that often helps chromosomes reach separate poles. Flux can be achieved by pushing microtubules outward from the center, by pulling them in from their ends, or by a combination of the two.

In fly S2 cells and in frog extracts, Eg5 is found at the central spindle, where antiparallel microtubules overlap. By cross-linking these microtubules and sliding them toward the poles, Eg5 has been proposed to create flux.

As Eg5 pushes from the middle, kinesin 13 lops off tubulin subunits at the poles. Kinesin 13 inhibition lengthens spindles but does not prevent the sliding component of flux, suggesting that central pushing forces are the major components of flux. But Cameron and colleagues find that, in marsupial kidney cells, flux continues without pushing forces.

The authors made careful measurements of flux rates in PtK1 cells and found only a 25% dampening in the absence of Eg5 activity. Even monopolar spindles, which lack overlapping antiparallel microtubules, maintained almost normal flux rates.

Since pushing forces were not needed, the group tried to knock out pulling forces as well. Kinesin 13, however, was not easily removed from the equation. RNAi is not yet possible in PtK1 cells, and antibody-mediated inhibition was unsuccessful. The group even tried knocking the motor off poles, but it still clung to microtubule minus ends. Thus, although pulling forces seem to be dominant, in this cell type at least, it is unclear whether kinesin 13 is the motor responsible.

Future studies should also address what factors determine the flux method in different cell types. Perhaps spindle-cortex interactions, which are lacking in frog egg extracts, are necessary for pulling forces. Or maybe the use of centrosome—rather than chromatin-driven spindle formation mechanisms has different effects on the motors that propel flux. JCB