Yeast apoptosis debate continues

Yeast, as a unicellular organism, would seem to benefit most from self-preservation. But yeast altruism, in the form of apoptosis, is a new-found, if controversial, field of study. Many doubt the validity of experiments supporting programmed cell death in yeast and call for better controls. In this issue, the debate continues with two new articles that suggest that yeast cells do organize their own deaths—for the sake of their brethren.

Biologists often address how a phenomenon occurs, but seldom why. For the yeast apoptosis field, however, why is a painfully obvious question. On page 1055, Fabrizio et al. suggest a method to the madness. They show that yeast populations survive better in the long run when they initiate an early death program through superoxide.

Superoxides are produced by the everyday activities of life, but their mutational and death-inducing activities can be curtailed by superoxide dismutases (Sods). The authors find that Sods are normally down-regulated in older yeast cultures, which are surviving in nutrient-poor medium, leading to cell death. Mutants that circumvented this programmed death mechanism by maintaining high Sod activity had extended life spans. These long-lived populations, however, were unable to repopulate their culture once most of the cells died, a phenomenon known as adaptive regrowth.

As a result, in competition experiments, strains that initiated early death eventually outgrew the wild type.

Early death probably allows the best-adapted cells in a population to reproduce before they are too old by using nutrients left behind by the dead yeasts. Superoxides are mutation inducers. The higher mutation rates that the authors noted in wild-type and other short-lived populations might impart surviving cells with the ability to use newly available nutrients rather than rely on the vanishing original supply. Mathematical models of adaptive regrowth based on experimental measurements of growth and mutation rates confirmed that long-lived populations are less able to survive under changing growth conditions.

The group has shown before that aging is similar among yeast and higher eukaryotes. The finding that yeast programs its own aging for altruistic reasons raises the pessimistic possibility that our own life span is best left similarly limited. The authors do not insist that superoxide-mediated death must be apoptotic, but hallmarks of mammalian apoptosis were seen, including chromatin condensation, cytosolic acidification, and extracellular exposure of phosphatidyl serine.

Another parallel with mammalian apoptosis, AIF-induced cell death, is revealed in an article by Wissing et al. (page 969). AIF is a mitochondrial protein that moves to the nucleus in response to apoptosis-inducing stimuli and then triggers DNA degradation. Wissing et al. show that similar translocation and degradation events occur in yeast apoptosis and that its loss delays age- or peroxide-induced death, accompanied by chromatin condensation and DNA fragmentation.

Overexpression of yeast AIF sensitized cells to death in response to low levels of peroxide in a pathway that was partly dependent on the yeast caspase-like protein YCA1.

Although evidence of apoptosis was artifactual and that death is independent of YCA1. Proponents of yeast apoptosis counter that Wysocki and Kron used extreme death-inducing conditions, which could lead to nonapoptotic or caspase-independent death. They say that the identification of so many yeast counterparts of mammalian apoptotic proteins, including YCA1, Cdc48, Cdc6, and the caspase regulator Omi, suggests that the pathway is ancient and conserved.

Things may be more complicated for some of the mammalian proteins implicated in apoptosis. Past evidence, for instance, suggests that the loss of AIF in mammalian cells makes the cells more, not less, susceptible to death.

If yeast do undergo apoptosis, scientists will be better able to do experiments that would be difficult in mammalian cells. Wissing et al. hope to find suppressors of AIF overexpression, for example. For now, it seems, they are still fighting to prove that apoptosis is a real phenomenon in yeast.

We therefore await the next battle in this deadly war.

A force for holocentrics to reckon with

Holocentric chromosomes, like those of *C. elegans*, pose a dangerous attachment problem during mitosis. Their kinetochores are distributed along the length of the chromosomes and are thus easy targets for microtubules from both poles. If a single kinetochore is caught by two poles, the chromatid is held up at anaphase, causing segregation defects (as these merotelic attachments create tension, the mitotic checkpoint is not activated).

On page 991, Powers et al. uncover a chromosome-associated kinesin in worms that prevents persistent merotelic attachments. Although homologues of this plus-end microtubule motor, called KLP-19, are found in many systems, they may be especially critical in organisms with holocentric chromosomes.

Dividing worm cells that lacked KLP-19 had high rates of segregation errors due to merotelic attachments. Chromosomes congregated at the metaphase plate normally, but some then moved.
Scaffolds from blood to brain

Scaffolds that hold up membrane proteins in red blood cells also support the channels needed for neuronal signaling, as shown by Lacas-Gervais et al. on page 983.

Neurons fire when sodium channels clustered at the axonal initial segment (AIS) open. This depolarization is propagated by more channels clustered along axons in the Nodes of Ranvier (NR). The structure of these compartments is now shown to rely on a spectrin, relatives of which are needed for the characteristic concave shape of the red blood cell plasma membrane.

The AIS and NR are rich in two spectrins: \( \beta IV_1/IV_6 \). But loss of the \( \beta IV_1 \) isoform was sufficient to disrupt AIS and NR physiology. NRs in the mutants were longer and fatter and lacked the protein-dense region beneath the NR membrane, which probably corresponds to the \( \beta IV_1 \) scaffold. These changes interfered with membrane potential generation and propagation, thus causing deafness.

Recent results showed that sodium channels are concentrated in the AIS because of both anchoring to the AIS cytoskeleton and endocytosis elsewhere. The specialized AIS cytoskeleton may prevent endocytosis at this site. In the \( \beta IV_1 \) mutants, the NR contained membrane protrusions that were filled with vesicular organelles. If spectrins are involved in membrane trafficking, as has been proposed, the vesicles may be a result of increased endocytosis in the mutant NR.

Narcissistic CLIP-170 also attracts dynactin

CLIP-170 is the prototypical microtubule plus-end binding protein. It changes microtubules dynamics by rescuing them from shrinking. Using RNAi, the authors now demonstrate that CLIP-170 is also needed to recruit dynactin to plus ends through the p150\(^{Glued}\) dynactin subunit.

But first, CLIP-170 has to let go of itself. The authors found that CLIP-170 folds on itself through binding of its NH\(_2\) and COOH termini. In this position, its p150\(^{Glued}\) binding site in the COOH terminus was inaccessible. Microtubules bound to CLIP-170 at the NH\(_2\) terminus near the site needed for the self-interaction. Once mounted on plus ends, CLIP-170 is probably open, thus freeing its COOH terminus for binding to p150\(^{Glued}\). CLIP-170 phosphorylation may regulate the microtubule binding.

Part of dynactin’s job is to recruit the minus end–directed motor dynein. But being permanently stuck on a plus-end binding protein would be trouble for a motor. Release from plus ends may be brought about by LIS1. Although LIS1 is known as a dynein-associated protein, it also competed with p150\(^{Glued}\) for binding to CLIP-170. Once LIS1 releases dynactin–dynein from CLIP-170, direct binding of dynein to microtubules may take over. Dynein could then work its way to the minus end.