Survival is sweet

Nurtition and cell death are integrated in a single mitochondrial complex, according to Nika Danial, Stanley Korsmeyer (Harvard Medical School, Boston, MA), and colleagues.

The complex was discovered after gel filtration of the pro-apoptotic BAD protein, and contains BAD, a phosphatase, kinase, and kinase-anchoring protein directed at BAD, and glucokinase. In cells lacking BAD, the complex falls apart, respiration is compromised, and blood glucose regulation is abnormal. A nonphosphorylatable BAD leaves the complex intact but otherwise nonresponsive to glucose.

The results are consistent with a simple model: glucose induces phosphorylation of BAD, thus ensuring both cell survival and activation of glucokinase. The active glucokinase clears blood glucose and feeds the mitochondrion with necessary intermediates.

The presumption was always that the cell’s two major survival pathways—glycolysis and apoptosis—were independent. But the complex hints at integration. Korsmeyer speculates that early cells may have relied on this direct integration with sugar levels, as the cells probably lacked fancy growth factors for modulating cell survival. “We could be looking at a primordial role between nutrition and cell death,” he says. “The growth factors may have come later.” This hypothesis is consistent with the ideas of Craig Thompson (University of Pennsylvania, Philadelphia, PA), who has suggested that growth factors act not directly on cell survival but via modulation of glucose levels.

Reference: Danial, N.N., et al. 2003. Nature. 424:952–956.

A daughter’s size is not critical

The critical size model of cell division is so well established for budding yeast that, as Warren Heideman says, “it’s on the wall of the Guinness Brewery.” But now Tracy Laabs, Heideman (University of Wisconsin, Madison, WI), and colleagues have found that one of the pillars of the model has an alternative explanation.

The model states that cells only divide once they reach a critical size, which is why smaller daughters delay their division until they reach sizes comparable to those of their mothers. The Madison team found instead that daughters delay thanks to a daughter-localized G1 inhibitor called Ace2.

After elimination of Ace2, mothers and daughters divided at the same time, so daughters divided at a smaller size than usual. An Ace2 mutant that was no longer localized to daughters also showed simultaneous division because both mothers and daughters were delayed.

Ace2 works at least in part by controlling levels of the G1 cyclin Cln3. In theory Ace2 could be resetting the critical size in daughters. But, says Heideman, “if you stick with critical size you have so many modifications that you are left with something very cumbersome.”

He believes the cell couples growth rate and cell division rate without sensing size. “The critical size model was easily accepted by our minds because it was so elegant,” he says, “but it may be hard [for the cell] to engineer.”

Reference: Laabs, T.L., et al. 2003. Proc. Natl. Acad. Sci. USA. 100:10275–10280.

Pulling to the protease

Before destroying proteins, proteases such as bacterial ClpXP and the related eukaryotic proteasome must denature them. Jon Kenniston, Robert Sauer (MIT, Cambridge, MA), and colleagues now show that ClpX denatures by repeatedly applying a uniform unfolding force. “The way the enzyme works is to keep trying,” says Sauer.

This strategy works because proteins fluctuate around an average structure over time. Even a very stable protein will, very infrequently, be surprised in a relatively susceptible state. When this happens, the standard pulling force by ClpX is enough to unravel the protein. The enzyme then quickly threads the denatured protein through a narrow hole, toward the protease active site, before the substrate can refold.

The MIT group discovered the repetitive pulling phenomenon by studying stability variants of the muscle protein titin. This allowed “us to deconvolute how much ATP hydrolysis is used for unfolding versus translocating,” says Sauer.

During denaturation of different variants, the ATP hydrolysis rate was constant, but the amount of time taken to denature varied widely. Thus, although unstable variants were destroyed by a handful of ATP cycles, the destruction of a wild-type titin domain took more ATP molecules than were used in the protein’s biosynthesis.

When it fails, the ClpX unfoldase probably lets the pulling process cycle back to a ground state. This slipping may be inevitable given the protein’s construction. “The enzymes aren’t very stable proteins by themselves, so we don’t think they have any way to store energy,” says Sauer. For that reason, he says, “there’s no way of making unfolding a cumulative process.”

Reference: Kenniston, J.A., et al. 2003. Cell. 114:511–520.