Spaced just right

Mitochondria and ER membranes are directly tethered to one another, Csordás et al. report on page 915. Changes in tether length make the cell more or less vulnerable to apoptotic triggers.

Indirect evidence suggested that the mitochondria and ER were physically tied to one another, but what such a connection might be was obscure. Using electron tomography, Csordás et al. saw thin threads that ran between the organelles, ranging in size from 6 to 15 nm at the smooth ER, and 19 to 30 nm at the rough ER.

Limited protease digestion lengthened the ties and made the mitochondria less sensitive to Ca\(^{2+}\) release from the ER. By contrast, when the group engineered a 5-nm linker to narrow the gap between the organelles, mitochondria took in apoptosis-inducing amounts of Ca\(^{2+}\).

When wild-type cells were exposed to ER stress, the interorganelle tethers appeared to shorten before the cells entered apoptosis. The researchers speculate that the decreased distance enhances Ca\(^{2+}\) transfer from the ER to the mitochondria by keeping the organelles in immediate proximity. Whether other conditions push the organelles further apart—to safeguard mitochondria and prevent cell death—is unknown as yet.

It is also not yet clear what proteins comprise the tethers, but given their varied lengths, the team predicts that it will not be a single protein. In addition to organelle spacing, tether components might also help to control ER and mitochondria fusion and fission. JCB

Speeding nuclear import

Faster, better import is gained by increasing levels of the importin β nuclear transport receptor, according to Yang and Musser (page 951).

Current nuclear pore models do not consider the possibility that transport time might vary under different conditions. But that is just what Yang and Musser found when they increased the concentration of importin β in an in vitro system. Transport speed increased as much as sevenfold. Transport was also more efficient—more of the molecules that entered the pore passed through it successfully.

Structure-based studies suggest that long strands of phenylalanine–glycine (FG) repeats extend from the edge of the nuclear pore into the channel, creating a spaghetti-like network that molecules must wiggle through as they traverse the pore. A single importin β protein can bind to several of these FG repeats at the same time. Yang and Musser hypothesize that, as importin β moves through the channel, it may temporarily rearrange and open up the FG meshwork.

Higher importin β concentrations also increased the rate and efficiency of dextran movement through the pore, even though dextran is small enough to move through the pore without a transport receptor. The team is currently studying the effect of hyperactive import on the rate and efficiency of nuclear export. If excess importin β structurally disrupts the meshwork, it might facilitate movement in both directions. JCB

Trimming ERAD

Ubiquitins are zip codes for proteins heading to the proteasome. But misfolded ER proteins must be deubiquitinated before they are degraded, as shown by Wang et al. on page 963.

Misfolded ER proteins are sent back through the ER membrane into the cytosol by the p97 ATPase. Upon reaching the membrane’s cytosolic side, the substrates are modified by ubiquitin ligases. Wang et al. found that an enzyme that undoes the work of the ligases, a deubiquitinase called ataxin-3 (atx3), associates with p97 and the rest of this ER-associated degradation (ERAD) complex.

Overexpression of an atx3 mutant that lacks its deubiquitinase activity blocked degradation of at least two ERAD substrates and thus induced ER stress. The mutant also led to an accumulation of ubiquitinated substrates that were bound to p97, suggesting that substrates must shed ubiquitins before they can be moved to the proteasome. As a few ubiquitins are needed to target proteins to the proteasome, atx3 probably trims, rather than removes, the ubiquitin chains.

The atx3 protein is also compromised by polyQ expansions that cause spinocerebellar ataxia. Preliminary data from Wang et al., as well as data from Zhong and Pittman (Hum. Mol. Genet. 2006. 15:2409), show that these mutations effectively block degradation of some ERAD substrates. The resulting ER stress likely leads to cell death and may be the cause of neurodegeneration. JCB