Specialized chaperones

According to Véronique Albanèse, Judith Frydman, and colleagues (Stanford University, Stanford, CA), yeast evolved two distinct chaperone networks—one to fold newly synthesized proteins, and another to deal with stress-induced misfolding. The dedication is a departure from the prokaryotic chaperone system.

Bacteria have only one ribosome-bound chaperone and use primarily the same two chaperones to fold proteins after translation and then again after stress. But bioinformatic analyses by the authors suggested that yeast are different; whereas stresses such as heat and oxidation induced one set of cytosolic chaperones, they repressed another. The proteins from the repressed set were associated with ribosomes, and mutant lines lacking in this set were hypersensitive to translation inhibitors.

The authors propose that eukaryotes have a set of chaperones dedicated to nascent polypeptide folding during translation. This task splitting might have allowed for a better optimization of chaperone duties. “Eukaryotic cells have much larger, multidomain proteins than bacteria,” says Frydman. “Maybe this [advancement] was helped by the evolution of a chaperone machinery dedicated to ribosomes.”

Some overlap in duties might occur, as the slow growth of a mutant line lacking the major translation-linked chaperone, SSB, was partially rescued by high levels of stress-induced chaperones. Evidence suggests, however, that the replacements are more likely to be helping by cleaning up the mess of unfolded proteins rather than by contributing to cotranslational folding. JCB

Reference: Albanèse, V., et al. 2006. Cell. 124:75–88.

XX meetings

An interphase meeting between X chromosomes, revealed by Na Xu, Chia-Lun Tsai, and Jeannie Lee (Harvard Medical School, Boston, MA), ensures that one and only one is silenced.

Silencing of one of the two X chromosomes in a female somatic cell brings the gene dosage level down to that of male cells. Inactivation is controlled by several noncoding RNAs transcribed from, and acting in cis upon, the X inactivation center (XIC). But the field has been perplexed as to how one chromosome knows what the other is doing to keep inactivation mutually exclusive.

The new results suggest that a prior meeting between X chromosomes sets the decision. Although mammalian chromosomes normally only pair during meiosis, the authors saw transient contact between X chromosomes just before the inactivation of one.

Pairing required only the gene sequences of two of the silencing RNAs. Addition of either of these sequences to an autosome drew X chromosomes away from each other and into autosomal pairings. Deletion of the sequences from the X chromosome also interfered with pairing and resulted in none, one, or both X chromosomes being inactivated.

The big next step for the field will be to identify the molecules behind this choice. Thinking on a larger scale, Lee imagines that other epigenetic events might also be preceded by transient chromosomal pairings. In support of this idea, close proximity in late S phase of the two copies of an imprinted locus has been reported. JCB

Reference: Xu, N., et al. 2006. Science. doi:10.1126/science.1122984.

APC’s order of business

The anaphase-promoting complex (APC) has a hectic schedule. From mitosis through the G1/S transition, the APC is busily targeting cell cycle regulators for degradation. Yet it must keep an ordered degradation schedule for proper cell cycle progression. Now, results from Michael Rape, Sashank Reddy, and Marc Kirschner (Harvard Medical School, Boston, MA) suggest that the APC lets its substrates determine their own death order.

The degradation order of cell cycle regulators correlates with the kinetics of their ubiquitination by the APC. In vitro, securin—one of the first of the APC’s substrates to be degraded—rapidly obtained full-length polyubiquitin chains, which are required for proteasome recognition. The late-degraded substrates took much longer for multiubiquitination.

The kinetics reflects differences in substrate processivity—that is, how many ubiquitins are added in a single APC binding event. The most processive substrate outcompeted the rest in vitro for polyubiquitination and thus degradation.

“Why do we need so many ubiquitins in the first place?” asks Kirschner. “Isn’t it overboard?” Not according to the group’s new results. “We argue that by having multiple steps, chances for things to come off, you could accentuate very small differences in kinetic processes.”

Differences are probably further compounded by deubiquitinating enzymes. Nonprocessive substrates easily lost ubiquitin moieties upon dissociation from the APC. JCB

Reference: Rape, M., et al. 2006. Cell. 124:89–103.