Highly goes slowly

Rates of protein evolution vary widely. Very little of this variation is explained by dispensability (essential proteins evolving slowly), but up to a third is explained by expression levels. For an entirely mysterious reason, highly expressed proteins evolve slowly. Now, Allan Drummond and colleagues (Caltech, Pasadena, CA; and Keck Graduate Institute, Claremont, CA) argue that this correlation is based on the severe selective pressure on highly expressed proteins to avoid misfolding even when they are mistranslated. More abundant proteins are a greater misfolding threat because even a low misfolding rate would result in many misfolded, potentially toxic proteins—what Drummond calls “glue-covered monkey wrenches.”

Genes encoding abundant proteins therefore get stuck, say the authors, in the few sequences that are “translationally robust”: they usually fold correctly even when there are translational errors.

The study started not with experiments but theory. “The ‘aha!’ moment was lying in bed,” says Drummond. For the theory to work, however, the threat of errors would have to be large enough. Drummond checked his references for translation error rates. “They were absurdly high,” he says.

Ribosomes make ~5 errors per 10,000 codons translated. “When you convert that into how many proteins are translated,” says Drummond, “it becomes much more interesting to look at the cost.” With this error rate, ~19% of average-length yeast proteins should have a missense error; conservatively, 5% of the proteins might misfold. For the abundant PMA1 transporter that raises the scary prospect of ~63,000 misfolded molecules per cell.

The team found that misfolding matters not because it takes proteins out of circulation, but because it creates a potentially damaging molecule. What mattered most for evolution rate was not absolute abundance (the more abundant, the more activity that can potentially be lost by misfolding) but translation frequency (the more translation events, the more opportunities for creating troublesome and long-lived misfolded proteins).

The theory also makes sense of proteins such as the plant enzyme Rubisco, perhaps the most abundant protein on Earth. It is highly conserved but the result of this slow evolution is not functional fragility but, the authors hypothesize, translational robustness—surprisingly few inactivating mutations have been found in its gene.

Reference: Drummond, D.A., et al. 2005. Proc. Natl. Acad. Sci. USA. doi:10.1073/pnas.0504070102.

Fate trafficking

A symmetric cell fates can be defined by creating an endocytic compartment in one incipient daughter but not the other, say Gregory Emery, Juergen Knoblich (IMB, Vienna, Austria), and colleagues. Only the daughter with a functioning recycling endosome can direct Delta back to the plasma membrane so that it can activate Notch on the other daughter.

Knoblich studies fly sensory organ precursor (SOP) cells, which divide to form two cells—pIIa and pIIb—with different fates. Those fates are decided largely by Notch and its binding partner Delta. In pIIb, the asymmetry determinants Numb and Neuralized turn off Notch and increase the endocytosis that somehow activates Delta activity.

The Austrian team found that only in pIIb did Delta travel to a compartment resembling a recycling endosome. From here it could be sent back to the plasma membrane to activate Notch on pIIa. Some Delta endocytosis also happens in pIIa but, with no recycling endosome available, this Delta is sent to its destruction in a lysosome.

The recycling endosome protein Rab11 was present in both of the daughter cells, but only pIIb had centrosome-localized recycling endosomes labeled with Rab11 and the Rab11-binding protein Nuf. Overriding both the Numb and Rab11 pathways, but not either one by itself, resulted in a complete loss of asymmetry.

The work has uncovered not only a new pathway for asymmetric cell division but a more dramatic mode of regulation by the endocytic system. Endocytosis of select cargos has been known for some time to regulate signal transduction.

“What is new,” says Knoblich, “is that for the first time a cell can regulate the endocytic pathway itself—the cell shuts off the recycling endosome. That is unprecedented.”

Reference: Emery, G., et al. 2005. Cell. 122:763–773.