How to become a generalist again

If life seems like one inexorable process of specialization, take a closer look at the Dictyostelium slug. After forming from aggregated single cells, it is on its way to becoming a specialized fruiting body. But if its cells are dispersed and given nutrients they revert to their primitive, proliferative state. This dedifferentiation, say Mariko Katoh, Gad Shaulsky (Baylor College of Medicine, Houston, TX), and colleagues, is not a simple reversal of differentiation but a carefully regulated process. Similar regulation may ensure that dedifferentiating cells in a mammalian wound, for example, can fill in the wound without causing cancers or distorting the shape of the body part that was carefully crafted during development.

The group’s claim is based on microarray results. Many of the transcriptional changes in dedifferentiating cells are a mirror image of those taking place in differentiating cells, but over 100 genes show changes specific to dedifferentiation. The set of genes is similar even when cells start dedifferentiating from different developmental stages.

One of the genes turned on during dedifferentiation encodes DhkA. Mutants lacking DhkA are slower to reinitiate cell division, but not DNA synthesis, during dedifferentiation. DhkA is a histidine kinase that, as part of a two-component system, is also required for the late differentiation event of sporulation. Shaulsky suggests that DhkA may be part of a checkpoint system in which completion of differentiation is contingent on accumulation of proteins (such as DhkA) necessary for dedifferentiation, thus ensuring that development is reversible.

Reference: Katoh, M., et al. 2004. Proc. Natl. Acad. Sci. USA. 101:7005–7010.

Metabolism as a production line

Metabolic pathways might be smarter than we think, according to Alon’s team. At least in bacterial amino acid biosynthesis pathways, the production schedules are designed using two principles that, according to theory, optimize the pathways for the fastest output using the least amount of enzymes.

“Life is just in time” propagation needs some help in propagating through a cell cycle, according to Attila Becskei, Monica Boselli, and Alexander van Oudenaarden (MIT, Cambridge, MA).

Each transcriptional wave from a yeast cell cycle promoter lasts 20–25 min; so stringing together 3 or 4 of them should allow the construction of a simple 90-min cell cycle. But, says van Oudenaarden, “if you didn’t optimize the system, the cell cycle waves get washed out very easily. Within a quarter or a third of a 90-minute cycle, the waves are almost completely gone.”

Rather than investigating every last detail of real cell cycle oscillators, the MIT group built, both in yeast cells and in silico, a simple circuit that transmits cell cycle-like oscillations. They found that a slow process such as transcription (and the lengthy persistence of the resulting mRNA) led to a loss of the initial periodicity information from a cell cycle promoter.

A faster process, such as accelerated nuclear import, gave a shorter delay but maintained the high peak-to-trough information of the original oscillation. Stringing together a series of such fast processes, such as protein modifications, should give accurate oscillations of approximately the correct duration. The high peak-to-trough ratio can also be restored with feedback loops and nonlinear activation and degradation steps. All of these tricks were known to exist in the cell cycle, but the MIT group has now established why they are necessary.

Reference: Becskei, A., et al. 2004. Nat. Cell Biol. 6:451–457.