Fine-tuning gene expression

Controlling transgene expression levels beyond the removal or duplication of a gene is a challenging task. Smithies and colleagues provide a potential solution by appending to genes of interest a selection of natural and modified 3′ untranslated region (UTR) sequences that affect mRNA stability. To test their system, they placed each UTR downstream of a green fluorescent protein marker gene inserted into the hypoxanthine phosphoribosyltransferase (HPRT) locus in mouse embryonic stem (ES) cells and then assessed transcript level by fluorescence. Depending on the UTR inserted, over a 100-fold difference in gene expression could be obtained. The authors go on to show that ES cells undergoing differentiation maintain the same range of gene expression as undifferentiated cells, indicating the potential utility of the approach in animals. They also modify the 3′ UTRs of two endogenous mouse genes and accurately predict their expression levels in cell lines from ES cell–derived mice. (*Dev. Cell* **6**, 597–606, 2004) *NC*

Peptide fatbuster

If the latest wave of fad diets has failed you, hope glimmers on the horizon. Kolonin *et al.* have developed an antiobesity strategy that avoids surgery, drugs acting on your brain or even old-fashioned diet and exercise. Taking their cue from efforts to shrink tumors with angiogenesis inhibitors, the authors slimmed down obese mice by targeting an apoptotic molecule to the vasculature of white fat tissue. This molecule is a fusion of a peptide, found by *in vivo* phage panning, that homes to the membrane protein prohibitin (identified as a vascular marker of white fat tissue) with another peptide known to induce apoptosis in tumor blood vessels. Injection of the fusion peptide into wild-type mice rendered obese through a high-calorie diet resulted in >30% weight loss over four weeks of treatment. Treated mice also experienced a loss of excess fat deposits in the liver, reduced lipid content in the skeletal muscles and increased metabolism, with no apparent negative side effects. The researchers believe that this concept may hold promise for clinical development. (*Nat. Med.* **10**, 625–632, 2004) *MZ*

Networks in a spin

Reconstructing whole (*e.g.*, genetic, metabolic) networks of an organism has remained a challenge despite the increasing availability of massive data sets. In a first crack at this conundrum, Palsson and colleagues have applied an iterative approach to modeling the integrated transcriptional regulatory and metabolic network of the bacterium *Escherichia coli*. First, the authors created an *in silico* Version 1 strain of *E. coli* that incorporated existing information from databases and the literature. Once the robustness of the model was characterized by determining the accuracy of different predictions generated by it, the authors then went on to test several new predictions related to *E. coli*'s response to oxygen deprivation. These data were then applied toward refining the model, resulting in an *in silico* Version 2 strain of *E. coli* in which the prediction coverage increased from 15% to 66% and the accuracy of the predictions increased from 49% to 98%. These results show the potential of applying iterative schemes to network reconstruction. (*Nature* **429**, 92–96, 2004) *GTO*

Research Notes written by Nadia Cervoni, Laura DeFrancesco, Andrew Marshall, Gaspar Taroncher-Oldenburg and Mark Zipkin.

Rx/Dx oligonucleotides

DNA oligonucleotides that liberate a drug or a drug suppressor depending on the levels of four mRNAs specific to a disease may open the path to nucleic acid molecules that act both as diagnostic and drug. In their ingenious approach, Shapiro and colleagues rely on encryption of sequences specific to each mRNA into two double-stranded (ds) hairpin DNA 'diagnostic' oligos: one that liberates an embedded single-stranded (ss)DNA drug and another that liberates a ssDNA drug suppressor. Sequential cleavage of these diagnostic oligos by *Fok*I is regulated in a stepwise manner by duplexes formed as a result of cross hybridization between each specific mRNA and an additional set of cleverly designed dsDNA and ssDNA molecules. When an mRNA is expressed at disease levels, excess 'activating' duplexes produced by cross hybridization stimulate single *Fok*I digestion of the drug oligo and at the same time halt a single digestion of the drug suppressor oligo; in contrast, when mRNA levels are normal, the reverse effect is seen. Thus, as each of the four mRNAs associated with disease is detected at the relevant level, the *Fok*I enzyme consecutively removes a sequence in the diagnostic oligo that corresponds to that mRNA, so that the diagnostic oligo's stem structure (before the hairpin) becomes shorter and shorter. After four successive digestions, either the ssDNA drug or its suppressor is released from the hairpin. The system was validated using mRNA signatures characteristic of small-cell lung cancer and prostate cancer. (*Nature* **428**, doi:10.1038/nature02551, published online 28 April 2004). *AM*

Nitrogen booster

Agriculture in the developed world relies heavily on nitrogen fertilizers, which are costly and inefficient in economic and ecological terms. Until now, alternative strategies aiming to make plants assimilate nitrogen more effectively by manipulating levels of individual enzymes have had only limited success, perhaps because the demand for carbon skeletons required for extra nitrogen creates an imbalance in metabolites. To solve this problem, Japanese researchers have introduced into *Arabidopsis thaliana* the maize *Dof 1* gene, encoding a transcription factor that regulates an entire metabolic pathway involved in carbon metabolism. Transgenic *A. thaliana* containing *Dof1* had higher levels of multiple genes involving carbon metabolism (nontarget genes such as β-tubulin were unchanged). In addition, they had higher concentrations of glutamine, glutamate and free amino acids, 30% greater nitrogen accumulation and, importantly, grew well under low nitrogen conditions. The same maize transcription factor gene works in potatoes, suggesting that this one factor could be useful in producing nitrogen-efficient varieties of many plant species. (*Proc. Natl. Acad. Sci. USA* **101**, 7833–7838, 2004) *LD*