A-maize-ing agronomic loci?

The striking differences between ears of contemporary maize (right), its wild ancestor teosinte (left) and their hybrid (center) illustrate but one aspect of the extraordinary transformation of maize from its humble progenitor to the world's highest-yielding grain crop. To identify the genes that account for the striking improvements in yield and biochemical composition that accompanied the domestication of maize, McMullen and colleagues identified 35 genes that displayed no sequence diversity among 14 inbred maize lines. Assuming that genes that have been targeted by artificial selection are likely to display the lowest levels of variation, the authors sequenced these candidates in several maize landraces and teosintes. Six genes that have functions consistent with productivity and nutritional quality displayed strong selection throughout their lengths. As these loci appear to have contributed to the improvement of maize, their manipulation in the future might be important in further enhancement of the agronomic performance, palatability or nutritional quality of the crop. They are also excellent candidates for introgression from wild relatives to increase the diversity that breeders can exploit. (*Plant Cell* 17, 2859–2872,

Rapid resolution X-rays

A technology that allows improved resolution of the kinetics of state transitions driving metalloenzyme-based redox reactions in living systems may appear to be of academic interest only, but it isn't. Haumann *et al.* apply time-resolved X-ray absorption spectroscopy to monitor the kinetics of photosynthetic oxygen evolution by photosystem II, a key process in solar energy transduction during photosynthesis. Previously, it was impossible to measure the precise sequence of events in enzymatic reactions over submillisecond time scales. But the authors took advantage of recently available, high-intensity X-ray beams at 'third-generation' synchrotron facilities to achieve a time-resolution of 10 μs—two orders of magnitude better than the previous resolution limit (3 ms). As improved resolution X-ray absorption spectroscopy can facilitate kinetic analysis, it is likely to facilitate advances in the design of solar-converting fuel cells, biofuel cells or even industrial enzymes with improved activities. (*Science* **310**, 1019–1021, 2005). *GTO*

Structure meets pharmacology

High drug failure rates can be traced in part to an inability to connect data on the effects of drugs on isolated proteins with their effects on whole animals or organs. A group of Pfizer researchers are trying to bridge the gap between those two universes. In previous publications, they created 'biospectra' for 1,567 chemical entities by measuring their effect on the activity of 92 proteins that represent a cross-section of druggable targets. In the current work, they categorized side effects taken from the labels of 1,045 prescription drugs and propose that together these two data sets could predict the behavior of untested drugs. They defined 591 possible effects (e.g., nausea, headache), binarized the drug effect data for each drug (0 is no effect, 1 is effect) and entered such descriptors into hierarchical clustering to create 'effect spectra.' This revealed six clusters of side effects, as well as seven clusters of drugs with similar side-effect profiles. Using a set of 19 hypnotic-anxiolytic small molecules with low biospectrum similarity, they found that they also fell into several side-effect classes, suggesting a correlation between structural and pharmacological properties. The authors feel that quantifying these relationships could help determine clinical effects early in drug development. They also suggest that the creation of public databases of preclinical data will facilitate these analyses in the future. (*Nat. Chem. Biol.*, **1**, 389–397, 2005) *LD*

Research Highlights written by Kathy Aschheim, Laura DeFrancesco, Peter Hare, Teresa Moogan & Gaspar Taroncher-Oldenburg.

Silencing microRNAs

MicroRNAs (miRNAs) have joined mRNAs as potential targets of knockdown technology. By conjugating 2′-*O*-methyl single-stranded oligoribonucleotides with cholesterol, Markus Stoffel and colleagues obtain RNA analogs with "drug-like properties" that are amenable to *in vivo* delivery. One of these oligoribonucleotides (antagomir-122), designed to be complementary to an miRNA abundant in liver (miR-122), completely suppressed the miR-122 signal and continued to do so for up to 23 days when administered to mice. To further explore the role of miR-122 in liver function, the authors studied effects of the knockdown on gene expression, identifying 363 upregulated transcripts and 305 downregulated ones. Examination of the 3′ untranslated regions of the genes whose expression was altered revealed that upregulated mRNAs were directly repressed by miR-122, but that downregulated genes were also likely activated by this miRNA. According to their Gene Ontology classification, downregulated genes belonged most often to 'cholesterol biosynthesis.' Indeed, compared with control animals, treated mice had a 45% and 40% decrease in cholesterol biosynthesis enzyme and plasma cholesterol, respectively. The findings demonstrate that oligoribonucleotide knockdown is likely to be a useful tool in investigating miRNA function and ultimately may be useful in therapy for diseases in which miRNA regulation plays a part. (*Nature*, published online 30 October 2005; doi:10.1038/nature04803) *TM*

Sorting out stem cell gene correction

Methods for targeted genetic modification of stem cells by homologous recombination are still too inefficient to be used without a subsequent step to isolate the corrected cells. This isolation step is often carried out by positive-negative drug selection, a procedure that can take more than 10 days and may be especially problematic if the cells are difficult to culture in an undifferentiated state. In addition, drug selection doesn't eliminate feeder cells, which must be drug resistant. Smithies and colleagues have devised an approach for purifying genetically modified stem cells in 3–5 days using fluorescent markers and fluorescence-activated cell sorting. Their gene-correction vector includes a gene encoding green fluorescent protein that is expressed in corrected cells and used for positive selection, and a gene encoding cyan fluorescent protein that is excluded by homologous recombination and used for negative selection. The approach was tested on mouse embryonic stem cells bearing a mutation in the hypoxanthine phosphoribosyl transferase gene. Corrected cells could be isolated after 5 days with a purity of >30% and a recovery of ~20%. (*Proc. Nat. Acad. Sci. USA* **102**, 16357–16361, 2005) *KA*