Chromosome shuffle

Jonathan Singer and colleagues report the completion of a 7-year effort to produce a complete panel of chromosome substitution strains (CSSs) of mice (*Science* advance online publication, 18 March 2004; doi:10.1126/science.1093139). The CSS approach was proposed as a shortcut to identify quantitative trait loci (QTLs). There are 22 mouse strains in the panel, each of which carries a single chromosome from the A/J donor background, with the rest of the chromosomes from a common C57BL/6J host background. These strains were chosen because of the abundant physiological differences between them. With the CSSs, any phenotypic difference between the two inbred backgrounds can immediately be ascribed to QTLs on the particular A/J chromosome. Subsequent crosses and fine-mapping can then be carried out with a fraction of the usual effort needed to identify QTLs. To demonstrate the approach, the authors used the CSSs to study 53 complex traits related to sterol levels, diet-induced obesity, anxiety and amino-acid levels, and found evidence for 150 QTLs. Some overlapped with regions previously reported to harbor QTLs for these traits; others were new. The CSS panel will be preserved and distributed by the Jackson Laboratory. ***AP***

Common haplotype confers asthma risk

Juha Kere and colleagues (*Science* **304**, 300–304; 2004) identified a common haplotype on chromosome 7 associated with asthma-related phenotypes in three different populations of European descent. The common haplotype, which spans 133 kb, was associated with high immunoglobulin E (IgE) levels in two Finnish populations and with asthma in a population from Northeastern Quebec. The risk-associated genomic segment contains two genes, one of which encodes an orphan G protein–coupled receptor designated GPRA. Two main isoforms of GPRA are expressed in the adult lung: isoform A, predominantly in bronchial smooth muscle cells, and isoform B, restricted to bronchial epithelial cells. Although it is not yet known whether differences in GPRA expression are correlated with different *GPRA* haplotypes, isoform B was upregulated in smooth muscle cells in biopsy samples from asthmatic individuals, suggesting that the functional variants underlying the association might alter the balance between the two GPRA isoforms. Notably, GPRA was also expressed in the epithelium of the gut and the epidermis of the skin, suggesting that this receptor might have a role in other IgE-mediated allergic diseases. *KV*

Combination therapy for APL

The t(15;17)(q22;q21) translocation in acute promyelocytic leukemia (APL) fuses the gene encoding retinoic acid receptor alpha (*RARA*) with the gene *PML*, which regulates myeloid differentiation. The chimeric protein arrests the maturation of myeloid cells before terminal cell differentiation, leading to increased proliferation of promyelocytes. In addition to cytotoxic chemotherapy, Zhu Chen and colleagues (*Proc. Natl. Acad. Sci. USA* **101**, 5328–5335; 2004) used a triple combination of differentiation therapy with all-*trans* retinoic acid (ATRA) and arsenic trioxide; 20 individuals achieved complete remission with this treatment. In addition to promoting apoptosis, the arsenic contributed to increased downregulation of the PML-RARα fusion protein beyond that previously attributed to ATRA. Apart from recommending trials of the triple therapy in newly diagnosed cases of APL, the authors recommend further analysis of the molecular changes wrought by the combination in order to understand the two modes of action of ATRA and the multiple cellular effects of arsenic. Though this analysis emphasized oncoprotein stability, transcriptome analysis of cells under the three treatment regimens will probably also be informative, as the fusion protein downregulates a number of genes by sequestering the RXR retinoid receptor and promoting histone deacetylation. *MA*

Research Notes written by Myles Axton, Alan Packer and Kyle Vogan

Tailored gene expression in mice

Oliver Smithies and colleagues (*Dev. Cell* **6**, 597–606; 2004) developed a method for altering gene expression levels in mice by introducing specific modifications into the 3′ untranslated region (UTR) of target genes. The authors designed a series of modified 3′ UTR sequences linked to green fluorescent protein (GFP) and inserted them into the *Hprt* locus by homologous recombination in mouse embryonic stem (ES) cells. They found that the modified 3′ UTRs altered reporter activity over a 100-fold range in ES cells by influencing steady-state levels of the modified transcripts. Consistent differences in reporter activity were also seen after the ES cells differentiated into specific cell types. Moreover, predicted changes in transcript levels were observed in mice derived from ES cells carrying targeted alterations in two different genes, *Agtr1* and *Pparg*. Targeting the 3′ UTR in this manner leaves most regulatory elements unchanged, producing quantitative changes in transcript levels without altering the temporal or spatial expression pattern of the targeted gene. This system can thus be applied to studying the effect of varying gene dosage over a wide range of expression levels *in vivo*. *KV*

Interfering with siRNAs

Small RNAs produced by the Dicer endoribonuclease form two distinct forms of ribonucleoprotein complex in animal cells. siRNAs are associated with the RISC complex mediating specific mRNA cleavage. The four known animal microRNAs block translation of their complementary target mRNAs, but the functions of hundreds more miRNAs are not known. Hutvágner *et al.* (*PLoS Biology* 2, 465–475; 2004) report that ribonuclease-resistant 2′-O-methyl oligoribonucleotides can act as irreversible stoichiometric inhibitors of small RNA function. In extracts of fruit fly embryos, these oligos specifically blocked RNAi-dependent cleavage of a firefly luciferase mRNA. Injection of a 2′-O-methyl oligonucleotide complementary to the *let-7* miRNA induced a *let-7* phenocopy in *C. elegans*. The modified oligos, tethered to magnetic beads, were used to isolate *let-7* RNA complexes with RNA binding proteins, including two previously identified Argonaute proteins, showing that they were serviceable affinity reagents with which to investigate the roles of the associated proteins in RNA-mediated silencing events. The 2′-O-methyl oligonucleotide bound to RISC was much more effective at inhibiting RNA cleavage than was the modified oligo bound to the RISC recognition site on target RNA. The authors interpret this result to mean that there is more to the specific recognition mechanism of RNAi than RNA-RNA hybridization followed by duplex stabilization. ***MA***