IN BRIEF

FUNCTIONAL GENOMICS

Integration of transcriptomics and metabolomics for understanding of global responses to nutritional stresses in *Arabidopsis thaliana*.

Hirai, M. Y. *et al. Proc. Natl Acad. Sci. USA* 15 June 2004 (doi:10.1073/pnas0403218101)

Few studies have managed to integrate global analyses of gene expression and metabolism. Masami Hirai and colleagues do just that for *Arabidopsis thaliana*, specifically focussing on the effects of sulphur deficiency. Their multidimensional analyses of DNA macroarray and mass-spectrometry data allowed them to identify metabolic pathways that respond to nutrient deficiencies. The expression of genes in the glucosinolate metabolic pathway is particularly tightly coordinated with this pathway's metabolites.

MOUSE GENETICS

Unexpected complexity in the haplotypes of commonly used inbred strains of laboratory mice.

Yalcin, B. *et al. Proc. Natl Acad. Sci. USA* 29 June 2004 (doi:10.1073/pnas0401189101)

Variation between the genomes of inbred mouse strains was thought to be structured into high- and low-frequency segments that might be useful for quantitative trait locus (QTL) mapping. Richard Mott and colleagues show that, for one region at least, this picture is inaccurate: while the distribution of variation between mouse strains is not random, the definition of haplotype blocks is problematic. Complete sequences might be needed to map QTLs from the distribution of SNP variants among strains.

COMMUNITY RESOURCE

The BDGP Gene Disruption Project: single transposon insertions associated with 40% of *Drosophila* genes.

Bellen, H. J. *et al. Genetics* **167**, 761–781 (2004)

The Berkeley *Drosophila* Genome Project (BDGP) aims to disrupt each fly gene with a single *P*-transposon insertion. This article reports the expansion of the collection from 1,045 to 7,140 lines — targeting ~5,362 (or 39%) of annotated *D. melanogaster* genes — which are freely available to the community. This is a valuable resource for fly geneticists that also provides insight into how transposons interact with the eukaryotic genome.

COMMUNITY RESOURCE

Mutagenic insertion and chromosome engineering resource (MICER).

Adams, D. J. *et al. Nature Genet.* 4 July 2004 (doi:10.1038/ng1388)

The manipulation of mouse embryonic stem cells remains the preferred way to assess the function of mouse genes. To overcome the limitation caused by gene targeting — which requires unique vectors to be designed for each target allele — the authors have created a public resource (MICER) that consists of 93,960 insertional targeting vectors. A total of 5,925 of these, which were indexed from 2 existing vector libraries, can be readily used to inactivate specific genes or to engineer larger genomic alterations.

TECHNOLOGY

Mouse functional genomics in full bloom

It is the question that everyone is asking: we have the completed genome sequence — now how do we use it effectively? In the case of the mouse, one answer lies in high-throughput functional genomics. Two recent reports — one from Japan, one from the UK — describe the generation of mutant embryonic stem (ES) cell libraries that could enable functional studies for years to come.

Recessive screens in mice require breeding of heterozygous mutations, which is both time-consuming and expensive. Knowing that screens in mammalian cell lines would be cheaper and quicker, both sets of authors have exploited properties of mouse stem cells that are homozygous for mutations in *Blm* (Bloom syndrome homologue). With each generation, these cells are more likely to make the mutations that occur on one chromatid homozygous, presumably through increased mitotic recombination. Guo and colleagues mutagenized the $Blm^{-/-}$ ES cells with a retroviral gene-trap vector to create a library of homozygous mutant cell lines. They first looked for genes that are involved in the mismatch repair (MMR) pathway, which is often mutated in cancer. The use of 6-thioguanine allowed for the selection of cells that are defective in MMR, and the gene-trap method allowed for quick mutant gene identification. Indeed, one of the famous *Msh* genes was picked up, as was *Dnmt1* — a surprise because it is normally thought of as a methylase. But re-examination of *Dnmt1* knockout cells confirmed that they had a higher level of microsatellite instability, qualifying *Dnmt1* as a new MMR pathway member.

Yusa *et al.* used a tetracycline-induced *Blm* ES-cell knockout line. They mutagenized these cells with *N*-ethyl-*N*-nitrosourea (ENU) and used doxycycline selection to make the mutations biallelic. As a proof of principle, they screened for cell lines that were deficient in one pathway — glycosylphosphatidylinositol (GPI)-anchor biosynthesis — which is easier than it might sound, because exposing cells to aerolysin kills those with GPI anchors and leaves the mutants behind. Unlike in the Guo *et al.* library, here expression cloning is needed to find the genes; Yusa *et al.* achieved this through complementation analysis of the known genes in the pathway. A total of 12 of the 23 known genes in this pathway were mutated in both alleles after just one round of screening.

The strengths of both studies are the selection for cell lines with recessive mutations and an easy transition from mutant ES cells to new mice for further study. Given that both libraries are available to other scientists, mouse geneticists have hit the jackpot.

Chris Gunter, Senior Editor, Nature

References and links

ORIGINAL RESEARCH PAPERS Guo, G. *et al.* Mismatch repair genes identified using genetic screens in Blm-deficient embryonic stem cells. *Nature* **429**, 891–895 (2004) | Yusa, K. *et al.* Genome-wide phenotype analysis in ES cells by regulated disruption of Bloom's syndrome gene. *Nature* **429**, 896–899 (2004)