GENE EXPRESSION

Genetic landscape in 3D

Last year, data from several yeast DNA microarray experiments were pooled to create a compendium of gene expression profiles in *Saccharomyces cerevisiae*. Data comparisons on such a massive scale can provide rich insights into gene function and biology. Kim *et al.* have now pooled data from 30 different laboratories to create a similar compendium that covers ~93% of the *Caenorhabditis elegans* genome. By visualizing data in three dimensions to create a gene expression landscape — in which genes that share expression patterns cluster together to form expression mountains — the authors were able to obtain a comprehensive view of how genes are co-regulated in the worm.

Motivated by the need to develop high-throughput functional genomics approaches to analyse gene function, Stuart Kim and colleagues combined data from 553 microarray experiments, in which gene expression was compared between wild-type and mutant worms, and between worms grown under different conditions. To identify genes that are co-regulated, they first assembled a gene expression matrix that contains the relative expression level for each gene in each microarray experiment programme. A two-dimensional scatter plot, in which genes with similar expression profiles lie close to each other, was converted into a three-dimensional map, in which the *z* axis corresponds to gene density in a given area. Each gene was then assigned to a cluster, or expression mountain, and each of these was numbered — the biggest mountain was zero and the smallest was 43.

The expression landscape is visually impressive, but is it biologically meaningful? Overlaps between certain expression mountains and groups of genes that are known to share a common function are significant. In addition, the authors confirmed the validity of this representation, for example by randomizing the data and adding noise.

Once satisfied with their method, Kim *et al.* went off to explore the genetic landscape they had generated. They found that some mountains group together genes that are expressed in similar tissues, so for example there is a muscle mountain and a germ-line mountain. Other mountains are made up of genes with similar cellular functions — there is a histones mountain and a ribosomal genes mountain. By showing that the mountains were enriched in particular sets of genes, Kim *et al.* were able to attribute physiological significance for 30 out of 44 of the mountains. Zooming in on particular mountains confirmed and augmented already known genetic links between genes. For example, 89% of previously identified sperm-enriched genes clustered on mountain 4 and genes that encode principal sperm proteins, protein kinases and phosphatases fell into three separate subclusters on mountain 4.

The exploratory trips of Kim and colleagues into this expression landscape have already yielded much information on gene co-regulation, and they have amply shown the superiority of this visual data representation. New gene interactions, unexpected gene co-regulation, assignment of function to new genes and much more await future explorers.

Magdalena Skipper

References and links

ORIGINAL RESEARCH PAPER Kim, S. K. *et al.* A gene expression map for *Caenorhabditis elegans*. *Science* **293**, 2087–2092 (2001)

FURTHER READING Gifford, D. K. Blazing pathways through genetic mountains. *Science* **293**, 2049–2051 (2001)

WEB SITE

Stuart Kim's lab: http://cmgm.stanford.edu/~kimlab/topomap/c._elegans_topomap.htm

IN BRIEF

GENE REGULATION

Identifying regulatory networks by combinatorial analysis of promoter elements.

Pilpel, Y. *et al. Nature Genet.* **29**, 153–159 (2001)

The use of microarray technology for transcriptional profiling and cluster analysis is a powerful approach for finding co-regulated genes and the promoter motifs that control transcription. Pilpel *et al.* have extended this approach by studying the combinatorial action of regulatory motifs in *Saccharomyces cerevisiae*. They identified pairs of motifs that act in a synergistic manner to provide tighter transcriptional regulation than either motif alone. The resulting network of interactions shows how a relatively small number of transcription factors might act in concert to regulate gene expression under a broad range of growth conditions.

DEVELOPMENT

A murine model of the Holt–Oram syndrome defines roles of the T-box transcription factor Tbx5 in cardiogenesis and disease.

Bruneau, B. G. *et al. Cell* **109**, 709–721 (2001)

Several T-box (Tbx) gene family members are involved in dominant congenital heart disorders — *TBX5* in Holt–Oram syndrome (HOS) and probably *TBX1* in DiGeorge syndrome (see Elizabeth Lindsay's review, p858). This *Tbx5*-knockout study provides new insight into how *Tbx5* haploinsufficiency causes HOS-like heart defects in mice. $Tbx^{+/-}$ mice show the reduced expression of many genes, most markedly that of atrial natriuretic factor (*Anf*) and connexin 40 (*Cx40*). The authors discovered that *Anf* and *Cx40* are activated when Tbx5 and Nkx2-5 interact at their promoters, indicating a mechanism for the haploinsufficient effects of *Tbx5*. Misregulation of *Cx40* could underlie the heart-conduction defects in $Tbx5^{+/-}$ mice and HOS patients. Their findings also shed light on the condition's variability and on cardiac malformations caused by other transcription factor mutations.

TRANSPOSABLE ELEMENTS

Mobilization of a *Drosophila* transposon in the *Caenorhabditis elegans* germ line.

Bessereau, J.-L. *et al. Nature* **413**, 70–74 (2001)

Although *C. elegans* has several native transposon types, they cannot be used to manipulate the worm genome because they are too numerous to serve as unique gene tags and because different transposon types can be activated at the same time, making them difficult to trace. This paper shows the successful mobilization of a foreign element — the *Drosophila* mariner element, *Mos1* — in the worm. *Mos1* has the essential qualities of a regulable transposon: it can be mobilized in the soma and germ line — where its insertion point can be identified by PCR — and it can be mutagenic by imperfect excision.