IN BRIEF

TECHNOLOGY

Functional annotation and network reconstruction through cross-platform integration of microarray data.

Zhou, X. J. *et al. Nature Biotechnol.* 16 January 2005 (doi:10.1038/nbt1058)

Zhou *et al.* designed a method for microarray analysis that combines data from different microarray platforms. The key to the approach lies in the two-step analysis: expression patterns are extracted as meta-information from each data set, and only then are they analysed across data sets. The method identified yeast genes with the same function without the need for co-expression data, and transcription factors that co-operate with each other, without the need to quantify their levels.

EVO–DEVO

Chance caught on the wing: *cis*-regulatory evolution and the origin of pigment patterns in *Drosophila*.

Gompel, N., Prud'homme, B. *et al*. *Nature* **433**, 481–487 (2005)

This work lends support to the view that morphological variation can be attributed to changes in gene-regulatory regions. The wings of *Drosophila melanogaster* are uniformly pigmented, but those of *Drosophila biarmipes* males feature a single dark spot that is caused by the accumulation of the Yellow protein. *Cis*-coding regions of the *yellow* locus from *D. biarmipes* induced spot-specific expression when introduced into *D. melanogaster*; further analyses showed that the spot-specific control region arose by mutation of an ancestral element.

GENE THERAPY

Protective effect of DNA vaccine during chemotherapy on reactivation and reinfection of *Mycobacterium tuberculosis*.

Ha, S.-J. *et al*. *Gene Ther.* 3 February 2005 (doi:10.1038/sj.gt.3302465)

Tuberculosis (TB) can re-emerge years after the initial active disease, either through reactivation of latent viruses or reinfection. These authors have shown that delivery of a double-gene DNA vaccine against TB (containing the genes *Ag85A* and *PstS3*), combined with immunotherapy, blocks the reactivation of TB and significantly reduces reinfection.

HUMAN GENETICS

Restoration of tolerance in lupus by targeted inhibitory receptor expression.

McGaha, T. L. *et al. Science* **307**, 590–593 (2005)

The breakdown of checkpoints that control the ability of the immune system to maintain tolerance results in the development of autoimmune disorders. McGaha and colleagues showed that the inhibitory Fc receptor FcγRIIB in mice regulates a B-cell checkpoint that is required for tolerance maintenance and autoimmunity prevention. Changes in the expression of this receptor influence disease progression and could provide the basis for novel therapeutic approaches against autoimmune diseases.

RNA WORLD

The wide reach of microRNAs

Despite the recent rapid progress in understanding the roles of microRNAs (miRNAs), it seems that we still have a lot to learn. Two recent studies of animal miRNAs not only reveal a new mode of action for these molecules, but also indicate that they might have a far wider regulatory role than was previously appreciated.

In animals, miRNAs are thought to regulate gene expression by inhibiting translation. Lee Lim and colleagues investigated whether, like their plant equivalents, animal miRNAs also trigger transcript degradation. They transfected human cells with two miRNA sequences and examined their effects on gene expression using microarrays. For both miRNAs, many transcripts were downregulated, indicating widespread effects at the mRNA level.

Is this transcript downregulation direct, or is it a secondary effect that is caused by decreased expression of regulatory genes? Using a computational method, the authors identified motifs that were over-represented in the 3′ untranslated regions of the downregulated transcripts. These motifs showed complementarity to 5′ regions of the miRNAs, indicating that downregulation is mediated by a direct interaction between the miRNAs and their target transcripts.

Further support for this conclusion came from examining the sets of transcripts that were downregulated by the two miRNAs, both of which have specific expression patterns *in vivo*. The transcripts they regulated in the microarray experiments correspond to genes that are expressed at lower levels in the tissues with the highest abundance of the miRNAs. This correlation between *in vivo* expression patterns and *in vitro* activities provides strong evidence that the results of the microarray analysis are biologically relevant.

In a second study, Benjamin Lewis and colleagues provide evidence that more than a third of human genes are regulated by miRNAs. The authors reasoned that, for genuine targets, sites of interaction with the regulatory miRNA would be preserved in orthologous genes from other vertebrates much more frequently than similarly abundant sites that lack complementarity to the miRNA. This requirement for conservation allowed them to refine other constraints in searches for potential target genes. In the gene set that was analysed by the authors, more than a third of the genes were identified as conserved miRNA targets, a much larger figure than previously estimated.

Our knowledge of the regulatory importance of miRNAs and their mechanisms of action is increasing all the time; the next challenge will be to assimilate this information to understand how miRNAs define specific patterns of gene expression.

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References and links

ORIGINAL RESEARCH PAPERS

Lim, L. P. *et al.* Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. *Nature* 30 January 2005 (doi:10.1038/nature03315) | Lewis, B. P., Burge, C. B. & Bartel, D. P. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. *Cell* **120**, 15–20 (2005)

FURTHER READING

He, L. & Hannon, G. J. MicroRNAs: small RNAs with a big role in gene regulation. *Nature Rev. Genet.* **5**, 522–531 (2004) | Bartel, D. P. & Chen, C. Z. Micromanagers of gene expression: the potentially widespread influence of metazoan microRNAs. *Nature Rev. Genet.* **5**, 396–400 (2004)

WEB SITES

David Bartel's laboratory: http://web.wi.mit.edu/bartel/pub

Christopher Burge's laboratory: http://genes.mit.edu/burgelab