Web watch

WOULD MENDEL HAVE BEEN A BLOGGER?

The web is undergoing a revolution. Web 2.0, or the 'social web', is much talked about, but are geneticists ready to make the most of it?

Web 2.0 describes internet environments — such as social networking, wikis and blogs — that allow users to collaborate and share information online. Blogs have, by now, become almost ubiquitous. A Google search for blogs related to genetics reveals some interesting sites that, as well as being informative, provide a glimpse of how geneticists use this communication tool.

Mendel's Garden is run by Hsien-Hsien Lei, and offers monthly instalments on topics that range from science policy (such as the story about a biological sample repository on the moon!) to the history of genetics.

A blog from our colleagues at *Nature Genetics* — Free Association — focuses on newly published primary papers, interviews, and so on.

The Daily Transcript, subtitled "Daily news and views from a postdoctoral fellow in cell biology", offers yet more discussion on recent publications; in August it also had a posting on laboratory fashion, which featured photos of the 'socks and sandals' look. Among other offerings are the Genomics Policy weblog from the University of Glamorgan, UK, and Pharyngula, subtitled "Evolution, development, and random biological ejaculations from a godless liberal".

Based on this survey, most genetics blogs tend to discuss general topics sparked off by recent scientific publications or general press coverage. But another potential application of blogging springs to mind. Benefits of such rapid exchanges of information are clear to anyone who has struggled with experiments that don't work for no apparent reason, or with problematic data analysis. In fact, the 'world wide lab' concept predates blogging itself: BIOSCI/Bionet is a set of newsgroups and parallel e-mail lists used by biological scientists worldwide.

Magdalena Skipper

GENE REGULATION

The insulating role of an RNAi architect

> This study adds the control of chromatin architecture to the growing list of skills of the RNAi machinery.

Small RNA pathways are skilled multi-taskers, regulating gene expression in various ways. A study of insulator activity has now uncovered a new role for the RNAi machinery: in organizing chromatin structure.

The *gypsy* transposable element of *Drosophila melanogaster* is widely used to study insulator function in assays because of its ability to shield genes from enhancers when it is inserted between them. *gypsy* recruits a protein complex that is thought to promote the formation of higher-order chromatin structures that prevent enhancers and promoters from meeting.

Lei and Corces identified a putative RNA helicase, Rm62, as a new component of the *gypsy* insulator complex that only interacts with the other components in the presence of an RNA molecule. Rm62 is essential for dsRNA-mediated silencing in flies, providing a potential link between the RNAi pathway and insulator function.

To check the functional significance of their finding, the authors tested the effects of mutating either Rm62 or other RNAi-pathway components on the insulating abilities of *gypsy*. *Rm62* mutations increased insulator activity, indicating that the encoded helicase somehow inhibits *gypsy* function. By contrast, mutations in *piwi* and *aubergine* — which encode Argonaute proteins that are needed for RNAi-induced chromatin modifications — had the opposite effect. Epistasis analysis that used

SYSTEMS BIOLOGY

Network fundamentals, via hub genes

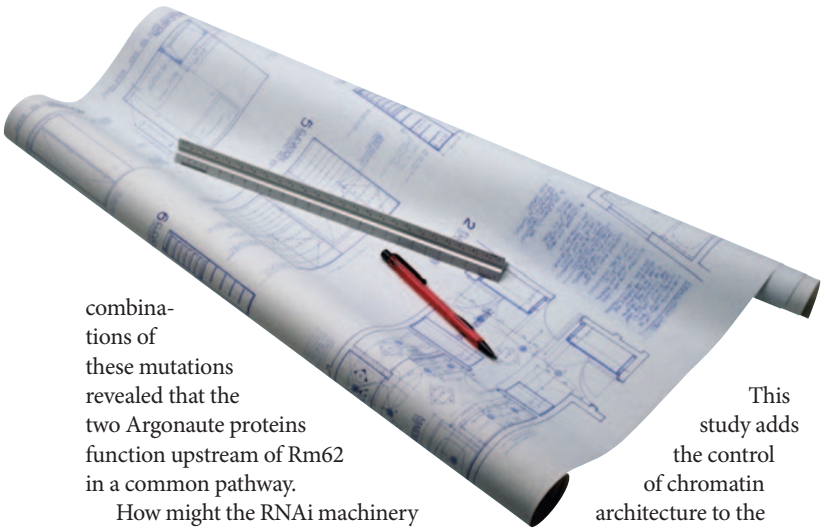
A thorough investigation of the molecular interactions that take place in, arguably, the most interesting of animal cells — our own — is currently beyond our practical means. But while technologies catch up, simpler eukaryotes can tell us a great deal about the nature of genetic networks in animals. The first systematic study of such interactions to be carried out on a large scale in any animal has now been reported for *Caenorhabditis elegans*. The most striking general finding to emerge from this RNAi screen — which tested ~65,000 pairwise interactions — is that a handful of genes interact with an unexpectedly large number of signalling pathways, and so might be common modifiers of different developmental processes.

The new screen, reported by Ben Lehner and colleagues, was designed to detect interactions between a member of an RNAi library and genes that were individually mutated in 'query' strains. In practice, one of a library of RNAi reagents was delivered to both mutant and wild-type worms, and the treated animals were then scored for a synthetic phenotype. The assay, therefore, involved asking: is the phenotype caused by combining a library RNAi reagent and any mutant allele more severe than the product of the phenotype seen in the mutant and in the library-treated wild-type worm alone? If the answer is yes, then an interaction between the two genes is deemed to be likely.

> If genetic hub genes also exist in humans (and they most probably will) then they might function as modifier genes in seemingly unrelated genetic diseases.

The authors were particularly interested in assessing the interaction between components of signalling pathways, as there is much evidence that, when mutated, these molecules cause disease in mammals. The RNAi library consisted of about 1,750 genes that, based on sequence homology, are involved in signal transduction; likewise, each of the 37 query strains carried a mutation in a known signalling molecule. Of the 65,000 pairwise interactions that were tested ~350 interactions, involving 162 genes, were identified.

The resulting interaction map is notable for two reasons. First, it highlights an unexpected level of sharing between pathways: six genes



combinations of these mutations revealed that the two Argonaute proteins function upstream of Rm62 in a common pathway.

How might the RNAi machinery physically affect insulator function? Mutations in *piwi*, *aubergine* and *Rm62* had no effect on the chromosomal localization of *gypsy* complex proteins, ruling out a role in recruitment. However, they did have an impact on the higher-order organization of insulator complexes, which usually form foci known as insulator bodies. Piwi and aubergine were found to be needed for these foci to form, whereas Rm62 seems to negatively regulate their accumulation. This study adds the control of chromatin architecture to the growing list of skills of the RNAi machinery. Precisely how it does this — and how Rm62 carries out its counteracting role — awaits further investigation.

Louisa Flintoft

ORIGINAL RESEARCH PAPER Lei, E. P. & Corces, V. G. RNAi machinery influences the nuclear organization of a chromatin insulator. *Nature Genet.* 23 July 2006 (doi: 10.1038/ng1850)
FURTHER READING Matzke, M. A. & Birchler, J. A. RNAi-mediated pathways in the nucleus. *Nature Rev. Genet.* **6**, 24–35 (2005)

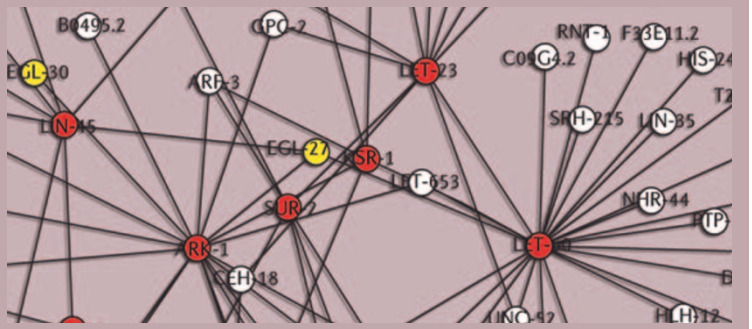
interacted with all the pathways tested, and so might modify more than one signalling network. Second, all of these six so-called 'hub' genes are chromatin-modifying proteins. These genes are conserved across animals and there is evidence to suggest that they can enhance the strength or penetrance of loss-of-function phenotypes of genes with diverse biological functions in other animals in addition to *C. elegans*.

If genetic hub genes also exist in humans (and they most probably will) then they might function as modifier genes in seemingly unrelated genetic diseases. Hub genes, therefore, make excellent candidate genes for disease association studies.

The genetic interaction map also has a direct application in identifying genes that were unknown to interact with a pathway. The functional characterization of these interactors should open up opportunities for developing testable hypotheses about the biological basis of cellular signalling and disease.

Tanita Casci

ORIGINAL RESEARCH PAPER Lehner, B. *et al.* Systematic mapping of genetic interactions in *Caenorhabditis elegans* identifies common modifiers of diverse signalling pathways. *Nature Genet.* **38**, 896–903 (2006)
FURTHER READING Echeverri, C. J. and Perrimon, N. High-throughput RNAi screening in cultured cells: a user's guide. *Nature Rev. Genet.* **7**, 373–384 (2006) | Barabási, A. L. and Oltvai, Z. N. Network biology: understanding the cell's functional organization. *Nature Rev. Genet.* **5**, 101–113 (2004)
WEB SITE
Andrew Fraser's laboratory: http://www.sanger.ac.uk/Teams/Team37/



Reproduced from *Nature Genet.* **38**, 896–903 © (2006) Macmillan Publishers.

IN BRIEF

EVOLUTIONARY GENETICS

High-resolution mutation mapping reveals parallel experimental evolution in yeast.

Segre, A. V., Murray, A. W. & Leu, J. Y. *EMBO J.* **25**, 28–36 (2006)

This paper describes a strategy for the efficient mapping of adaptive mutations in yeast experimental evolution studies. A strain in which a trait has evolved is crossed to a second strain, and DNA from the progeny of this cross is hybridized to a microarray to identify polymorphisms between the two strains. Linkage analysis is used to map the differences between the two that underlie the adaptive trait. The authors successfully used this strategy to map mutations that enabled yeast to adapt to fluctuating sugar sources, identifying an example of parallel adaptation.

GENE REGULATION

An RNA-dependent RNA polymerase is required for paramutation in maize.

Alleman, M. *et al. Nature* **442**, 295–298 (2006)

This study shows that an RNA molecule underlies paramutation in maize. In paramutation, an allele interacts with its homologue and somehow causes a heritable epigenetic change in it. The authors cloned the gene that is involved in paramutation at the *b1* locus in maize: this gene, *mop1* (*mediator of paramutation 1*) encodes an RNA-dependent RNA polymerase, and it is proposed here that MOP1 transcribes RNA from a repeat region close to *b1* that is required for paramutation at this locus.

GENE EXPRESSION

Tissue-specific expression and regulation of sexually dimorphic genes in mice.

Yang, X. *et al. Genome Res.* **16**, 995–1004 (2006)

Microarray analysis of over 23,000 transcripts identified thousands of genes in liver, muscle and adipose tissue, and hundreds in the brain, that were differentially expressed between the sexes in a highly tissue-specific fashion. Most of these genes, which mapped to several autosomes and the sex chromosomes, associate with tissue-specific transcription factor binding sites. Linkage analysis provided evidence of tissue-specific genetic control mediated by several expression QTL hot spots. Such differences could provide clues to gender disparities in disease susceptibility and drug metabolism.

GENOME EVOLUTION

Hemizygous subtelomeres of an African trypanosome chromosome may account for over 75% of chromosome length.

Callejas, S. *et al. Genome Res.* 10 August 2006 (doi:10.1101/gr.4565806)

The considerable size variation among the megabase chromosomes of *Trypanosoma brucei* is poorly understood. A high-resolution DNA microarray analysis of chromosome 1 homologues identified regions that showed copy number polymorphisms, in particular the subtelomeres. More than half of an enlarged chromosome 1 consisted of arrays of genes encoding variant surface glycoproteins (VSGs), which form the molecular cloak that shields trypanosomes from the immune system. Subtelomeric amplification could, therefore, significantly enlarge the VSG repertoire and provide trypanosomes with additional capacity for immune evasion.