

## WEB WATCH

**Integr8 genome and proteome browser**

• <http://www.ebi.ac.uk/integr8>

With the explosion in genomic and proteomic data stored in a variety of databases, there is an increasing need for this information to be brought together in a way that is easy to access and intuitive to use. In response to this need, the European Bioinformatics Institute has recently launched the Integr8 web site, providing a one-stop shop for researchers exploring gene and protein function.

Integr8 currently houses data on more than 180 species of archaeans, bacteria and eukaryotes, providing information on taxonomy, genome structure and proteomics. For each species, proteins are classified according to sequence similarity, structure and function, giving the user an overview of proteome content. There is also the option of comparing this information across several species. Alternatively, if you have a particular gene or protein in mind, a simple search pulls out a wealth of information, including links to entries in gene and protein databases, structural data, key references from the published literature and a summary of expression patterns and function.

The site also provides several other useful resources. For example, the BioMart tool allows complex searches of several databases using a range of criteria, such as species name, chromosomal region, and protein structure and function. There is also access to FASTA similarity and homology searching, enabling comparisons with sequences from proteome and genome databases.

So, Integr8 truly lives up to its name, and should allow researchers from diverse fields to make the most of the increasing availability of genomic and proteomic information.

Louisa Flintoft

## GENOME EVOLUTION

# Give and take

With some parasites it's just "take... take... take" and this can include the host's genes! However, other unwelcome guests actually make generous DNA donations to their hosts.

Independent studies of *Trypanosoma cruzi* — the protozoan that causes Chagas disease — and the Rafflesiaceae — a family of plants that rely entirely on their hosts for nutrition — show that there have been horizontal gene transfers between these parasites and their respective vertebrate and plant hosts.

Following up on the hypothesis that frequent integration of *T. cruzi* DNA into the host genome might underlie Chagas disease, Nadjar Nitz and colleagues extracted genomic DNA from 13 patients with Chagas disease. A probe derived from components of the *T. cruzi* mitochondrial DNA (kinetoplast minicircles; kDNA) was then Southern hybridized to these extracts. This hybridization showed

that there were smaller fragments of kDNA than would be expected if it were present in its native form, which indicated that kDNA had integrated into the host genome.

Using 5'-RACE (rapid amplification of cDNA ends), the authors isolated the genomic integration sites in each patient that they studied, identifying integration sites in a total of 5 loci. But could such integration events be observed in an experimental system?

To address this question, the authors examined rabbits that had been experimentally infected with *T. cruzi* for up to 3 years. These rabbits had *de novo* kDNA integrations, which indicated that horizontal transfer of parasite DNA to the host could be a normal part of the infection process. The rabbit and human data also indicated that  $\beta$ -globin loci and long interspersed nuclear elements (LINE-1) are frequent targets for kDNA integrations.

## RNA WORLD

# RNA stories on a mythical scale

RNA interference (RNAi) hardly disappears off the science headlines. Most recently, the spotlight has been on Argonaute proteins — some of which are involved in the small interfering RNA (siRNA) and microRNA (miRNA) pathways. Okamura and colleagues reveal an interesting division of labour between the Argonautes in *Drosophila melanogaster*: Argonaute1 (AGO1) is required for miRNA maturation and miRNA-directed RNA cleavage, whereas Argonaute2 (AGO2) acts in the siRNA pathway.

siRNA... miRNA... the difference is more than semantic. siRNAs are the key agents for RNAi and mediate RNA destruction in a sequence-specific manner. Although miRNAs

can direct RNA cleavage, they can also block translation of their targets. Both species of small RNAs carry out their functions as part of the RNA-silencing complex (RISC), a multi-protein complex that mediates RNA cleavage. Given that both types of small RNAs associate with the same RISC, do the two pathways converge at this level, or do they differ?

Prompted by previous studies in the worm, Okamura and colleagues decided to resolve the issue by looking at *Ago1* and *Ago2* mutants in *Drosophila*. They mobilized *P*-elements to delete *Ago2* and found that it is required for RNAi *in vivo* and for RISC assembly; in particular, AGO2 is required for the



Interestingly, the authors went on to show that kDNA was also integrated in the genomes of the offspring of chronically infected rabbits and in chickens hatched from *T. cruzi*-inoculated eggs. Importantly, they also found kDNA integrations in the germline of F<sub>2</sub> chickens without persistent infections, conclusively showing vertical transfer to infection-free progeny and so quashing any chance that their results could be artefactual.

unwinding of the siRNA, which is a prerequisite for siRNA-mediated cleavage. Although the RISC is associated with both siRNAs and miRNAs, *Ago2* is required exclusively for the siRNA pathway.

AGO1, on the other hand, seems to be involved only in the miRNA pathway. *Ago1* mutant flies die as larvae with many developmental defects, and miRNA cleavage does not occur in lysates from *Ago1* mutant embryos. *In vivo* analysis indicates that AGO1 directly interacts with Dicer-1, which is required for miRNA production from larger precursors, and that the role of *Ago1* is to stabilize mature miRNAs.

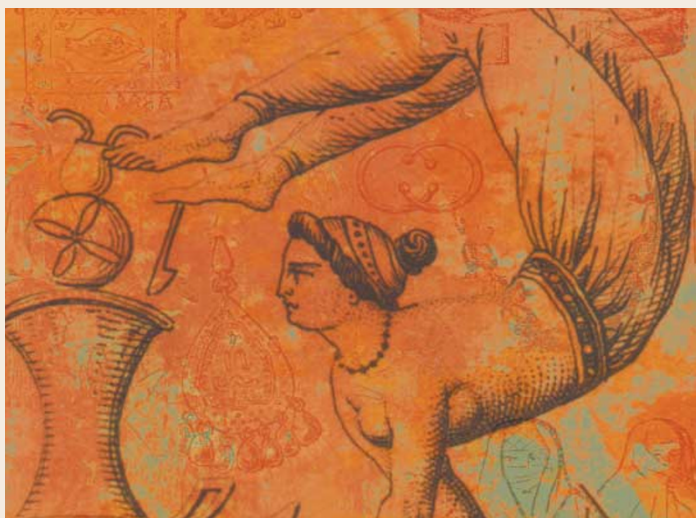
In mammals, siRNA and miRNA pathways seem to converge downstream of Dicer. This is not the case in other organisms, such as worms and flies. Okamura and colleagues have elegantly shown that it is *Ago1* and 2 (as part of RISC) at



Charles Davis and Kenneth Wurdack took an entirely different, but no less convincing, approach to their analysis of horizontal gene transfer between plants. Their phylogenetic analyses showed that, although Rafflesiaceae are close relatives of members of the order Malpighiales, the rafflesian mitochondrial *nad1B-C* gene is more closely related to the homologue in its obligate host, *Tetrastigma* (Vitaceae). Clearly, this is strong evidence

the heart of the difference between siRNA- and a miRNA-mediated RNA cleavage. Undoubtedly, the small RNA world has many more equally elegant stories to tell us.

Magdalena Skipper



that a section of the host mitochondrial genome was transferred to the parasite.

The huge significance of horizontal gene transfer for the evolution of prokaryotes has been known for a long time, as has the large contribution that intracellular endosymbiont ancestors of mitochondria and chloroplasts have made to eukaryotic genomes (see further reading). Studies such as these show that ongoing horizontal gene transfer from a range of parasites and endosymbionts might be more important for eukaryotic evolution than we previously realized — just how important remains to be seen.

Nick Campbell

### References and links

**ORIGINAL RESEARCH PAPERS** Nitz, N. *et al.* Heritable integration of kDNA minicircle sequences from *Trypanosoma cruzi* into the avian genome: insights into human Chagas disease. *Cell* **118**, 175–186 (2004) | Davis, C. C. & Wurdack, K. J. Host-to-parasite gene transfer in flowering plants: phylogenetic evidence from Malpighiales. *Science* 15 July 2004 (doi:10.1126/science.1100671)

**FURTHER READING** Brown, J. R. Ancient horizontal gene transfer. *Nature Rev. Genet.* **4**, 121–132 (2003) | Timmis, J. N. *et al.* Endosymbiotic gene transfer: organelle genomes forge eukaryotic chromosomes. *Nature Rev. Genet.* **5**, 123–135 (2004)

#### WEB SITE

Multidisciplinar de Pesquisa em Doença de Chagas: <http://www.unb.br/ib/cel/pg/pt-br/laboratorios/chagas.php>

### References and links

**ORIGINAL RESEARCH PAPER** Okamura, K. *et al.* Distinct roles for Argonaute proteins in small RNA-directed RNA cleavage pathways. *Genes Dev.* **18**, 1655–1666 (2004)

**FURTHER READING** Liu, J. & Carmell, M. A. *et al.* Argonaute2 is the catalytic engine of mammalian RNAi. *Science* 29 July 2004 (doi:10.1126/science.1102514)

## IN BRIEF

### PLANT GENETICS

#### Plant Reproduction

*Plant Cell* **16** Supplement (2004)

This supplement to the June issue of *Plant Cell* is entirely devoted to plant reproduction, and comprises 19 review articles on flowering, fertilization and on the development of the gametophyte, seed and fruit. The previous supplement was published in 1993, so this is a valuable update on our mechanistic understanding of plant reproduction and its application to agriculture. It will be a great resource for those who teach developmental biology or genetics, for researchers in the plant field and those generally interested in sexual reproduction.

### GENE EXPRESSION

#### Role of transposable elements in heterochromatin and epigenetic control.

Lippman, Z. & Gendrel A.-V. *et al. Nature* **430**, 471–476 (2004)

Making use of microarrays, these authors show that, as predicted from research on other organisms, *Arabidopsis* heterochromatin is composed of transposable elements (TEs) and other related tandem repeats. Their expression is regulated by a chromatin-remodelling protein DDM1 that might be guided by small interfering (si) RNAs that are complementary to the heterochromatic sequences. In addition, TEs can epigenetically regulate individual genes if they lie close to the locus in question, indicating that euchromatic loci such as *FWA* might be imprinted by a siRNA-guided DDM1-dependent mechanism.

### PHARMACOGENETICS

#### Breed distribution and history of canine *mdr1-1Δ*, a pharmacogenetic mutation that marks the emergence of breeds from the collie lineage.

Neff, M. W. *et al. Proc. Natl Acad. Sci. USA* **101**, 11725–11730 (2004)

When treated with the anti-parasitic drug ivermectin some dogs, including collies, can die from neurotoxicosis. To investigate the origin of the 4-bp-deletion in the drug transporter gene *mdr1* that underlies this adverse response, Mark Neff and colleagues surveyed dog populations. The causal allele was isolated in seven new dog breeds and found to have originated prior to dog breeds being isolated.

### GENETIC DISEASE

#### *Pms2* is a genetic enhancer of trinucleotide CAG·CTG repeat somatic mosaicism: implications for the mechanism of triplet repeat expansion.

Gomes-Pereira, M. *et al. Hum. Mol. Genet.* **13**, 1815–1825 (2004)

The expansion of trinucleotide repeats causes several progressive genetic disorders, but the genetic mechanism underlying repeat instability is unclear. These authors have addressed the issue by studying a transgenic CAG·CTG repeat in somatic tissue in the mouse. The rate of expansion is reduced by 50% in animals that are mutant for the DNA mismatch repair gene *Pms2*, implicating inappropriate mismatch repair in repeat instability.