RNA WORLD

MicroRNAs: defenders of the mammalian cell

RNA silencing has been billed as a second form of immune system, allowing the cell to destroy viruses by recognizing their nucleic acids. But although this role is well-established in plants and insects, evidence in vertebrates has been harder to come by. Olivier Voinnet and colleagues now show that mammals do use small RNAs for antiviral defence, but with some intriguing differences.

The authors showed that P19, a potent suppressor of RNA silencing from a plant virus, increases the accumulation of primate foamy virus type 1 (PFV-1) in human cells. This indicated that RNA silencing normally has a role in defence against PFV-1 and prompted the authors to investigate whether small interfering RNAs (siRNAs), which trigger the antiviral response in plants and insects, are also required in human cells. To do this, they tagged sequences from throughout the viral genome with *GFP* and co-transfected them with PFV-1 into human cells. Any siRNAs derived from the viral genome would be expected to target the corresponding construct for degradation, leading to a decrease in *GFP* mRNA levels. However, for all the constructs, these levels were the same in the presence or absence of PFV-1, indicating that there was no production of viral siRNAs.

Interestingly, however, one of the constructs, F11, showed a decrease in *GFP* protein expression — in both the presence and absence of the virus — that was disproportionate to the corresponding mRNA levels. MicroRNAs, which are best known for their role in regulating cellular gene expression, function by inhibiting translation, leading the authors to ask whether an miRNA might be responsible for this effect.

Voinnet and colleagues found that miR-32, a human miRNA, matched the F11 viral sequence, and that expression of the predicted miR-32 target sequence inhibited F11 translation. Direct confirmation of the antiviral role of this miRNA came from the use of miR-32 antisense oligonucleotides, which specifically blocked inhibition of translation by the miRNA. Finally, to discount the possibility that miR-32 exerts its antiviral effects indirectly — for instance, by downregulating the expression of a cellular protein required for viral infection — the authors modified the miR-32 target sequence in PFV-1. This was designed to have no effect on the proteins expressed by the virus, but to prevent miR-32 binding. The result was a threefold increase in viral mRNA levels, demonstrating that, besides its cellular function, miR-32 exerts direct antiviral effects against PFV-1.

The use of cellular miRNAs rather than virally derived siRNAs is an important difference between the antiviral defence strategies used in mammals and those used by plants and insects. However, it is possible that mammalian cells do produce siRNAs, but that these have not yet been identified. miRNAs are likely to recognize viral sequences initially by chance, owing to a match between their sequences, but it might well be that certain miRNAs have co-evolved with endogenous viruses so that their original cellular functions are lost — a possibility that future studies will need to explore.

Louisa Flintoft

References and links

ORIGINAL RESEARCH PAPER Lecellier, C.-H. *et al.* A cellular microRNA mediates antiviral defence in human cells. *Science* **308**, 557–560 (2005)

FURTHER READING Voinnet, O. Induction and suppression of RNA silencing: insights from viral infections. *Nature Rev. Genet.* **6**, 206–220 (2005)

IN BRIEF

CIRCADIAN GENETICS

Association of the length polymorphism in the human *Per3* gene with the delayed sleep-phase syndrome: does latitude have an influence on it?

Pereira, D. S. *et al.* *Sleep* **28**, 29–32 (2005)

Obesity and metabolic syndrome in circadian *Clock* mutant mice.

Turek, F. W. *et al.* *Science* 21 April 2005 (doi:10.1126/science.1108750)

These papers highlight intriguing aspects of the role of circadian genetics in disease. Pereira *et al.* investigated the role of *PER3*, a circadian gene, in human delayed sleep-phase syndrome (DSPS). The association of a specific *PER3* polymorphism with the syndrome was found to vary with latitude, indicating that the same circadian genotype responds differently to the distinct environmental cues provided at different geographical locations. Turek and colleagues showed that mice that are mutant for *Clock*, another circadian gene, develop obesity and a metabolic-syndrome phenotype. Levels of neurotransmitters involved in regulating energy balance were altered in these mice, indicating a direct link between the circadian system and metabolism.

EVOLUTIONARY GENETICS

Genetic variance in female condition predicts indirect genetic variance in male sexual display traits.

Petfield, D. *et al.* *Proc. Natl Acad. Sci. USA* **102**, 6045–6050 (2005)

Indirect genetic effects (IGEs) occur when the genotype of one individual affects the phenotype of another. Although IGEs between related individuals are well studied, less is known about their importance in interactions between unrelated individuals. Using *Drosophila serrata* as a model, these authors demonstrated that the production of male pheromones, a sexual display trait, varies in response to genetic variance in the condition of unrelated females. IGEs might therefore have an important impact on sexual selection.

GENE EXPRESSION

Interchromosomal associations between alternatively expressed loci.

Spilianakis, C. G. *et al.* *Nature* 8 May 2005 (doi:10.1038/nature03574)

Recent work described how the T-helper-cell 2 (T_H2) locus control region (LCR) co-ordinately regulates T_H2 cytokine genes, which are spread over 120 kb, through interchromosomal interactions between the LCR and the cytokine loci in question. Spilianakis *et al.* used a chromosome-conformation capture technique to show that interactions between loci on different chromosomes (in this case, mouse chromosomes 10 and 11) also occur. This phenomenon might function in coordinating gene expression, and might also apply to other genes, such as those that encode olfactory receptors and globin proteins.