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URLs

IN BRIEF

RNA INTERFERENCE

Fatality in mice due to oversaturation of cellular microRNA/short hairpin RNA pathways.

Grimm, D. *et al. Nature* 25 May 2006 (doi:10.1038/nature04791)

RNAi has shown great promise as a tool for functional genomics and in therapy. These authors have looked into the long-term effects of expressing high levels of short hairpin RNAs (shRNAs) in livers of mice, delivered using adeno-associated viral vectors. In 36 of 49 cases, this expression caused liver damage, resulting in death in 23 animals. The authors show that this morbidity is due to the downregulation of liver-derived microRNA, probably because shRNA overexpression depletes the cellular pool of factors required for processing small RNAs.

DISEASE GENETICS

Impaired control of IRES-mediated translation in X-linked dyskeratosis congenital.

Yoon, A., Peng, G. & Brandenbyrg, Y. *et al. Science* **312**, 902–906 (2006)

X-linked dyskeratosis congenital (X-DC) is a human disease associated with mutations in *DCK1*, a gene that encodes a pseudouridine synthase. Using a mouse model of the disease and an unbiased proteomics approach, the authors show that translation of mRNAs that contain internal ribosomal entry sites is impaired in these mice and in cells of patients. These findings point to defective ribosome activity as a potential disease mechanism and explain some of the X-DC phenotypes.

TECHNOLOGY

Computational redesign of endonuclease DNA binding and cleavage specificity.

Ashworth, J. *et al. Nature* **441**, 656–659 (2006)

These authors have used a computational approach to reprogram the DNA-cleavage specificity of the endonuclease I-*Mso*I. To understand how this endonuclease functions, a model was generated that incorporated various physical properties of the protein–DNA interface. Based on this information, a virtual host of mutated proteins was created, then screened for enzymes that alter the binding affinity or specificity of I-*Mso*I. One such enzyme had 10,000-fold higher affinity for an altered template, while maintaining high target specificity; structural studies confirmed that the modified properties were indeed determined by the predicted amino-acid substitution. Practical applications of such work include gene therapy.

EVO–DEVO

Regulatory blueprint for a chordate embryo.

Imai, K. S. *et al. Science* **312**, 1183–1187 (2006)

This study presents the first whole-embryo gene-regulatory network for a chordate. Gene-circuit diagrams were constructed for all 76 zygotically expressed transcription factors and signalling molecules expressed in the ascidian *Ciona intestinalis* at the stage when the fates of the embryonic blastomeres are established. Interesting differences between networks in vertebrate and echinoderm embryos were revealed; for example, *C. intestinalis* contains fewer highly connected subnetworks and makes more use of negative autoregulatory loops. This study provides a basis for investigating the evolution of the chordate body plan as similar networks from other species are established.