Support for the functional importance of this retrotransposon-mediated transcription comes from phylogenetic conservation — the positioning of some of the retrotransposons associated with chimeric transcripts is conserved between two distantly related strains of mice and, in some cases, between rat and mouse. Unfortunately, what their function is remains an open question. The authors propose that sequential activation and silencing of retrotransposons might underlie stage-specific, potentially RNAi-mediated, chromatin remodelling at specific genomic locations at early stages of development and during oogenesis — an attractive model that urgently needs further testing.

*Magdalena Skipper*

**References and links**

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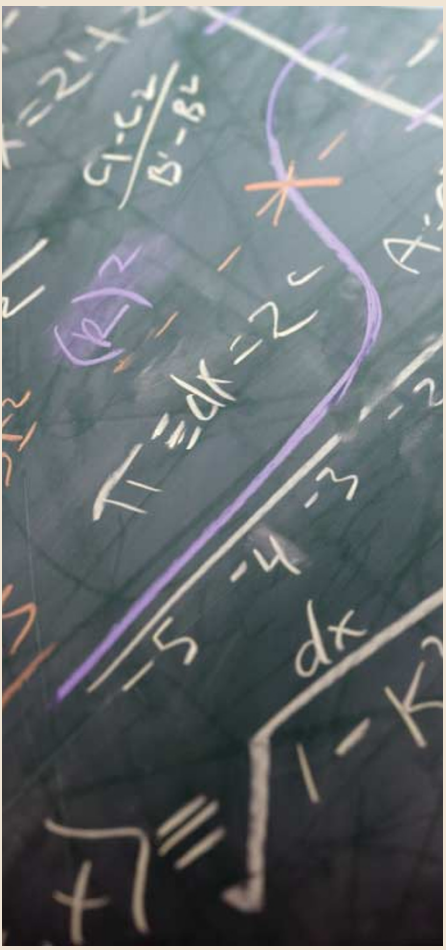

RNA INTERFERENCE

# Silencing the sceptics

We've all heard of the promise of RNA interference (RNAi) as a potential approach to treating disease, but how close are we to delivering on this promise? Writing in *Nature*, Vornlocher and colleagues now take us a step closer to the goal of selectively modifying gene activity for a clinical benefit.

Vornlocher and colleagues have demonstrated the *in vivo* silencing of an endogenous gene that encodes a protein of therapeutic relevance, apolipoprotein B (APOB), which is essential for the formation of low-density lipoprotein (LDL) and therefore implicated in a range of cardiovascular disorders. Although RNAi has been demonstrated *in vivo* before, previous models have either not targeted an endogenous gene or have been administered in a way that is not applicable to the human therapeutic setting. In this study, small interfering RNA (siRNA) molecules, which induce RNAi of genes with complementary sequences, were administered to mice by tail-vein injection, a route that can be readily translated to human patients.

Just as gene therapy and antisense approaches have been held back by problems of delivery, so too has RNAi. In the past, viral vectors have been used, among other delivery vehicles, to get siRNA to the target tissue. This study used chemical modifications to render the siRNA molecules more drug-like and stable within the body, and more likely to be taken up by cells. The conjugation of cholesterol to the 3′ end of siRNA molecules significantly improved their *in vivo* pharmacological properties, such as cellular delivery and half-life. Such improvements lend credence to the idea that further chemical modifications could improve the prospects of siRNA-based therapeutics.

To explore the *in vivo* effect of these *ApoB*-targeting, cholesterol-modified siRNAs, they were injected into mice that were fed a normal diet. Levels of the target mRNA were then measured in the liver and jejunum, key sites of APOB expression. The modified siRNA caused a significant reduction of *ApoB* mRNA in both tissues, which was reflected as a diminution of APOB protein levels. Desirable effects were seen at the physiological level too: siRNA treatment resulted in a 25% reduction in high-density lipoprotein levels, and a 40% reduction in LDL levels.

A key concern with studies of RNAi is that the observed results might be caused by nonspecific 'off-target' effects or the interferon response. Vornlocher and colleagues were able to eliminate this possibility, because two *ApoB*-specific siRNAs that target different regions of the *ApoB* mRNA resulted in similar effects. Furthermore, control siRNA, although present in the liver and jejunum at levels comparable to those of therapeutic siRNA, had no effect. The authors were also able to establish, through an analysis of APOB degradation products, that an RNAi mechanism of action was responsible for the experimental findings.

With the first demonstration of the *in vivo* silencing by siRNA of an endogenous gene through an RNAi mechanism — and using an administration route that could readily be applied to humans — in the bag, RNAi looks set to gain even further prominence as a research tool and potential therapeutic.

*Daniel Jones*

**References and links**

**ORIGINAL RESEARCH PAPER** Soutschek, J. *et al.* Therapeutic silencing of an endogenous gene by systemic administration of modified siRNAs. *Nature* 11 November 2004 (doi:10.1038/nature)

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