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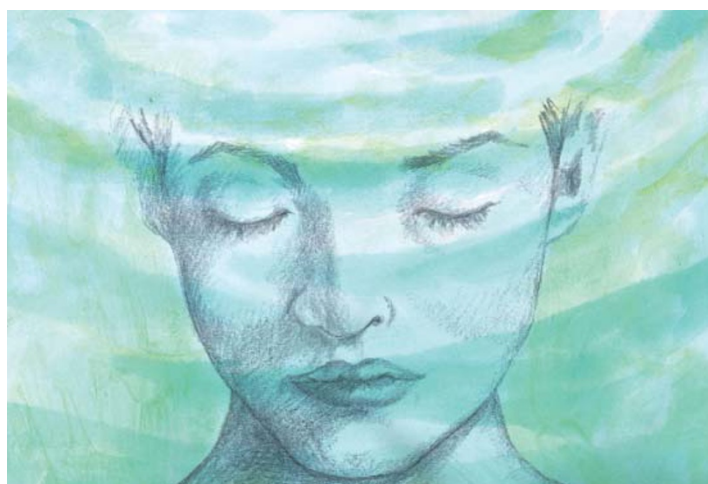
RNA INTERFERENCE

Have our dreams been shattered?

RNA interference (RNAi) has revolutionized biology — it has changed the way in which we view gene regulation and is a heaven-sent tool for studies of gene function and, potentially, for gene therapy. But, has the time come for us to re-evaluate the ‘power’ of RNAi? Two recent reports, one by Bridge *et al.* and the other by Sledz *et al.*, show that RNAi might not be as specific as we had thought and that small interfering (si) RNAs, either chemically synthesized or transcribed from vectors, induce an interferon response.

When RNAi was first reported in worms and flies, the enthusiasm of those working with mammals was marred by the fact that long 500-bp RNAs, which worked so well in invertebrates, induced a nonspecific interferon response that resulted in a transcriptional shut down of the cell. This problem was overcome by the direct use of short RNAs, into which the 500-bp fragments are cut anyway to mediate RNAi.

Bridge *et al.* used microarray analysis of cells that had been infected with viruses that express short hairpin RNAs (shRNAs), which are intracellularly processed into siRNAs. Although several siRNAs specifically silenced their target genes, the transduced cells also activated the interferon target genes. Despite their findings, the authors do not rule out future use of RNAi, but suggest that the lowest effective concentration should be used to minimize the non-specific interferon response.



Sledz *et al.* show that the non-specific effects extend to chemically synthesized siRNAs. Also using microarrays, they conclude that siRNAs activate the JAK-STAT signalling pathway, which is implicated in interferon-mediated stress responses.

Sledz *et al.* also reveal some of the mechanism by which siRNAs activate the interferon pathway. They show that PKP — a dsRNA recognition protein that is part of the signal transduction pathway that regulates cell growth and stress responses — is activated by siRNAs in a concentration-dependent manner, and is required for the interferon response. By using cell lines that lack the interferon response, the authors show that this pathway is not normally required for specific gene silencing by siRNA. As Bridge *et al.* point out, interferon induction

by siRNA might have eluded us so far because tissue-‘culture experiments use cell lines that are derived from tumours in which the interferon pathway is defective.

Neither group suggests that their findings mean the end of RNAi as a basic research tool, but we will need to be more cautious when interpreting RNAi results. There is a different take home message for those who want to develop RNAi as a therapeutic tool — it will be interesting to see their response.

Magdalena Skipper

References and links

ORIGINAL RESEARCH PAPERS Bridge, A. J. *et al.* Induction of an interferon response by RNAi vectors in mammalian cells. *Nature Genet.* **34**, 263–264 (2003) | Sledz, C. A. Activation of the interferon system by short-interfering RNAs. *Nature Cell Biol.* (10.1038/ncb1038)

FURTHER READING McManus, M. T. & Sharp, P. A. Gene silencing in mammals by small interfering RNAs. *Nature Rev. Genet.* **3**, 737–747 (2002)