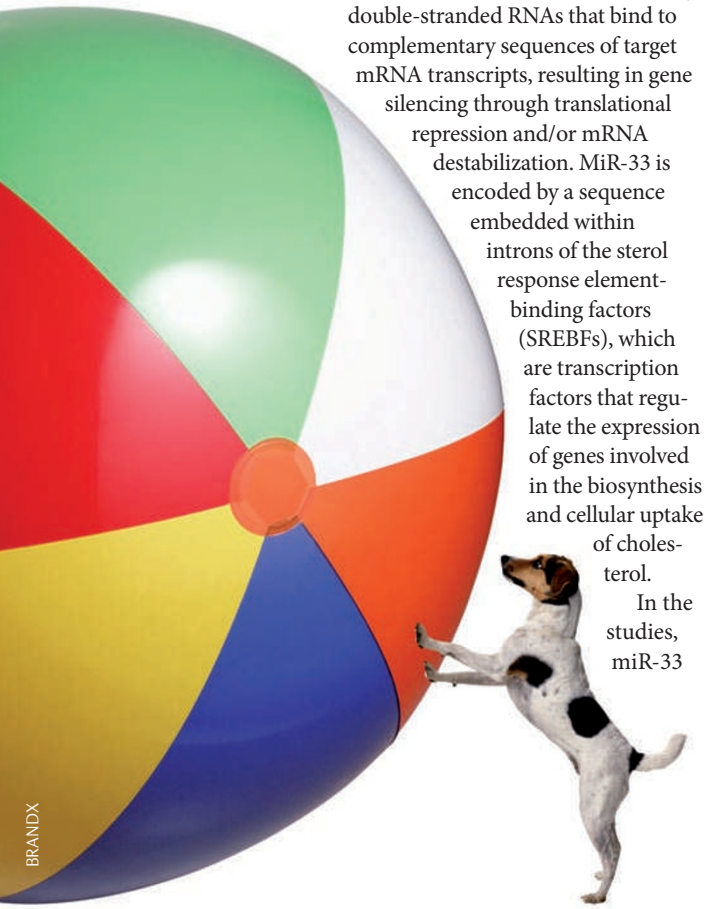
CARDIOVASCULAR DISORDERS

MicroRNA modulation of cholesterol

Two independent papers published in *Science* have shown that microRNA-33 (miR-33) helps to regulate the homeostasis of high density lipoprotein (HDL; 'good') cholesterol, suggesting that it might be a possible target for cardiovascular and metabolic disorders.

MicroRNAs are small non-coding double-stranded RNAs that bind to complementary sequences of target mRNA transcripts, resulting in gene silencing through translational repression and/or mRNA destabilization. MiR-33 is encoded by a sequence embedded within introns of the sterol response element-binding factors (SREBFs), which are transcription factors that regulate the expression of genes involved in the biosynthesis and cellular uptake of cholesterol.



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In the studies, miR-33 was identified by two different routes. Rayner and colleagues used a genome-wide screen of microRNAs that were differentially modulated by cellular cholesterol depletion and enrichment, whereas Najafi-Shoushtari and colleagues undertook studies of gene regulation by SREBFs.

Both groups reported similar or complementary findings. Expression of miR-33 was found in various cells and tissues, including macrophages, hepatic cells, endothelial cells, brain, liver, colon, small intestine and skeletal muscle. The predominant target identified for miR-33 was the gene encoding the ATP binding cassette transporter *ABCA1*, which is involved in cellular cholesterol mobilization. Moreover, overexpression of miR-33 reduced ABCA1 protein levels. In mice, hepatic miR-33 levels correlated inversely with cholesterol levels and *Abca1* expression, and positively correlated with *Srebf2* mRNA levels, suggesting that miR-33 and *SREBF2* expression are co-transcribed and that miR-33 is regulated by dietary cholesterol.

The studies next investigated whether miR-33 could modulate cholesterol efflux from macrophages — which is an important anti-atherosclerotic mechanism in plaques. Under conditions of cholesterol depletion, expression of miR-33 and the *SREBF2* host gene were increased, together with a concomitant decrease in the levels of ABCA1 protein and cholesterol efflux. Conversely, antagonism of endogenous miR-33 (using miR-33 antisense oligonucleotides) increased ABCA1 protein levels and cholesterol efflux, showing that manipulation of cellular miR-33 levels alters cholesterol efflux from macrophages.

Last, the authors investigated the effects of reducing miR-33 levels in mice. Rayner *et al.* used lentiviral delivery of anti-miR-33, and showed that this increased plasma HDL levels. Similar results were seen by Najafi-Shoushtari *et al.*, who used locked nucleic acid miR-33-specific antisense RNA and also demonstrated that antisense RNA-treated animals had no changes in the levels of low-density lipoprotein cholesterol, triglyceride or glucose.

Together, these studies show a new role for miR-33 in the epigenetic regulation of cholesterol homeostasis. Although further work is needed — including optimization of the knockdown strategy and proof of concept in animal models of disease — miR-33 might represent a novel target in cardiovascular disorders.

Charlotte Harrison

ORIGINAL RESEARCH PAPERS Rayner, K. J. *et al.* miR-33 contributes to the regulation of cholesterol homeostasis. *Science* 13 May 2010 doi:10.1126/science.1189122 | Najafi-Shoushtari, S. H. *et al.* MicroRNA-33 and the SREBP host genes cooperate to control cholesterol homeostasis. *Science* 13 May 2010 doi:10.1126/science.1189123