Nature Reviews Drug Discovery | AOP, published online 18 November 2011; doi:10.1038/nrd3605

CARDIOVASCULAR DISORDERS

microRNA modulation elevates HDL

BRANDX

The development of novel cardiovascular disease therapies that harness the atheroprotective functions of high-density lipoprotein (HDL) is an area of intense investigation. However, achieving safe and effective HDL-targeted agents has so far proved challenging. Now, writing in *Nature*, Rayner and colleagues show that inhibiting microRNA-33a (miR-33a) and miR-33b in non-human primates increases circulating HDL levels and promotes anti-atherosclerotic mechanisms, supporting the development of antagonists of these microRNAs as a novel therapeutic approach.

miR-33a and miR-33b are intronic microRNAs with their encoding regions embedded within the genes encoding the sterol regulatory element-binding proteins SREBP1 and SREBP2, which regulate cholesterol and fatty acid metabolism together with their host genes. Although they differ by two nucleotides, their seed regions are identical, which indicates that they repress the same set of genes. Previous studies have shown that silencing miR-33a in mice increases levels of the hepatic cholesterol transporter ATP-binding cassette transporter A1 (ABCA1) and circulating HDL, promoting the anti-atherosclerotic efflux of cholesterol from macrophages. However, the translational relevance of these findings is limited as mice lack miR-33b, which is likely to contribute substantially to human miR-33 levels. With this in mind, Rayner and colleagues set out to investigate the effects of silencing miR-33a and miR-33b in a model highly related to humans.

> “This study in non-human primates is the first to show that inhibiting miR-33a and miR-33b has a profound and sustained effect on circulating HDL levels.”

To do this, the authors treated African green monkeys with a 2′-fluoro/methoxyethyl-modified, phosphorothioate backbone-modified antisense miR-33 oligonucleotide (anti-miR-33) that equally inhibits miR-33a and miR-33b; this oligonucleotide was subcutaneously injected biweekly for the first 2 weeks and then weekly for the remaining 10 weeks of the study. Microarray profiling of mRNA isolated from liver biopsy samples revealed that the treatment increased expression of ABCA1 and miR-33 target genes involved in fatty acid oxidation but reduced the expression of genes involved in fatty acid synthesis. Plasma HDL cholesterol levels were elevated in monkeys treated with anti-miR-33 for the entire duration of the study, attaining a maximal increase of 50% by 8 weeks; by contrast, levels of very-low-density lipoprotein (VLDL) cholesterol and VLDL triglycerides were significantly reduced — a finding that has not been observed in mice. Importantly, there appeared to be no toxicity associated with the anti-microRNA treatment.

Next, the authors characterized the HDL from the plasma of monkeys treated with anti-miR-33. There was an increase in plasma concentrations of the primary apolipoproteins carried on HDL — APOA1 and APOA2 — which are associated with large and very large HDL particles. Examination of the atheroprotective properties of the HDL generated by anti-miR-33 demonstrated that it induced greater macrophage cholesterol efflux than that of control monkeys, and it protected endothelial cells from cytokine-induced inflammation.

Interestingly, this inhibition of miR-33 in monkeys also increased the hepatic expression of insulin receptor substrate 2, which is a key component of insulin signalling that is dysfunctional in individuals suffering from metabolic syndrome, who also exhibit low HDL and high VLDL levels.

This study in non-human primates is the first to show that inhibiting miR-33a and miR-33b has a profound and sustained effect on circulating HDL levels. These findings support the development of antagonists of miR-33 as potential therapeutics for dyslipidaemia, atherosclerosis and related metabolic diseases.

Sarah Crunkhorn

ORIGINAL RESEARCH PAPER Rayner, K. J. *et al.* Inhibition of miR-33a/b in non-human primates raises plasma HDL and lowers VLDL triglycerides. *Nature* **478**, 404–407 (2011)