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Genetics and molecular biology: miRNAs take the HDL ride

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MicroRNAs (miRNAs) are small non-coding RNAs that interact with 3'UTR regions of target mRNAs resulting in translational repression and/or messenger destabilization [1]. These small RNA molecules hold a huge regulatory potential since each of them controls the level of hundreds of targets. Alterations of expression or activity of miRNAs have a major impact on cellular functions and contribute to the development of human diseases [1]. Recent studies highlighted an unsuspected interconnection between miRNAs and blood lipoproteins that opens new therapeutic perspectives for the treatment of dyslipidemias.

Regulation of fatty acid metabolism is an important component in homeostasis maintenance. This is achieved by master controllers such as SREBPs (sterol regulatory element-binding proteins) that are transcription factors governing the expression of key enzymes in the lipid synthesis pathways and the production of blood lipid carriers (e.g. very low density lipoproteins [VLDLs], high density lipoproteins [HDLs]) [2]. miRNAs are now also emerging as key players in lipid metabolism regulation (reviewed in [3]). A series of recent articles unveiled an important connection between, on one hand, fatty acid and cholesterol metabolism and transport and, on the other hand, miR-33, a miRNA encoded by an intron of the gene coding for SREBP-2 that positively regulates the expression of many genes involved in cholesterol biosynthesis [2]. Mice lacking miR-33 express more of the ABCA1 transporter that loads cholesterol on HDLs and display higher serum HDL levels [4]. miR-33 represses at least two sets of genes relevant for lipid homeostasis: those involved in cholesterol metabolism and cellular efflux to HDLs (ABCA1, ABCG1, and NPC1) and those implicated in fatty acid metabolism (CPT1α, CROT, HADHB, and AMPK1α) [5-7, 8**]. Consequently, miR-33 participates in lowering HDL

levels by diminishing the efflux of cholesterol to nascent HDL particles and decreases fatty acid oxidation, favoring lipid and triglyceride accumulation. miR-33 also perturbs proper insulin signaling by targeting the insulin receptor substrate 2-encoding mRNA [8**].

These properties make miR-33 an ideal target for the development of compounds to treat the metabolic syndrome characterized by decreased HDL levels, increased triglyceride and glucose blood levels. Increasing HDLs levels would also be beneficial in the context of atherosclerosis as HDLs can remove cholesterol from atheromatous plaques [9]. The clinical relevance of antagonizing miR-33 was demonstrated in mice and African green monkeys treated with an anti-miR-33 oligonucleotide. In mice, this resulted in increased circulating levels of HDLs and regression of atherosclerosis [10**]. In African green monkey, HDL levels were also raised with a concomitant decrease in VLDL levels [11*].

SREBP-2 is activated post-transcriptionally when cells are low in cholesterol but the transcription of its own gene is also turned on in these conditions [2]. As indicated above, miR-33 is encoded by an SREBP2 intron. Hence, when SREBP-2 is induced to promote cholesterol synthesis, the concomitant expression of miR-33 ensures, via down-regulation of ABCA1 for example, that cholesterol is not exported out from cells that are in need of this lipid. This is not the only interconnection between HDLs and miRNAs. Indeed, miRNAs use HDLs to travel in the blood and to reach distant tissues [12**]. Transfer of miRNAs from HDLs to the acceptor cells requires the scavenger receptor class B type I (SR-BI) [12**]. Interestingly, the HDL-miRNA profile of healthy subjects differs from that of patients suffering from atherosclerosis [12**]. Determination of which miRNAs are carried by HDLs represents therefore an

attractive diagnostic tool to determine if a person has developed, or is at risk of developing, a given metabolic pathology.

As demonstrated in the studies described above, miR-33 controls HDL production which in turn favors the transport of miRNAs in the circulation. Even though miR-33 itself seems not to be incorporated in newly produced HDL particles [12**], it increases the capacity of other miRNAs to take a ride on HDLs to act on distant tissues. Thus, the partnership between HDLs and miR-33 would extend the response to changes in lipid homeostasis far beyond the cells initially producing the lipoprotein particles. From this point of view, HDL-associated miRNAs would elevate their statute from useful biomarkers to a new class of hormones.

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11. Rayner KJ, Esau CC, Hussain FN *et al*. Inhibition of miR-33a/b in non-human primates raises plasma HDL and lowers VLDL triglycerides. Nature 2011; 478**:**404-407.

12. Vickers KC, Palmisano BT, Shoucri BM *et al*. MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. Nat Cell Biol 2011; 13**:**423-433.

Recommended reading

Two bullets: 8. Davalos A, Goedeke L, Smibert P et al. miR-33a/b contribute to the regulation of fatty acid metabolism and insulin signaling. Proc Natl Acad Sci U S A 2011; 108:9232-9237.

This study provides evidence that miR-33 is co-expressed with his hosting gene SREBP-2 and that it targets ABCA1 and ABCG1 mRNAs. Overexpression of miR-33 reduces HDL levels and cholesterol efflux while silencing of this miRNA has opposing effects. The importance of this work is that it shows a two-tiered control of a given metabolic pathway – lipid synthesis in the present case – from a single locus via the expression of a transcription factor (SREBP-2) and a miRNA (miR-33).

Two bullets: 10. Rayner KJ, Sheedy FJ, Esau CC et al. Antagonism of miR-33 in mice promotes reverse cholesterol transport and regression of atherosclerosis. J Clin Invest 2011; 121:2921-2931.

This study demonstrates that blockade of miR-33 in mice leads to increased circulating HDL levels and to enhanced cholesterol transport to liver and feces. Moreover, mice treated with anti-miR-33 displayed reduced atherosclerotic plaque sizes and decreased inflammation. This work and the data presented in reference 11 support the notion that miRNA inhibition is a potential therapeutic tool to treat metabolic diseases.

One bullet: 11. Rayner KJ, Esau CC, Hussain FN et al. Inhibition of miR-33a/b in non-human primates raises plasma HDL and lowers VLDL triglycerides. Nature 2011; 478:404-407.

In contrast to mice, large mammals express two miR-33 isoforms. This study demonstrates that inhibition of both miR-33 isoforms permits to raise HDL and lower VLDL levels in African monkeys. These beneficial effects further confirm the therapeutic potential of anti-miR-33 for the treatment of dyslipidemias in primates.

Two bullets: 12. Vickers KC, Palmisano BT, Shoucri BM et al. MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. Nat Cell Biol 2011; 13:423-433.

This is the first demonstration that circulating HDLs transport a large number of miRNAs that can be delivered in active form to recipient cells through a receptor-dependent process. These original findings suggest that HDL-mediated delivery of miRNAs represents a novel cell-to-cell communication mechanism. The HDL-miRNA profile differs between healthy and hypercholesterolemia subjects and may potentially be used as a new diagnostic tool.