MiR-1200 Differentially Modulates Plasma LDL and HDL-cholesterol Levels to Reduce Hyperlipidemia and Atherosclerosis in Mice

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High LDL and low HDL are risk factors for heart disease. Drugs that can lower LDL and increase HDL might be ideal for the treatment of cardiovascular diseases. We performed a high throughput screening of human microRNA (miR) mimic library to identify miRs that regulate apoB (LDL scaffolding protein) and apoAI (major HDL protein) secretion in human hepatoma Huh-7 cells. MiR-1200 potently decreased apoB and increased apoAI secretion. We found that seed sequence of miR-1200 interacts with the 3´-untranslated region of apoB mRNA to enhance posttranscriptional degradation and reduce apoB secretion. In contrast, miR-1200 increased apoAI protein and mRNA levels by increasing transcription. Mechanistic studies revealed that miR-1200 reduced the expression of B-Cell Lymphoma 11B (BCL11B), a repressor of apoAI transcription, to increase apoAI expression. *In vivo* studies showed that overexpression of miR-1200 significantly reduced LDL-cholesterol and increased HDL-cholesterol levels without causing hepatic steatosis in Western diet fed C57Bl6J mice. Additionally, miR-1200 reduced atherosclerosis in Western diet fed *Apoe*$^{-/-}$ mice. Physiologic studies showed that miR-1200 reduced VLDL production. Further, HDL from miR-1200 injected mice showed increased cholesterol efflux capacity from lipid loaded macrophages suggesting increases in functionally adept HDL. In short, we have identified a novel miR-1200 that reduces dyslipidemia by reducing apoB-containing lipoproteins and increasing functional HDL and suggest that it can be useful in treating hyperlipidemia and atherosclerosis.

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