Arteriosclerosis, Thrombosis, and Vascular Biology 2016 vol.35 N2, pages 323-331

MicroRNA 302a is a novel modulator of cholesterol homeostasis and atherosclerosis

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Abstract

© 2014 American Heart Association, Inc.OBJECTIVE - : Macrophage foam cell formation is a key feature of atherosclerosis. Recent studies have shown that specific microRNAs (miRs) are regulated in modified low-density lipoprotein-treated macrophages, which can affect the cellular cholesterol homeostasis. Undertaking a genome-wide screen of miRs regulated in primary macrophages by modified low-density lipoprotein, miR-302a emerged as a potential candidate that may play a key role in macrophage cholesterol homeostasis. APPROACH AND RESULTS - : The objective of this study was to assess the involvement of miR-302a in macrophage lipid homeostasis and if it can influence circulating lipid levels and atherosclerotic development when it is inhibited in a murine atherosclerosis model. We found that transfection of primary macrophages with either miR-302a or anti-miR-302a regulated the expression of ATP-binding cassette (ABC) transporter ABCA1 mRNA and protein. Luciferase reporter assays showed that miR-302a repressed the 3′ untranslated regions (UTR) activity of mouse Abca1 by 48% and human ABCA1 by 45%. In addition, transfection of murine macrophages with miR-302a attenuated cholesterol efflux to apolipoprotein A-1 (apoA-1) by 38%. Long-term in vivo administration of anti-miR-302a to mice with low-density lipoprotein receptor deficiency (Ldlr) fed an atherogenic diet led to an increase in ABCA1 in the liver and aorta as well as an increase in circulating plasma high-density lipoprotein levels by 35% compared with that of control mice. The anti-miR-302a-treated mice also displayed reduced atherosclerotic plaque size by ≈25% and a more stable plaque morphology with reduced signs of inflammation. CONCLUSIONS - : These studies identify miR-302a as a novel modulator of cholesterol efflux and a potential therapeutic target for suppressing atherosclerosis.

http://dx.doi.org/10.1161/ATVBAHA.114.304878

Keywords

ABCA1 protein, atherosclerosis, cholesterol-efflux regulatory protein, HDL cholesterol, macrophages, microRNA