Inhibition of miR-155-5p reduces NADPH oxidase expression and oxidative stress in the aorta of hypercholesterolemic ApoE-deficient mice; potential implication in human atherosclerosis

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NADPH oxidase (Nox)-derived reactive oxygen species are important molecular effectors underlying oxidative stress and inflammation in atherosclerosis. miR-155-5p has been implicated in a number of human malignancies as key regulator of inflammatory and immune responses. Yet, the role of miR-155-5p in atherogenesis is poorly defined. The aim of this study was to determine the role of miR-155-5p in mediating Nox up-regulation and the ensuing oxidative stress in the aorta of hypercholesterolemic ApoE-/- mice. Non-atherosclerotic and atherosclerotic human arterial samples, and ApoE-/- mice were employed. After 10 weeks on normal or high-fat, cholesterol-rich diet, male ApoE-/- mice, were randomized to receive via intraperitoneal injection miR-155-5p inhibitor, or its negative control, once per week for 4 weeks. Human and mouse specific miRCURY LNA™ miRNome real-time PCR panels were employed to determine the expression of 752 miRNAs in arterial tissues. miRNA expression profiling revealed that miR-155-5p was significantly up-regulated both in human atherosclerotic tissue samples and in atherosclerotic aorta of ApoE-/- mice. TargetScanTM analysis predicted that miR-155-5p interacts with genes (e.g., SHIP-1, IKBKE, SOCS) that may control Nox expression. Treatment of atherosclerotic ApoE-/- mice with miR-155-5p inhibitor reduced significantly the progression of atherosclerosis, the aortic expression of Nox1, Nox2, and Nox4 protein levels, and the formation of 4-HNE-protein adducts (oxidative stress marker). Moreover, inhibition of miR-155-5p led to a marked reduction in CD45, CD68, and NOS2 protein levels (markers of immune cell infiltration and inflammation). The data of this study point to miR-155-5p as potential therapeutic target to reduce oxidative stress and inflammation in atherosclerosis-related cardiovascular disorders. Work supported by PN-III-P1-1.1-TE-2016-0851, PN-III-P2-2.1-PED-2019-2512, PN-III-P2-2.1-PED-2019-2497.