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Robert L Raffai

University of California, USA

Therapeutic control of inflammation & atherosclerosis with apoE-regulated microRNA expression in macrophages and their exosomes

Monocytes and macrophages participate in the process of atherosclerosis. Although generally believed to be culprits of atherosclerosis, results of recent studies including from our laboratory have shown that subsets of monocytes and macrophages can suppress and even reverse atherosclerosis. An important feature of such protective monocytes and macrophages include the expression of the ApoE gene. Findings from our lab uncovered that ApoE expression causes an increase in levels of cellular microRNA that suppress NF- κ B activation in monocytes and macrophages and thereby atherosclerosis in hyperlipidemic mice. Among the upregulated microRNA include miR146a. Furthermore, we reported that a systemic delivery of miR146a in lipid microparticles can suppress systemic inflammation and atherosclerosis in hyperlipidemic mice. In more recent studies, we explored whether apoE expression by monocytes and macrophages modulates miRNA content in exosomes to suppress atherosclerosis via their communication to cells of the immune system and vascular wall. To this end, exosomes were isolated from cultured bone marrow derived macrophages (BMDM) harvested from wildtype (WT) and ApoE deficient (ApoE^{-/-}) mice. An absence of ApoE expression in BMDM resulted in a 30% increase in the secretion of exosomes with an average size of 85 nm. Such ApoE^{-/-} exosomes were less effective than WT exosomes in reducing IL-6 mRNA expression in cultured endothelial cells exposed to TNF- α . Ongoing sequencing studies reveal major changes in the microRNA content of WT and ApoE^{-/-} exosomes. Future studies will test the hypothesis that WT-BMDM derived exosomes can communicate protective microRNA signaling to cells of the immune system and vascular wall to suppress inflammation and atherosclerosis in mice with hyperlipidemia.

Biography

Robert L Raffai earned a PhD from the University of Ottawa and pursued Post-doctoral studies at the J David Gladstone Institutes with Dr. Karl H Weisgraber and Robert W Mahley. He has published more than 25 papers on the topic of apolipoprotein metabolism and its influence of atherosclerosis. More recently, his laboratory has reported the first evidence that apoE regulates microRNA controlled NF- κ B activation in macrophages and monocytes to suppress atherosclerosis in mice with hyperlipidemia. More recent studies from the laboratory uncovered evidence that apoE regulates the microRNA content and anti-inflammatory capacity of exosomes secreted by macrophages.

Robert.Raffai@ucsf.edu