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# Role of extracellular rna in atherosclerotic plaque formation in mice

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## Abstract

BACKGROUND -: Atherosclerosis and vascular remodeling after injury are driven by inflammation and mononuclear cell infiltration. Extracellular RNA (eRNA) has recently been implicated to become enriched at sites of tissue damage and to act as a proinflammatory mediator. Here, we addressed the role of eRNA in high-fat diet-induced atherosclerosis and neointima formation after injury in atherosclerosis-prone mice. METHODS AND RESULTS -: The presence of eRNA was revealed in atherosclerotic lesions from high-fat diet-fed low-density lipoprotein receptor-deficient (Ldlr) mice in a time-progressive fashion. RNase activity in plasma increased within the first 2 weeks (44±9 versus 70±7 mU/mg protein; P=0.0012), followed by a decrease to levels below baseline after 4 weeks of high-fat diet (44±9 versus 12±2 mU/mg protein; P<0.0001). Exposure of bone marrow-derived macrophages to eRNA resulted in a concentration-dependent upregulation of the proinflammatory mediators tumor necrosis factor-α, arginase-2, interleukin-1β, interleukin-6, and interferon-γ. In a model of accelerated atherosclerosis after arterial injury in apolipoprotein E-deficient (ApoE) mice, treatment with RNase1 diminished the increased plasma level of eRNA evidenced after injury. Likewise, RNase1 administration reduced neointima formation in comparison with vehicle-treated ApoE controls (25.0±6.2 versus 46.9±6.9×10 μm, P=0.0339) and was associated with a significant decrease in plaque macrophage content. Functionally, RNase1 treatment impaired monocyte arrest on activated smooth muscle cells under flow conditions in vitro and inhibited leukocyte recruitment to injured carotid arteries in vivo. CONCLUSIONS -: Because eRNA is associated with atherosclerotic lesions and contributes to inflammation-dependent plaque progression in atherosclerosis-prone mice, its targeting with RNase1 may serve as a new treatment option against atherosclerosis. © 2013 American Heart Association, Inc.

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## Keywords

atherosclerosis, inflammation, nucleic acids, vascular diseases