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miR-155 inhibits oxidized low-density lipoprotein-induced apoptosis of RAW264.7 cells

Guo-fu Zhu · Li-xia Yang · Rui-wei Guo · Hong Liu · Yan-kun Shi · Hong Wang · Jin-shan Ye · Zhi-hua Yang · Xing Liang

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Abstract Macrophage apoptosis is a prominent feature of advanced atherosclerotic plaques. Here, we examined the hypothesis that the apoptotic machinery is regulated by microRNA-155 (miR-155). Constitutive expression of miR-155 was detected in RAW264.7 cells, which was increased following stimulation with oxidized low-density lipoprotein (OxLDL) in a dose- and time-dependent manner. OxLDL-treated RAW264.7 cells showed a marked time- and dose-dependent increase in apoptosis, which was suppressed in the presence of mimics and increased with antagonists of miR-155. Bioinformatics analysis revealed Fas-associated death domain-containing protein (FADD) as a putative target of miR-155. Luciferase reporter assay and Western blot further disclosed that miR-155 inhibits FADD expression by directly targeting the 3′-UTR region. We propose that miR-155 attenuates the macrophage apoptosis, at least in part, through FADD regulation, since forced expression of FADD blocked the ability of miR-155 to inhibit apoptosis. Our results collectively suggest that miR-155 attenuates apoptosis of OxLDL-mediated RAW264.7 cells by targeting FADD, supporting a possible therapeutic role in atherosclerosis.

Keywords miR-155 · FADD · Macrophage apoptosis · Atherosclerosis

Introduction

Macrophage apoptosis has been identified as a prominent feature of advanced atherosclerotic plaques [1]. Pathological studies of advanced atherosclerotic lesions have revealed a strong correlation between macrophage apoptosis and large necrotic cores, thought to promote plaque rupture and acute vascular events [2]. Oxidized low-density lipoprotein (OxLDL) is an important pathogenetic factor in atherosclerosis and a potential inducer of cell apoptosis [3–6]. Previous studies have demonstrated OxLDL-induced apoptosis in a variety of tissues and cells, including endothelial cells, smooth muscle cells (SMCs) and macrophages [6]. An extrinsic pathway mediated by the death receptor family, mainly involving Fas/FasL signaling and downstream caspase-3, has been defined as the underlying mechanism in OxLDL-mediated apoptosis [7–9].

Since macrophage apoptosis plays an important role in atherogenesis and plaque destabilization, modulation of cell death may provide significant protection against advanced atherosclerotic plaque rupture. Accumulating evidence indicates that the apoptotic machinery is regulated by microRNAs (miRNAs) [10], which are 18–22 nucleotide non-coding RNA molecules that regulate gene expression post-transcriptionally by targeting 3′-untranslated regions (UTRs) and other regions of protein-coding mRNA sequences and triggering either translational repression or RNA degradation [11, 12]. Bioinformatics and cloning studies have estimated that miRNAs regulate 30 % of all human genes [13, 14]. To date, over 600 miRNAs have been identified in humans [15], some of

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G. Zhu
Department of Postgraduate, Third Military Medical University, Chongqing 400038, China

G. Zhu · L. Yang (✉) · R. Guo · H. Liu · Y. Shi · H. Wang · J. Ye · Z. Yang · X. Liang
Department of Cardiology, Kunming General Hospital of Chengdu Military Area, Yunnan 650032, China
e-mail: doctorlxyang@163.com