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Commentary

MiR-16 is promising to be a therapy target to alleviate atherosclerosis

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Atherosclerosis is characterized by formation of plaque containing cholesterol and fat-like substances in the intima of large and middle arteries, which is mostly caused by lipid metabolism disorder and neurovascular dysfunction [1]. Monocytes, one of the main participants in atherosclerosis, are involved in the initiation, progression and complications of atherosclerosis [2]. In the early stage of the pathogenesis of atherosclerosis, monocytes can enter the intima of blood vessel and differentiate into macrophages, mediated by adhesion molecules and cytokines, to engulf a large amount of oxidized low density lipoprotein and cholesterol and form foam cells, thus promoting the formation of atherosclerotic plaques [3]. Therefore, deepening the research on the mechanisms regulating the behaviors of monocytes may provide new clues for delaying the formation of atherosclerotic plaques and treating cardiovascular and cerebrovascular diseases.

MicroRNA (miRNA) is a kind of non-coding RNA that mainly controls gene expression at the post-transcriptional level; in recent years, with the deepening of research on non-coding RNA, more and more evidences show that miRNA has important effects on cell proliferation, migration, differentiation, inflammatory response and other biological processes [4]. Meanwhile, a variety of miRNAs can be used as biomarkers for clinical diagnosis of atherosclerosis [5]. Interestingly, microRNA-16 (miR-16) is revealed to be downregulated in the plasma and peripheral blood monocytes of the patients with cardiovascular disease [6], and the level of circulating miR-16 in peripheral blood is considered to be a risk factor of subsequent myocardial infarction after symptomatic coronary / carotid lesion [7]. Notably, miR-16 regulates the biological behaviors of vascular smooth muscle cells and inflammatory macrophages, both of which are crucial players in the pathogenesis of atherosclerosis. Specifically, Gu Qing et al. report that miR-16 participates in regulating the expression of cell cycle-related proteins in vascular smooth muscle cells induced by Ang II [8]. Liang X. et al. report that miR-16 can inhibit the activation of inflammatory macrophages in atherosclerosis by targeting PDCD4 protein [6]. Some recent studies have directly linked miR-16 with the pathogenesis of atherosclerosis. Mahjoubin-Tehran M, et al. reports that, miR-16 can modulate apolipoprotein B (APOB), proprotein convertase subtilisin/kexin type 9 (PCSK9), 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), all of which have been confirmed as therapy targets of atherosclerosis by clinical trials; importantly, this study preliminarily reveals that miR-16 represses interleukin-1 beta (IL-1β, another important player in inflammation during atherosclerosis), and miR-16 shows low cytotoxicity for both tested hepatic cell lines [9]. Wang M, et al. demonstrates that miR-16 was lowly expressed in the plasma and peripheral blood monocytes of patients with coronary artery disease, and in vivo experiments show that injection of miR-16 agomiR in ApoE-/- mice reduced the formation of atherosclerotic plaque and inhibits the release of proinflammatory factors including IL-6, TNF-α, MCP-1, and IL-1β [10]. Consistently, a recent study reports that artesunate suppresses the release of inflammatory cytokines of macrophages via repressing miR-16, and artesunate represses lipid accumulation and atherosclerotic plaque formation in rat model through decreasing miR-16 [11].

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Previous studies have shown that miR-16 inhibits the viability and migration of a variety of human cells. For instance, Ding Z et al. report that high-expression of miR-16 inhibits the viability and proliferation of cervical cancer cells and promotes apoptosis by specifically regulating KRAS [12]. Wang DW et al. demonstrates that miR-16 can inhibit the proliferation of pituitary adenoma cells by regulating ERK/MAPK signaling pathway [13]. Chen T et al. Reports that miR-16 can regulate the ERK/MAPK signaling pathway by inhibiting the expression of MEK1, thereby reducing the colony formation and migration / invasion of lung cancer cells [14]. Foam cell is a key hallmark of atherosclerotic plaque formation. Current studies have proven that foam cells are macrophages or smooth muscle cells that engulf a large amount of lipids, and they are mainly derived from blood mononuclear cells and smooth muscle cells in blood vessels [15,16], so the abnormal viability and migration ability of monocytes is associated with the formation of subendothelial foam cells. Nonetheless, the role of miR-16 in modulating the viability and migration of monocytes is rarely reported. With human mononuclear cell line THP-1, our group investigated the biological function of miR-16 on the phenotypes of monocytes. Compared with the control miRNA transfection group, the viability and migration of THP-1 cells in the miR-16 overexpression group was significantly reduced ($P < 0.05$) (Figure 1&2). Additionally, transfection of miR-16 mimics repressed the expression levels of matrix metalloproteinase (MMP)-2, MMP-9 and vimentin in THP-1 cells (Figure 3). These data suggest that miR-16 has the potential to repress the abnormal viability and migration of monocytes, supporting that miR-16 is a promising target for treating atherosclerosis.

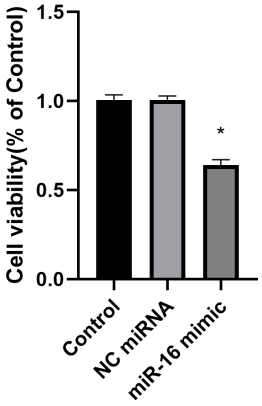

Figure 1. Detection of the viability of THP-1 cells after the transfection of miR-16. * $P < 0.05$ miR-16 mimic group vs. NC miRNA group

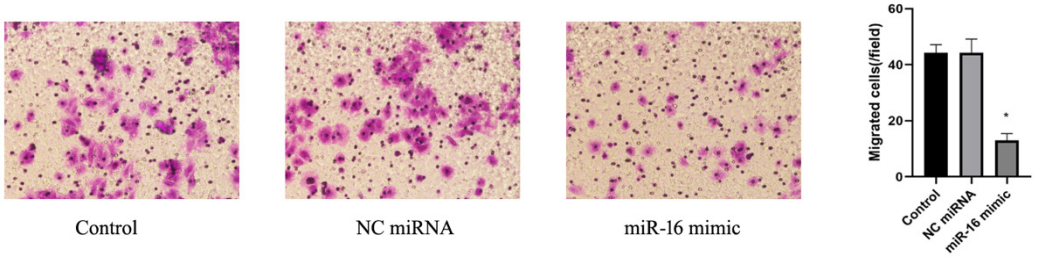

Figure 2. Detection of the migration of THP-1 cells after the transfection of miR-16. * $P < 0.05$ miR-16 mimic group vs. NC miRNA group

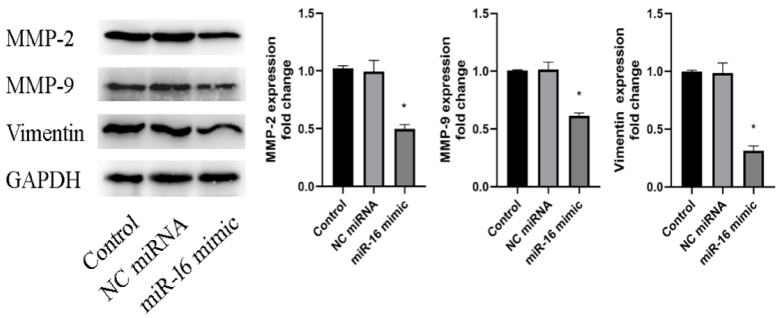

Figure 3. Expression levels of migration-related proteins in THP-1 cells after transfection of miR-16. * $P < 0.05$ miR-16 mimic group vs. NC miRNA group

There are some advantages of miRNA-based therapy over other potential therapeutic strategies. First of all, the procedures for miRNA synthesis is easy and the cost is low; additionally, compared with other drugs designed for suppressing gene expression (e.g. monoclonal antibody, small interfering RNAs and antisense oligonucleotides), miRNAs simultaneously targets multiple deleterious genes, which implies superior treatment efficacy. The published studies and our data based on THP-1 cells mentioned above suggest that increasing miR-16 expression is an attractive treatment option for atherosclerosis, however, an obstacle still exist before its clinical application. Considering there are almost no studies focusing on the role of miR-16 in normal cells, systemic introduction of miR-16 mimics carries the risk of disrupting the normal physiological function of healthy cells. Accordingly, safe and feasible administration routes and delivery systems for modulating miR-16 are required to be explored in the following work.

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Authors' Statement

The details and protocols of the experiments mentioned in this article can be obtained from the corresponding via e-mail author upon request.

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