MicroRNA-1185 Promotes Arterial Stiffness though Modulating VCAM-1 and E-Selectin Expression

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Key Words
miR-1185 • Arterial stiffness • Adhesion molecules • Atherosclerosis

Abstract

Background/Aims: Atherosclerosis is the primary cause of cardiovascular ischaemic events; arterial stiffness is a characteristic of the atherosclerotic process. MicroRNAs (miRNAs) have been revealed as crucial modulators of atherosclerosis. However, the role of arterial stiffness-related miRNAs in the atherosclerotic process is still unclear.

Methods: Four hundred six participants from Northern China were enrolled in this study. Circulating miR-1185 and adhesion molecule levels were measured. Multiple linear regression models were used to evaluate the association of miR-1185 levels with brachial-ankle pulse wave velocity (baPWV) and adhesion molecule levels. A mediation analysis was also performed to examine the mediating effect. Cell adhesion molecule levels were measured in primary human umbilical vein endothelial cells (pHUVECs) and human umbilical vein smooth cells (HUVSMCs) transfected with miR-1185 or co-transfected with a miR-1185 inhibitor.

Results: miR-1185 was independently correlated with arterial stiffness. A positive relationship between miR-1185 and vascular cell adhesion molecule-1 (VCAM-1) and E-selectin levels was observed. VCAM-1 and E-selectin partially mediated the correlation between miR-1185 and arterial stiffness. miR-1185 induced a significant increase in the VCAM-1 and E-selectin levels in pHUVECs and HUVSMCs in vitro. According to our mechanistic analysis, VCAM-1 and E-selectin mediated miR-1185-induced arterial stiffening.

Conclusions: miR-1185 modulated the expression of VCAM-1 and E-selectin to promote arterial stiffening, suggesting that miR-1185 plays a crucial role in the development of atherosclerosis and may serve as a novel therapeutic target for atherosclerosis.
process by which atherosclerosis develops is complex, arterial stiffness plays a crucial role in the process. In fact, arterial stiffness is increased in subjects with CVD [2, 3], which has been suggested to be a potential marker and predictor of atherosclerosis [4-6]. Because the association between arterial stiffness and atherosclerosis has been well established, the cause of arterial stiffening is gaining more attention. Several studies have revealed the characteristics of arterial stiffness, which include increased intima-media thickness, endothelial dysfunction, increased collagen production and elastin degradation [7, 8]. Although some mechanisms that are conducive to arterial stiffness increased have been suggested in previous studies [9-12], the mechanisms underlying arterial stiffening require further elucidation.

MicroRNAs (miRNAs) are small, non-coding RNAs that regulate target genes though degradation or the inhibition of post-transcriptional gene expression [13]. miRNAs are stably expressed in the circulatory system and are detected in the plasma, serum, platelets and nucleated blood cells [14, 15]. Recently, roles for miRNAs in the pathological and physiological processes of CVD, such as atherosclerosis, have been suggested [16-24]. Furthermore, accumulating evidence has indicated potential roles for miRNAs in endothelial function, angiogenesis and vascular remodelling [25-28]. However, the modulatory effects of miRNAs on arterial stiffness are still unclear.

Adhesion molecules, which are expressed in the endothelium, have been shown to mediate the process of monocyte recruitment [29], a characteristic of the early phase of atherosclerosis [30, 31]. Adhesion molecules are expressed in early atherosclerotic lesions [32, 33], and soluble adhesion molecules are considered risk predictors for cardiovascular events [34]. Furthermore, aberrant expression levels of adhesion molecules play crucial roles in arterial stiffness [35].

As shown in our previous study, miR-1185 induces endothelial dysfunction (unpublished data). Thus, the primary aim of this study was to determine whether the effect of miR-1185 on arterial stiffness could be mediated by adhesion molecules. We first examined the association between miR-1185 and arterial stiffness and adhesion molecule expression in a cross-sectional study to verify the effect of miR-1185 on arterial stiffness. Furthermore, we performed cellular experiments in two types of cells, primary human umbilical vein endothelial cells (pHUVECs) and human umbilical vein smooth muscle cells (HUVSMCs), to examine the effect of miR-1185 on the expression of adhesion molecules.

Materials and Methods

Study population

The Harbin Cohort Study on Diet, Nutrition and Chronic Noncommunicable Disease (HDNNCDS) was used in our study. The study design and recruitment of participants have been described previously [36]. In this study, participants with hepatitis, nephropathy, hormone therapy, taking medication for inflammatory or metabolic disorders or with missing data were excluded. Four hundred six participants were randomly selected from 8,142 eligible participants for enrolment in this study. The Ethical Committee of Harbin Medical University approved the study protocol, and written informed consent was obtained from all participants.

Anthropometric measurements

Participants’ heights and body weights were measured when they were wearing light, thin clothing and no shoes. Body weights and heights were measured to the nearest 0.1 kg and 0.1 cm, respectively. Each participant’s blood pressure was measured 3 times using a standard mercury sphygmomanometer placed on the right arm after 10-min of rest in a seated position, and the mean values were used for the analysis. Body mass index (BMI) was calculated as weight (kg) divided by the squared height in metres (m²) [36].

Biochemical analyses

Fasting blood glucose and 2-h glucose levels were measured using an automatic biochemistry analyser (Hitachi 7100, Tokyo, Japan). Serum vascular cell adhesion molecule-1 (VCAM-1), intercellular cell adhesion
molecule-1 (ICAM-1) and E-selectin levels were measured with enzyme-linked immunosorbent assay (ELISA) kit (Cusabio, Wuhan, China) according to the manufacturer's instructions.

**Assessment of brachial-ankle pulse wave velocity (baPWV)**

Participants’ baPWVs were measured after a 10-min rest in the supine position by well-trained examiners using an automated waveform analyser (Colin VP1000, Ormon, Japan). The participants were asked to wear loose clothing and no shoes when the measurements were performed. The mean baPWV from the measurements obtained on the left and right sides were used for the analysis.

**Outcomes**

Diabetes was defined as fasting blood glucose levels ≥ 7.0 mmol/L or 2-h glucose levels ≥ 11.0 mmol/L. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg.

**Cell culture and transfection**

The pHUVECs were obtained from AllCells (Shanghai, China) and cultured in complete medium (AllCells, Shanghai, China). The HUVSMCs were purchased from ScienCell (Carlsbad, CA, USA) and cultured in basal medium (ScienCell, Carlsbad, CA, USA) with smooth muscle cell growth supplement (ScienCell) and 10% FBS (PAA Laboratories, Pasching, Austria). The cells were cultured at 37°C in a 5% CO₂ and 95% air atmosphere.

All cells (pHUVECs and HUVSMCs) were transfected with 50 nM miR-1185 mimic (RiboBio Co., Guangzhou, China) or co-transfected with 50 nM miR-1185 and 100 nM miR-1185 inhibitor (RiboBio Co., Guangzhou, China) with the Lipofectamine 2000 reagent (Invitrogen, Carlsbad, USA) according to the manufacturer’s protocol. A scrambled sequence was used as a negative control (NC). Forty-eight hours after transfection, the cells were used for the subsequent experiments.

**RNA isolation and real-time quantitative polymerase chain reaction (qRT-PCR)**

miR-1185 was extracted from the plasma using an miRNeasy RNA Isolation Kit (Qiagen, Hilden, Germany), and the expression levels were normalized to U6 expression according to the manufacturer’s protocol. Primers (miR-1185 and U6) were purchased from Qiagen.

For the mRNA assessment, total RNA was isolated from the pHUVECs and HUVSMCs using TRIzol reagent (Invitrogen) according to the manufacturer’s instructions, and β-actin expression was used as an internal control. Primers (VCAM-1, ICAM-1, E-selectin, and β-actin) were synthesized by Invitrogen. Primer sequences are listed in Table 1. Real-time PCR was performed with the SYBR Green PCR Master Mix (Applied Biosystems, Foster City, CA, USA) [37].

**Immunofluorescence staining**

Cells (pHUVECs and HUVSMCs) were washed with PBS and fixed with 4% paraformaldehyde. Cells (pHUVECs and HUVSMCs) were incubated with a fluorescein isothiocyanate (FITC)-conjugated VCAM-1 antibody (BD, Franklin Lakes, NJ, USA) for 30 min, and then the cell nuclei were counterstained with DAPI (Beyotime Biotechnology, Jiangsu, China) for 15 min. The fluorescent signal was detected with a confocal microscope (Nikon, Tokyo, Japan).

**Table 1. Primer sequences used for real-time PCR**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Primer sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCAM-1</td>
<td>Sense 5'-TTCCCTAGAGATCCAGAATTCGAG-3'</td>
</tr>
<tr>
<td></td>
<td>Antisense 5'-CTTTGCACTTTGACGAGGAGC-3'</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>Sense 5'-CTCAATGTGCGCCGGCTT-3'</td>
</tr>
<tr>
<td></td>
<td>Antisense 5'-CAGTGGGAAATGCGCATCTC-3'</td>
</tr>
<tr>
<td>E-selectin</td>
<td>Sense 5'-AGAGCTCCACCTGAGTCCAA-3'</td>
</tr>
<tr>
<td></td>
<td>Antisense 5'-GCTGCTTATGGTGGAGAGGAGA-3'</td>
</tr>
<tr>
<td>β-actin</td>
<td>Sense 5'-ACTATCGGCAATGAGCC-3'</td>
</tr>
<tr>
<td></td>
<td>Antisense 5'-GAGCCAGGCGATCTAT-3'</td>
</tr>
</tbody>
</table>
**Statistical analysis**

Data are presented as means ± standard deviations (SD) and medians (interquartile ranges) for the continuous variables with normal and skewed distributions and frequencies for the categorical variables. Participants were stratified into low and high miR-1185 groups based on their median circulating miR-1185 levels. Continuous variables were compared using t-tests, and chi-square tests were used to compare the categorical data between two groups. Normal distributions were obtained after log transformation of the circulating miR-1185 levels, and the transformed data were used for the subsequent analysis. Multiple linear regression models were performed; Model 1 was performed without covariates, and Model 2 was adjusted for age, sex, BMI, smoking rate, and alcohol consumption rate. A mediation model was constructed to examine whether the association between miR-1185 and baPWV was mediated by VCAM-1 and E-selectin after adjusting for age, sex, BMI, smoking rate, and alcohol consumption rate. miR-1185 was the predictor variable, VCAM-1 and E-selectin were the mediators, and baPWV was the outcome variable. Four steps were conducted in the mediation analysis: 1) examining the association between the predictor variable and outcome (Model Y = β\textsubscript{tot}X); 2) examining the association between the predictor variable and mediators (Model M1 = β\textsubscript{1}X; Model M2 = β\textsubscript{2}X) (β\textsubscript{1} = indirect effect 1; β\textsubscript{2} = indirect effect 2); 3) examining the association between the mediators and outcome variable while controlling for the predictor (Model Y = β\textsubscript{y}M1+β\textsubscript{y}M2+β\textsubscript{dir}X) (β\textsubscript{3} = indirect effect 3; β\textsubscript{4} = indirect effect 4; β\textsubscript{dir} = direct effect); and 4) calculating the percentage of mediation: mediation effect for M1 (%) = (β\textsubscript{1} × β\textsubscript{3}/β\textsubscript{tot}) × 100% and mediation effect for M2 (%) = (β\textsubscript{2} × β\textsubscript{4}/β\textsubscript{tot}) × 100%. A mediation analysis was performed using structural equation modelling (SEM) and a path diagram analysis with IBM SPSS Amos as described in a previous study [38].

For the cell-based experiments, the values are shown as the means ± SD obtained from at least three separate experiments. Significance was determined using one-way ANOVA followed by the Student-Newman-Keuls (SNK) test.

SPSS v20.0 (Chicago, IL, USA) was used for all statistical analysis. A two-sided P-value < 0.05 was considered statistically significant.

**Results**

**Characteristics of the participants according to their circulating miR-1185 levels**

Compared with participants in the low miR-1185 group, participants in the high miR-1185 group were significantly older and exhibited markedly increased baPWV and VCAM-1 and E-selectin levels. A significant difference in the prevalence of hypertension between the two groups was observed (Table 2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Group</th>
<th>High Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-1185 levels</td>
<td>0.13 (0.03, 0.48)</td>
<td>4.44 (2.02, 9.02)</td>
<td>0.018</td>
</tr>
<tr>
<td>Age (y)</td>
<td>53.27 ± 7.76</td>
<td>55.07 ± 7.56</td>
<td>0.018</td>
</tr>
<tr>
<td>Male (%)</td>
<td>27.09</td>
<td>25.12</td>
<td>0.735</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>24.54 ± 3.09</td>
<td>25.10 ± 3.31</td>
<td>0.081</td>
</tr>
<tr>
<td>baPWV (cm/s)</td>
<td>1536.38 ± 486.31</td>
<td>1781.66 ± 505.47</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>VCAM-1 (ng/ml)</td>
<td>134.08 ± 70.20</td>
<td>152.95 ± 92.43</td>
<td>0.038</td>
</tr>
<tr>
<td>ICAM-1 (ng/ml)</td>
<td>241.80 ± 155.92</td>
<td>262.23 ± 173.83</td>
<td>0.259</td>
</tr>
<tr>
<td>E-selectin (ng/ml)</td>
<td>52.17 ± 20.37</td>
<td>57.09 ± 21.51</td>
<td>0.031</td>
</tr>
<tr>
<td>Smoking rate (%)</td>
<td>16.26</td>
<td>13.30</td>
<td>0.484</td>
</tr>
<tr>
<td>Alcohol consumption rate (%)</td>
<td>32.54</td>
<td>31.53</td>
<td>0.830</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>23.16</td>
<td>27.58</td>
<td>0.362</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>45.32</td>
<td>62.56</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
**Table 3.** Relationship between circulating miR-1185 levels and baPWV and adhesion molecule expression. β represents the standard coefficient. Model 1 was crude; Model 2 was adjusted for age, sex, BMI, smoking rate, and alcohol consumption rate. baPWV: brachial-ankle pulse wave velocity; VCAM-1: vascular cell adhesion molecule-1; ICAM-1: intercellular cell adhesion molecule-1.

<table>
<thead>
<tr>
<th></th>
<th>baPWV (cm/s)</th>
<th>VCAM-1 (ng/ml)</th>
<th>ICAM-1 (ng/ml)</th>
<th>E-selectin (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β</td>
<td>P value</td>
<td>β</td>
<td>P value</td>
<td>β</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.407</td>
<td>&lt; 0.001</td>
<td>0.224</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.284</td>
<td>&lt; 0.001</td>
<td>0.174</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Table 4.** Associations of adhesion molecule levels with baPWV. β represents the standard coefficient. Model 1 was crude; Model 2 was adjusted for age, sex, BMI, smoking rate, and alcohol consumption rate. VCAM-1: vascular cell adhesion molecule-1; ICAM-1: intercellular cell adhesion molecule-1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>P value</td>
</tr>
<tr>
<td>VCAM-1 (ng/ml)</td>
<td>0.364</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICAM-1 (ng/ml)</td>
<td>0.134</td>
<td>0.014</td>
</tr>
<tr>
<td>E-selectin (ng/ml)</td>
<td>0.475</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**Fig. 1.** Mediating effects of VCAM-1 and E-selectin on the association between miR-1185 and baPWV. Structural equation modelling was used after adjusting for age, sex, BMI, smoking rate, and alcohol consumption rate. β represents the standard regression coefficient. *P < 0.05, **P < 0.001.

**Association between the circulating miR-1185 levels and baPWV and adhesion molecule levels**

A significant positive correlation between miR-1185 levels and baPWV (P < 0.001), VCAM-1 (P < 0.001) and E-selectin (P < 0.001) in Model 1 was observed. In the multiple linear regression models, Model 2 revealed a positive correlation between the miR-1185 levels and baPWV (P < 0.001) and VCAM-1 (P = 0.001) and E-selectin levels (P = 0.002) after adjusting for age, sex, BMI, smoking rate and alcohol consumption rate. However, a significant correlation between the miR-1185 and ICAM-1 levels was not observed (Table 3).

**Relationship between adhesion molecule levels and baPWV**

In Model 1 adhesion molecules, including VCAM-1 (P < 0.001), ICAM-1 (P = 0.014) and E-selectin (P < 0.001) levels resulted positively associated with baPWV. Based on multiple linear regression Model 2, the levels of the adhesion molecules VCAM-1 (P = 0.001), ICAM-1 (P = 0.005), and E-selectin (P < 0.001) were significantly associated with baPWV after adjusting for age, sex, BMI, smoking rate and alcohol consumption rate (Table 4).

**Direct and indirect effects of miR-1185 on baPWV**

As shown in Figure 1, the total effect of miR-1185 on baPWV, which was measured as a standardized regression coefficient (β_{tot} = 0.284; P < 0.001), was estimated without VCAM-1...
miR-1185 modulated adhesion molecule expression in pHUVECs

We examined the effect of miR-1185 on adhesion molecule expression in pHUVECs to assess the potential effect of miR-1185 on endothelial cell dysfunction. Cells transfected with miR-1185 exhibited a significant increase in the expression of the VCAM-1 mRNA, but co-transfection with the miR-1185 inhibitor eliminated this increase (Fig. 2a). The expression of the E-selectin mRNA was increased in pHUVECs transfected with miR-1185 compared with that in the NC group, whereas co-transfection with the miR-1185 inhibitor reversed the effect (Fig. 2b). miR-1185 did not significantly affect the expression of the ICAM-1 mRNA (Fig. 2c). Additionally, we examined the effect of miR-1185 on the accumulation of the VCAM-1 protein using immunofluorescence staining. The miR-1185-transfected pHUVECs exhibited a marked increase in the levels of the VCAM-1 protein compared with the levels in the NC group, and co-transfection with the miR-1185 inhibitor almost completely reversed the effect of miR-1185 (Fig. 2d).

miR-1185 modulated adhesion molecule expression in HUVSMCs

The effect of miR-1185 on adhesion molecule expression in HUVSMCs was detected. HUVSMCs transfected with miR-1185 exhibited a significant increase in the expression of the VCAM-1 and E-selectin mRNAs; however, co-transfection with the miR-1185 inhibitor
restored the mRNA levels (Fig. 3a and b). The levels of the ICAM-1 mRNA were not changed in HUVSMCs transfected with miR-1185 (Fig. 3c). The accumulation of VCAM-1 protein, which was measured using immunofluorescence staining, was dramatically increased in the miR-1185-transfected group, and co-transfection with the miR-1185 inhibitor significantly abrogated the effect of miR-1185 (Fig. 3d).

**Discussion**

As shown in the present study, miR-1185 plays a key role in the pathological and physiological processes of atherosclerosis. For the first time, we showed that miR-1185 was independently correlated with arterial stiffness. We also observed a positive correlation between miR-1185 and VCAM-1 and E-selectin levels. Furthermore, VCAM-1 and E-selectin partially mediated the relationship between miR-1185 and arterial stiffness. miR-1185 significantly induced the expression of VCAM-1 and E-selectin in pHUVECs and HUVSMCs in vitro. Thus, we conclude that miR-1185 may increase arterial stiffness by promoting VCAM-1 and E-selectin expression.

According to studies, vascular dysfunction is required to increase arterial stiffness [39-41]. In recent years, aberrant miRNA expression has been suggested to be involved in vascular dysfunction [42, 43]. Specifically, miRNA-induced vascular dysfunction increased arterial stiffness in the study by Liao et al. [44]. Freedman et al. reported that miR-1185 was expressed at high levels in plasma and predicted to modulate both transcription factor expression and the cell cycle [45]. Importantly, we found that miR-1185 induced endothelial dysfunction in previous study (unpublished data). In this study, miR-1185 levels were
positively associated with arterial stiffness. Thus, we proposed that increased miR-1185 levels lead to increased arterial stiffness.

Aberrant adhesion molecules have been considered characteristic for vascular dysfunction [46], and the modulatory effects of adhesion molecules on arterial stiffness have been explored. Arterial stiffness arises from a complex process involving structural alterations in the extracellular matrix (ECM) and changes in vascular tone [44]. Adhesion molecules have been shown to increase the arterial stiffness by participating in the remodelling of the ECM [35, 47]. The mediators of this process include matrix metalloproteinases (MMPs), which play a crucial role in the remodelling ECM, and adhesion molecules stimulate MMP activity and increase fragmentation of elastin molecules, a characteristic of arterial stiffness [47-49]. In addition to structural changes in the ECM, adhesion molecules also increase vascular tone. Vascular tone is directly modulated by factors regulating the smooth muscle layer or indirectly modulated by factors that regulate smooth muscle cells by stimulating the release of bioactive substances from endothelial cells [50]. The up-regulation of adhesion molecule expression in endothelial cells recruits circulating leukocytes to the vessel wall, which induces endothelial dysfunction and affects vascular tone [51, 52]. Similarly, vascular smooth muscle cells also express adhesion molecules to guide migrating monocytes to the vessel wall [53]. Importantly, VCAM-1 has been shown to regulate the proliferation and migration of monocytes towards smooth muscle cells [54]. In our study, we also identified a significant association between adhesion molecule levels and arterial stiffness.

Adhesion molecules can be regulated by pro-inflammatory cytokines, which activate nuclear factor-κB and interferon regulatory factor-1 [55]. However, unknown factors that affect the stability of adhesion molecule mRNAs also modulate mRNA expression [56, 57]. In this study, miR-1185 promoted the expression of VCAM-1 and E-selectin, suggesting the effect of miR-1185 on vascular dysfunction. The mechanism by which miR-1185 modulates adhesion molecule expression may include some currently unidentified target genes of miR-1185, which could regulate the signalling pathways related to the adhesion molecules, involved in the process. Nevertheless, the precise mechanism by which miR-1185 induced changes in VCAM-1 and E-selectin expression is still not completely understood.

To our knowledge, this study is the first to show that miR-1185 influences arterial stiffness by promoting VCAM-1 and E-selectin expression. Specifically, our study illustrates a novel mechanism by which arterial stiffness is increased: increased miR-1185 levels promote VCAM-1 and E-selectin expression, which induce endothelial dysfunction and lead to arterial stiffening and the development of atherosclerosis. Our findings contribute to the understanding of the pathogenesis of atherosclerosis and provide evidence that miR-1185 may be a promising therapeutic target and novel biomarker for atherosclerosis.

Limitations

Because species-specific miR-1185 was not expressed in mice and rats, we did not further explore the effect and mechanism of miR-1185-induced arterial stiffening in animal model. However, a cross-sectional design and different cell types, including pHUVECs and HUVMSCs, were used in this study to confirm the effect of miR-1185 on arterial stiffness and its related mechanisms. Our study reflects the effects of miR-1185 on arterial stiffness and the atherosclerotic process.

Another limitation is that all participants in this study were ethnic Chinese; therefore, further studies are needed to determine whether the relationship between miR-1185 levels and arterial stiffness can be extended to other ethnic groups.

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Disclosure Statement

The authors declare no conflict of interests.

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