MicroRNA-134 Promotes the Development of Atherosclerosis Via the ANGPTL4/LPL Pathway in Apolipoprotein E Knockout Mice

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Aims: Atherosclerosis is the most common cause of cardiovascular disease, such as myocardial infarction and stroke. Previous study revealed that microRNA (miR)-134 promotes lipid accumulation and proinflammatory cytokine secretion through angiopoietin-like 4 (ANGPTL4)/lipid lipoprotein (LPL) signaling in THP-1 macrophages.

Methods: ApoE KO male mice on a C57BL/6 background were fed a high-fat/high-cholesterol Western diet, from 8 to 16 weeks of age. Mice were divided into four groups, and received a tail vein injection of miR-134 agomir, miR-134 antagonim, or one of the corresponding controls, respectively, once every 2 weeks after starting the Western diet. After 8 weeks we measured aortic atherosclerosis, LPL Activity, mRNA and protein levels of ANGPTL4 and LPL, LPL/low-density lipoprotein receptor related protein 1 Complex Formation, proinflammatory cytokine secretion and lipid levels.

Results: Despite this finding, the influence of miR-134 on atherosclerosis in vivo remains to be determined. Using the well-characterized mouse atherosclerosis model of apolipoprotein E knockout, we found that systemic delivery of miR-134 agomir markedly enhanced the atherosclerotic lesion size, together with a significant increase in proinflammatory cytokine secretion and peritoneal macrophages lipid contents. Moreover, overexpression of miR-134 decreased ANGPTL4 expression but increased LPL expression and activity in both aortic tissues and peritoneal macrophages, which was accompanied by increased formation of LPL/low-density lipoprotein receptor-related protein 1 complexes in peritoneal macrophages. However, an opposite effect was observed in response to miR-134 antagonim.

Conclusions: These findings suggest that miR-134 accelerates atherogenesis by promoting lipid accumulation and proinflammatory cytokine secretion via the ANGPTL4/LPL pathway. Therefore, targeting miR-134 may offer a promising strategy for the prevention and treatment of atherosclerotic cardiovascular disease.

Key words: MiR-134, ANGPTL4, LPL, Atherosclerosis
LPL in both macrophages and apolipoprotein E knock-out (apoE KO) mice.

Angiopoietin-like 4 (ANGPTL4), a novel member of the ANGPTL family, acts as a potent LPL inhibitor. Recently, Lichtenstein et al. reported that induction of macrophage ANGPTL4 can suppress foam cell formation and inflammatory gene expression. Moreover, overexpression of ANGPTL4 dramatically reduces lesion area in atherosclerosis-prone ApoE3-Leiden transgenic mice. MiR-134, a polyphenic miRNA, is associated with cardiovascular disease. The levels of miR-134 are significantly increased in peripheral blood mononuclear cells isolated from patients with coronary artery disease. Our group found that miR-134 upregulates LPL expression by directly binding to the 3’ UTR of ANGPTL4 in THP-1 macrophages, leading to increased lipid accumulation and proinflammatory cytokine secretion. However, it remains unclear whether miR-134 can aggravate atherosclerosis in apoE KO mice fed a high-fat/high-cholesterol diet.

The aim of the present research was to investigate the effects of miR-134 on the development of atherosclerosis and its underlying mechanisms. Our results showed that miR-134 downregulated ANGPTL4 expression and then increased LPL expression and activity in apoE KO mice fed a high-fat/high-cholesterol diet. Moreover, upregulation of LPL promoted lipid accumulation and the inflammatory response, leading to a significant increase of atherosclerotic lesions. Our findings collectively support the utility of an miR-134 inhibitor as a novel therapeutic approach for atherosclerosis.

Materials and Methods

Animal Models
ApoE KO male mice (8 weeks old) on a C57BL/6 background were obtained from Beijing University of Medicine Laboratory, China. All experimental procedures were approved by the institutional animal care committee (University of South China, Hunan, China). These mice were randomly divided into four groups: miR-134 agomir negative control (AG-NC), miR-134 agomir (AG), miR-134 antagonist negative control (AN-NC), and miR-134 antagonist (AN). The agomir (2’ OMe+5’ chol modified) and antagonist (2’ OMe+5’ chol modified) of miR-134 are locked nucleic acids, purchased from RiboBio (Guangzhou, China). All sequences are as follows: miR-134 agomir: UCUCAGUGUUCAGAGAGGG, miR-134 antagonist: CUCUCAGGGCCCGCACUCUGC, miR-134 agomir negative control: UCACAACCUCAAGAAAGAGUAG, and miR-134 antagonist negative controls: UUUGUACUACAAAAGUACUG. Each group included 10 animals. Each mouse received a tail vein injection of miR-134 agomir, miR-134 antagonist, or one of the corresponding controls, respectively, at a dose of 80 mg/kg wt in 0.2 ml saline once every 2 weeks after starting the high-fat/high-cholesterol Western diet (15% fat wt/wt, 0.25% cholesterol wt/wt). After 8 weeks on the Western diet, and after fasting for 12-14 h, mice were euthanized. The blood was collected and assayed for plasma lipids and inflammatory cytokine expression using commercially available enzymatic methods and enzyme-linked immunosorbent assay (ELISA) kits (y-y (Shanghai) Chemical Reagent Co., Ltd, Shanghai, China), respectively. The expression of LPL mRNA and protein in the aorta and peritoneal macrophages was detected by real-time polymerase chain reaction (RT-PCR) and Western blot analysis, respectively. Images of lesions in aortic sinuses were obtained by performing hematoxylin and eosin (HE) staining, Oil red O staining, and Masson’s trichrome staining.

Atherosclerosis Analysis
The mice were perfused by cardiac puncture with 4% (w/v) paraformaldehyde to wash out blood from the heart and all vessels after euthanasia. The surrounding fat and connective tissues were removed carefully from the aorta and heart, followed by observation under a stereomicroscope. Tissues, including hearts and aortas, abdominal cavity macrophages, and blood samples were collected for further analyses and measurements. For en face analysis, the whole aorta was excised from the aortic arch to the common iliac artery and stained with Oil red O. To analyze the ather-
erosclerotic lesions in the aortic root, 8 µm frozen sections of the aortic root were prepared and also stained with hematoxylin-eosin (HE) and Oil red O. Images of the sections were obtained with a microscope. Lesion areas were quantified using IMAGEPRO PLUS software.

LPL Activity

The activities of LPL in peritoneal macrophages and aortic tissues isolated from apoE KO mice were determined using the LPL activity assay kit as described previously. Briefly, 0.5 U/ml heparin was added to the medium at the end of the incubation period. LPL activity was normalized to total cell proteins. In the reaction system, production of 1 µmol FFA per mg of protein per hour in the reaction system is expressed as one active unit.

RT-PCR Analyses

Total RNA was isolated by TRIzol reagent (Invitrogen) in accordance with the manufacturer’s instructions. Relative quantitative RT-PCR (qPCR) with the use of SYBR Green detection chemistry was performed with a LightCycler Run 5.32 Real-Time PCR System (Roche). The melting curve analyses of all RT-PCR products were conducted and shown to produce a single DNA duplex. The DDCt method was used to determine quantitative measurements. In the experiments, β-actin was used as the internal control. The sequences of the RT-PCR primers were as follows: LPL, forward: 5’-GGGAGTTTGGCTCCAGAGT-TT-3’ and reverse: 5’-TGTGTCTTCTCAGGGGTCC-TTAG-3’; ANGPTL4, forward: 5’-GAGGTCCCTTCACAGCCTGCA-3’ and reverse 5’-TGGGCCACCTTGTGGAAGAG-3’; GAPDH, forward: 5’-AAGAAGACGGGAGGTGAT-3’ and reverse: 5’-ACATGGGGTAGGAACA-3’.

Western Blot Analysis

Aortic tissues and peritoneal macrophages were lysed for protein extraction using RIPA buffer containing proteinase inhibitor cocktails (Sigma). The expression of LPL protein was examined using Western blot assay. In brief, 20 µg protein from each lysate from isolated aortic tissues was loaded into a separate lane for analysis. The resulting blots were probed with primary antibodies against LPL or β-actin (1:1000, Sigma) and antibodies against ANGPTL4 or β-actin (1:1000, Sigma), followed by incubation with the appropriate secondary antibodies (1:2000, Sigma). Protein signals were visualized by chemiluminescence and quantified by densitometry.

High-Performance Liquid Chromatography (HPLC) Assays

The blood samples were collected from apoE KO mice fasted for 12–14 h by retro-orbital venous plexus puncture. Plasma was separated by centrifugation and stored at -20°C. According to the manufacturer’s instructions, total plasma cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and lipids were enzymatically measured with the amplex red cholesterol assay kit (Molecular Probes, Invitrogen). The sterol analyses were performed using an HPLC system (Model 2790, controlled with Empower Pro software, Waters Corporation, PerkinElmer, Milford, MA). Analysis of cholesterol was conducted after elution and detection by absorbance at 210 nm.

Cytokine Expression Analysis by ELISA

The quantitation of secreted proinflammatory cytokines was conducted by ELISA (BioSource). The levels of monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-6 were analyzed from aliquots of conditioned medium from peritoneal macrophages and plasma according to the manufacturer’s instructions.

Co-Immunoprecipitation and Immunoblotting Analysis

Co-immunoprecipitation was conducted to determine the interaction between LPL and LRP1. Protein extracts from peritoneal macrophages were first incubated with anti-LRP1 antibody or anti-LPL antibody overnight at 4°C with gentle rotation and subsequently incubated with protein A/G agarose slurry. After washing, the samples were mixed with sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) sample buffer. The mixture was then heated for 10 min and centrifuged. The supernatants containing LRP1 or LPL immunoprecipitates were removed and subjected to Western blot analysis. Whole cell extracts were subjected to immunoblot analysis as a control, and polyclonal goat IgG was used as a negative control.

Statistical Analysis

All data are expressed as mean ± standard deviation (SD) of at least three independent experiments. Statistically significant differences among groups were analyzed by one-way analysis of variance (ANOVA) or Student’s t-test using SPSS 18.0 software. A difference with P<0.05 was considered to be statistically significant.
Fig. 1. MiR-134 aggravates atherosclerosis development

Male 8-week-old apoE KO mice (n = 10 mice per group) fed a high-fat diet were given a tail vein injection with miR-134 agomir negative control (AG-NC), miR-134 agomir (AG), miR-134 antagomir negative control (AN-NC), or miR-134 antagomir (AN), respectively. A: MiR-134 accelerated the development of atherosclerotic plaques in apoE KO mice. Plaques in aortic arches of representative apoE KO mice are marked by the blue arrows. B: MiR-134 increased atherosclerotic lesion areas in apoE KO mice. The images show atherosclerotic lesion areas of the whole aorta with Oil red O staining. C: The Oil red O staining of atherosclerotic lesion areas at aortic sinuses. D: The HE staining of cross-sections of the proximal aorta in apoE KO mice. E: Microscopic images of atherosclerotic plaque collagen content in cross-sections of the proximal aorta of apoE KO mice with Masson’s trichrome staining. Original magnification: 10×. All results are expressed as mean±S.D. *P<0.05 vs AG-NC group. ‡P<0.01 vs AN-NC group.
Fig. 2.
Effects of miR-134 on ANGPTL4 and LPL expression in apoE KO mice
MiR-134 regulated ANGPTL4 expression and LPL activity and protein expression. A: ANGPTL4 mRNA and protein levels in aortic tissues and peritoneal macrophages of apoE KO mice were analyzed by qRT-PCR and Western blot analyses, respectively. B: LPL mRNA and protein levels in aortic tissues and peritoneal macrophages of apoE KO mice were analyzed by RT-qPCR and Western blot analyses, respectively. Effects of MiR-134 on LPL activity levels in the aortic tissues and macrophages of apoE KO mice were determined by ELISA. *P<0.05 vs. AG-NC. **P<0.05 vs. AN-NC.
**Results**

**MiR-134 Aggravates Atherosclerosis in ApoE KO Mice**

The formation of plaques is the hallmark of atherosclerosis. Our results show that administration of miR-134 agomir elevated the number and size of plaques in the aortic arch, thoracic aorta region, and whole aorta, whereas an opposite effect appeared in the presence of miR-134 antagonim (Fig. 1A and B). We then examined atherosclerotic plaque development of aortic root lesions by HE staining and observed that the agomir group developed significantly more lesion areas than the agomir negative control group (Fig. 1C). To further investigate the effects of miR-134 on lipid deposition, quantification of lipid accumulation in aortic sinus lesions by Oil red O staining was conducted. We found a significant increase of lipid accumulation in miR-134 agomir-treated mice but a significant decrease of lipid accumulation in miR-134 antagonim-treated mice, when compared with their respective control mice (Fig. 1D). Finally, we determined atherosclerotic plaque collagen content in cross-sections of the proximal aorta of apoE KO mice with Masson's trichrome staining. Treatment with miR-134 agomir significantly increased necrotic core areas when compared with those in control mice. In contrast, the necrotic core area was significantly decreased when mice were treated with miR-134 antagonim (Fig. 1E). Taken together, these results indicate that overexpression of miR-134 accelerates atherosclerosis development.

**MiR-134 Decreases ANGPTL4 Expression but Elevates LPL Expression and Activity**

Our previous experiments identified ANGPTL4 as a target gene of miR-134. We thus explored the effects of miR-134 on ANGPTL4 expression in vivo. As expected, in both peritoneal macrophages and the aortas of apoE KO mice, miR-134 agomir decreased, but miR-134 antagonim increased, the mRNA and protein levels of ANGPTL4 (Fig. 2A). Given the fact that absence of ANGPTL4 results in accumulation of the mature glycosylated form of LPL and increases LPL secretion, we next investigated whether miR-134 could impact LPL expression and activity in the above-mentioned peritoneal macrophages and aortas. As shown in Fig. 2B, overexpression of miR-134 markedly raised LPL expression and activity; however, knockdown of miR-134 inhibited its expression and activity.

**MiR-134 Promotes LPL/LRP1 Complex Formation in Peritoneal Macrophages**

LRP1 is enriched at the lipid rafts on the surface of macrophages and usually forms a complex with its ligand protein, LPL. Thus, a co-immunoprecipitation assay was used to explore the effects of miR-134 on LPL/LRP1 complex formation in peritoneal macrophages isolated from apoE KO mice. As demonstrated in Fig. 3, administration of miR-134 agomir markedly facilitated LPL/LRP1 complex production, whereas miR-134 antagonim inhibited complex production.
subsequently measured the effects of miR-134 on the contents of lipids and proinflammatory cytokines using ELISA. Increased total cholesterol (TC), cholesterol ester (CE), TNF-α, IL-6, IL-1β, and MCP-1 contents, but decreased free cholesterol (FC) content, were subsequently measured the effects of miR-134 on the contents of lipids and proinflammatory cytokines using ELISA. Increased total cholesterol (TC), cholesterol ester (CE), TNF-α, IL-6, IL-1β, and MCP-1 contents, but decreased free cholesterol (FC) content, were

### Table 1. Effect of miR-134 on lipid accumulation in the peritoneal macrophages of apoE KO mice

<table>
<thead>
<tr>
<th></th>
<th>TC</th>
<th>FC</th>
<th>CE</th>
<th>CE/TC (%)</th>
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<tbody>
<tr>
<td>AG-NC</td>
<td>518 ± 30.1</td>
<td>185 ± 24.8</td>
<td>318 ± 21.6</td>
<td>61.4</td>
</tr>
<tr>
<td>AG</td>
<td>620 ± 28.8*</td>
<td>230 ± 30.2</td>
<td>391 ± 28.9*</td>
<td>63.1</td>
</tr>
<tr>
<td>AN-NC</td>
<td>503 ± 22.6#</td>
<td>189 ± 21.7</td>
<td>331 ± 26.8#</td>
<td>65.8</td>
</tr>
<tr>
<td>AN</td>
<td>405 ± 22.6#</td>
<td>150 ± 17.6</td>
<td>267 ± 23.6#</td>
<td>65.9</td>
</tr>
</tbody>
</table>

Each group contained 10 mice. Unit: (mg/g protein). TC: total cholesterol; FC: free cholesterol; CE: cholesterol ester. All the results are expressed as mean ± S.D. *p < 0.05, vs AG-NC; #p < 0.05, vs AN-NC.

**Fig. 4.** Effects of miR-134 on inflammatory cytokine expression of apoE KO mice

MiR-134 promoted inflammatory cytokine production and increased lipid levels. Effects of miR-134 on inflammatory cytokine production were determined for the blood plasma and peritoneal macrophages of apoE KO mice.

**MiR-134 Facilitates Lipid Accumulation and the Inflammatory Response**

Upon binding of LPL to LRP1, LPL can promote abnormal lipid metabolism and the inflammatory response, two key events in atherogenesis. We subsequently measured the effects of miR-134 on the contents of lipids and proinflammatory cytokines using ELISA. Increased total cholesterol (TC), cholesterol ester (CE), TNF-α, IL-6, IL-1β, and MCP-1 contents, but decreased free cholesterol (FC) content, were
observed in peritoneal macrophages from mice dosed with miR-134 agomir (Table 1 and Fig. 4). Similarly, the plasma levels of TC, LDL-C, TNF-α, IL-6, IL-1β, and MCP-1 were raised, but plasma TG and HDL-C levels were reduced, in response to treatment with miR-134 agomir (Table 2 and Fig. 4). Notably, an opposite effect was observed in the presence of miR-134 antagonim. All these results suggest that overexpression of miR-134 enhances lipid accumulation and the inflammatory response in apoE KO mice, which may be responsible for the proatherosclerotic action of miR-134.

### Discussion

Atherosclerosis has been regarded as the most common cause of heart attack, stroke, and peripheral vascular disease. MiR-134, which is located in chromosome region 14q32.31, was initially identified by cloning research on rats. Recently, several lines of evidence have demonstrated that miR-134 is closely related to the risk of heart failure and might act as a potential biomarker of myocardial infarction. Overexpression of miR-134 induces the formation of atherosclerotic lesions in apoE KO mice, whereas its downregulation produced an opposite effect. These results suggest that overexpression of miR-134 contributes to atherogenesis.

The major pathogenic events of atherosclerosis are foam cell formation and an excessive inflammatory response. More recently, our group reported that overexpression of miR-134 significantly promotes intracellular lipid accumulation and the secretion of proinflammatory cytokines including TNF-α, IL-6, and MCP-1 in THP-1 macrophages. Similar to the in vitro experimental results, apoE KO mice overexpressing miR-134 showed a significant increase in plasma levels of LDL-C, TC, CE, TNF-α, IL-6, IL-1β, and MCP-1. Our results show that knockdown of ANGPTL4 by miR-134 AG increased plasma TC levels. However, mice lacking Angptl4 exhibited a significant decrease in plasma TC levels. This discrepancy may be attributed to the differences in the degree of Angptl4 inhibition and the experimental protocols. Further studies will be required to explain the opposite effects. The LPL/LRP1 complex is primarily localized to the cell surface of macrophages. It has already been reported that treatment of THP-1 macrophages with either miR-134 mimic or miR-155 inhibitor markedly increases intracellular lipid contents and proinflammatory cytokine generation by promotion of the formation of this complex.

In the current study, we found that the formation of the LPL/LRP1 complex was significantly increased in peritoneal macrophages from apoE KO mice treated with miR-134 agomir. All of these results suggest that miR-134 promotes LPL/LRP1 complex production and then increases lipid accumulation and proinflammatory cytokine secretion, which may be the main mechanism for miR-134-induced atherosclerosis.

LPL, a protein containing 448 amino acids, is encoded by the gene located in chromosome region 8p22. LPL is primarily synthesized in the heart, skeletal muscle, and adipose tissue. Other tissues with measurable LPL activity include lungs, brain, lactating mammary glands, brain, and kidney, and macrophages also exhibit LPL activity. In all tissues, LPL is found to line the capillary endothelial lumen, and its main function is to hydrolyze the core triglycerides in the TG-rich lipoproteins, such as the chylomicrons and the very-low-density lipoproteins, into glycerol and FFAs for uptake by tissues. Macrophage LPL contributes to the formation of foam cells via a “molecular bridge” between lipoproteins and receptors on peritoneal macrophages surface. The nonenzymatic activity of LPL is essential to maintain normal plasma lipid levels in the face of excessive fat intake or dysregulated lipid metabolism. In addition, macro-

### Table 2. The Effects of miR-134 on body weight and plasma lipid profile in apoE KO mice

<table>
<thead>
<tr>
<th></th>
<th>AG-NC</th>
<th>AG</th>
<th>NG-NC</th>
<th>NG</th>
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<tbody>
<tr>
<td>BW (g)</td>
<td>27.62 ± 2.33</td>
<td>29.33 ± 3.99</td>
<td>28.62 ± 2.67</td>
<td>29.13 ± 2.56</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>2.56 ± 0.49</td>
<td>1.89 ± 0.46*</td>
<td>2.45 ± 0.52</td>
<td>3.38 ± 0.59*</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>15.65 ± 3.04</td>
<td>19.98 ± 3.54*</td>
<td>14.98 ± 2.89</td>
<td>12.15 ± 2.34*</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>3.52 ± 0.95</td>
<td>2.25 ± 0.98*</td>
<td>3.51 ± 1.15</td>
<td>5.12 ± 0.98*</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>11.98 ± 1.07</td>
<td>14.34 ± 1.23*</td>
<td>12.13 ± 1.22</td>
<td>10.15 ± 1.02*</td>
</tr>
</tbody>
</table>

Each group contained 10 mice. AG-NC: miR-134 agomir negative control, AG: miR-134 agomir, AN-NC: miR-134 antagomir negative control, AN: miR-134 antagomir, BW: body weight, TG: triglyceride, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol. HPLC method was used for determination of blood lipid levels. The data are the means ± SEM from the indicated numbers of male apoE KO mice in each group. *p < 0.05, vs AG-NC, **p < 0.05, vs AN-NC.
In summary, on the basis of in vitro experiments, our studies further suggest that overexpression of miR-134 facilitates lipid accumulation and the inflammatory response, leading to increased atherosclerotic lesions in apoE KO mice. Mechanistically, miR-134 upregulation enhances the LPL level by targeting ANGPTL4, which accelerates the formation of the LPL/LRP1 protein complex (Fig. 5). Thus, inhibition of miR-134 may become a novel and promising strategy for the prevention and treatment of atherosclerotic cardiovascular disease.

Conflict of Interest

We have no actual or potential conflict of interest.

Acknowledgments

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