Abstract. Numerous reports have shown that dysfunction of vascular smooth muscle cells (VSMCs) serves a critical function in the development of cardiovascular disease, including coronary heart disease (CHD). microRNAs (miRNAs/miRs) have been reported to play important roles in regulating the function of VSMCs. The present study aimed to determine the role of miR-24-3p in VSMCs and to uncover the underlying mechanism. The expression of miR-24-3p in the peripheral blood samples of CHD patients was measured by reverse transcription-quantitative (RT-q) PCR. It was found that the level of miR-24-3p in the peripheral blood of patients with CHD was significantly upregulated compared with that in healthy controls. A dual luciferase reporter assay was performed to determine whether Bcl-2-like protein 11 (Bcl-2L11) was a target gene of miR‑24‑3p, and it was identified that Bcl‑2L11 was a direct target of miR-24-3p. The mRNA level and protein expression of Bcl-2L11 in the peripheral blood of patients with CHD were measured by RT-qPCR and western blotting, respectively. The findings suggested that Bcl-2L11 was downregulated in the peripheral blood of patients with CHD. In addition, it was found that downregulation of miR-24-3p suppressed VSMC proliferation and promoted VSMC apoptosis, while the effects of the miR-24-3p inhibitor on cell viability and apoptosis were reversed by Bcl-2L11-small interfering (si)RNA. Additionally, downregulation of miR-24-3p increased the levels of Bel-2L11, caspase-3 and Bax, and decreased Bel-2 expression in VSMCs; these changes were abolished by Bcl-2L11-siRNA. In conclusion, the aforementioned results indicated that miR-24-3p was an important regulator in VSMC proliferation and apoptosis by targeting Bcl-2L11, which suggested that miR-24-3p might be a potential therapeutic target for the treatment of CHD.

Introduction

Cardio- and cerebrovascular disease incidence has increased due to improved living standards (1,2). Coronary heart disease (CHD) is one of the leading causes of death in the world and adversely affects public health (3,4). An increasing number of studies have indicated that vascular smooth muscle cells (VSMCs) serve vital functions in the development of CHD (5,6). However, the molecular mechanisms of VSMCs in CHD have yet to be elucidated.

MicroRNAs (miRNAs/miRs) are a class of non-coding RNAs of 20-22 nucleotides in length that are able to regulate 30-50% of all genes by binding to the 3'-untranslated regions (3'-UTRs) (7). miRNAs regulate various biological functions, including cell proliferation, apoptosis and signal transduction (8). Previous studies have suggested that miRNAs participate in the pathological processes of a number of diseases, including cardiac hypertrophy (9), heart failure (10), myocardial ischemia (11) and reperfusion (12). Previous studies have demonstrated that miR-24 is a vital molecule in mediating vascular endothelial cells (13,14). miR-24-3p has been shown to play an important role in regulating cell growth and metastasis in various types of cancer (15-17). In addition, miR-24-3p is involved in ischemia/reperfusion injury in cardiomyocytes (18). However, the function of miR-24-3p in VSMCs in coronary heart disease remains to be elucidated.

The Bcl-2 and caspase protein families serve different and vital roles in cell apoptosis (19). Bcl-2-like protein 11 (Bcl-2L11; Bim) is a pro-apoptotic member of the Bcl-2 family, which induces cytochrome c release from the mitochondria (20). Previous studies have reported that Bcl-2L11 mediates the biological processes of cell growth and apoptosis (21-23). Therefore, the present study investigated the modulating effect of miR-24-3p in VSMCs. Furthermore, the underlying mechanism by which miR-24-3p regulated the apoptosis of VSMCs was clarified.

The purpose of the present study was to investigate the expression of miR-24-3p in the blood samples of CHD patients, examine the role of miR-24-3p in VSMCs, and further to explore the molecular mechanism.
Materials and methods

Clinical specimen collection. Blood samples were collected from 30 patients with coronary heart disease (22 male, 8 female; age range, 37-75 years) and 30 healthy volunteers (22 male, 8 female; age range: 34-73 years) from Renmin Hospital (Shijian, China) between February 2016 and June 2018. The specimens were rapidly frozen and stored at -80°C until use. All patients provided written informed consent and approved the use of their samples in the present study. The study procedures obtained approval from the Ethics Committee at Renmin Hospital.

Cell culture. Human VSMCs were obtained from the American Type Culture Collection (cat. no. ATCC® PCS-100-012). Cells were cultured in DMEM (Gibco; Thermo Fisher Scientific, Inc.) containing 10% FBS (Gibco; Thermo Fisher Scientific, Inc.) and 1% penicillin/streptomycin (Sigma-Aldrich; Merck KGaA) at 37°C in a 5% CO₂ incubator.

Cell transfection and reagents. In total, 100 nM miR-24-3p inhibitor (antagonist of miR-24-3p; 5'-CUGUUCUCUGCGACUGAAGCCA-3'), 100 nM inhibitor control (5'-CAGUACUUGUGAGUACAA-3'), 100 nM miR-24-3p mimic (sense: 5'-UGGCUCCAGUCAGGAACAG-3'; anti-sense: 5'-GUUCUGCUAGACCCAUU-3'), 100 nM mimic control (sense: 5'-UCUUCUGACUGAGUCAGTT-3'; anti-sense: 5'-ACGUGACACAGGUGGAAT-3'; all from Shanghai GenePharma Co., Ltd.), 1 µM control small interfering (si)RNA (cat. no. sc-36869; Santa Cruz Biotechnology, Inc.), 0.2 µM Bcl-2L11-siRNA (cat. no. sc-29802; Santa Cruz Biotechnology, Inc.), 100 nM miR-24-3p inhibitor + 1 µM control-siRNA, or 100 nM miR-24-3p inhibitor + 0.2 µM Bcl-2L11-siRNA were transfected into VSMCs using Lipofectamine® 2000 (Invitrogen; Thermo Fisher Scientific, Inc.) for in accordance with the manufacturer's protocol. Reverse transcription-quantitative (RT-q) PCR was performed to detect the efficiency of cell transfection 48 h after incubation, at 37°C.

CCK-8 assay. A Cell Counting Kit-8 (Beyotime Institute of Biotechnology) was employed to detect the cell viability of VSMCs, according to the manufacturer's protocol. Cells were seeded into 96-well culture plates (6x10⁴ cells/well) and then incubated in DMEM for 24 h at 37°C. Then, the cells were transfected with inhibitor control, miR-24-3p inhibitor, miR-24-3p inhibitor + control-siRNA, or miR-24-3p inhibitor + Bcl-2L11-siRNA for 48 h. Subsequently, CCK-8 reagent was added into each well and the cells were incubated at 37°C for another 2 h. The absorbance (optical density) at a wavelength of 450 nm was measured using a microplate reader (Eon; BioTek Instruments, Inc.).

Flow cytometry analysis. VSMCs were transfected with inhibitor control, miR-24-3p inhibitor, miR-24-3p inhibitor + control-siRNA, or miR-24-3p inhibitor + Bcl-2L11-siRNA for 48 h. Then, Annexin V-FITC/propidium iodide (PI) dual staining was performed to evaluate cell apoptosis, according to the manufacturer's protocol (cat. no. KGA106; Nanjing KeyGen Biotech Co., Ltd.). Briefly, VSMCs were digested with 0.2% trypsin, washed with PBS and fixed with 70% ethanol overnight at 4°C. Then, the cells were stained with 5 µl Annexin V-FITC and 5 µl PI for 30 min at room temperature. Finally, the stained cells were quantified using a FACScalibur flow cytometer (BD Biosciences) and the data were analyzed with FlowJo 7.6.1 software (FlowJo LLC).

Dual-luciferase reporter assay. A bioinformatics prediction program (TargetScan 7.2; http://www.targetscan.org/vert_72/) was used to predict the relationship between miR-24-3p and Bcl-2L11, and binding sites between miR-24-3p and Bcl-2L11 were observed. To confirm the prediction, the wild-type (WT-Bcl-2L11: 5'-CCCUCGACUGGAAACUCGGCA-3') and mutant (MUT-Bcl-2L11: 5'-CCAAAGCAUGGGAAACUCGGCA-3') 3'UTR of Bcl-2L11, containing the miR-24-3p-binding elements, were generated by RT-PCR using a Transcriptor First Strand cDNA Synthesis Kit (Roche Molecular Systems, Inc.) from total RNA preps extracted from VSMCs, using the temperature protocol of 5 min at 25°C followed by 60 min at 42°C. The sequences were then cloned into a pmir-RB-Report™ dual luciferase reporter gene plasmid vector (Guangzhou RiboBio Co., Ltd.). Then 100 ng Bcl-2L11-WT or 100 ng Bcl-2L11-MUT were co-transfected with 100 nM miR-24-3p mimic or 100 nM mimic control into VSMCs using Lipofectamine® 2000 (Invitrogen; Thermo Fisher Scientific, Inc.), according to the manufacturer's protocols. Dual-Luciferase® Reporter Assay kit (Promega Corporation) was used to measure luciferase activity 48 h after cell transfection, which were normalized to that of Renilla luciferase.

RT-qPCR. TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.) was used to isolate the total RNA from cells or blood samples, respectively, according to the manufacturer's protocol. Then, 200 ng total RNA was reverse transcribed into cDNA using the miScript RT kit (Applied Biosystems; Thermo Fisher Scientific, Inc.), following the manufacturer's protocol. The temperature protocol for the reverse transcription reaction was as follows: Initial annealing at 25°C for 5 min, followed by extension at 42°C for 60 min and termination at 80°C for 2 min. The expression levels of miR-24-3p and Bcl-2L11 were quantified using a SYBR Green PCR Master Mix kit (Takara Biotechnology Co., Ltd.). GAPDH and U6 were used to normalize mRNA and miR-24-3p expression, respectively. The reaction conditions of the qPCR were as follows: 95°C for 5 min; 35 cycles of denaturation at 94°C (15 sec), annealing at 50°C for 30 sec and chain extension at 72°C for 30 sec; and a final extension step at 72°C for 10 min. Primers were purchased from Sangon Biotech Co., Ltd. (Shanghai, China): U6 forward, 5'-GCTTGCAGCAGCAATACTAAAT-3'; and reverse, 5'-CGCTTACGAATTTGCGTGTCAT-3'; GAPDH forward, 5'-TGTTGCTCATCAAGACCCCGCTT-3'; and reverse, 5'-CTCAGACGGTGTGTCTGCGGAGTCGAGGCAATTCGAT-3'; miR-24-3p forward, 5'-ACATCCACGTTGGTGCCTAGTTCAGCAG-3'; and reverse, 5'-CTCAGCTGGTCTGCGGAGTCGAGGCAATTCGAT-3'; Bcl-2L11 forward, 5'-CACAAA CCCCAAGTCTCCTCCT-3'; and reverse, 5'-ACACACACAGCCGAATGTTAA-3'; caspase-3 forward, 5'-TGTGCAATGACACAAAGCCCTCA-3'; and reverse, 5'-GACTTTCTACAACGATCTCCCCTTC-3'; Bax forward, 5'-CGTCCACAAAGGCTGAGC-3'; and reverse, 5'-CGTCCACAAAGGCTGAGC-3'; and Bcl-2 forward, 5'-TTGGATCGAGGAGTTGGAAG-3'; and reverse, 5'-TTGGATCGAGGAGTTGGAAG-3'; The 2^(-ΔΔCq) method (24) was used to calculate the relative expression levels. The assay was repeated three times.

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Western blot analysis. Proteins from VSMCs or blood samples were extracted using RIPA buffer (Beyotime Institute of Biotechnology). The protein concentration was detected by BCA Protein Assay kit (Thermo Fisher Scientific, Inc.). Then, the extracted protein samples were mixed with 5X loading buffer, boiled at 100°C for 5 min, centrifuged at 1,000 x g at 4°C for 2 min. Protein samples (30 µg protein/lane) were separated by 10% SDS-PAGE and subsequently transferred onto a PVDF membrane. Then, the membranes were blocked with 5% skimmed milk at room temperature for 1.5 h and subsequently incubated with the primary antibodies at 4°C overnight: Bcl-2L11 (cat. no. 2933; dilution 1:1,000), caspase-3 (cat. no. 14220; dilution 1:1,000), Bcl-2 (cat. no. 4223; dilution 1:1,000), Bax (cat. no. 5023; dilution 1:1,000) and GAPDH (cat. no. 5174; dilution 1:1,000; all from Cell Signaling Technology Inc.). After washing with TBS with Tween-20, the membranes were incubated with horseradish peroxidase-conjugated anti-rabbit immunoglobulin G secondary antibody (cat. no. 7074; dilution: 1:2,000; Cell Signaling Technology, Inc.) for 2 h at room temperature. Finally, the protein bands were visualized using ECL reagent (EMD Millipore), according to the manufacturer’s protocols.

Statistical analysis. All the aforementioned experiments were performed in triplicate. Data are expressed as the mean ± SD. Statistical analysis was performed using SPSS 19.0 software (IBM Corp.). Comparisons between groups were estimated by Student’s t-test or one-way analysis of variance followed by Tukey’s post hoc test. P<0.05 was considered to indicate a statistically significant difference.

Results

miR-24-3p expression is upregulated in blood samples from patients with CHD. The present study first evaluated miR-24-3p expression levels in peripheral blood samples from 30 patients with CHD and normal controls. The results from RT-qPCR indicated that the miR-24-3p expression was significantly higher in the peripheral blood samples of patients with CHD than that in the healthy volunteers (Fig. 1).

Bcl-2L11 is a direct target of miR-24-3p. To investigate potential miR-24-3p target sites, TargetScan was used to analyze the target genes of miR-24-3p. It was found that Bcl-2L11 was a possible target of miR-24-3p and the binding sites are shown in Fig. 2A. To better understand the interaction between miR-24-3p and Bcl-2L11, a luciferase reporter gene assay was performed. The results suggested that miR-24-3p mimic markedly suppressed the luciferase activity of cells co-transfected with miR-24-3p mimic and Bcl-2L11-WT, whereas no significant differences were observed in luciferase activity in cells co-transfected with miR-24-3p mimic and Bcl-2L11-MUT (Fig. 2B).

Bcl-2L11 mRNA and protein levels were then detected in the blood samples of patients with CHD using RT-qPCR and western blotting. As shown in Fig. 2C, the mRNA level of Bcl-2L11 was significantly reduced in the blood samples of patients with CHD compared with healthy controls. In addition, a relatively decreased protein expression level of Bcl-2L11 was observed in the blood samples of CHD patients via western blot analysis (Fig. 2D). In summary, it was concluded that Bcl-2L11 was a direct target of miR-24-3p. The expression levels of Bcl-2L11 in patients with CHD were reduced.

Bcl-2L11-siRNA reverses the incremental effects of miR-24-3p inhibitor on VSMCs. The functional relevance of Bcl-2L11 in miR-24-3p-regulated effects in VSMCs was explored. Control-siRNA, Bcl-2L11-siRNA, inhibitor control, miR-24-3p inhibitor, miR-24-3p inhibitor + control-siRNA, or miR-24-3p inhibitor+Bcl-2L11-siRNA were transfected into VSMCs for 48 h. RT-qPCR was performed to evaluate the transfection efficiency. As presented in Fig. 3A, compared to the control group, the levels of miR-24-3p were significantly decreased in VSMCs transfected with miR-24-3p inhibitor. The Bcl-2L11 mRNA level was significantly decreased in VSMCs transfected with Bcl-2L11-siRNA compared with the control group (Fig. 3B). The results of the RT-qPCR and western blotting demonstrated that the mRNA and protein levels of Bcl-2L11 increased in the VSMCs transfected with miR-24-3p inhibitor compared with the control group, and this increase was reversed by Bcl-2L11-siRNA (Fig. 3C and D). Taken together, it was found that Bcl-2L11 was negatively regulated by miR-24-3p in VSMCs.

Bcl-2L11-siRNA reverses the effect of miR-24-3p inhibitor on cell proliferation and apoptosis in VSMCs. In order to further investigate the effect of miR-24-3p on VSMCs, a CCK-8 assay and flow cytometry were performed to assess VSMC viability and apoptosis. VSMCs were transfected with an inhibitor control, miR-24-3p inhibitor, miR-24-3p inhibitor + control-siRNA, or miR-24-3p inhibitor + Bcl-2L11-siRNA for 48 h. The results of the CCK-8 analysis indicated that cell viability was significantly decreased in the miR-24-3p inhibitor group compared with the control group, whereas this decrease was reversed by Bcl-2L11-siRNA (Fig. 4A). Flow cytometry analysis demonstrated that compared with the control group, miR-24-3p inhibitor significantly induced
Figure 3. Effect of miR-24-3p inhibitor on Bcl-2L11 expression in VSMCs. VSMCs were co-transfected with the control-siRNA, Bcl-2L11-siRNA, inhibitor control or miR-24-3p inhibitor, miR-24-3p inhibitor + control-siRNA, or miR-24-3p inhibitor + Bcl-2L11-siRNA for 48 h. RT-qPCR was performed to evaluate the transfection efficiency. (A) The level of miR-24-3p was detected when VSMCs were transfected with the miR-24-3p inhibitor or inhibitor control for 48 h. (B) The Bcl-2L11 mRNA level was tested by RT-qPCR in VSMCs transfected with Bcl-2L11-siRNA or control-siRNA. (C) RT-qPCR and (D) western blotting were performed to measure the Bcl-2L11 mRNA and protein expression in different groups. All experiments were performed three times. Data are presented as the mean ± SD. **P<0.01 vs. control. ##P<0.01 vs. inhibitor control. miR, microRNA; Bcl-2L11, Bcl-2-like protein 11; VSMCs, vascular smooth muscle cells; si, small interfering; RT-qPCR, reverse transcription quantitative PCR.
apoptosis in VSMCs, while Bcl-2L11-siRNA clearly reversed these effects (Fig. 4B and C). These data demonstrated that miR-24-3p inhibitor could inhibit VSMC viability and induce VSMC apoptosis by targeting Bcl-2L11.

**miR-24-3p affects VSMC apoptosis by regulating Bcl-2L11/Bcl-2/Bax/caspase-3 expression.** To further explore the underlying mechanism of miR-24-3p inhibitor-induced cell apoptosis, the expression levels of Bcl-2L11, caspase-3, Bcl-2 and Bax were determined by western blot analysis and RT-qPCR. VSMCs were transfected with inhibitor control, miR-24-3p inhibitor, miR-24-3p inhibitor + control-siRNA or miR-24-3p inhibitor + Bcl-2L11-siRNA for 48 h. As shown in Fig. 5A, miR-24-3p inhibitor increased the protein levels of Bcl-2L11, caspase-3 and Bax, while it decreased the protein levels of Bcl-2 in VSMCs, and these changes were reversed by Bcl-2L11-siRNA. RT-qPCR assay indicated that miR-24-3p inhibitor significantly increased the mRNA levels of Bcl-2L11, caspase-3 and Bax, while it decreased the mRNA levels of Bcl-2 (Fig. 5). All these changes were reversed by Bcl-2L11-siRNA.

**Discussion**

VSMCs are the main cell type in blood vessels and, abnormal proliferation and apoptosis of VSMCs may result in the rapid development of disease (25,26). Recently, growing evidence has identified miRNAs as new biomarkers for a number of cardiovascular diseases (27,28). It is necessary to identify disease-specific miRNAs and their targets to understand their roles in disease (29-31). It has been reported that various miRNAs participate in mediating the functions of VSMCs, including miR-21, miR-214 and miR-146a (32-34). In the present study, the expression level of miR-24-3p in the blood samples of 30 patients with CHD was explored using RT-qPCR and it was found that the miRNA-24-3p level was higher in the blood samples of patients with CHD compared with the normal controls. The results demonstrated that miRNA-24-3p might play a vital role in modulating CHD. Luciferase reporter analysis identified that Bcl‑2L11 was a direct target of miRNA-24-3p in VSMCs. The measurements of the mRNA and protein Bcl-2L11 expression in peripheral blood samples of CHD patients and normal volunteers showed that Bcl-2L11 was downregulated in the blood samples of CHD patients. However, the relationship between miRNA-24-3p expression and Bcl-2L11 expression in patients with CHD was not analyzed. This might be a limitation of the present study, and is something to explore in the future.

Then, the role and mechanism of miRNA-24-3p in regulating VSMCs was investigated. It has been reported that Bcl-2L11 is a pro-apoptotic Bcl-2 family member and it is activated in a number of activities, including mediating excitotoxic apoptosis, mitochondrial depolarization and factor
translocation (35-37). As Bcl-2L11 was found to be a direct target of miRNA-24-3p in VSMCs, it was hypothesized that altering the expression of miRNA-24-3p in the VSMCs of CHD patients could change the Bcl-2L11 expression and the growth of VSMCs. To test this hypothesis, inhibitor control, miRNA-24-3p inhibitor, miRNA-24-3p inhibitor + control-siRNA, or miRNA-24-3p inhibitor + Bcl-2L11-siRNA were transfected into VSMCs. The results showed that miRNA-24-3p inhibitor significantly increased Bcl-2L11 expression in VSMCs, while this increase was eliminated by Bcl-2L11-siRNA. miRNA-24-3p inhibitor significantly suppressed cell viability and induced apoptosis in VSMCs. However, Bcl-2L11-siRNA significantly reversed the effects of miRNA-24-3p inhibitor on cell viability and cell apoptosis in VSMCs. These data indicated that miRNA-24-3p regulated the apoptosis of VSMCs in patients with CHD. This was in accordance with the observations of previous studies (38,39). However, the effect of miR-24-3p upregulation on VSMCs was not investigated and this might be a limitation of the present study, to be addressed in the future.

Cell apoptosis occurs through two pathways: The death receptor-regulated external signaling pathway and the mitochondria-regulated internal signaling pathway (40). The present study investigated the signaling pathway in which miRNA-24-3p regulated apoptosis in the VSMCs of patients with CHD. It was observed that miRNA-24-3p inhibitor significantly upregulated the expression of Bcl-2L11, caspase-3 and Bax in VSMCs, and the expression of Bcl-2 was suppressed. The effects of miR-24-3p inhibitor on the expression of these genes were reversed by Bcl-2L11-siRNA.

In conclusion, the present study suggested that miRNA-24-3p exhibited a vital role in regulating the viability and apoptosis of VSMCs by targeting Bcl-2L11. This may provide potential therapeutic targets for the interference and treatment of CHD. However, the current study is only a preliminary study of the expression of miRNA-24-3p in CHD patients and its role in VSMCs. To substantiate the role of miRNA-24-3p in CHD in vivo needs further study.
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Availability of data and materials

All data sets used and/or generated during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HXZ and SZX contributed to study design, data collection, statistical analysis, data interpretation and manuscript preparation. YF contributed to data collection, statistical analysis and manuscript preparation. JS and JXZ contributed to data collection and statistical analysis. All authors approved the final version of the manuscript.

Ethics approval and consent to participate

All patients provided written informed consent and approved the use of their samples in the present study. The study procedures obtained approval from the Ethics Committee at Renmin Hospital.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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