MicroRNAs (miRNAs) play critical roles in the development of vascular diseases. However, the effects of miR-130a-5p and its functional targets on atherosclerosis (AS) are still largely unknown. In this regard, our aim is to explore the potentially important role of miR-130a-5p and its target gene during the progression of endothelial cell injury. We first found oxidized low-density lipoprotein (ox-LDL) induced FAS and cell apoptosis in HUVECs. Subsequently, miR-130a-5p expression was verified to be downregulated after ox-LDL treatment and negatively correlated with FAS, and FAS was identified as substantially upregulated in the ox-LDL-treated HUVEC cells. After that, the knockdown of FAS and overexpression of miR-130a-5p together were observed to aggregate ox-LDL-induced reduction of cell viability and apoptosis, cell cycle progression, cell proliferation, cell migration and invasion. In conclusion, we detected that miR-130a-5p contributed to the progression of endothelial cell injury by regulating of FAS, which may provide a new and promising therapeutic target for AS.

Key words: Atherosclerosis; ox-LDL; miR-130a-5p; FAS.
Introduction

Atherosclerosis (AS), a chronic inflammatory disease, is a major cardiovascular disease that is characterized by the deposition of oxidized low-density lipoprotein (ox-LDL), endothelial cell injury, and plaque accumulation in the vascular walls.\textsuperscript{1,2} Its prevention and treatment are all important in medical research. ox-LDL within plaques has been reported to be able to induce apoptosis of endothelial cells, and it is considered to contribute to the inflammatory state of AS and to play a key role in its pathogenesis.\textsuperscript{3,4} It leads to considerable morbidity and mortality in most countries. Therefore, improved understanding of the potential biological mechanisms underlying endothelial cell injury could facilitate the development of novel treatments for AS.

miRNAs, also widely found in humans, are a group of 19-22 nucleotides. They comprise of non-coding, single-stranded RNA molecules that participate in sequence-specific post-transcriptional regulation of gene expression.\textsuperscript{5} miRNAs have emerged as crucial players in many biological processes of human diseases, such as apoptosis, cell proliferation, cell migration and invasion.\textsuperscript{6} It has been verified that many miRNAs also play important roles in AS. For instance, miR-146-5p has been reported to protect against AS by inhibiting vascular smooth muscle cell proliferation and migration.\textsuperscript{7} miR-200b-3p has been validated to promote endothelial cell injury, as well as the potential inhibition of miR-130a-5p and FAS on endothelial cell injury, as well as the potential inhibition during the early stages of obesity development.\textsuperscript{13} However, it is still unclear about the potentially important role of miR-130a-5p during the development of AS.

FAS (also known as APO-1 or CD95) belongs to the subgroup of the tumor necrosis factor receptor (TNF-R) family that contain the face death receptor.\textsuperscript{14} Activated FAS recruits FAS-associated protein death domain (FADD) adaptor protein. FADD further recruits caspase-8, caspase-10, and cellular FADD-like interleukin-1-β-converting enzyme-inhibitory protein (c-FLIP) to form the death-inducing signaling complex (DISC), which mediates both apoptotic and non-apoptotic signaling pathways.\textsuperscript{15,16} However, to date, little is known about the important role of miR-130a-5p and FAS, and this needs to be further explored.

In this study, we aimed to investigate the effects of miR-130a-5p and FAS on endothelial cell injury, as well as the potential molecular pathways involved in cultured human umbilical vein endothelial cells (HUVECs) in vitro.

Materials and Methods

Cell culture

HUVEC cells have played a major role as a model system for the study of the regulation of endothelial cell function. HUVEC cells (Shanghai Al!Cells Biotech Co., Ltd. Shanghai, China) were cultured at 37°C and 5% CO\textsubscript{2} in HyClone M-199 media (GE Healthcare Life Sciences, South Logan, UT, USA) with 1% antibiotics-antimicrobial (Gibco, Carlsbad, CA, USA), and 15.3 units of heparin (Sigma-Aldrich, St. Louis, MO, USA), one vial of endothelial cell growth supplement (Millipore, Bedford, MA, USA), and 10% FBS (Sigma-Aldrich). Cells were cultured up to 80% confluency, and growth media was replaced every other day.

The cellular model of AS was constructed using HUVEC stimulated by 100 μg/mL of oxidized low-density lipoprotein (ox-LDL, Solarbio, Beijing, China) ox-LDL (Solarbio, Beijing, China) for 24 h.\textsuperscript{4} ox-LDL at 100 μg/mL was diluted in PBS.

RNA interference

For the RNA interference assay, the siFAS and negative siCtrl were from GenePharma Co., Ltd. (Shanghai, China). We tested 3 siFAS sequences. The siFAS-1 sequence was composed of the sense strand 5’-CCCCUGACCCAUGUGAATT-3’ and the antisense strand 5’-UUCAACUUGGCGAAGGGTT-3’. The siFAS-2 sequence was composed of the sense strand 5’-GCCAUAUCCACUAUUGUUTT-3’ and the antisense strand 5’-AACAUUUAGUGGAUUGGCTT-3’. The siFAS-3 sequence was composed of the sense strand 5’-GGUUCAUGAAUCUC-CAAATT-3’ and the antisense strand 5’-UUGGAAGAUUCAUGA-GAACCTT-3’. The sequence of siCtrl consisted of the sense strand UUCCUGAAACGUGUCACGUTT and the antisense strand ACGUGACACGUUCGGGAAAGAT. HUVECs were transfected with 3 siRNAs mixture using RNAiMAX (Invitrogen, Carlsbad, CA, USA) according to the manufacturer’s instructions. We seeded the cells into 6-well plate to be 80% confluent at transfection; 9 μL of RNAiMAX was diluted with 150 μL of Opti-MEM medium (Gibco); 3 μL of siRNA (10 μM) was diluted in 150 μL of Opti-MEM medium. The diluted siRNA was added to diluted RNAiMAX at 1:1 ratio and incubated for 5 min at room temperature. After that, 250 μL of siRNA-lipid complex was added into per well and incubated for 2 days at 37°C.

miR-130a-5p overexpression

Negative control oligonucleotide (miR NC) and miR-130a-5p mimic (miR mimic) overexpression lentiviral systems were commercially available at RiboBio Co. Ltd. (Guangzhou, China). Cells were plated at 20-30% confluence for 24 h. After that, 50 pmol/mL RNA oligonucleotides were transfected using the Lipofectamine 2000 reagent (Invitrogen) according to the manufacturer’s instructions.

qRT-PCR

Total RNA from the cells was prepared by TRIzol reagent (Invitrogen). Then, 1 μg of total RNA was subjected to reverse transcription using PrimeScript RT Master Mix (Perfect Real Time) (Takara, Shiga, Japan). Quantitative real-time PCR was carried out using the TB Green Premix Ex Taq II (Tli RNaseH Plus) (Takara) to detect FAS gene mRNA level (forward: 5’-AGATTGTGGTGTGAAAGGACATGG-3’, reverse: 5’-GTGGTGCTGTGATGTTGCAATT-3’) on StepOnePlus Real-Time PCR System (Applied Biosystems, Waltham, MA, USA). GAPDH (forward: 5’-AGAAGGCTGCGGGCTCAATTG-3’, reverse: 5’-AGGGGCCATCCACAGTCCTTC-3’) was used as the internal reference gene.

For miRNA quantification, the Taqman advanced miRNA cDNA synthesis kit was used to implement reverse transcription following the manufacturer’s instruction (Applied Biosystems, Carlsbad, CA, USA). The Taqman microRNA reverse transcription kit was used for U6 small nuclear RNA (snRNA) to perform reverse transcription according to manufacturer’s protocol (Applied Biosystems). All probes were purchased from ThermoFisher Scientific (Waltham, MA, USA). The comparative \(2^{-ΔΔCt}\) method\textsuperscript{4} was used to analyze the relative expression level of FAS and miR-130a-5p.

Western blotting

The total protein of the cells was extracted with T-PER tissue protein extraction reagent (Thermo Fisher, Rockford, IL, USA).
with 1% fetal bovine serum and 1% penicillin-streptomycin (Thermo Pierce).

5-ethyl-2'-deoxy-uridine (EdU) incorporation assay

The 5-ethyl-2'-deoxy-uridine (EdU) incorporation assay (Beyotime) was performed to evaluate cell proliferation. Cells were treated with 100 μg/mL of ox-LDL for 24 h and transfected with siCtrl or siFAS for 24 h. In the next step of the study, we transfected the cells with siCtrl or siFAS with miR NC or miR mimic for 24 h, separately. Subsequently, cells were digested and seeded into a 96-well plate at a density of 2X10^3 cells per well. Cells were cultured with 20 μM of EdU diluent at 37°C with 5% CO₂ for 2 h. After that, 4% paraformaldehyde was used to fix cells for 15 min. After cells were washed with PBS, 1 mL of permeabilization solution was added to each well and incubated for 15 min at room temperature. Cells were incubated with endogenous peroxidase blocking solution at room temperature for 20 min, and washed with PBS 3 times. 50uL of Click reaction solution was added into each well and incubated for 30 min at room temperature in the dark. After that, cells were washed with PBS 3 times. Streptavidin-HRP working solution was added to the sample, incubated at room temperature for 30 min, and washed with PBS 3 times. After that, 0.1 mL of TMB color developing solution was added, and incubated at room temperature for 30 min. The absorbance was directly measured at 370 nm.

Wound scratch assay analysis

Cells were treated with 100 μg/mL of ox-LDL for 24 h. After that, cells were first transfected with siCtrl or siFAS for 24 h. Next, we transfected the cells with siCtrl or siFAS with miR NC or miR mimic for 24 h, Wound scratch assay was performed as previously described.20-22 Subsequently, cells were seeded into 12-well plates at a density of 5x10^3 cells per well with medium, and they were cultured for 24 h to reach ~90% confluence. A 10 μL pipette tip was used to make a scratch line. Cells were washed with PBS 3 times to remove the scratched cells. After that, cells were cultured in a medium containing 0.5% FBS. The cells were incubated at 37°C and images were captured at 6 and 24 h using a light microscope (Olympus Corporation, Tokyo, Japan). PBS was used as a control.

Transwell assay

Cell invasion was assayed by Boyden chamber assay with a 24-well collagen-based cell invasion assay kit (Millipore); 200 μL of serum-free medium containing 5x10^5 cells for the invasion assay were added to the filter. The bottom chamber was prepared with 750 μL of complete cell culture medium in which the FBS was a chemoattractant. After being incubated for the indicated time, the non-invasive cells were cleaned by scrubbing with a cotton swab. The cells that adhered to the outside of the membrane were fixed and dyed with Cristal Violet solution. An Olympus optical microscope (Olympus Corporation) was used to observe migratory or invasive cells.

Dual-luciferase reporter assay

The wide type (WT) and mutant (MUT) binding sites of FAS were commercially available from General Biosystems (Chuzhou, Anhui, China) and were cloned into the psiCHECK-2 vector (Promega, Madison, WI, USA) downstream of a firefly luciferase reporter gene using the Xhol and EcoRI restriction sites.

Cells were seeded in a 24-well plate (2x10^5 cells/well). After being in culture for 24 h, plasmids were transfected using the X-tremeGene HP DNA transfection reagent (Roche Diagnostic, Basel, Switzerland) and 100 μL of Opti-MEM (Gibco) at a ratio of 1 μg plasmid to 2 μL X-tremeGene HP reagent. Following incubation at 37°C for 6 h, the medium was replaced with fresh culture medium containing 10% FBS. Following incubation for 24 h, the dual-luciferase reporter assay system (Beyotime, Shanghai, China)
was used to verify the transfection efficiency according to the manufacturer’s protocols.

**Statistical analysis**

Statistical analyses were performed using GraphPad Prism and all data were presented as mean ± SD from at least 3 independent experiments. Differences between two groups were analyzed by unpaired *t*-test. ANOVA was used to compare differences in multiple groups. A *p*-value of less than 0.05 is statistically significant.

**Results**

**ox-LDL-induced FAS and cell apoptosis in HUVEC cells**

ox-LDL was used to mimic endothelial injury caused by lipid accumulation in atherosclerosis. HUVEC cells were stimulated with several doses of ox-LDL (10, 20, 40, 80 and 100 μg/mL) for 24 h. The cell morphology changed from a spindle shape to a spherical or elliptical shape after being treated with 100 μg/mL of ox-LDL compared with the non-treatment control group (Figure 1A). Meanwhile, we found that FAS protein expression was altered by western blotting under the induction of different dose of ox-LDL (Figure 1B). As the dose of ox-LDL increased, FAS expression gradually increased (Figure 1B,C). We also observed that HUVEC cell apoptosis was significantly increased after treatment of 100 μg/mL (Figure 1D).

**FAS was repressed by miR-130a-5p**

To advance the understanding of the FAS involved in ox-LDL induced HUVEC cell apoptosis and discover the potential target gene network of early AS, we first verified the upstream regulators including miRNAs for FAS. MiR-130a-5p is one of the predicted upstream miRNAs. As shown in Figure 2A, miR-130a-5p expression decreased as the dose of ox-LDL increased. FAS mRNA and miR-130a-5p expression levels are negatively correlated (Figure 2A). To verify whether FAS is a potential target of miR-130a-5p, HUVEC cells were cotransfected with the FAS 3’-UTR wide type (WT) firefly luciferase reporter vectors with miR-130a-5p (miR mimic) or control miRNA (miR NC). We also cotransfected HUVEC cells with mutant (MUT) firefly luciferase reporter vectors with miR mimic or control miR NC. We found that miR-130a-5p repressed the activity of FAS 3’-UTR WT (Figure 2B). When we mutated the binding site in FAS, inhibition of the reporter activities by miR-130a-5p was less compared with FAS 3’-UTR WT (Figure 2B). Furthermore, NC had no effect on both of FAS 3’-UTR WT and MUT (Figure 2B). These results suggest that the FAS is directly repressed by miR-130a-5p and that both are involved in the endothelial cell injury.

**FAS knockdown and miR-130a-5p overexpression aggregated ox-LDL induced cell viability and apoptosis reduction**

SiFAS or and miR-130a-5p mimic were transfected into HUVECs to reduce FAS expression and overexpress miR-130a-5p.

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**Figure 1.** Ox-LDL-induced FAS and cell apoptosis in HUVECs. A) the cell morphology changed from a spindle shape to a spherical or elliptical shape after being treated with 100 g/mL of ox-LDL compared with the non-treatment control group; scale bar: 50 μm. B) Western blot analysis of FAS under different dose of Ox-LDL. C) The blotting bands were quantified by ImageJ. The relative FAS expression levels were normalized to α-tubulin; ***p<0.01 vs no Ox-LDL treatment. (D) 100 g/mL ox-LDL induced cell apoptosis. The apoptosis rate was detected through flow cytometry by using annexin V-FITC/PI double staining. The apoptotic rate was analyzed in terms of the percentage of the lower and upper right quadrants. Results are mean ± SD (n = 3). ***p<0.01 vs control.
HUVECs transfected with control siRNA and miRNA were treated with 100 μg/mL ox-LDL for 24h. These samples constituted the control group. The same control group was used in all of the subsequent assays. The effect of siFAS and miR-130a-5p mimic on the ox-LDL-induced reduction of HUVEC viability was detected with CCK-8. Figure 3A showed that the cell viability in the siFAS group or miR-130a-5p mimic with ox-LDL treatment was increased compared with the control group. The cell viability of the siFAS and miR-130a-5p mimic group with ox-LDL treatment was significantly increased more compared to either siFAS group or miR-130a-5p mimic group (Figure 3A).

The effect of siFAS and miR-130a-5p mimic on the ox-LDL-induced reduction of HUVEC apoptosis was determined by flow cytometry. We found that the cell apoptosis in the siFAS group or miR-130a-5p mimic with ox-LDL treatment was significantly decreased compared with the control group (Figure 3B). The cell apoptosis of the siFAS and miR-130a-5p mimic group with ox-LDL treatment was strongly decreased more compared to either siFAS group or miR-130a-5p mimic group (Figure 3B).

**FAS knockdown and miR-130a-5p overexpression promoted cell cycle at S and G2/M phases**

We subsequently examined the effect of FAS knockdown and miR-130a-5p overexpression on cell cycle progression. In ox-LDL treatment cells, the percentage of HUVECs in the G1 phase was obviously decreased in siFAS and miR-130a-5p mimic groups compared with that in control group, whereas the percentage of siFAS and miR-130a-5p mimic group was significantly increased more compared to either siFAS group or miR-130a-5p mimic group (Figure 3A).

![Figure 2. FAS was repressed by miR-130a-5p. A) miR-130a-5p expression decreased as the dose of ox-LDL increased. FAS mRNA and miR-130a-5p expression levels are negatively correlated; results are mean ± SD (n=3); **p<0.05 vs miR-130a-5p; ***p<0.01 vs miR-130a-5p. B) 3’-UTR luciferase reporter assays. HUVEC cells were co-transfected with WT FAS (FAS-3UTR-WT) or its mutant (FAS-3UTR-MUT), miRNA control (NC) or miR-135a-5p mimic (miR mimic) for 24 h; Firefly luciferase activity was normalized to Renilla luciferase activity; results are mean ± SD (n=3); **p<0.05 vs NC; ***p<0.01 vs NC.](image1)

![Figure 3. FAS knockdown and miR-130a-5p overexpression altered ox-LDL induced reduction of cell viability and apoptosis. A) The effect of siFAS and miR-130a-5p mimic on the ox-LDL-induced reduction of HUVEC viability was detected with CCK-8; **p<0.05 vs siFAS + miR NC; ***p<0.01 vs siCtrl + miR NC. B) The effect of siFAS and miR-130a-5p mimic on the ox-LDL-induced reduction of HUVEC apoptosis was determined by flow cytometry; results are mean ± SD (n=3); ***p<0.01 vs siCtrl + miR NC.](image2)
significantly decreased to a greater degree when compared with control group (Figure 4). Meanwhile, in ox-LDL treatment cells, the percentage of HUVECs in the S and G2/M phases was remarkably increased than the control group (Figure 4). In addition, the percentage of S and G2/M phases cells in siFAS and miR-130a-5p mimic group was more obviously enhanced than the control group (Figure 4).

Overall, these results suggested that the downregulation of FAS and upregulation of miR-130a-5p could lead to cell cycle arrest at the S and G2/M phases.

**FAS knockdown and miR-130a-5p overexpression increased ox-LDL-induced cell proliferation reduction**

We tested the alteration on the ox-LDL-induced reduction of cell proliferation after FAS knockdown or/and miR-130a-5p overexpression. Cell proliferation in live cells was slowly and significantly increased in D4 in ox-LDL treatment cells with siCtrl and miR NC (control group, Figure 5). Meanwhile, cell proliferation was significantly increased to a greater degree in both siFAS and miR NC (siFAS group), or siCtrl and miR-130a-5p mimic (miR-130a-5p mimic group) in D4 compared with that of the control group. Whereas the cell proliferation of siFAS and miR-130a-5p mimic group was significantly increased to a greater degree when compared with the controls: the siFAS and miR-130a-5p mimic groups (Figure 5).

**FAS knockdown and miR-130a-5p overexpression promoted ox-LDL-induced migration and invasion reduction**

Enhanced migration and invasion are another key feature across the metastatic cascade. To assess the effect of FAS knockdown and miR-130a-5p overexpression on the migration and invasion of HUVEC cells, wound scratch and transwell assays were performed, respectively.

As shown in Figure 6 A,B, the rate of gap closure and invasion were significantly increased in the siFAS and miR-130a-5p mimic
groups compared with that of the control group, whereas the rate of gap closure and invasion of siFAS and miR-130a-5p mimic group was also significantly enhanced to a greater degree when compared with the siFAS and miR-130a-5p mimic control groups (Figure 6 A,B).

**Discussion**

In this study, our goal was to explore the potential important roles of miR-130a-5p and FAS during the progression of endothelial cell injury and provide the rationale for novel potential therapeutical tools of AS. We used ox-LDL to treat HUVEC cells and build up a cell model of AS. Then we found that FAS was repressed by miR-130a-5p. In addition, FAS knockdown and miR-130a-5p overexpression together were found to play important roles on ox-LDL induced reduction of cell viability, apoptosis, cell cycle progression, cell proliferation, migration and invasion.

miR-130a-5p has emerged as an important regulator in different human diseases. miR-130a-5p has been found to affect cell growth, migration and invasion by targeting CRIR via the Wnt/β-catenin signaling pathway in gastric carcinoma. In addition, the miRNA-130a-5p/RUNX2/STK32A network modulates tumor invasive and metastatic potential in non-small cell lung cancer. Moreover, FAM225A promotes soralfenib resistance in hepatocarcinoma cells by modulating the miR-130a-5p–CCNG1 interaction network. In this study, we found that miR-130a-5p expression decreased as the dose of ox-LDL increased. FAS mRNA and miR-130a-5p expression levels are negatively correlated. In addition, miR-130a-5p overexpression was found to aggregate ox-LDL induced reduction of cell viability and apoptosis, cell cycle progression, cell proliferation, migration and invasion.

Currently, miRNAs and FAS have been reported to work together and play important roles in human diseases. MiR-196b-5p-mediated downregulation of FAS promotes NSCLC progression by activating IL6-STAT3 signaling. MiR-19-3p has also been observed to induce tumor cell apoptosis via targeting FAS in rectal cancer cells. Especially, miRNAs have been attracted more attention in AS study. miR-302c-3p has been reported to inhibit endothelial cell pyroptosis via directly targeting NO-, LRR-and pyrin domain-containing protein 5 in AS. MiRNA-30e has been determined to regulate TGF-β-mediated NADPH oxidase 4-dependent oxidative stress by Snail in AS. Although those previous studies, the biological activities of miR-130a-5p in AS still remains largely unknown. In this regard, we determined that miR-130a-5p contributed to the progression of endothelial cell injury by regulating of FAS. FAS is the direct target of miR-130a-5p. FAS knockdown and miR-130a-5p overexpression together were found to aggregate to a greater extent ox-LDL induced reduction of cell viability and apoptosis, cell cycle progression, cell proliferation, migration and invasion compared to FAS knockdown itself. However, further studies should be performed in vivo. Once the role of miR-130a-5p had been confirmed in vivo, miR-130a-5p would become a novel therapeutic target for AS patients.

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