MiR-193-3p inhibits the malignant progression of atherosclerosis by targeting WDR5

Kai Yang, MD, Chunjun Yu, MD, Lin Ruan, MD, Shengpeng Hu, MD, Wenjie Zhu, MD, and Feng Xia, MD

Abstract

Background: The aberrantly increased proliferation and migration of vascular smooth muscle cells (VSMCs) was critically associated with atherosclerosis (AS) progression. MiR-197-3p has been confirmed to regulate various biological processes, such as tumorigenesis; however, whether miR-197-3p is involved with the pathological development of AS remains largely unknown.

Methods: The serum levels of miR-197-3p in AS patients and healthy donors were determined by polymerase chain reaction (PCR) assay. The transfection efficacies of miR-197-3p mimic or inhibitor in VSMCs were evaluated by PCR assay. The effects of miR-197-3p on VSMC proliferation and migration were determined by EdU cell proliferation and Traswell migration assays. Western blotting was conducted to evaluate the effect of miR-197-3p on WDR5 expression in VSMCs.

Results: In the present study, we found that the expression of miR-197-3p was decreased in the serum of AS patients compared to healthy donors. Overexpression of miR-197-3p inhibited the proliferation and migration of VSMCs, while silencing miR-197-3p showed opposite effects. Mechanistical study revealed that WD Repeat Domain 5 (WDR5) was a target of miR-197-3p. Moreover, miR-197-3p was downregulated in VSMCs upon IL6 treatment and inhibited IL6-induced proliferation and migration in VSMCs.

Conclusions: These findings indicate that miR-197-3p could serve as a promising diagnostic marker for AS and that targeting IL6/miR-197-3p/WDR5 axis might be a potential approach to treat AS.

Keywords
ATHEROSCLEROSIS, VASCULAR SMOOTH MUSCLE CELLS, MiR-197-3P, WDR5, IL6

Date received: 29 April 2022; revised: 17 July 2022; accepted: 26 July 2022.

Introduction

Atherosclerosis (AS), characterized by the formation of fatty plaques in the intima of arteries, has become the leading cause of morbidity and mortality all around the world.1,2 The occurrence of luminal stenosis or thrombogenesis leads to the obstruction of blood flow to the heart, brain and lower extremities, resulting in coronary heart disease, ischemic stroke, and peripheral vascular disease, respectively.1,2 It has been confirmed that the aberrantly increased proliferation and migration of vascular smooth muscle cells (VSMCs) critically contribute to the pathogenesis and progression of AS.3,4 These VSMC behaviors can be induced by various growth factors, such as platelet-derived growth factor BB (PDGF-BB), as well as non-coding RNAs,3,4 including microRNAs (miRNAs). Therefore, targeting VSMC dysfunctions might be a promising therapeutic strategy to manage AS-related vascular diseases.

Currently, increasing studies have demonstrated that a variety of miRNAs are dysregulated in AS and play an important role in AS progression via regulating VSMC functions.5,6 For example, miR-186-5p regulated VSMC behaviors and can be served as diagnostic biomarker in AS.7 MiR-128 targeted KLF4 to inhibit the proliferation and migration of VSMCs and reduce neointima formation in the injured carotids.6 Of note, miR-197-3p functions as a tumor-suppressive miRNA in various types of tumors by inhibiting tumor cell proliferation.

Department of Cardiovascular Surgery, WuHan Asia General Hospital, Wuhan City, Hubei Province, China

Corresponding Author:
Feng Xia, WuHan Asia General Hospital, No. 300, Taizihu North Road, Hanyang District, Wuhan City, Hubei Province, 430050, China.
Email: xiafeng030@163.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (https://us.sagepub.com/en-us/nam/open-access-at-sage).
and migration.\textsuperscript{8,9} MiR-197-3p was also a target of circ_USP36 that was upregulated in AS patients,\textsuperscript{10} indicating that miR-197-3p might be associated with AS progression. However, the expression of miR-197-3p in AS patients and the effects and mechanisms of miR-197-3p on VSMC proliferation and migration are largely unknown.

In the present study, we found that the expression of miR-197-3p was decreased in the serum of AS patients. MiR-197-3p targeted WD Repeat Domain 5 (WDR5) to inhibit the proliferation and migration of VSMCs. IL6 induced miR-197-3p downregulation in VSMCs and miR-197-3p inhibited IL6-induced VSMC behaviors. Our study indicated that miR-197-3p/WDR5 axis could serve as a diagnostic biomarker and therapeutic target in AS patients.

\textbf{Materials and Methods}

\textbf{Patient Study}

The serum samples were obtained from 52 patients with stable AS (age, 42.6 ± 8.2, 32 male and 20 female) and the degree of AS was evaluated by the Gensini scoring system. The serum samples of healthy donors were obtained from 30 volunteers without AS (age, 40.2 ± 6.3, 17 male and 13 female). AS patients with diabetes or tumors, or with complications or infections of liver or kidney, were excluded. All the serum samples were obtained from January 2017 to December 2020 at WuHan Asia General Hospital.

\textbf{Cell and Cell Culture}

Human aortic smooth muscle cells (HASMCs) were purchased from ScienCell Research Laboratories and cultured in Smooth Muscle Cell Medium (SMCM) containing 2% fetal bovine serum, 1% Smooth Muscle Cell Growth Supplement (SMCGS), and 1% penicillin-streptomycin. The cells were maintained in a 37°C humidified atmosphere with 5% CO\textsubscript{2}.

\textbf{Cell Transfection}

HASMCs were seeded in 6-well plates and cultured overnight. Then, miR-197-3p mimic, negative control (NC) mimic, miR-197-3p inhibitor, NC inhibitor, and WDR5 overexpression plasmid (GenePharma) were transfected into HASMCs using Lipofectamine\textsuperscript{TM} 3000 Transfection Reagent according to the manufacturer’s instructions. The miR-197-3p mimic and inhibitor sequences were showed as follow: miR-197-3p mimic (5′-UUCCACCCUUCUUCCACCAGC-3′, 5′-UCGGGG GAGAGGGGUGGAAU-3′), NC mimic (5′-UUCCUGCGA GGUGACCGUTT-3′, 5′-ACGUGACACGUUGCGAGA ATT-3′), miR-197-3p inhibitor (5′-UCGUGGGGUGAAG GUGGGUGA A-3′), and NC inhibitor (5′-UCGGGGUGG AGAAGGGUGGGUGA-3′). After transfection for 24 h, HASMCs were subjected to further experiments as indicated.

\textbf{Quantitative polymerase chain reaction (PCR) (qPCR) Assay}

The total RNA of transfected HASMCs was isolated with Total RNA Extraction Kit (Solarbio) according to the manufacturer’s instructions. Then, cDNA was generated using All-in-One cDNA Synthesis SuperMix (Bimake). Primers and cDNA were mixed with 2 × SYBR Green PCR Mastermix (Solarbio), followed by amplification and quantification with LightCycler 480 real-time PCR system (Roche). 2\textsuperscript{−ΔΔCt} method was used to calculate the relative expression of targeted genes, which was normalized to the expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in HASMCs.

\textbf{Cell Proliferation Assay}

Cell proliferation was determined by EdU cell proliferation and CCK8 assays. Briefly, HASMCs were seeded in 96-well plates and transfected for 48 h as indicated. For EdU cell proliferation assay, the culture medium was replaced by fresh medium containing 10 μM EdU for 2 h at 37°C, followed by EdU cell proliferation assay (Beyotime Biotechnology) according to the user guide. For CCK8 assay, the cells were further incubated with fresh medium containing 10% CCK8 solution (Beyotime Biotechnology) for 2 h and then the absorbances were detected with a microreader at a wavelength of 450 nm.

\textbf{Transwell Migration Assay}

Briefly, transfected HASMCs were trypsinized and resuspended in serum-free medium. 100 μl of serum-free medium containing HASMCs was seeded in the upper filters of chambers and 600 μl fresh medium was added into the lower chambers. After a 24-h incubation, the cells were fixed with 4% paraformaldehyde (Sigma) and stained with 0.2% crystal violet (Sigma). The migrated HASMCs were photographed and quantified.

\textbf{Western Blot Assay}

HASMCs after different transfections were harvested and total proteins were extracted with radio-immunoprecipitation assay lysis buffer containing protease inhibitor cocktails (Bimake). Then, the concentrations of proteins were determined and proteins were electrophoretically separated by 10% sodium dodecyl sulfate-polyacrylamide gels and analyzed with Western blot assay. Antibodies against WDR5 and GAPDH were purchased from Cell Signaling Technology.

\textbf{Luciferase Reporter Assay}

HASMCs were seeded into 6-well plates and cultured overnight. The wild type (wt) or mutant (mut) 3′UTR fragments of WDR5 containing miR-197-3p binding sites was cloned into a luciferase reporter vector (GenePharma). Then, the vectors were co-transfected with miR-197-3p or NC mimic into HASMCs. After 48 h, the cells were harvested and the relative luciferase activity was measured by
the Dual-Luciferase Reporter Assay System (Promega), which was normalized to the Renilla luciferase activity.

**Statistical Analysis**

The data are shown as mean ± SEM and analyzed with GraphPad Prism 7.0 software. The statistical differences between two groups were analyzed by unpaired two-tail Student’s *t* test and the statistical differences among more than two groups were analyzed by One-way analysis of variance (ANOVA) followed by Tukey’s multiple comparisons test. *P* < .05 indicated a significant difference.

**Results**

*The Expression of miR-197-3p is Decreased in the Serum of Patients with AS*

To investigate whether miR-197-3p is associated with AS progression, the levels of miR-197-3p in the serum from AS patients and healthy volunteers were determined. We found that the expression of miR-197-3p was significantly lower in patients with AS than in healthy donors (Figure 1). The result indicates that miR-197-3p might regulate the development of AS.

*Ectopic Expression of miR-197-3p Inhibits the Proliferation and Migration of VSMCs*

To functionally explore the effect of miR-197-3p on the proliferation and migration of VSMCs, the cells were transfected with miR-197-3p mimic. Our results showed that miR-197-3p mimic treatment significantly promoted the expression of miR-197-3p in VSMCs (Figure 2A). Then, cell proliferation and migration were determined. CCK8 assay showed that miR-197-3p mimic significantly suppressed the growth of VSMCs (Figure 2B). We found that overexpression of miR-197-3p inhibited the proliferation of VSMCs, as determined by EdU cell proliferation assay (Figure 2C). Moreover, ectopic expression of miR-197-3p also decreased the number of migrated VSMCs (Figure 2D). These results demonstrate that miR-197-3p negatively regulates the proliferation and migration of VSMCs.

*Silencing miR-197-3p Promotes VSMC Proliferation and Migration*

Then, VSMCs were transfected with miR-197-3p inhibitor to further confirm the effect of miR-197-3p on the proliferation and migration of VSMCs. PCR assay showed that miR-197-3p inhibitor downregulated miR-197-3p in VSMCs (Figure 3A). CCK8 (Figure 3B) and EdU cell proliferation (Figure 3C) assays showed that inhibition of miR-197-3p dramatically enhanced the proliferation of VSMCs. We also found that silencing miR-197-3p increased the migration capacity of VSMCs (Figure 3D). Our data further suggest that downregulation of miR-197-3p promote the proliferation and migration of VSMCs.

*WDR5 is a Target of miR-197-3p*

Next, we searched for candidate target genes of miR-197-3p by the databases, such as the Encyclopedia of RNA Interactomes and miRBD (Figure 4A). We found that a complementary miR-197-3p sequence was present in the 3′-UTR of WDR5 mRNA (Figure 4B), and studies have shown that WDR5 also critically regulates the phenotypic changes of VSMCs;11–13 thus, WDR5 was selected for further study. Our result revealed that the luciferase activity of a reporter fused to the wild-type (WT) 3′-UTR of WDR5 was significantly decreased in the VSMCs transfected with miR-197-3p mimic, which was increased in the mutant (MUT) reporter (Figure 4C). Additionally, the expression of WDR5 mRNA was dramatically decreased in miR-197-3p-overexpressing VSMCs, while increased in VSMCs transfected with miR-197-3p inhibitor (Figure 4D). More importantly, similar results were also confirmed by Western blotting assay (Figure 4E). These results suggest that WDR5 might be a potential target of miR-197-3p.

*Overexpression of WDR5 Reverses miR-197-3p-Mediated Suppression of Proliferation and Migration in VSMCs*

Then, to further investigate whether overexpression of WDR5 reverses the miR-197-3p-mediated inhibition of proliferation and migration in VSMCs, VSMCs were co-transfected with WDR5 overexpression plasmid and miR-197-3p mimic. We found that the protein (Figure 5A) and mRNA (Figure 5B) expressions of WDR5 were increased in the VSMCs co-transfected with WDR5 overexpression plasmid and miR-197-3p mimic compared to cells transfected with miR-197-3p. Then, cell proliferation and migration were
explored. Our result showed that the proliferation rate was decreased in the miR-197-3p-overexpressing VSMCs, which was significantly increased in the VSMCs co-transfected with WDR5 overexpression plasmid and miR-197-3p mimic (Figure 5C and D). We also found that overexpression of WDR5 reversed the miR-197-3p-mediated inhibition of VSMC migration (Figure 5E). Our results further demonstrate that miR-197-3p inhibits the proliferation and migration of VSMCs by targeting WDR5.

**IL6 Decreases the Expression of miR-197-3p in VSMCs**

Next, we tried to figure out the mechanisms conferring miR-197-3p downregulation in VSMCs. Since pro-inflammatory factors are also crucial to AS progression, a well-known pro-inflammatory factor IL6 was selected. We found that IL6 treatment significantly downregulated miR-197-3p in VSMCs (Figure 6A). STAT3 is a key downstream effector of IL6-meidated inflammatory signaling
pathway, and then VSMCs were treated with a STAT3 inhibitor (STAT i) cryptotanshinone in the presence of IL6. Our results showed that the expression of miR-197-3p was increased in VSMCs treated with IL6 + cryptotanshinone compared to IL-6-treated VSMCs (Figure 6B). Then, we also determined whether ectopic expression of miR-197-3p affects the effect of IL6 on VSMC proliferation and migration. As expected, our results showed that IL6 treatment significantly promoted the proliferation (Figure 6C) and migration (Figure 6D) of HASMC, which was attenuated in cells transfected with miR-197-3p. These findings indicate that IL6/STAT3 signaling pathway might be responsible for miR-197-3p down-regulation in VSMCs and that miR-197-3p inhibits IL6-induced proliferation and migration in VSMCs.

Discussion

AS is one of the most common vascular diseases and is the underlying cause of clinical manifestation of various vascular
disorders, such as myocardial infraction and stroke. Endothelial cell damage, the accumulation of inflammatory cells and VSMCs, and the deposition of lipid and fibrous tissues are the key characteristics of AS, which are critically associated with AS progression.14–16 VSMCs are the major type of cells present at all stages of an atherosclerotic plaque and aberrant proliferation and migration of VSMCs crucially regulate the development of AS.3,4 In addition to known growth factors, including transforming growth factor beta (TGF-β) and platelet-derived growth factor (PDGF)-BB, emerging evidence has showed that non-coding RNAs, such as miRNA6,17 and lncRNA18,19 played an important role in AS progression via regulating VSMC behaviors. In our study, we found that miR-197-3p was downregulated in the serum of patients with AS. EdU cell proliferation assay showed that ectopic expression of miR-197-3p significantly inhibited the proliferation of VSMCs. Transwell migration assay revealed that overexpression of miR-197-3p suppressed the migration capacity of VSMCs. Whereas, silencing

Figure 4. WDR5 might be a target of miR-197-3p. (A) The bioinformatic databases were used to predict the potential targets of miR-197-3p. (B) The predictive binding sites of miR-197-3p in the 3'-UTR of WDR5. (C) HASMCs were co-transfected with WT or MUT luciferase reporter vectors and miR-197-3p mimic, and the relative luciferase activity was determined. (D) The expression of WDR5 was measured by qPCR assay. (E) Western blot assay for the effect of miR-197-3p on WDR5 expression. Quantification of blots is shown. Data are shown as mean ± SEM. n = 3. **P < .01, ***P < .001.
miR-197-3p showed opposite effects. These results indicated that miR-197-3p might function as an atheroprotective miRNA and could serve as a novel diagnostic biomarker of AS progression.

MiRNA is a class of highly conserved small non-coding RNA with 19-25 nucleotides and regulates various cellular biological processes, such as proliferation and migration.\(^\text{17,20}\) MiRNA mediates post-transcriptional regulation mainly by inhibiting mRNA translation or facilitating mRNA degradation through base-pairing with the 3’-UTR of target genes.\(^\text{20}\) In the present study, we found that miR-197-3p negatively regulated the proliferation and migration of VSMCs. To explore the mechanisms of miR-197-3p on VSMC behaviors, we used several bioinformatic databases. We found that WDR5 was a target of miR-197-3p. WDR5, a highly conserved WD40-repeat protein, existed as part of several chromatin-regulatory complexes\(^\text{21}\) and participated in numerous chromatin-centric processes.\(^\text{22}\) WDR5 has been confirmed to regulate the proliferation,\(^\text{23,24}\) chemoresistance,\(^\text{24}\) and metastasis\(^\text{25}\) of tumor cells. Studies also

**Figure 5.** MiR-197-3p targets WDR5 to inhibit VSMC proliferation and migration. (A) HASMCs were co-transfected with miR-197-3p mimic and WDR5 overexpression plasmid, and the level of miR-197-3p and WDR5 were determined by PCR and Western blot assays. (B) qPCR assay for the expression of WDR5 in HASMCs co-transfected with miR-197-3p mimic and WDR5 overexpression plasmid. (C and D) The proliferation of HASMCs co-transfected with miR-197-3p mimic and WDR5 overexpression plasmid was determined by (C) EdU cell proliferation assay and (D) CCK8 assay. (E) Representative images of migrated HASMC and quantification of the number of migrated HASMCs are shown. Data are shown as mean ± SEM. n = 3. **P < .01, ***P < .001.
showed that WDR5 critically participated in the development of AS, particularly the phenotypic changes of VSMCs, via various mechanisms. A previous study revealed that lncRNA NEAT1 sequestered WDR5 from vascular smooth muscle cell (VSMC)-specific gene loci, resulting in phenotypic switching of VSMCs.12 LncRNA antisense non-coding RNA at the INK4 locus (ANRIL) acted as a potential modular scaffold that interacted with WDR5/HDAC3, which led to NOX1 upregulation by histone modification and consequently increased reactive oxygen species level and promoted the phenotypic alteration of VSMCs.11 This study also showed WDR5 silence downregulated the levels of NOX1 and inhibited the ANRIL-induced NOX1 expression in VSMCs.11 Thus, whether WDR5 was responsible for miR-197-3p-mediated inhibition of proliferation and migration in VSMCs was further investigated. Our results showed that WDR5-3p overexpression decreased the proliferation and migration in VSMCs, which was attenuated by WDR5 overexpression. These data confirmed that miR-197-3p might targets WDR5 to suppress VSMC proliferation and migration and our study further suggested that WDR5 could serve as a potential therapeutic target of AS.

It has been reported that the downregulation of atheroprotective miRNA was regulated by various factors, such as oxidative stress,26 inflammation, excessive growth factor, and lncRNA upregulation. SNHG16 was upregulated by ox-low-density lipoprotein (LDL) treatment, and it promoted the formation of atherosclerotic plaque and enhanced ox-LDL-induced proliferation and migration in VSMCs by targeting miR-22-3p/HMGB2 axis.27 PDGF-BB treatment decreased the expression of miR-233 in HASMCs and miR-233 inhibited PDGF-BB-induced proliferation and migration of HASMC.28 IL6 has showed to regulate inflammation, atherogenesis,29,30 and VSMC behaviors.31 Inhibition of IL6 can alleviate atherosclerosis in ApoE−/− mice.32,33 In our study, we found that IL6 treatment significantly downregulated the expression of miR-197-3p in VSMCs and that blockade of STAT3 inhibited IL6-mediated miR-197-3p downregulation as well as WD repeat domain upregulation in VSMCs. Notably, miR-197-3p abrogated the IL6-induced proliferation and migration in VSMCs. These finding indicated that an inflammatory factor IL6 might be responsible for the downregulation of atheroprotective miRNA miR-197-3p and suggested a potential role of IL6/STAT3 axis in the development of AS. However, whether the expression of miR-197-3p had a negative correlation with IL6 in the serum of AS patients needed to be further investigated.

Figure 6. IL6/STAT3 axis decreases the expression of miR-197-3p in VSMCs. (A) HASMCs were treated with IL6 (50 ng/ml) for 24 h, and the expression of miR-197-3p was measured by qPCR assay. (B) HASMCs were treated with IL6 in the presence or absence of STAT3 inhibitor (STAT3 i) cryptotanshinone, and the level of miR-197-3p was determined by qPCR assay. (C) The effect of IL6 and miR-197-3p on HASMC proliferation was detected by EdU cell proliferation assay. (D) Transwell migration assay was used to evaluate the effect of IL6 and miR-197-3p on HASMC migration. Data are shown as mean ± SEM. n = 3. *P < .05, **P < .01, and ***P < .001.
Additionally, since miR-197-3p inhibited IL6-induced VSMC proliferation and migration, miR-197-3p might also suppress other inflammation-associated signaling pathways, such as nuclear factor-kB axis, and downregulate the levels of other pro-inflammatory factors, such as IL1β and TNFα. A prior study showed that oxidized low-density lipoprotein (ox-LDL) induced the expression of lncRNA ANRIL in VSMCs and that knockdown of lncRNA ANRIL inhibit the ability of ox-LDL to promote proliferation, migration, and phenotypic changes in VSMCs, which was associated with WDR5. Thus, miR-197-3p might also regulate the function of ox-LDL in AS induction. These issues were still remained largely unknown in the present study and were required to be further investigated in the near future, which will further unravel the roles and mechanisms of miR-197-3p in the development and progression of AS.

**Conclusion**

In conclusion, this study found that miR-197-3p was decreased in the serum of AS patients. MiR-197-3p inhibited the proliferation and migration of VSMCs by targeting WDR5. The IL6/STAT3 axis might be critically associated with miR-197-3p downregulation in VSMCs. These finding indicated that miR-197-3p/WDR5 axis could serve as a diagnostic biomarker for AS and that IL6/STAT3/miR-197-3p/WDR5 pathway might be a potential therapeutic target to treat AS.

**Author contributions**

Kai Yang conceived the project and wrote the manuscript. Chunjun Yu, Lin Ruan, Shengpeng Hu, and Wenjie Zhu participated in experiments and data analysis. Feng Xia reviewed the manuscript.

**Availability of Data and Materials**

The data supporting the conclusions of this study are included in this article.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Wuhan Municipal Health Commission, (grant number WX21Z46).

**Ethics Approval and Consent to Participate**

Prior patient consent and approval from WuHan Asia General Hospital were obtained for the use of these clinical tissues in the patient study. The present study was authorized by the Ethics Committees of WuHan Asia General Hospital.

**ORCID iD**

Kai Yang https://orcid.org/0000-0002-0015-4531

**References**

1. Kobiyama K, Ley K. Atherosclerosis. Circ Res. 2018;123(10):1118-1120.
2. Libby P, Buring JE, Badimon L, et al. Atherosclerosis. Nat Rev Dis Primers. 2019;5(1):56.
3. Bennett MR, Sinha S, Owens GK. Vascular smooth muscle cells in atherosclerosis. Circ Res. 2016;118(4):692-702.
4. Basatemur GL, Jørgensen HF, Clarke MCH, Bennett MR, Mallat Z. Vascular smooth muscle cells in atherosclerosis. Nat Rev Cardiol. 2019;16(12):727-744.
5. Zhu J, Liu B, Wang Z, et al. Exosomes from nicotine-stimulated macrophages accelerate atherosclerosis through miR-21-3p/PTEN-mediated VSMC migration and proliferation. Theranostics. 2019;9(23):6901-6919.
6. Farina FM, Hall IF, Serio S, et al. miR-128-3p is a novel regulator of vascular smooth muscle cell phenotypic switch and vascular diseases. Circ Res. 2020;126(12):e120-e135.
7. Sun B, Cao Q, Meng M, Wang X. MicroRNA-186-5p serves as a diagnostic biomarker in atherosclerosis and regulates vascular smooth muscle cell proliferation and migration. Cell Mol Biol Lett. 2020;25:27.
8. Huang Q, Ma B, Su Y, et al. miR-197-3p represses the proliferation of prostate cancer by regulating the VDAC1/AKT/β-catenin signaling axis. Int J Biol Sci. 2020;16(8):1417-1426.
9. Chen Z, Ju H, Zhao T, et al. Hsa_circ_0092306 targeting miR-197-3p promotes gastric cancer development by regulating PRKCB in MKN-45 cells. Mol Ther Nucleic Acids. 2019;18:617-626.
10. Zhang Y, Li W, Li H, et al. Circ_USP36 silencing attenuates oxidized low-density lipoprotein-induced dysfunction in endothelial cells in atherosclerosis through mediating miR-197-3p/ROBO1 axis. J Cardiovasc Pharmacol. 2021;78(5):e761-e772.
11. Zhang C, Ge S, Gong W, et al. LncRNA ANRIL acts as a modular scaffold of WDR5 and HDAC3 complexes and promotes alteration of the vascular smooth muscle cell phenotype. Cell Death Dis. 2020;11(6):435.
12. Ahmed ASI, Dong K, Liu J, et al. Long noncoding RNA NEAT1 (nuclear paraspeckle assembly transcript 1) is critical for phenotypic switching of vascular smooth muscle cells. Proc Natl Acad Sci U S A. 2018;115(37):E8660-E8667.
13. Xia J, Fang M, Wu X, et al. A2b adenosine signaling represses CIITA transcription via an epigenetic mechanism in vascular smooth muscle cells. Biochim Biophys Acta. 2015;1849(6):665-676.
14. Gimbrone MA Jr., García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ Res. 2016;118(4):620-636.
15. Sorokin V, Vickneson K, Kofidis T, et al. Role of vascular smooth muscle cell plasticity and interactions in vessel wall inflammation. Front Immunol. 2020;11:599415.
16. Schaftenaar F, Frodermann V, Kuiper J, Lutgens E. Atherosclerosis: the interplay between lipids and immune cells. Curr Opin Lipidol. 2016;27(3):209-215.
17. Lu Y, Thavarajah T, Gu W, Cai J, Xu Q. Impact of miRNA in atherosclerosis. Arterioscler Thromb Vasc Biol. 2018;38(9):e159-e170.
18. Shan K, Jiang Q, Wang XQ, et al. Role of long non-coding RNA-RNCR3 in atherosclerosis-related vascular dysfunction. Cell Death Dis. 2016;7(6):e2248.
19. Jian L, Jian D, Chen Q, Zhang L. Long noncoding RNAs in atherosclerosis. J Atheroscler Thromb. 2016;23(4):376-384.
20. Feinberg MW, Moore KJ. MicroRNA regulation of atherosclerosis. Circ Res. 2016;118(4):703-720.
21. Thomas LR, Foshage AM, Weissmiller AM, Tansey WP. The MYC-WDR5 nexus and cancer. Cancer Res. 2015;75(19):4012-4015.
22. Bryan AF, Wang J, Howard GC, et al. WDR5 Is a conserved regulator of protein synthesis gene expression. Nucleic Acids Res. 2020;48(6):2924-2941.
23. Huang D, Chen X, Chen X, et al. WDR5 Promotes proliferation and correlates with poor prognosis in oesophageal squamous cell carcinoma. Onco Targets Ther. 2020;13:10525-10534.
24. Gu P, Chen X, Xie R, et al. IncRNA HOXD-AS1 regulates proliferation and chemo-resistance of castration-resistant prostate cancer via recruiting WDR5. Mol Ther. 2017;25(8):1959-1973.
25. Malek R, Gajula RP, Williams RD, et al. TWIST1-WDR5-Hottip Regulates Hoxa9 chromatin to facilitate prostate cancer metastasis. Cancer Res. 2017;77(12):3181-3193.
26. Badran A, Nasser SA, Mesmar J, et al. Reactive oxygen species: modulators of phenotypic switch of vascular smooth muscle cells. Int J Mol Sci. 2020;21(22):8764.
27. Wang Y, Yang Y, Zhang T, et al. LncRNA SNHG16 accelerates atherosclerosis and promotes ox-LDL-induced VSMC growth via the miRNA-22-3p/HMGB2 axis. Eur J Pharmacol. 2022;915:174601.
28. Su F, Shi M, Zhang J, et al. MiR-223/NFAT5 signaling suppresses arterial smooth muscle cell proliferation and motility in vitro. Aging (Albany NY). 2020;12(24):26188-26198.
29. Tyrrell DJ, Goldstein DR. Ageing and atherosclerosis: vascular intrinsic and extrinsic factors and potential role of IL-6. Nat Rev Cardiol. 2021;18(1):58-68.
30. Tyrrell DJ, Blin MG, Song J, et al. Age-Associated mitochondrial dysfunction accelerates atherogenesis. Circ Res. 2020;126(3):298-314.
31. Lee GL, Wu JY, Tsai CS, et al. TLR4-Activated MAPK-IL-6 axis regulates vascular smooth muscle cell function. Int J Mol Sci. 2016;17(9):1394.
32. Luo P, Shi W, Wang Y, et al.Raloxifene inhibits IL-6/STAT3 signaling pathway and protects against high-fat-induced atherosclerosis in ApoE(-/-) mice. Life Sci. 2020;261:118304.
33. Luo P, Wang Y, Zhao C, et al. Bazedoxifene exhibits anti-inflammatory and anti-atherosclerotic effects via inhibition of IL-6/IL-6R/STAT3 signaling. Eur J Pharmacol. 2021;893:173822.