Abstract. Abdominal aortic aneurysm (AAA) is characterized as dilation of the aortic wall. Dysregulation of vascular smooth muscle cells (VSMCs) can contribute to the development of this phenotype. Circular RNAs and microRNAs (miRNAs) can regulate the proliferation and apoptosis of VSMCs. This present study aimed to identify the mechanisms of action behind the regulation of cerebellar degeneration-related protein 1 antisense RNA (CDR1as)/miRNA (miR)-7 in VSMCs. The expression levels of miR-7 were upregulated, whereas the levels of CDR1as and cytoskeleton-associated protein 4 (CKAP4) were downregulated in aortic specimens obtained from 10 patients who underwent surgery for AAA compared with aortic specimens from 10 control patients who underwent coronary artery bypass surgery. The molecular mechanism of action of CDR1as/miR-7 was investigated in primary VSMCs. The results of Cell Counting kit-8 and cell growth curve assays revealed that overexpression of CDR1as and knockdown of miR-7, increased VSMC proliferation, whereas knockdown of CDR1as and overexpression of miR-7 suppressed VSMC proliferation. In addition, overexpression of CDR1as and knockdown of miR-7, suppressed apoptosis in VSMCs, indicated by the decreased levels of reactive oxygen species (ROS) and lactate dehydrogenase (LDH) activity, whereas knockdown of CDR1as and overexpression of miR-7 exhibited the opposite effects. The results of luciferase reporter and biotin pull-down assays confirmed that CDR1as directly bound to miR-7 and suppressed its expression. Additionally, the miR-7-suppressed proliferation and increased ROS and LDH activity were reversed by the overexpression of CKAP4. CDR1as also increased caspase 3/7 activity, which was reversed by miR-7 mimics. miR-7 increased the activity of caspase 3/7, which was again reversed by the overexpression of CKAP4. Therefore, CDR1as, miR-7 and CKAP4 may act in the same pathway to regulate VSMC proliferation and apoptosis.

Introduction

Abdominal aortic aneurysm (AAA) is a disease characterized by the dilation of the aorta that mostly affects adult patients, especially those >65 years (1). AAA can be life-threatening when an acute rupture occurs (2). Histological studies have revealed that AAA is associated with the impairment of apoptotic and inflammatory functions of vascular smooth muscle cells (VSMCs). VSMCs are the key source of elastin, which provides the elasticity of the aortic wall (3). VSMC apoptosis can reduce the levels of elastin, leading to the expansion of the aortic wall and ultimately resulting in alterations to the elasticity and remodeling of the abdominal aortic wall (4).

Non-coding RNAs (ncRNAs) are a class of non-protein coding RNAs that participate in numerous cellular processes and pathological conditions. This class includes microRNAs (miRNAs/miRs) and circular RNAs (circRNAs), among others (5). miRNAs have been demonstrated to be major post-transcriptional regulators of gene expression (6) and serve critical functions in vascular biology (7).

circRNAs interact with other molecules or miRNAs to regulate gene expression at the post-transcriptional or transcriptional levels (8), thus modulating various biological processes such as cell proliferation, apoptosis, invasion and migration (9). Cerebellar degeneration-related protein 1 antisense RNA (CDR1as) contains >70 binding sites to sponge miR-7 and modulate its activity on target genes (10). The CDR1as/miR-7 axis has been investigated in several types of cancer, such as esophageal squamous cell carcinoma and colorectal carcinoma (11). However, the functions of the CDR1as/miR-7 axis in AAA have not been investigated in detail.

Cytoskeleton-associated protein 4 (CKAP4), also termed p63 or cytoskeleton-linking membrane protein of 63 kDa, is a plasma membrane protein presented by VSMCs (12). Previous studies have suggested that CKAP4 may promote...
tumor progression through the PI3K/AKT (12) and cyclin B signaling pathways (13). CKA4 and PI3K can form a complex at the proline-rich domain of CKA4 and the Src homology 3 domain, which accelerates the production of phosphatidylinositol-3,4,5-triphosphate, leading to the activation of AKT and the proliferation of normal and cancer cells (13). Furthermore, the upregulation of CKA4 increases the levels of cyclin B1 and cyclin B2, which in turn decreases cell population at the G2/M phase and increases cell population at the S phase, leading to the progression of clear cell renal cell carcinoma (14).

Previous studies have demonstrated that CDR1as can sponge miR-7 in osteosarcoma and hepatocellular carcinoma (11,15); therefore, the present study used bioinformatics analysis to predict that CKA4 may be targeted by miR-7. The aim of the present study was to determine the relationship among CDR1as, miR-7 and CKA4 in the pathogenesis of AAA, which may ultimately serve as a potential treatment target for AAA.

Materials and methods

Patient tissues. Aortic specimens were collected from 10 patients who underwent ascending aortic aneurysm surgery (mean age, 63.25±6.24; men, 7; women, 3) and from 10 control patients who underwent coronary artery bypass graft with non-aneurysmal aortas (mean age, 57.80±6.56; men, 8; women, 2) between January 2017 and December 2018 at Tianjin Chest Hospital. Patients with bicuspid aortic valves or hereditary connective tissue disorders were excluded from the control group. The obtained aortic specimens were split into two parts, which were snap-frozen in liquid nitrogen for RNA isolation or primary VSMCs isolation. All patients signed written informed consent, and ethical approval was obtained from the Institutional Review Board of Tianjin Chest Hospital.

Cell culture and transfection. Primary VSMCs were isolated from the aforementioned 10 clinical aortic specimens who underwent ascending aortic aneurysm surgery as previously described with modifications (16). Following removal of fat and connective tissue, the tissues were cut into 3-mm long sections under 5% CO2 and centrifugation at 120 x g for 15 min at 4˚C to obtain VSMCs. Following washing with PBS, the obtained pelleted VSMCs cells were used to measure the activities of firefly and Renilla luciferase was used as internal control.

Reverse transcription-quantitative PCR (RT-qPCR) analysis. TRIzol® (Invitrogen; Thermo Fisher Scientific, Inc.) was used for total RNA extraction from aortic specimens or VSMCs. Briefly, 1 μg of the RNA was reverse transcribed using the High-Capacity cDNA reverse transcription kit (cat. no. 4368813; Thermo Fisher Scientific, Inc.). The temperature protocol for reverse transcription was as follows: Incubation at 25˚C for 5 min, 37˚C for 120 min and 85˚C for 5 min. qPCR was then performed using SYBR Green Master mix (Thermo Fisher Scientific, Inc.) using the following parameters: 95˚C for 5 min; 40 cycles of 10 sec at 95˚C, 20 sec at 55˚C and 15 sec at 72˚C, followed by a melting curve of 10 sec at 95˚C, 60 sec at 60˚C and a continuous increase up to 95˚C at a rate of 0.15˚C/sec for 15 sec with a continuous reading of the fluorescence. The 2-ΔΔCq method was used to quantify the target gene expression (17).

Bioinformatics analysis. StarBase v3.0 (http://starbase.sysu.edu.cn) was used for predicting the potential long ncRNA (lncRNA) that can bind miR-7. TargetScan 7.1 (http://www.targetscan.org/vert_72/) was used to predict the downstream target genes of miR-7.

Luciferase reporter assay. Briefly, 1.5x104 cells were seeded in a 24-well plate. After 24 h, the cells were transfected with miR-7 mimics, miR-7 ASO, miR-NC or ASO NC as well as the pmirGLO vector (Promega Corporation), which was inserted with the wild-type (WT) 3'-untranslated region (UTR) of CKA4 or a mutant (mut) form of CKA4 3'-UTR which contained a mutated seed sequence (from 5'-GUCUUC-3' into 5'-GUGUUGG-3'). At 48 h following transfection, the cells were used to measure the activities of firefly and Renilla luciferase using a Dual Luciferase reporter assay kit (Promega Corporation). The activity of Renilla luciferase was used as internal control.

Biotin pull-down assay. Cells were transfected with 50 μM of biotinylated miR-7 mimic or miR-NC (as aforementioned; GeneCopoeia, Inc.) for 24 h and lysed in 500 μl lysis buffer at 4˚C for 30 min, followed by the addition of 50 μl blocked streptavidin magnetic beads and incubation for 4 h at 4˚C. TRIzol® was used to extract the miR-7 that interacted with ncRNAs and the CDR1as expression levels were subsequently determined using RT-qPCR.

Western blot analysis. Following transfection for 48 h, the VSMCs were lysed using RIPA buffer (150 mM Tris-HCl,
50 mM NaCl, 1% Nonidet P-40 and 0.1% Tween-20), followed by determining the protein concentration using Bradford assays (Bio-Rad Laboratories, Inc.). Proteins (30 μg) were separated by 10% SDS-PAGE, followed by transferring to PVDF membranes at 250 mA for 2.5 h. After blocking for 1 h with 3% w/v skimmed milk at room temperature, the membranes were incubated with the following primary antibodies overnight at 4°C: Anti-CKAP4 (cat. no. ab84712; 1:2,000; Abcam), anti-cleaved-caspase 3 (cat. no. 9661; 1:1,000; Cell Signaling Technology, Inc.) and anti-GAPDH (cat. no. 2118; 1:10,000; Cell Signaling Technology, Inc.). The next day, the membranes were washed with Tris-buffered saline containing 0.1% Tween 20, three times and incubated with a secondary antibody conjugated with horseradish peroxidase (cat. no. A0208, Beyotime Institute of Biotechnology) at 1:1,000 for 1 h at room temperature. Chemiluminescence was detected with an ECL kit (GE Healthcare Life Sciences), then quantified using ImageQuant software version 5.2 (GE Healthcare Life Sciences). GAPDH was used as an internal control.

**Cell Counting Kit-8 (CCK-8) assay.** To detect cell viability, a CCK-8 assay was performed. Treated and untreated VSMCs were cultured in a 96-well plate at 3x10^4 cells/well. After 48 h, 10% CCK-8 solution (DOJINDO Molecular Technologies, Inc.) was added to each well and incubated for 1 h at 37°C, as per the manufacturer's instructions, followed by analysis using a microplate reader at a wavelength of 450 nm.

**Lactate dehydrogenase (LDH), reactive oxygen species (ROS) and caspase 3/7 detection assays.** To detect the extent of VSMC apoptosis, LDH, ROS and caspase 3/7 assays were performed. For the LDH assay, transfected cells were cultured at 5x10^4 cells/well in 96-well plates for 48 h. After centrifuging at 350 x g for 5 min at 4°C and discarding of the supernatant, 150 μl LDH release regent (cat. no. C0016; Beyotime Institute of Biotechnology) was added to each well and incubated for 1 h at 37°C. The signal was detected using a microplate reader (Bio-Rad Laboratories, Inc.) at excitation/emission wavelengths of 488/525 nm.

Caspase 3/7 activity was quantitated using a Caspase-Glo® 3/7 Assay kit (Promega Corporation) according to the manufacturer's instructions.

**Statistical analysis.** Data are presented as the mean ± standard error of the mean. When comparing the AAA aortic tissues and normal controls, data are presented using box and whiskers plots. Statistical analysis was performed using GraphPad Prism 8 software (GraphPad Software, Inc.) with one-way ANOVAs followed by Tukey's test. *P*<0.05 was considered to indicate a statistically significant difference. All experiments were repeated at least three times.

**Results**

**miR-7 is upregulated, whereas CDR1as and CKAP4 are downregulated in AAA tissues.** The results of RT-qPCR demonstrated that miR-7 was expressed at higher levels in AAA aortic tissues compared with the normal controls (Fig. 1A). The expression levels of CDR1as and CKAP4 were notably downregulated in AAA (Fig. 1B and C).

**Effects of CDR1as and miR-7 on the function of primary VSMCs.** Transfection efficiency of CDR1as overexpression plasmids and siRNA, and miR-7 mimics and ASO was evaluated using RT-qPCR. The results revealed that CDR1as overexpression increased CDR1as RNA levels 2-fold, whereas si-CDR1as downregulated the expression of this RNA by 60%. miR-7 mimics upregulated miR-7 expression 1.8-fold, whereas miR-7 ASO downregulated its expression by 70% (Fig. 2A). The results of the CCK-8 assay revealed that cell viability was increased following transfection with either CDR1as or miR-7 ASO, but decreased following transfection with siRNA CDR1as or miR-7 mimics, compared with their respective controls (Fig. 2B). Similarly, Cell growth curve assay showed that cell proliferative ability was increased following transfection with CDR1as or miR-7 ASO, but decreased following transfection with siRNA CDR1as or miR-7 mimics (Fig. 2C and D). In addition, CDR1as and miR-7 ASO decreased the ROS generation and LDH activity, which was increased following transfection with siRNA CDR1as or...
Figure 2. Effect of CDR1as and miR-7 on the phenotype of primary vascular smooth muscle cells. (A) The expression levels of CDR1as following transfection with a CDR1as overexpression vector and siRNA targeting CDR1as, as well as miR-7 following transfection with miR-7 ASO and mimics were detected by reverse transcription-quantitative PCR. (B) Cell viability was detected using Cell Counting Kit-8 assays. Cell growth curve assay was performed following transfections altering (C) CDR1as and (D) miR-7 expression levels. (E) The ROS generation and (F) the LDH activity were detected.

*P<0.05; #P<0.05, NC vs. CDR1as; ^P<0.05, siRNA NC vs. siRNA CDR1as; %ASO NC vs. miR-7 ASO, &mimics NC vs. miR-7 mimics). ASO, antisense nucleotide; CDR1as, cerebellar degeneration-related protein 1 antisense RNA; LDH lactate dehydrogenase; miR, microRNA; NC, negative control; ROS, reactive oxygen species; siRNA, small interfering RNA.

Figure 3. miR-7 mediates the effects of CDR1as. (A) Bioinformatics predicted the binding sites of CDR1as that are targeted by miR-7. (B) VSMCs were co-transfected with miR-7 mimics and CDR1as-WT or CDR1as-mut. (C) The pull-down assay was performed in cells transfected with Bio-miR-7 mimic or Bio-NC, followed by reverse transcription-quantitative PCR detection of CDR1as. (D) miR-7 expression levels were detected in VSMCs co-transfected with NC + mimics NC, CDR1as + mimics NC and CDR1as + miR-7 mimics. (E) Cell Counting Kit-8 assays were performed to detect cell viability. (F) Cell growth curves were produced to detect cell proliferation. (G) ROS concentration and (H) LDH activity were detected.

*P<0.05; #P<0.05, NC + mimics NC vs. CDR1as + mimics NC; ^P<0.05, CDR1as + mimics NC vs. CDR1as + miR-7 mimics. Bio, biotinylated; CDR1as, cerebellar degeneration-related protein 1 antisense RNA; LDH, lactate dehydrogenase; miR, microRNA; mut, mutant sequence; NC, negative control; OD, optical density; ROS, reactive oxygen species; VSMCs, vascular smooth muscle cells; WT, wild-type sequence.
miR-7 mimics, compared with the respective control groups (Fig. 2E and F). These results suggested that CDR1as and miR-7 exerted opposing effects on VSMCs.

Overexpression of miR-7 reverses the effects of CDR1as in VSMCs. The WT version of CDR1as was found to contain a potential binding site of miR-7 (Fig. 3A). To further investigate whether miR-7 can be sponged by CDR1as in VSMCs, a CDR1as luciferase reporter was constructed. The results demonstrated that miR-7 significantly reduced the luciferase intensity of CDR1as-WT, but had no significant effect on the luciferase intensity of CDR1as-mut (Fig. 3B). In addition, the biotin pull-down assay results revealed that CDR1as was pulled down in biotinylated miR-7-transfected cells by 11-fold compared with cells transfected with biotinylated miR-NC (Fig. 3C). As presented in Fig. 3D, miR-7 expression was suppressed by CDR1as in VSMCs, which could be reversed by co-transfection with miR-7 mimics. CCK-8 and cell proliferation curve assays revealed that the CDR1as-facilitated cell viability and proliferation was reversed by co-transfection with miR-7 (Fig. 3E and F). Additionally, CDR1as-mediated suppression of ROS generation and LDH activity was reversed by co-transfections with miR-7 (Fig. 3G and H). Therefore, these data suggested that miR-7 may be sponged by CDR1as and mediate the downstream effects of CDR1as in VSMCs.

CKAP4 serves as a direct target of miR-7. Bioinformatics analysis was performed using TargetScan to predict the potential target of miR-7, with CKAP4 being identified as a target for miR-7 (Fig. 4A). To confirm whether CKAP4 was regulated by miR-7, RT-qPCR and western blot analysis were performed, which demonstrated that overexpression of miR-7 notably downregulated the expression of CKAP4 compared with mimics NC, whereas knockdown of miR-7 upregulated the expression of CKAP4 compared with ASO NC (Fig. 4B and C). In addition, luciferase reporter assays confirmed that miR-7 mimics notably decreased the luciferase activity of CKAP4-3'UTR, whereas this was not observed with miR-7 ASO. The expression of miR-7 mimics and ASO had no significant effects on the luciferase activity of the CKAP4-3'UTR mut reporter plasmid (Fig. 4D). These data confirmed that CKAP4 was a direct target of miR-7 in VSMCs.

CDR1as/miR-7/CKAP4 axis is involved in the regulation of the apoptosis proteins, caspase-3/7. To investigate whether CDR1as/miR-7/CKAP4 regulated the function of VSMCs, the present study investigated the impact of miR-7 on CKAP4. Firstly, pcDNA3-CKAP4 was verified to have an effective transfection efficiency (Fig. 5A). It was then confirmed that miR-7-mediated suppression of CKAP4 could be rescued by transfection with pcDNA3-CKAP4 (Fig. 5B). miR-7 mediated induction of caspase 3/7 activity can be rescued by co-transfection with pcDNA3-CKAP4 with miR-7 mimics (Fig. 5C), which suggested that miR-7-induced apoptosis may be rescued by CKAP4. In addition, the results demonstrated that CDR1as upregulated the expression of CKAP4, which was reversed by co-transfection with CDR1as and miR-7 mimics (Fig. 5D). The CDR1as-reduced caspase 3/7 activity by was rescued following co-transfection with miR-7 mimics (Fig. 5E), suggesting that the CDR1as-mediated suppression of apoptosis was dependent on the downregulation of miR-7. In summary, CDR1as mediated the downregulation of miR-7, resulting in the upregulation of CKAP4 and leading to the inhibition of caspase 3/7 activity (Fig. 5F).

**Discussion**

A previous study has demonstrated that miR-7 can be sponged or inhibited by CDR1as in the developing midbrain of zebrafish, suggesting a newly identified mechanism of action for miRNA regulation (19). Further studies have confirmed that CDR1as promotes cell proliferation in hepatocellular carcinoma (15) and osteosarcoma (11) by suppressing miR-7 expression levels. The results of the present study demonstrated that CDR1as was expressed at a lower level, whereas miR-7 was upregulated in aortic tissue from patients with AAA compared with that of...
In addition, the predicted miR-7 target CKAP4 was downregulated in AAA tissue compared with normal tissue. A previous study has identified that AAAs are associated with apoptosis of VSMCs (20). Therefore, the upregulated miR-7 and the downregulated CDR1as and CKAP4 may affect apoptosis in VSMCs.

Primary VSMCs were used in the present study to investigate the mechanism of action of CDR1as/miR-7, aiming to identify the mechanisms behind the pathogenesis in AAAs. In a myocardial infarction (MI) study, CDR1as promoted MI injuries by reducing miR-7a activity (21). CDR1as is also downregulated and miR-7 is upregulated in patients with Alzheimer's disease (22). In tumorigenesis, CDR1as commonly serves as an oncogene in hepatocellular carcinoma (15), osteosarcoma (11) and non-small cell lung cancer (23). The results of the present study suggested that CDR1as may promote the proliferation and suppress the ROS generation and LDH activity of VSMCs, whereas co-expression of miR-7 can reverse the CDR1as-mediated effects. In addition, the results suggested that CDR1as may directly bind miR-7 in VSMCs. A previous study has demonstrated that ROS dysregulates the function of the extracellular matrix, thus promoting the apoptosis of VSMCs (24), which suggested that the CDR1as/miR-7 axis may contribute to the remodeling of AAA.

Studies on miR-7 have been conducted in different types of tumors, and its function as a tumor suppressor has been demonstrated in pancreatic cancer (25) and glioma (26). In VSMCs derived from AAA in the present study, miR-7 suppressed proliferation and promoted the generation of ROS as well as LDH activity. In addition, CKAP4 was confirmed to be a direct target for miR-7. Overexpression of CKAP4 reversed the miR-7-mediated effects on VSMCs. As the receptor of dickkopf-related protein 1 (DKK1), CKAP4 mediates downstream signaling to promote cellular proliferation and inhibit apoptosis through the activation of the PI3K/AKT pathway (27). Apoptosis of VSMCs is crucial for normal vascular remodeling (28). The PI3K/AKT signaling pathway is implicated in the proliferation of VSMCs, thus modulating vascular remodeling by decreasing the pro-apoptotic functions of Bcl2-associated death promoter (29,30).

The results of the present study demonstrated that CKAP4 suppressed the activity of caspase 3/7 and that miR-7-mediated increase in caspase 3/7 activity could be reversed by the overexpression of CKAP4 in VSMCs. In addition, CDR1as-suppressed caspase 3/7 activity was rescued by miR-7 overexpression. Thus, the activation of CDR1as in AAA may result in the downregulation of miR-7 and upregulation of CKAP4. This in turn may activate the PI3K/AKT pathway and result in the interference in the function of DKK1, leading to VSMC remodeling.

In conclusion, the results of the present study identified the functions of the CDR1as/miR-7/CKAP4 axis in VSMC proliferation and apoptosis. As the receptor of dickkopf-related protein 1 (DKK1), CKAP4 mediates downstream signaling to promote cellular proliferation and inhibit apoptosis through the activation of the PI3K/AKT pathway (27). Apoptosis of VSMCs is crucial for normal vascular remodeling (28). The PI3K/AKT signaling pathway is implicated in the proliferation of VSMCs, thus modulating vascular remodeling by decreasing the pro-apoptotic functions of Bcl2-associated death promoter (29,30).

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FZ and TC performed the experiments, FZ wrote the manuscript. NJ designed the experiments. All authors read and approved the final manuscript.

Ethics and approval

Ethics and approval were obtained from the Institutional Review Board of Tianjin Chest Hospital. All patients signed written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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