MEDICAL SCIENCE MONITOR

LAB/IN VITRO RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 3958-3965
DOI: 10.12659/MSM.910000

Received: 2018.03.16
Accepted: 2018.03.26
Published: 2018.06.11

Long Noncoding RNA (lncRNA) n379519 Promotes Cardiac Fibrosis in Post-Infarct Myocardium by Targeting miR-30

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BEF 1 Xiaxia Wang
BD 1 Chunming Yong
CE 2 Kai Yu
CDF 1 Renchao Yu
CF 1 Rui Zhang
BC 1 Lingfan Yu
DG 1 Shan Li
AG 1 Shanglang Cai

1 Department of Cardiology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, P.R. China
2 Department of Cardiology, Qingdao Municipal Hospital, Qingdao, Shandong, P.R. China

Corresponding Author: Shanglang Cai, e-mail: caishanglang_666@126.com
Source of support: This work was supported by the Basic Laboratory of Qingdao University Medical School

Background: Abnormally expressed long noncoding RNAs (lncRNAs) are recognized as one of the key causes of cardiac diseases. However, the role of lncRNA in cardiac fibrosis remains largely unknown.

Material/Methods: The experiment was divided into 4 groups: a sham operation group, a myocardial infarction (MI) group, a lentivirus group (LV-si-n379519), and a lentivirus control (LV-NC) group. The adenovirus expression vectors LV-si-n379519 and LV-NC were constructed and transfected into mice. Echocardiography, HE staining, and Masson staining were performed to detect the heart function and collagen volume fraction in each group. RT-PCR was used to detect the expression level of n379519, miR-30, collagen I, and collagen III. *In vitro*, cardiac fibroblasts (CFs) were cultured and the relationship between n379519 and miR-30 was verified using luciferase reporter vector, n379519 siRNA, and miR-30 inhibitor.

Results: The expression of n379519 was markedly upregulated in the hearts of mice with MI and in the fibrotic CFs. Knockdown of endogenous n379519 by its siRNA improved the heart function and reduced collagen deposition and the process of cardiac fibrosis. Further experiments showed the opposite trend of expression between n379519 and miR-30. Bioinformatics analysis and luciferase reporter assay indicated that n379519 directly binds to miR-30. Moreover, miR-30 inhibitor abrogated the collagen synthesis inhibition induced by n379519.

Conclusions: These findings reveal a novel function of n379519-miR-30 axis as a negative regulator for the treatment of MI-induced cardiac fibrosis and the associated cardiac dysfunction.

MeSH Keywords: Endomyocardial Fibrosis • MicroRNAs • Myocardial Infarction • RNA, Long Noncoding

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/910000

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Myocardial infarction (MI) is an ischemic cardiomyopathy caused by the lesion of the coronary arteries or its branches, leading to stenosis or occlusion of the lumen. This occurs despite a wide appreciation that cardiomyocytes necrosis triggers inflammatory cell infiltration, which in turn activates proliferation of fibroblasts, transforms into myofibroblasts, producing large amounts of collagen fibers, eventually leading to cardiac fibrosis and ventricular remodeling [1]. The essence of cardiac fibrosis is the imbalance between extracellular matrix (ECM) synthesis and degradation, resulting in increased collagen deposition, the imbalance between various types of collagen (collagen I and collagen III increased), and the disordered tissues [2]. However, antifibrotic drug therapy (guideline-recommended for chronic heart failure treatment drugs, including ACE inhibitor, beta blockers and aldosterone receptor antagonists) in clinical practice has little effect [3] and the underlying mechanism of cardiac fibrosis is still unclear. Considering the important role of cardiac fibroblasts (CFs) differentiating into myofibroblasts in the progression of fibrosis [4], a more in-depth study of CF gene program and regulatory mechanism is needed to slow the progression of this disease.

lncRNAs are defined as RNA transcripts of >200 nucleotides that lack protein-coding potential [5], but base-pair with DNA or RNA in a sequence-specific manner, thus regulating gene expression and biological progress. Many studies have revealed that lncRNAs adjust the origination and progression of cardiac disease through transcriptional and posttranscriptional control and by competitively-binding miRNAs [6–8]. However, research on the biological role of lncRNAs in cardiac fibrosis is still in its infancy, and only a few articles have reported on the association between lncRNAs and cardiac fibrosis [9,10]. Therefore, further research on the role of lncRNAs in myocardial fibrosis is necessary to better understand the regulation of cardiac disease.

Members of the miR-30 family (including miR-30a, miR-30b, miR-30c-1, miR-30c-2, miR-30d, and miR-30e) are expressed in various tissues and act as indispensable regulators in different cancers [11]. miR-30 has been proved to be downregulated in hypertrophic myocardium and fibroblasts, whereas overexpressed miR-30 can decrease connective tissue growth factor levels and reduce collagen deposition [12]. In animal models, the repression of pro-fibrotic genes was enhanced when the expression of miR-30 decreases [13]. In addition, the expression level of miR-30 in human serum was found to be significantly correlated with collagen volume fraction [14].

In this study, n379519, an lncRNA that is pro-fibrotic and regulates the expression and function of ECM, as reported by Huang et al. [15], was used to further explore whether silencing it can affect specific binding to the 3'-UTR of miR-30 to improve cardiac function and reduce the process of cardiac fibrosis in MI rats.

Material and Methods

Animal experiment

Male Sprague-Dawley rats (age 8–10 weeks, weight 200–250 g) were purchased from Vital River Laboratory Animal Company (Beijing, China) and housed for 1 week at room temperature. This study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University. Sixty rats (each group n=15) were divided into a sham group, an MI group, a lentivirus group (LV-si-n379519), and a lentivirus control (LV-NC) group. Rats were anesthetized and intubated, then connected to a standard limb lead II electrocardiogram (ECG). The heart was exposed by thoracotomy and pericardiotomy at the 3rd to 4th ribs. A segment of saline-soaked 6–0 suture was looped around the left anterior descending coronary artery. When the left ventricular myocardial turns white and the ECG ST segment is greater than 0.1 mv, the model is successfully established. The sham operation group did not receive ligation of the anterior descending branch. Twenty minutes after surgery, a lentivirus vector plasmid (Genepharma, Shanghai, China) 40 µl of 1×10^9 UT/ml carrying si-n379519 or si-NC (Genepharma, Shanghai, China) was injected into myocardium of rats. At the second week and the fourth week after the operation, 3 rats in the sham operation group and the MI group were sacrificed to detect the expression of miR-30, and the remaining rats were fed until the fourth week for further study.

Cardiac function and histopathological examination

Four weeks after surgery, small-animal transthoracic echocardiography (Visualsonics, Inc., Toronto, Canada) was used to take the M-ultrasonography of the heart to detect left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS). After echocardiography, the rats were sacrificed and the hearts were removed and placed 10% formalin, then tissues were embedded in paraffin for Masson Trichrome staining and HE staining.

Isolation and culture of CFs cells

The ventricular tissues of 1–3-day-old SD neonatal rats were cut into 1.0-mm pieces and placed in D-Hank's mixed solution of 0.03% trypsin and 0.05% collagenase for 10 min. Subsequently, cells in the supernatant were isolated by centrifugation (1000 rpm, 5 min) at room temperature and cultured in Dulbecco's modified Eagle's medium (DMEM, 11965092, Gibco, USA) supplemented with 10% fetal bovine serum (FBS,

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

10099141, Gibco, USA), 100 IU/ml penicillin, and 100 μg/ml streptomycin. After 48-h culture, CFs were treated with TGF-β1 (PeproTech, New Jersey, USA) 10 ng/ml for 24 h to induce cell fibrosis, which has been proven to stimulate fibroblast proliferation and transformation [16].

Cell transfection

lncRNA n379519 siRNA (si-n379519), miR-30 mimics, and miR-30 inhibitor/NC inhibitor were synthesized by GenePharma Co., Ltd (Shanghai, China). The sequences were: si-n379519, 5'-CCTCTCATTCTTCATTCCTTTCTTA-3'; miR-30 mimics, 5'-GCAUCUGGAACUGACGCCU-3'; miR-30 inhibitor, 5'-UCUCCCGGACCUGAGACGU-3'; NC inhibitor, 5'-UCCUCCGAACCUGGCACGU-3'. Cells were transfected with indicated nucleotides or plasmid using Lipofectamine 2000 (Invitrogen, CA, USA) according to the manufacturer's instructions. After a 36-h transfection, CFs were harvested for further experiments.

Luciferase assays

The 3'-UTR of n379519 contained the conserved miR-30 binding sites and was amplified using PCR. The 3'-UTR sequences were amplified and cloned downstream of the firefly luciferase gene in the pMIR-Report luciferase vector (Ambion, Cambridge, MA, USA) to construct a luciferase reporter vector. Wild-type (WT) or mutant (Mut) fragments of the 3'-untranslated region (3'-UTR) of the n379519 containing the predicted miR-30 binding sites. Cells were transfected with miR-30 inhibitor/NC with Lipofectamine 2000 (Invitrogen, America) for 48 h. Luciferase activity was measured using the Bright-Glo™ Luciferase Assay System (Promega, USA) and normalized to that of Renilla.

RNA extraction and quantitative reverse transcription-PCR (qRT-PCR)

Total RNA was extracted from tissues or cells using Trizol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocol. Reverse transcription polymerase chain reaction was performed using the PrimeScript™ RT reagent Kit (TAKARA, Otsu, Shiga, Japan). Reverse transcription was performed according to the reagent instructions. The expression levels of n379519 and miR-30 were detected using SYBR Premix Ex Taq (TAKARA, Otsu, Shiga, Japan). The amplification conditions were: at 94°C for 15 min, followed by 40 cycles (94°C for 10 s; 60°C for 32 s; 72°C for 60 s). GAPDH was used as an internal control and the relative expressions of genes were calculated using the $2^{-\Delta\Delta Ct}$ method. The primers are presented in Supplementary Table 1.

Western blotting

The peri-infract regions of myocardial or CFs were lysed in RIPA buffer containing PMSF (Beyotime, Shanghai, China). After being homogenized and centrifuged (12 000 rpm, 10 min), the supernatant protein was transferred to another tube and subjected to standard BCA assay (Solarbio, Beijing, China). We separated 50 μg of proteins to SDS-PAGE on 12% polyacrylamide gels, transferred it to a PVDF microporous membrane (Millipore, Bedford, MA, USA), then blocked it with buffer containing TBST and 5% fat-free milk for 2 h at room temperature. The PVDF membrane was incubated in the primary antibodies (diluted by TBST with 0.1% tween) at 4°C overnight. After washing 3 times, the PVDF membrane was incubated with horseradish peroxidase (HRP)-conjugated anti-rabbit (1: 1000, Cell Signaling Technology, Inc., Danvers, MA, USA) for 2 h at room temperature. High-sensitivity chemiluminescence (Bio-Rad, Hercules, CA, USA) was used to detect the protein bands. The relative band densities were normalized to β-actin (1: 1000, Cell Signaling Technology, Inc., Danvers, MA, USA). The primary antibodies Anti-Collagen I (ab34710, 1: 1000) and Anti-Collagen III (ab7778, 1: 1000), purchased from Abcam (USA).

Statistical analysis

Data are expressed as the mean ±SD. Statistical analyses were performed using SPSS 19.0 (IBM, Armonk, NY, USA). The differences between individual groups were analyzed by one-way ANOVA followed by Fisher's LSD test. $P<0.05$ was considered statistically significant.

Results

LncRNA n379519 is up-regulated in infracted myocardium and TGF-β1-induced CFs

As shown in Figure 1, the myocardium in the left ventricle anterior turned pale and the ST segment elevation in the lead II of ECG showed that the model was successful. Compared with the sham group, the expression of n379519 was significantly upregulated at 2 and 4 weeks following MI (Figure 1B). After the induction by TGF-β1, the expression of n379519 was significantly increased, consistent with the *in vivo* experimental results (Figure 1C, 1D).

Suppression of n379519 improved heart function and attenuated fibrotic changes in myocardium.

To investigate the role of n379519 in the process of ventricular remodeling *in vivo*, we injected a siRNA-containing lentiviral plasmid into rat myocardium to suppress the n379519 gene. The echocardiography showed that knockdown of n379519

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

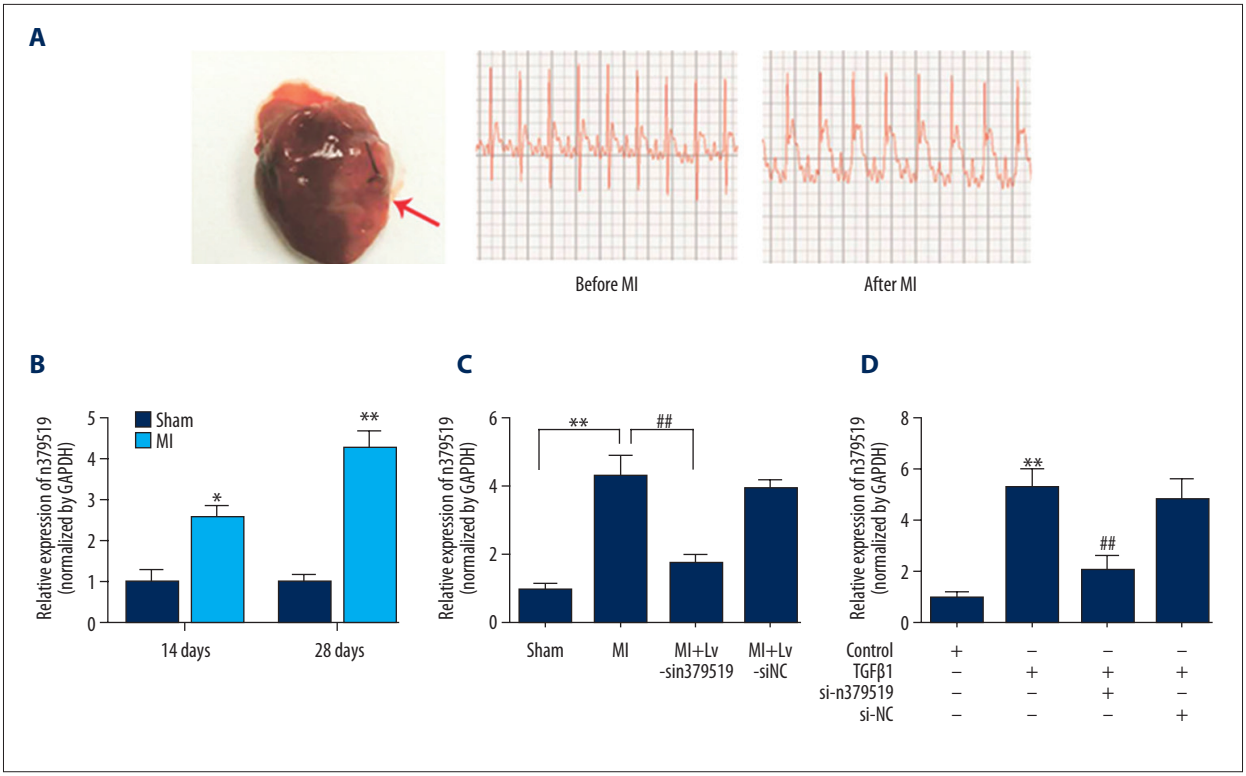

Figure 1. LncRNA n379519 is up-regulated in infarcted myocardium and TGF-β1-induced CFs. (**A**) Establishment of a myocardial infarction model in SD rats. (**B**) RT-PCR was used to detect the expression of n379519 on day 14 and day 28. (**C**) Relative expression levels of n379519 in the peri-infarct region of myocardial and TGF-β1 treatment CFs. Data are expressed as mean ±SD. * $P<0.05$, ** $P<0.01$ *vs.* sham operation group or control group. # $P<0.05$, ## $P<0.01$ *vs.* MI group or TGF-β1 group.

notably restored the LVEF and LVFS (Figure 2A–2C). Meanwhile, pathological staining indicated that transfection of n379519 siRNA resulted in a smaller infarct size and a more robust left ventricular wall (Figure 2 D–2F). Furthermore, the collagen volume fraction was significantly decreased in the Lv-sin379519 group (Figure 2G). Similarly, collagen I and collagen III expression in the Lv-sin379519 group were reduced at the transcriptional level (Figure 2H, 2I).

LncRNA n379519 function as an miR-30 sponge in myocardial fibrosis

Our study revealed the fibrosis-promoting effect of n379519 in MI rat myocardium. Next, we wanted to determine the potential mechanism of n379519 in cardiac fibrosis. Through *in vivo* and *in vitro* experiments, we consistently observed significant decreases of miR-30, and this down-regulation was reversed when we injected Lv-sin379519 into the peri-infract region of myocardia or transfected si-n379519 into the CFs (Figure 3A, 3B). Moreover, we found that n379519 expression was downregulated when transfected with miR-30 inhibitor, which directly indicates that there is a mutual regulation between the miR-30 and n379519 (Figure 3C). Bioinformatics analysis (Starbase v2.0) was used to predict lncRNA-mRNA interaction pathway, showing that miR-30 had binding sites with n379519 (Figure 3D). Dual-luciferase reporter assay further validated the alignment of complementary binding of miR-30 and n379519 (Figure 3E).

lncRNA n379519 regulated myocardial collagen deposition by targeting miR-30

Our data demonstrate that collagen I and collagen III were significantly upregulated at the transcriptional level in MI hearts (Figure 2H, 2I) after TGF-β1 treatment of CFs (Figure 4A, 4B). However, knockdown of n379519 obviously reversed collagen deposition. To explore the potential mechanism, CFs were incubated with miR-30 inhibitor and the result indicated that miR-30 inhibitor reversed the anti-collagen deposition effect of n379519 silencing at the protein level (Figure 4C, 4D).

Discussion

As the main component of the myocardial cell mesenchyme, type I collagen accounts for 80–85%, functioning to maintain the structural strength of the heart, and type III collagen accounts for 10–12%, which can maintain the elasticity

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

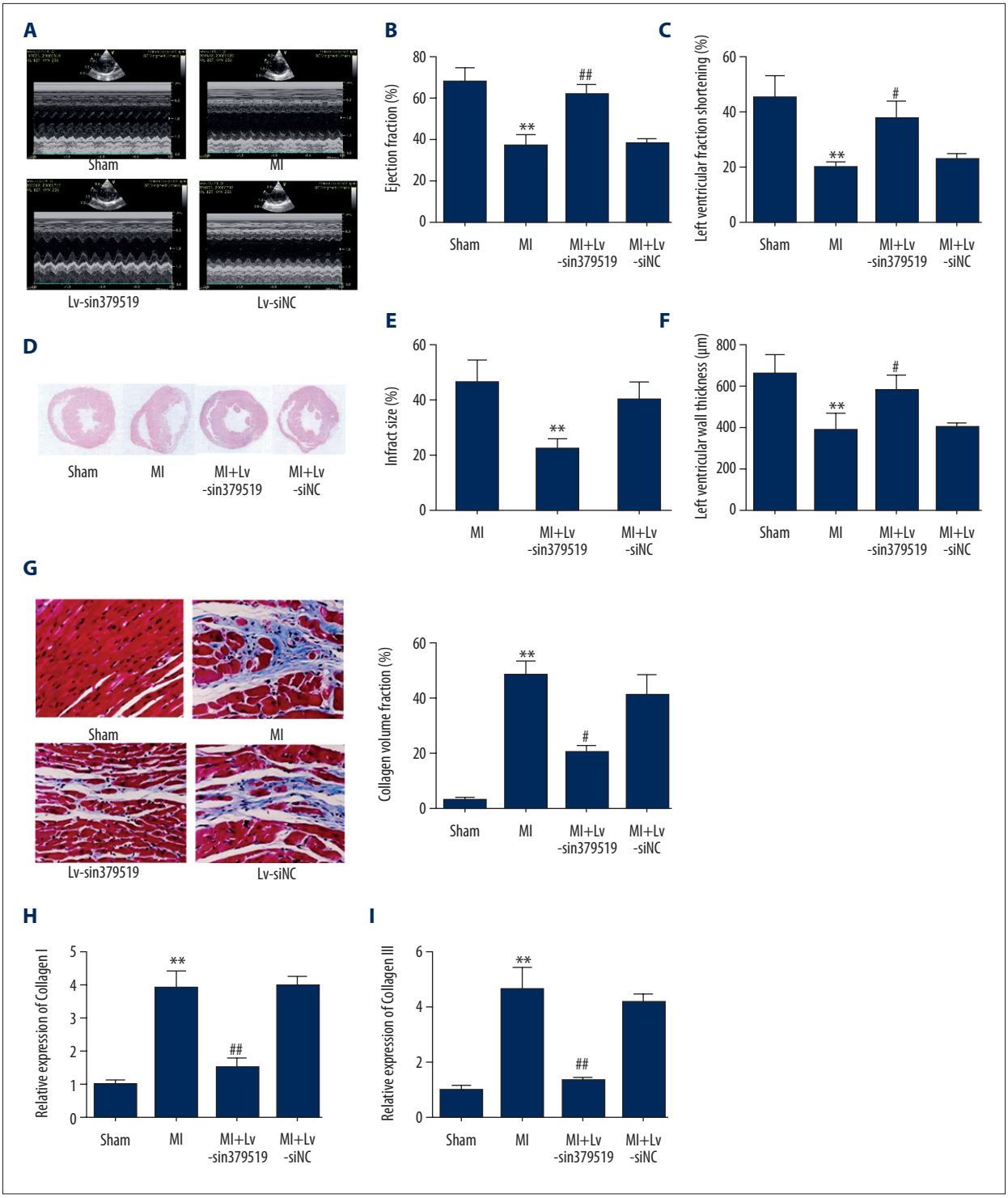

Figure 2. Suppression of n379519 improved heart function and attenuates fibrotic changes of myocardium. (**A**) Echocardiography images of each group. (**B**) Ejection fraction. (**C**) Left ventricular fractional shortening. (**D**) HE staining of crosses sections of the heart. (**E**) Comparison of infarct size. (**F**) Comparison of left ventricular wall thickness. (**G**) Masson staining and Collagen Volume Fraction were used to compare the severity of myocardial fibrosis. (**H**) The mRNA expression level of collagen I. (**I**) The mRNA expression level of collagen III. Data are expressed as mean ±SD. * $P<0.05$, ** $P<0.01$ *vs.* sham operation group. # $P<0.05$, ## $P<0.01$ *vs.* MI group.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

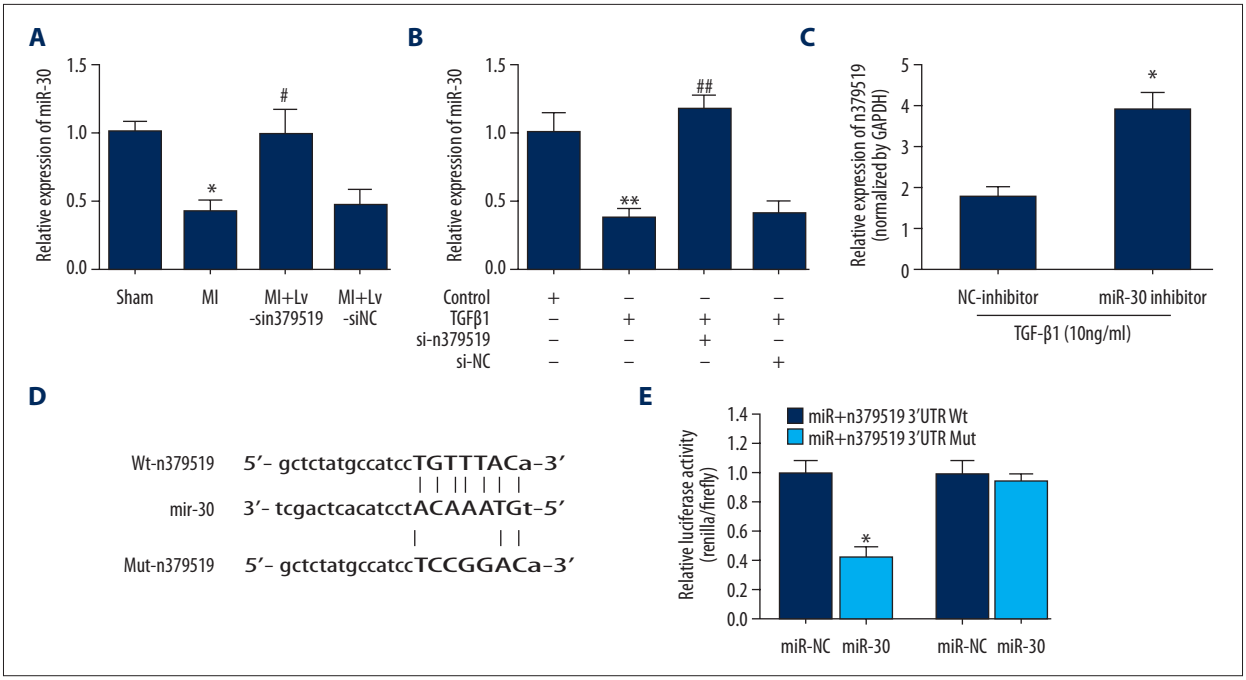

Figure 3. lncRNA n379519 functions as an miR-30 sponge in myocardial fibrosis. (**A**) The relative expression level of miR-30 in the peri-infract region of myocardium. (**B**) The relative expression level of miR-30 in TGF-β1 treatment CFs. (**C**) CFs was transfected with miR-30 inhibitor and the expression of n379519 was measured using RT-PCR. (**D**) Putative complementary sites within miR-30 and 3′-UTR of n379519 predicted using Starbase. (**E**) The miR-30 mimics and WT/Mut n379519 vectors were co-transfected into CFs and the probability of binding of miR-30 with the 3′-UTR of n379519 was assessed by luciferase reporter assay. Data are expressed as mean ±SD. * P <0.05, ** P<0.01 *vs.* sham operation group or control group or miR-NC/inhibitor group. # P<0.05, ## P<0.01 *vs.* MI group or TGF-β1 group.

and tension of the myocardium [17]. The primary pathological changes of post-myocardial infarction are the activation, proliferation, and conversion of fibroblasts into myofibroblasts, which then synthesize and secrete large amounts of extracellular matrix proteins [18]. Hence, Masson staining and collagen are the common detection index of myocardial fibrosis.

Long noncoding RNAs are not only critical for regulating cell proliferation, differentiation, metabolism, apoptosis, and other important biological processes, but are also related to the occurrence, development, and diagnosis of diseases [19]. Although many studies have reported the regulating function of lncRNA on cardiovascular disease, little is known about myocardial fibrosis. *Wisper* has been shown act as a specific regulator of cardiac fibroblasts proliferation, migration, survival, and extracellular matrix deposition [20]. Liang et al. found that lncRNA PEL was upregulated in the hearts of myocardial infarction mice, and knockdown of PEL significantly alleviates myocardial interstitial fibrosis and improved cardiac function [21]. Piccoli et al. observed that preventive inhibition of lncRNA Meg3 in CFs decreased myocardial fibrosis and hypertrophy and reversed diastolic function [16]. In the present study, we found that n379519 expression was upregulated both in the hearts of MI rats and TGF-β1 treatment CFs. Knockdown of n379519 significantly improved cardiac function and inhibited collagen overproduction. Based on the above results, we believe that silencing n379519 is cardioprotective and improves myocardial interstitial fibrosis and systolic function.

lncRNAs can be used as competitive endogenous RNAs to regulate multiple biological functions of cells. They often contain complements of the sequence domain of miRNAs that allow them to act as natural sponges to bind with multiple miRNAs [22]. lncRNA n379519 has been shown to be abundantly expressed in human left ventricle myocardium and mouse CFs, and knockdown of n379519 significantly reduced α-SMA and fibrosis genes (collagen 3A1, collagen 8A1, and fibronectin) expression [15]. n379519 and miR-30 have been found to be related with TGF-β signaling pathway [23,24]. Therefore, we explored whether n379519 regulates TGF-β to further regulate the expression of miR30. We demonstrated that alignment of complementary regions between n379519-3′UTR and miR-30 indicated a putative miR-30 target site in the n379519 gene. Dual-luciferase reporter assay identified the interaction between n379519 and miR-30. Furthermore, rescue experiments showed that miR-30 inhibitor reverses the increased expression of collagen caused by silencing n379519. These results provide powerful evidence that n379519 interacts with miR-30.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

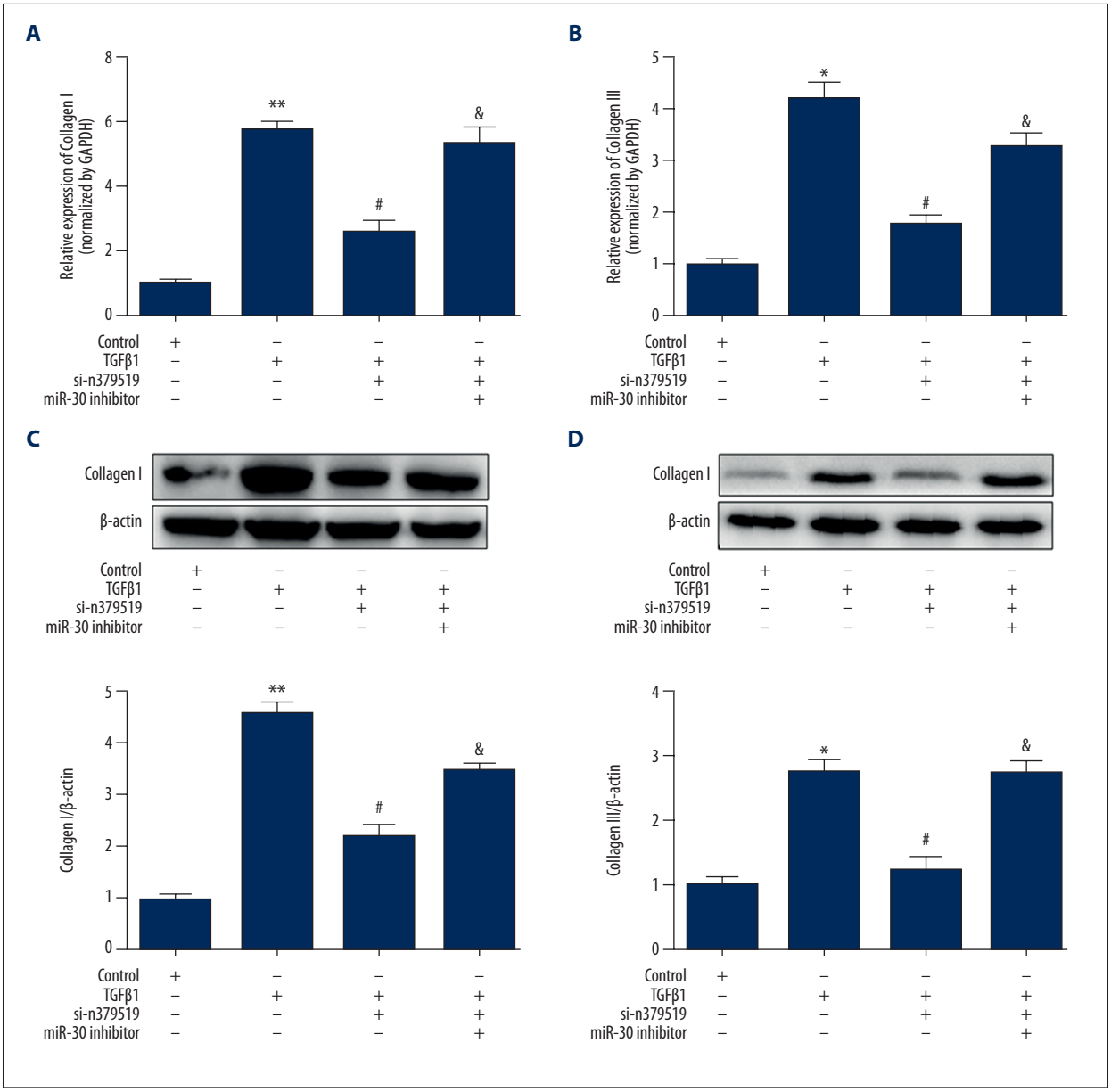

Figure 4. lncRNA n379519 regulated myocardial collagen deposition by targeting miR-30. (**A, B**) CFs were co-transfected with si-n379519 and miR-30 inhibitor. Expressions of collagen I and collagen III were detected using RT-PCR. (**C, D**) Protein expressions of collagen I and collagen III in CFs transfected with si-n379519 and miR-30 inhibitor were measured by Western blot. Data are expressed as mean ±SD. * $P<0.05$, ** $P<0.01$ *vs.* control group. # $P<0.05$, ## $P<0.01$ *vs.* TGF-β1 group. & $P<0.05$ *vs.* si-n379519 group.

Conclusions

Our results reveal the role and mechanism of n379519/miR-30 axis in the regulation of cardiac fibrosis after MI and provide advanced insight into the pathogenesis of lncRNAs in cardiac fibrosis.

Conflict of interest

None.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Supplementary Table

Supplementary Table 1. Sequence of primers used for RT-PCR.

RNA name		Sequence
GAPDH	Forward	5'-TGTGTCCGTCGTGGATCTGA-3'
	Reverse	5'-CCTGCTTCACCACCTTCTTGA-3'
n379519	Forward	5'-CTTCACTCCTGCAAATGTGTT-3'
	Reverse	5'-TTATAGTGGGATGGGCAGTTT-3'
miR-30	Forward	5'-TGTAAACATCCTCGAC-3'
	Reverse	5'-ACATCCAGTGTAGCATA-3'
Collagen I	Forward	5'-CAATGGCACGGCTGTGTGCG-3'
	Reverse	5'-CACTCGCCCTCCCGTCTTTGG-3'
Collagen III	Forward	5'-TGGCACAGCAGTCCAACGTA-3';
	Reverse	5'-AAGGACAGATCCTGAGTCACAGACA-3'

Refrerences:

1. Prabhu SD, Frangogiannis NG: The biological basis for cardiac repair after myocardial infarction: From inflammation to fibrosis. Circ Res, 2016; 119: 91–112
2. de Haas HJ, Arbustini E, Fuster V et al: Molecular imaging of the cardiac extracellular matrix. Circ Res, 2014; 114: 903–15
3. Schelbert EB, Fonarow GC, Bonow RO et al: Therapeutic targets in heart failure: Refocusing on the myocardial interstitium. J Am Coll Cardiol, 2014; 63: 2188–98
4. Lighthouse JK, Small EM: Transcriptional control of cardiac fibroblast plasticity. J Mol Cell Cardiol, 2016; 91: 52–60
5. Maruyama R, Suzuki H: Long noncoding RNA involvement in cancer. BMB Rep, 2012; 45: 604–11
6. Wang JX, Zhang XJ, Li Q et al: MicroRNA-103/107 regulate programmed necrosis and myocardial ischemia/reperfusion injury through targeting FADD. Circ Res, 2015; 117: 352–63
7. Li N, Ponnusamy M, Li MP et al: The role of MicroRNA and lncRNA-microRNA interactions in regulating ischemic heart disease. J Cardiovasc Pharmacol Ther, 2016; 6: 1024–32
8. Wang K, Liu F, Zhou LY et al: The long noncoding RNA CHRF regulates cardiac hypertrophy by targeting miR-489. Circ Res, 2014; 114: 1377–88
9. Tao H, Yang JJ, Hu W et al: Noncoding RNA as regulators of cardiac fibrosis: Current insight and the road ahead. Pflugers Arch, 2016; 468: 1103–11
10. Thum T: Noncoding RNAs and myocardial fibrosis. Nat Rev Cardiol, 2014; 11: 655–63
11. Wang C, Cai L, Liu J et al: MicroRNA-30a-5p inhibits the growth of renal cell carcinoma by modulating GRP78 expression. Cell Physiol Biochem, 2017; 43: 2405–19
12. Duisters RF, Tijsen AJ, Schroen B et al: miR-133 and miR-30 regulate connective tissue growth factor: Implications for a role of microRNAs in myocardial matrix remodeling. Circ Res, 2009; 104: 170–78, 6p following 8
13. Vegter EL, van der Meer P, de Windt LJ et al: MicroRNAs in heart failure: From biomarker to target for therapy. Eur J Heart Fail, 2016; 18: 457–68
14. Rubis P, Toton-Zuranska J, Wisniowska-Smialek S et al: Relations between circulating microRNAs (miR-21, miR-26, miR-29, miR-30 and miR-133a), extracellular matrix fibrosis and serum markers of fibrosis in dilated cardiomyopathy. Int J Cardiol, 2017; 231: 201–6
15. Huang ZP, Ding Y, Chen J et al: Long non-coding RNAs link extracellular matrix gene expression to ischemic cardiomyopathy. Cardiovasc Res, 2016; 6: 2514–27
16. Piccoli MT, Gupta SK, Viereck J et al: Inhibition of the cardiac fibroblast-enriched lncRNA Meg3 prevents cardiac fibrosis and diastolic dysfunction. Circ Res, 2017; 121: 575–83
17. Ladouceur M, Baron S, Nivet-Antoine V et al: Role of myocardial collagen degradation and fibrosis in right ventricle dysfunction in transposition of the great arteries after atrial switch. Int J Cardiol, 2018; 58: 108–22
18. Talman V, Ruskoaho H: Cardiac fibrosis in myocardial infarction-from repair and remodeling to regeneration. Cell Tissue Res, 2016; 365: 563–81
19. Ono K, Kuwabara Y, Horie T, Kimura T: Long non-coding RNAs as key regulators of cardiovascular diseases. Circ J, 2018; 28: 383–96
20. Micheletti R, Plaisance I, Abraham BJ: The long noncoding RNA Wisper controls cardiac fibrosis and remodeling. Sci Transl Med, 2017; 9(395): pii: eaai9118
21. Liang H, Pan Z, Zhao X et al: LncRNA PFL contributes to cardiac fibrosis by acting as a competing endogenous RNA of let-7d. Theranostics, 2018; 8: 1180–94
22. Cesana M, Cacchiarelli D, Legnini I et al: A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous RNA. Cell, 2011; 147: 358–69
23. Roy S, Benz F, Vargas Cardenas D et al: miR-30c and miR-193 are a part of the TGF-beta-dependent regulatory network controlling extracellular matrix genes in liver fibrosis. J Dig Dis, 2015; 16: 513–24
24. Tu X, Zheng X, Li H et al: MicroRNA-30 protects against carbon tetrachloride-induced liver fibrosis by attenuating transforming growth factor beta signaling in hepatic stellate cells. Toxicol Sci, 2015; 146: 157–69

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]