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LncRNA NEAT1 promotes cardiac hypertrophy through microRNA-19a-3p/SMYD2 axis

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Abstract. – OBJECTIVE: The role of NEAT1 in cancers has been demonstrated. But the role of NEAT1 in cardiac hypertrophy still remains unknown. This study aimed to elucidate the specific function of long non-coding RNA (lncRNA) NEAT1 in cardiac hypertrophy and its underlying mechanism.

PATIENTS AND METHODS: In this study, the *in vivo* and *in vitro* cardiac hypertrophy models were constructed by transverse aortic coarctation (TAC) procedure in rats and phenylephrine (PE) induction in primary cardiomyocytes, respectively. The expression levels of NEAT1, microRNA-19a-3p, SMYD2, and cardiac hypertrophic markers were detected by quantitative Real Time-Polymerase Chain Reaction (qRT-PCR). Cardiac hypertrophy was evaluated as calculating the surface area of hypertrophic cardiomyocyte by fluorescein isothiocyanate (FITC)-Phalloidin staining. Luciferase Reporter Gene Assay was conducted to detect the binding of NEAT1, SMYD2, and microRNA-19a-3p.

RESULTS: The results showed that NEAT1 and SMYD2 were highly expressed in myocardium of rats with cardiac hypertrophy and PE-induced primary cardiomyocytes, whereas microRNA-19a-3p was lowly expressed. Besides, NEAT1 overexpression markedly upregulated levels of the cardiac hypertrophic markers. Moreover, FITC-Phalloidin staining also revealed hypertrophic cardiomyocytes overexpressing NEAT1. On the contrary, microRNA-19a-3p overexpression reduced the cardiomyocyte surface area and downregulated the levels of the cardiac hypertrophic markers. As luciferase reporter gene assay demonstrated, NEAT1 and SMYD2 could bind to microRNA-19a-3p. Finally, the gain-of-function experiments were designed to verify whether NEAT1 exerted its functions in cardiac hypertrophy by modulating SMYD2 and microRNA-19a-3p. Furthermore, both microRNA-19a-3p overexpression or SMYD2 knockdown could inhibit and reduce the cardiomyocyte surface area, and downregulate the levels of the cardiac hypertrophic markers.

CONCLUSIONS: In summary, NEAT1 promotes the occurrence and progression of cardiac hypertrophy by upregulating SMYD2 by binding to microRNA-19a-3p.

Key Words:
NEAT1, MicroRNA-19a-3p, SMYD2, Cardiac hypertrophy.

Introduction

Cardiac hypertrophy is the increased contraction ability at a certain stage, which is the manifestation of normal growth and maturity of the heart. In the early stage, the cardiac hypertrophy is a compensatory performance against the increased working load. However, both diastole and systole impair the heart at the end-stage of hypertrophy, thus resulting in decompensation and further leading to heart failure[1]. Cardiac hypertrophy is an independent risk factor for unexplained sudden death. More importantly, hypertrophy is also an important risk factor for myocardial ischemia and arrhythmia[2].

Cardiac hypertrophy is morphologically characterized by the enlargement of heart size, structure, mass, and cardiomyocyte surface area, while the cell number maintains unchangeable. The pathological performances of the cardiac hypertrophy mainly include the proliferation of myocardial interstitial cells and alteration of the extracellular matrix. Molecular genetic studies[3,4] have shown that the expression levels of the myocardial markers, cardiomyocyte volume, and heart mass all increase during the development of cardiac hypertrophy. However, the molecular mechanism of cardiac hypertrophy is still not fully understood.

Long non-coding RNAs (lncRNAs) are a class of RNAs that are more than 200 nucleotides in length. They lack a specific open reading frame, and do not have the protein-encoding function. The biological functions of lncRNAs are achieved by mediating genetic imprinting, cell cycle progression, chromatin remodeling, mRNA degrada-

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tion, and translational regulation. The abnormal functions of lncRNAs can cause diseases[5]. As a kind of non-coding RNA, lncRNA cannot produce a protein with a specific function by translation, but it exerts a regulatory effect by affecting and changing the configuration of the specific target genes. So far, most studies on lncRNAs focused on their functions in malignancies. LncRNAs have been identified to regulate apoptosis and signaling pathways in multiple malignant tumors[6]. Abnormal proliferation is a specific feature in tumors, which is also observed in cardiac hypertrophy, which is present as increases in protein synthesis, cell volume, sarcomere number, and fibrous tissue proliferation. Previous studies[7,8] have shown that lncRNAs may also participate in the process of cardiac hypertrophy, affecting its occurrence and development.

The functional architecture of NEAT1 is an important component of the paraspeckle, which is essential for maintaining the morphology and function of paraspeckle[9,10]. In recent years, the abnormal expression of NEAT1 has been reported in many human malignancies, including leukemia, glioma, non-small cell lung cancer, and breast cancer[11]. NEAT1 is considered to promote tumorigenesis and tumor development. Some of the biological mechanisms of NEAT1 have been revealed. It is reported that NEAT1 interacts with a variety of nuclear RNA-binding proteins, such as the cleaving factor family proteins, thus transporting mRNAs out of the nucleus. In addition, NEAT1 affects the expression of some tumor-suppressor genes by interacting with miRNAs as a ceRNA[12,13]. However, the specific function of NEAT1 in cardiac hypertrophy has not been elucidated.

Materials and Methods

Experimental Animals

Healthy male Sprague-Dawley (SD) rats weighing 180-220 g and newborn (1-3 days old) SD rats were provided by the Experimental Animal Center of Beijing University. The rats were housed in a standard SPF environment with the temperature of 22°C and relative humidity of 50-60%. This experiment has been approved by the Animal Ethics Committee of the Beijing Hospital.

Cardiac Hypertrophy Model in Rats by Transverse Aortic Coarctation (TAC)

The rats were intraperitoneally injected with 10% chloral hydrate (4 mL/1000 g). After successful anesthesia, the rats were fixed and sterilized. A median longitudinal incision was made. Subsequently, the abdominal aorta at 0.5 cm above the left renal artery was ligated alongside the L-type syringe needle (0.6 mm inner diameter) using 4-0 suture. The needle was then carefully pulled out. The rats in the sham group received the same procedures except for ligation.

Culture of Primary Cardiomyocytes

The newborn rats were immersed in alcohol and the apex was taken out under aseptic conditions. The apex was gently torn with an ophthalmologist, and the ventricular muscles were cut into pieces of about 1 mm^3. The tissues were digested in a 37°C water bath and shaken at 100 rpm/min for 4-5 repeated digestion. The cells were resuspended in Dulbecco's Modified Eagle's Medium/F-12 (DMEM/F-12) medium (Gibco, Rockville, MD, USA) containing 5% fetal bovine serum (FBS) (Gibco, Rockville, MD, USA), 0.1 mM ascorbate, insulin-transferring-sodium selenite media supplement, 100 U/mL penicillin, 100 μg/mL streptomycin, and 0.1 mM bromodeoxyuridine. They were seeded in a 25 cm^2 culture bottle. After culturing for 1 h at 37°C, the purified primary cardiomyocytes were isolated due to the differential adherence of fibroblasts and cardiomyocytes. The phenotype of cardiac hypertrophy of the isolated primary cardiomyocytes were induced with 2.5 μg/mL PE treatment.

Transfection

The transfection was carried out according to the instructions of the Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). Briefly, the oligonucleotide sequence/overexpression plasmid or transfection reagent was diluted with serum-free medium (100 μmol oligonucleotide sequence / 50 ng DNA per 1×10^6 cells). After gentle mixture and maintenance for 20 min, the cells were incubated for 8 h. The medium was replaced and the transfected cells were cultured for 48 h until use. The small nucleotide sequences and plasmids used in the experiments were all provided by GenePharma (Shanghai, China).

RNA Extraction and Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

The total RNA of cells or tissues was extracted using TRIzol (Invitrogen, Carlsbad, CA, USA). The RNA concentration was determined as 500 ng. After the reverse transcription of the extracted RNA into complementary deoxyribose nucleic acid (cDNA), the 20 μL reaction system was prepared

using the SYBR Premix Ex Taq kit. The mRNA and miRNA were internally referenced by β-actin and U6, respectively. QRT-PCR reaction conditions were as follows: Pre-denaturation at 95°C for 30 s, followed by 40 cycles of 95°C for 5 s and 60°C for 30 s, and finally 94°C for 90 s, 60°C for 180 s. The PCR amplification product was subjected to 2% agarose electrophoresis (5 V/cm) for 30 minutes, and the results were observed on a UV detector. Each sample was tested twice. The primer sequences were as follows: NEAT1, F: TGGTAAGCCCGGGACAGT, R: CAGCGGGAAGGCCTCTCT; SMYD2, F: TACTGCAATGTGGAGTGTCAGA, R: ACAGTCTCCGAGGGATTCCAG; ANF, F: GCCGGTAGAAGATGAGGTCA, R: GGGCTCCAATCCTGTCAATC; SKA, F: GGCTCCCAGCACCATGAAGA, R: CAGCACGATTGTCGATTGTCG; β-MHC, F: GTGAAGGGCATGAGGAAGAG; R: AGGCCTTCACCTTCAGCTGC; BNP, F: GCTCTTGAAGGACCAAGGCCTCAC, R: GATCCGA TCCGGTCTATCTTGTGC; MicroRNA-19a-3p, F: ACACTCCAGCTGGGTGTGCAAATCTATGCAA; R: TGGTGTCGTGGAGTCG.

Determination of Cardiomyocyte Morphology

The cells were washed with Phosphate-Buffered Saline (PBS) twice, fixed in paraformaldehyde for 20 minutes and stained with fluorescein isothiocyanate (FITC)-Phalloidin for 30-60 min. After PBS wash, the nucleus was stained with Hoechst 33342 for 5 min. Five randomly selected fields containing 5-10 cardiomyocytes in each were captured using an inverted fluorescent microscope. The cardiomyocyte surface area was calculated by Image J Software (NIH, Bethesda, MD, USA).

Luciferase Reporter Gene Assay

WT-NEAT1, WT-SMYD2, MUT-NEAT1, and MUT-SMYD2 were purchased from Ribobio (Guangzhou, China). The Luciferase reporter vector was co-transfected with microRNA-19a-3p mimic into cells, followed by Luciferase activity determination.

Western Blot

The total protein was extracted from cell lysis, quantified and electrophoresed. After transferring on polyvinylidene difluoride (PVDF) membranes (Roche, Basel, Switzerland), they were incubated with primary antibodies at 4°C. At the other day, the membranes were incubated with the corresponding secondary antibody for 2 h. The bands were exposed with the enhanced chemiluminescence, and integral optical density was analyzed by gel imaging analysis system.

Statistical Analysis

The data were analyzed by Statistical Product and Service Solutions (SPSS) 17.0 statistical software (SPSS Inc., Chicago, IL, USA). The quantitative data were represented as mean ± standard deviation ($\bar{x}\pm s$) and analyzed by the *t*-test. $p<0.05$ was considered as statistically significant.

Results

Highly Expressed NEAT1 and Lowly Expressed MicroRNA-19a-3p in Cardiac Hypertrophy

First of all, we established an *in vivo* cardiac hypertrophy model by TAC procedure. NEAT1 was highly expressed, whereas microRNA-19a-3p was lowly expressed in myocardium of rats with cardiac hypertrophy than those of the sham group (Figure 1A). Subsequently, the primary cardiomyocytes were isolated from newborn SD rats and induced with PE for establishing the *in vitro* cardiac hypertrophy model. Identically, NEAT1 was highly expressed, whereas microRNA-19a-3p was lowly expressed in PE-induced hypertrophic cardiomyocytes than those of the controls (Figure 1B). By comparison, NEAT1 expression gradually decreased, and microRNA-19a-3p expression increased in normal cardiomyocytes with the prolongation of cell culture (Figure 1C). Besides, higher expression of NEAT1 was seen in cardiomyocytes than cardiac fibroblasts (Figure 1D). It is suggested that NEAT1 was closely related to cardiomyocyte hypertrophy.

High Expression of NEAT1 Promoted Cardiomyocyte Hypertrophy

To explore the biological function of NEAT1 in cardiac hypertrophy, we downregulated the expression of NEAT1 in cardiomyocytes by transfecting three lines of si-NETA1 and the most efficacy one was selected for subsequent experiments (Figure 2A). Compared with the control group, the cardiomyocyte surface area enlarged and levels of cardiomyocyte hypertrophic markers increased after PE treatment. However, NEAT1 knockdown reduced cardiomyocyte surface area (Figure 2B). Meanwhile, the expression levels of the cardiac hypertrophic markers ANF, SKA, β-MHC, and BNP were also reduced in cardiomyocytes with NEAT1 knockdown (Figures 2C-2F). Transfec-

tion efficacy of NEAT1 overexpression plasmid was then verified (Figure 2G). The overexpression of NEAT1 obtained the opposite results with enlarged cardiomyocyte surface area (Figure 2H) and increased the levels of cardiomyocyte hypertrophic markers (Figure 2I). These results suggested that the high expression of NEAT1 promoted hypertrophic growth of cardiomyocytes.

High Expression of MicroRNA-19a-3p Inhibited Cardiomyocyte Hypertrophy

Subsequently, we explored the biological function of microRNA-19a-3p by determining the cardiomyocyte surface area and cardiac hypertrophic marker levels. The surface area of cardiomyocytes overexpressing microRNA-19a-3p was reduced (Figure 3A). Besides, the overexpression of microRNA-19a-3p can remarkably downregulate the levels of ANF, SKA, β-MHC, and BNP (Figures 3B-3E). On the contrary, microRNA-19a-3p knockdown enlarged cardiomyocyte surface area and upregulated the levels of ANF, SKA, β-MHC, and BNP (Figures 3F-3G). These results revealed that high expression of microRNA-19a-3p inhibited hypertrophic growth of cardiomyocytes.

MicroRNA-19a-3p Bound to NEAT1 and SMYD2

To explore the potential role of microRNA-19a-3p in cardiac hypertrophy, we predicted the potential target gene of microRNA-19a-3p *via* TargetScan, StarBase, RNA22, and other bioinformatics websites, and SMYD2 was screened out (Figure 4A).

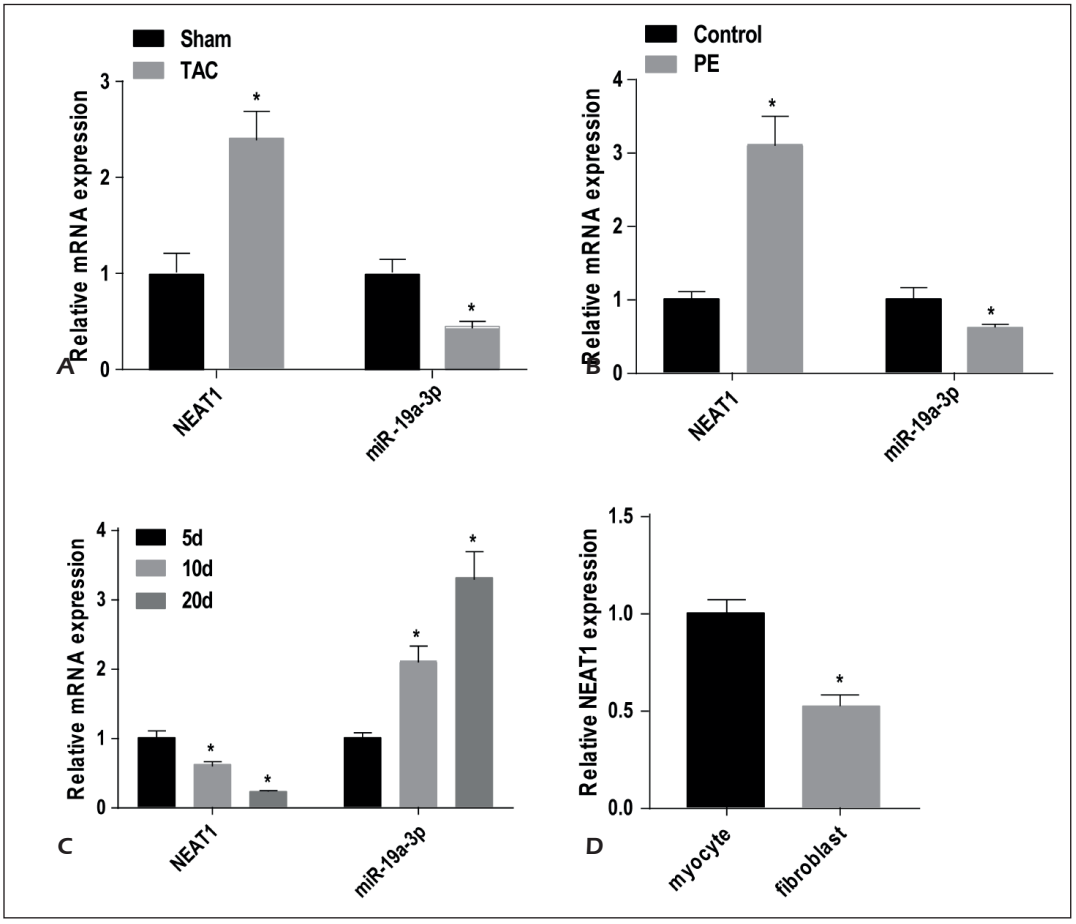

Figure 1. Highly expressed NEAT1 and lowly expressed microRNA-19a-3p in cardiac hypertrophy. **A**, NEAT1 was highly expressed, whereas microRNA-19a-3p was lowly expressed in myocardium of rats with cardiac hypertrophy than those of the sham group (n=3). **B**, QRT-PCR data showed that NEAT1 was highly expressed, whereas microRNA-19a-3p was lowly expressed in PE-induced hypertrophic cardiomyocytes than those of the controls. **C**, NEAT1 expression gradually decreased, and microRNA-19a-3p expression increased in normal cardiomyocytes with the prolongation of cell culture. **D,** NEAT1 was highly expressed in cardiomyocytes than cardiac fibroblasts.

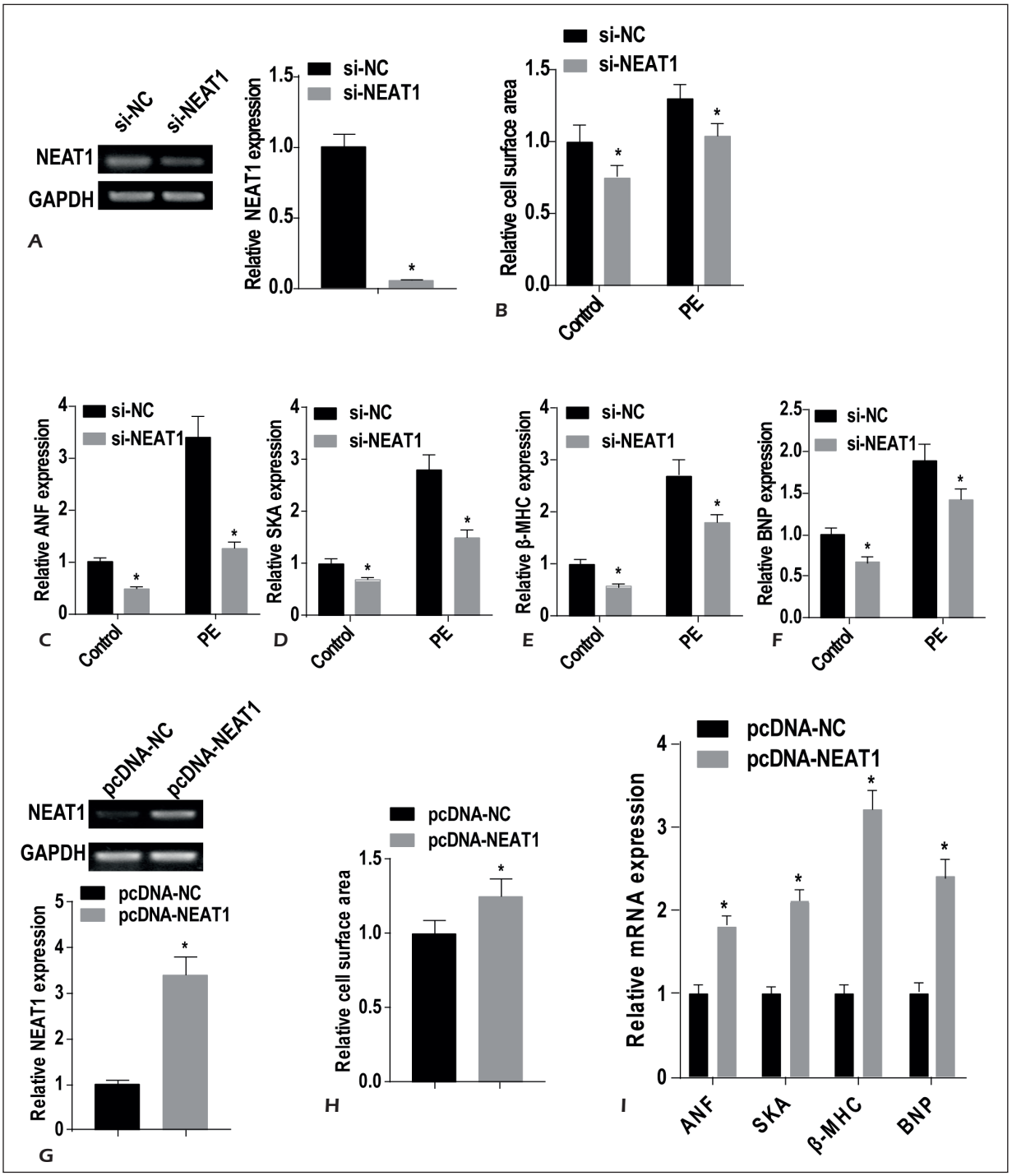

Figure 2. High expression of NEAT1 promoted cardiomyocyte hypertrophy. **A**, QRT-PCR data showed that NEAT1 expression was inhibited in cardiomyocytes transfected with si-NEAT1. **B**, Surface area became smaller in PE-induced cardiomyocytes with NEAT1 knockdown. **C**-**F**, QRT-PCR data showed that mRNA levels of ANF, SKA, β-MHC, and BNP decreased in PE-induced cardiomyocytes with NEAT1 knockdown. **G**, QRT-PCR data showed that NEAT1 expression increased in cardiomyocyte transfected with NEAT1 overexpression plasmid. **H,** The surface area became larger in PE-induced cardiomyocytes with NEAT1 overexpression. **I**, QRT-PCR data showed that mRNA levels of ANF, SKA, β-MHC, and BNP increased in PE-induced cardiomyocytes with NEAT1 overexpression.

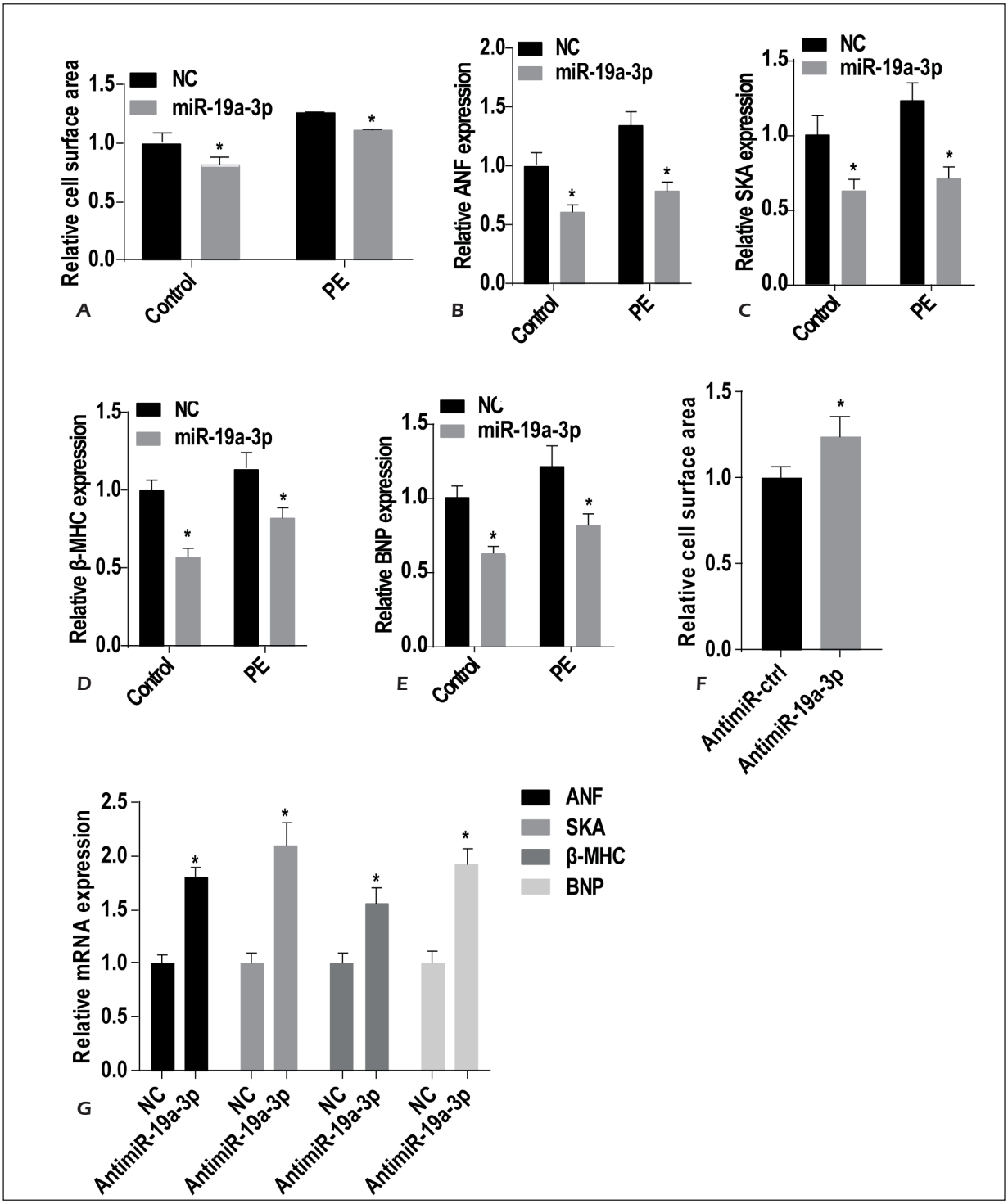

Figure 3. High expression of microRNA-19a-3p inhibited cardiomyocyte hypertrophy. **A**, Surface area became smaller in PE-induced cardiomyocytes with microRNA-19a-3p overexpression. **B**-**E**, QRT-PCR data showed that mRNA levels of ANF, SKA, β-MHC, and BNP decreased in PE-induced cardiomyocytes with microRNA-19a-3p overexpression. **F**, Surface area became larger in PE-induced cardiomyocytes with microRNA-19a-3p knockdown. **G**, QRT-PCR data showed that mRNA levels of ANF, SKA, β-MHC, and BNP increased in PE-induced cardiomyocytes with microRNA-19a-3p knockdown.

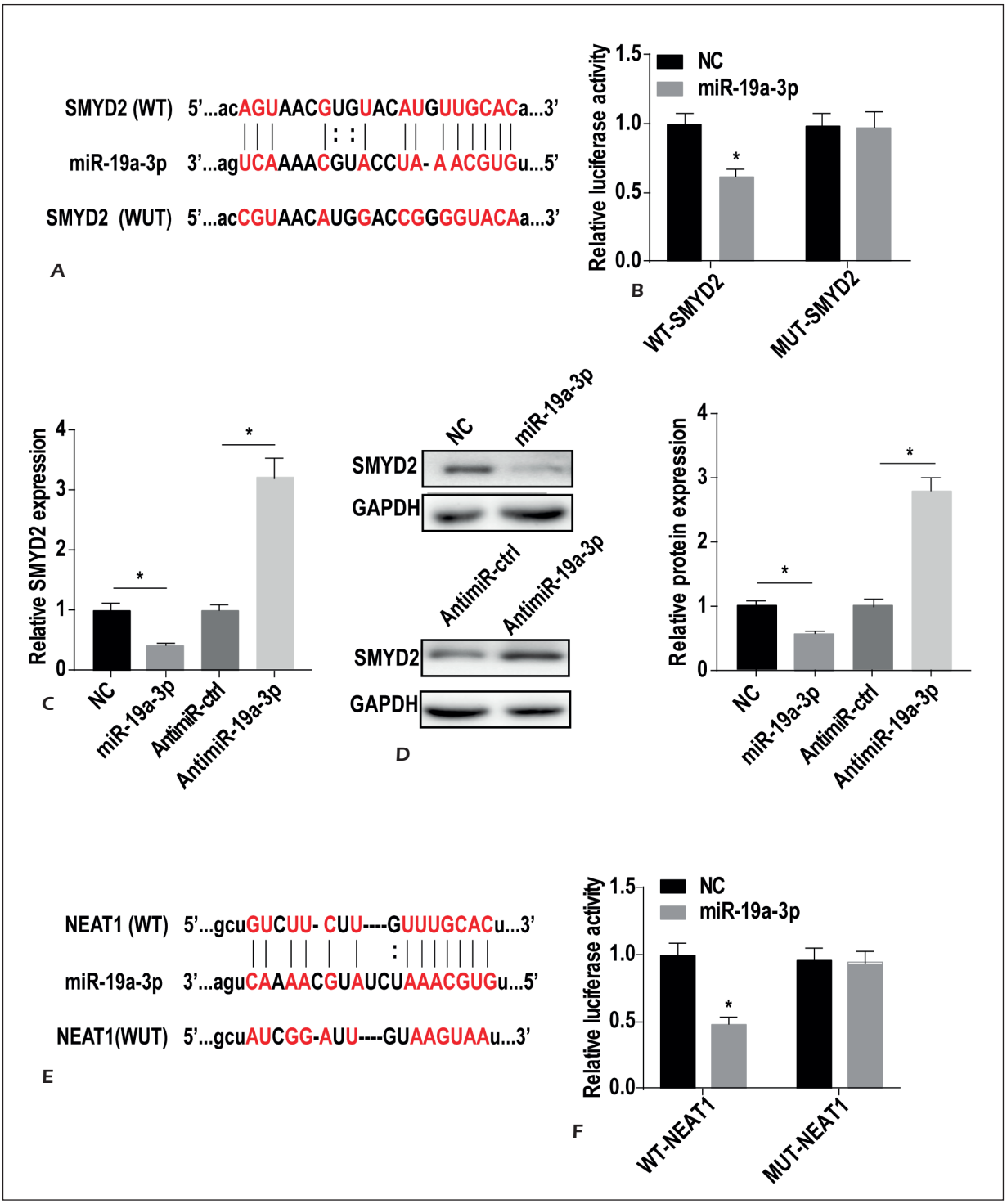

Figure 4. MicroRNA-19a-3p bound to NEAT1 and SMYD2. **A-B**, Binding sites of microRNA-19a-3p and SMYD2. The overexpression of microRNA-19a-3p quenched wild-type SMYD2 fluorescence in primary cardiomyocytes. **C**, QRT-PCR data showed that microRNA-19a-3p overexpression downregulated the SMYD2 expression, whereas microRNA-19a-3p knockdown upregulated the SMYD2 expression. **D**, Western blot results showed that microRNA-19a-3p overexpression downregulated SMYD2 expression, whereas microRNA-19a-3p knockdown upregulated SMYD2 expression. **E-F**, Binding sites of microRNA-19a-3p and NEAT1. Overexpression of microRNA-19a-3p quenched wild-type NEAT1 fluorescence in primary cardiomyocytes.

The Luciferase Reporter Gene Assay suggested that the overexpression of microRNA-19a-3p quenched the wild-type SMYD2 fluorescence in primary cardiomyocytes (Figure 4B). At the same time, both mRNA and protein levels of SMYD2 were negatively regulated by microRNA-19a-3p (Figures 4C and 4D). Similarly, we found a complementary binding site of microRNA-19a-3p to NEAT1. Overexpression of microRNA-19a-3p quenched the wild-type NEAT1 fluorescence, whereas mutant-type NEAT1 was not affected (Figures 4E and 4F).

MicroRNA-19a-3p Reversed Cardiac Hypertrophy Induced by NEAT1 Overexpression

To further verify that NEAT1 exerted its promotive function in cardiac hypertrophy through microRNA-19a-3p, we co-overexpressed NEAT1 and microRNA-19a-3p in hypertrophic cardiomyocytes. The co-overexpressed cardiomyocytes showed a smaller surface area than those only overexpressed NEAT1 (Figure 5A). Moreover, the expression levels of ANF, SKA, β-MHC, and BNP decreased in the co-overexpressed cardiomyocytes, as well compared with those only with NEAT1 overexpression (Figures 5B-5E). The protein levels of ANF and β-MHC obtained identical changing trends (Figure 5F).

NEAT1 Regulated Cardiac Hypertrophy Through SMYD2

To further verify whether NEAT1 can regulate the expression of SMYD2, we examined the expression changes of SMYD2 after altering NEAT1 expression. QRT-PCR results showed a positive relationship between the expressions of NEAT1 and SMYD2 in cardiomyocytes (Figure

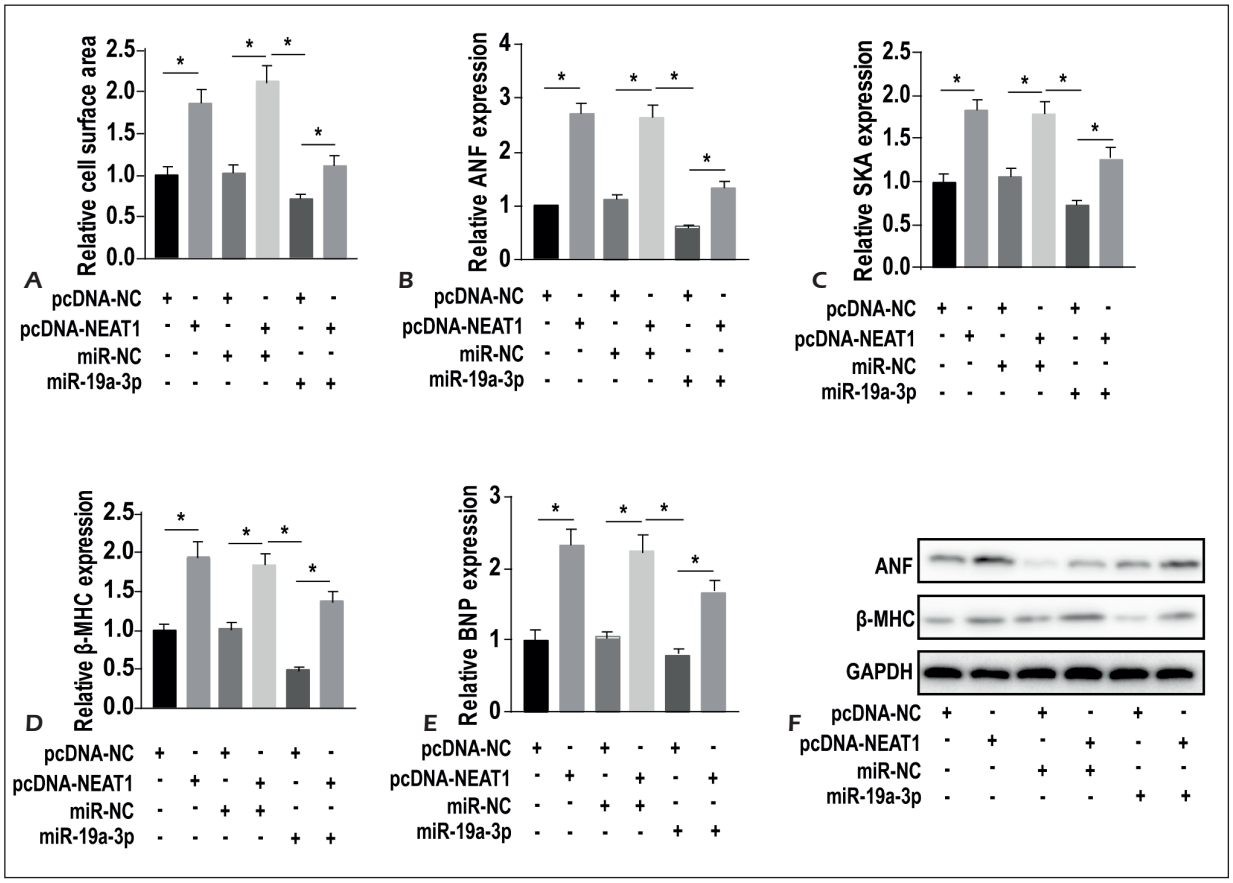

Figure 5. MicroRNA-19a-3p reversed cardiac hypertrophy induced by NEAT1 overexpression. **A**, Co-overexpressed NEAT1 and microRNA-19a-3p in cardiomyocytes showed smaller surface area than those only overexpressed NEAT1. **B**-**E**, QRT-PCR data showed that microRNA-19a-3p overexpression in cardiomyocytes reversed the promotive role of NEAT1 overexpression in upregulating mRNA levels of ANF, SKA, β-MHC, and BNP. **F**, Western blot results showed that microRNA-19a-3p overexpression in cardiomyocytes reversed the promotive role of NEAT1 overexpression in upregulating the protein levels of ANF and β-MHC.

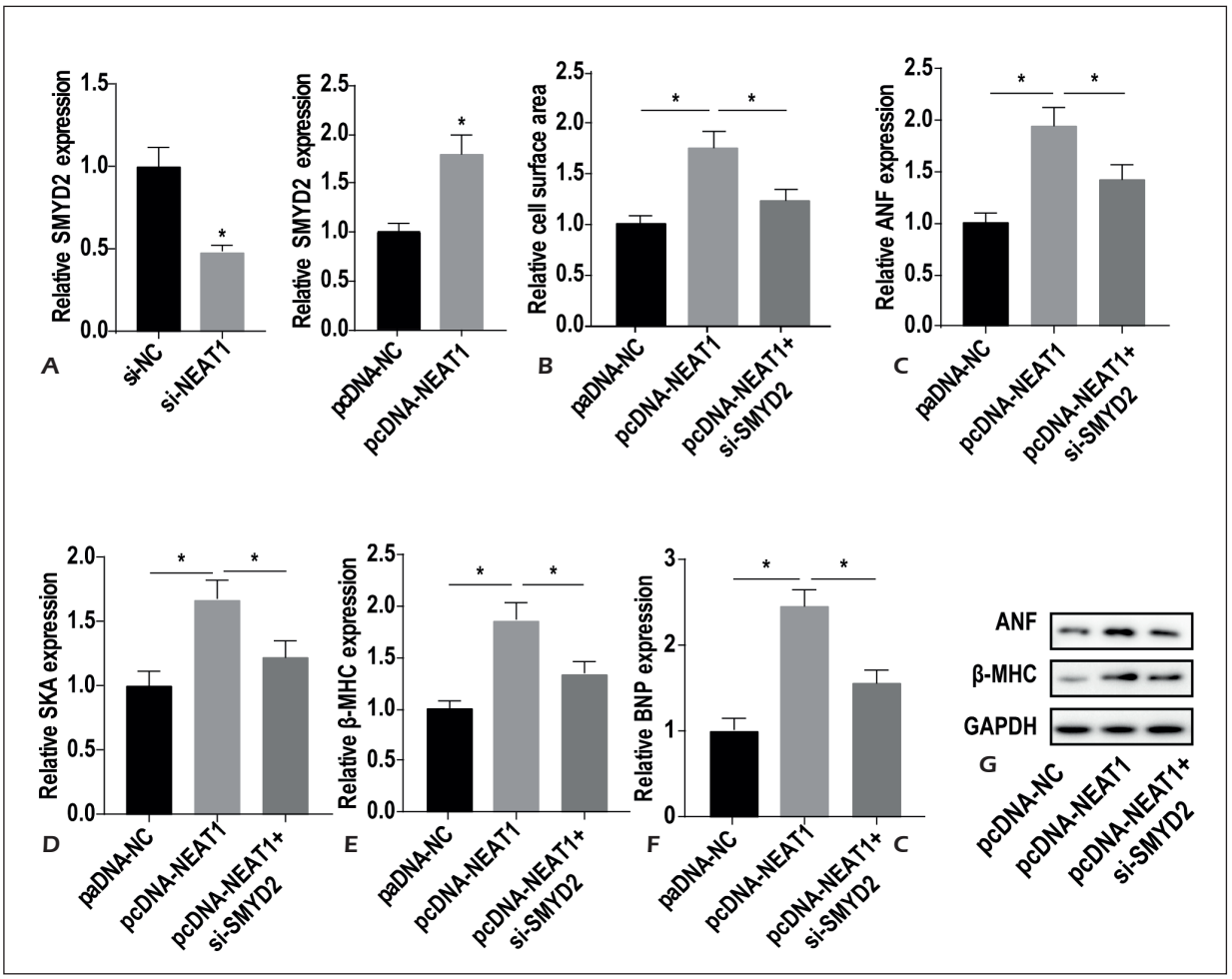

Figure 6. NEAT1 regulated cardiac hypertrophy through SMYD2. **A**, QRT-PCR data showed that NEAT1 knockdown downregulated SMYD2 expression, whereas NEAT1 overexpression upregulated SMYD2 expression. **B**, SMYD2 knockdown in cardiomyocytes reversed the enlarged surface area induced by NEAT1 overexpression. **C-F**, QRT-PCR data showed that SMYD2 knockdown in cardiomyocytes reversed the increased mRNA levels of ANF, SKA, β-MHC, and BNP induced by NEAT1 overexpression. **G**, Western blot results showed that SMYD2 knockdown in cardiomyocytes reversed the increased protein levels of ANF and β-MHC.

6A). Compared with the cardiomyocytes overexpressing NEAT1, the surface area became smaller in those co-overexpressing NEAT1 and SMYD2 (Figure 6B). The expression levels of ANF, SKA, β-MHC, and BNP were downregulated in the co-overexpressed cells as well (Figures 6C-6F). Identically, the protein levels of ANF and β-MHC showed decreased changes as same as their mRNA levels (Figure 6G).

Discussion

Cardiac hypertrophy is the increased biomechanical stress of heart responding to various external stimuli. Although cardiac hypertrophy ultimately normalizes ventricular wall tension, it often leads to many adverse outcomes, such as sudden death risk and severe heart failure[14].

Researches on lncRNAs relative to cardiovascular diseases are still insufficient. It is reported[15] that Bvht exerts a crucial function in stimulating the differentiation of mouse embryonic stem cells into cardiac cells. LncRNA-B130042P05 is lowly expressed in mice with heart failure[16]. It is believed that plasma lncRNAs may serve as potential biomarkers for evaluating the disease condition of heart failure[16]. LncRNA CHRF participates in the development of cardiac hypertrophy by mediating miR-489, further indicating the specific role of lncRNAs in cardiac hypertrophy[17]. In this study, lncRNA NEAT1 was highly expressed in both

in vivo and *in vitro* cardiac hypertrophy models. By comparison, NEAT1 expression gradually decreased in normal cardiomyocytes with the prolongation of cell culture. NEAT1 knockdown markedly reduced the cardiomyocyte surface area, and downregulated the cardiac hypertrophic markers ANF, SKA, β-MHC, and BNP. Overexpression of NEAT1 obtained the opposite trends. Our results demonstrated that NEAT1 was a significant risk factor for promoting cardiac hypertrophy. Further functional experiments suggested the binding between NEAT1 and microRNA-19a-3p.

MiRNAs are a class of 18-25 nt, highly conserved, single-stranded, non-coding RNAs. They are capable of regulating the eukaryotic gene expressions, cell development and differentiation, and individual development. MiRNAs have been identified for their functions in regulating cardiac hypertrophy. A great number of miRNAs negatively regulate cardiac hypertrophy. For example, miR-1, one of the key regulators of multiple signaling pathways found in human and experimental animal models, attenuates calcium signaling-dependent cardiac hypertrophy by negatively regulating CAM[18]. MiR-455 prevents cardiomyocyte hypertrophy induced by pressure overload by targeting calreticulin[19]. MiR-378 inhibits numerous growth-promoting receptors and signaling pathways related to cardiac hypertrophy[20]. MiR-155 alleviates cardiac hypertrophy and improves cardiac function by inhibiting the expression of the angiotensin II receptor and its downstream calcium signaling pathway[21]. There is also a part of miRNAs showing a positive correlation with cardiac hypertrophy. MiR-208a expression in the heart is positively related to cardiomyocyte hypertrophy and fiber production[22]. Similar to previous studies, our study showed decreased expression of microRNA-19a-3p in hypertrophic cardiomyocytes. The overexpression of microRNA-19a-3p remarkably reduced the cardiomyocyte surface area, and downregulated the levels of the cardiac hypertrophic markers, suggesting the negative regulatory effect of microRNA-19a-3p on cardiac hypertrophy. We subsequently verified the binding between miR-19a-3b and NEAT1. More importantly, microRNA-19a-3p overexpression could reverse the regulatory role of NEAT1 in cardiac hypertrophy. Previous studies considered ceRNAs as an important pathway for regulatory functions of lncRNAs. Hence, we further confirmed that microRNA-19a-3p could directly regulate SMYD2, which was regulated by microRNA-19a-3p and NEAT1.

SMYD (SET and MYND domain-containing protein) is essential in tumorigenesis and tumor development. SMYD2 is one of the members of the SMYD family and widely distributed in normal tissues and tumor tissues[23]. Expression level of SMYD2 in bladder cancer cells is higher than that in normal bladder epithelial cells[24]. SMYD2 expression is associated with gender, lymph node infiltration, TNM stage, and survival in esophageal squamous cell carcinoma[25,26].

SMYD2 transcripts are highly expressed in the heart, brain, liver, kidney, thymus, and ovary. They are especially important in maintaining the structure and function of skeletal muscles[27,28]. SMYD2 is present in the embryonic maternal gene until stage 40, which is mainly distributed in the dorsal medial lip, especially in the facial region of Xenopus laevis. Embryotic Xenopus with a low expression of SMYD2 presents abnormal body segment, mandibular tissue, and strong distortion[29]. In our study, we found that low expression of SMYD2 reversed the hypertrophic phenotype of cardiomyocytes caused by NEAT1 overexpression, fully demonstrating that NEAT1 promoted cardiac hypertrophy by positively regulating SMYD2.

However, there were still some shortcomings in this experiment. We did not specifically clarify the abnormal expression of NEAT1. The methylation level of NEAT1 in the promoter region or the expressions of the potential binding transcription factors may be further elucidated to fully explain the role of NEAT1 in cardiomyocyte hypertrophy.

In general, NEAT1 expression elevated in hypertrophic cardiomyocytes, which promoted the expression of SMYD2 by adsorbing miR-19a-3b, thereby accelerating cardiomyocyte hypertrophy. It provides a new target for the treatment of cardiac hypertrophy in the future.

Conclusions

In summary, NEAT1 promotes the occurrence and progression of cardiac hypertrophy by upregulating SMYD2 through binding to microRNA-19a-3p.

Acknowledgments

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Conflict of Interests

The authors declare that they have no conflict of interests.

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