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LncRNA MIAT enhances cardiac hypertrophy partly through sponging miR-150

X.-H. ZHU[1], Y.-X. YUAN[2], S.-L. RAO[3], P. WANG[4]

[1]VIP Ward, Zhumadian Central Hospital, Zhumadian, Henan, China
[2]Department of Cardiology, Zoucheng People's Hospital, Zoucheng, Shandong, China
[3]Department of Emergency, Binzhou People's Hospital, Binzhou, Shandong, China Shandong, China
[4]The 2nd Department of Cardiology, Feicheng mining industry Central Hospital, Feicheng, Shandong, China

Xiuhua Zhu and *Yuxiang Yuan* contribtued equally to this study

Abstract. – OBJECTIVE: In this work, we aimed to study whether myocardial infarction associated transcript (MIAT) exerts a regulative effect on cardiac hypertrophy via acting as a miR-150 sponge.

MATERIALS AND METHODS: Cardiac hypertrophy was induced using Angiotensin II (Ang II). MIAT and miR-150 expression were quantified using qRT-PCR. Rat heart-derived H9c2 cells were used as the in vitro model. Cardiac hypertrophic features were assessed by quantifying cardiac hypertrophic genes and measurement of cell surface, protein synthesis and total protein content.

RESULTS: MIAT is significantly increased in Ang II induced cardiac hypertrophy in a mouse model and in H9c2 cells. MIAT siRNA substantially alleviated the Ang II induced upregulation of ANP, BNP and β-MHC in H9c2 cells and markedly attenuated the Ang II induced increase of the cell surface area and the protein synthesis. MIAT overexpression in H9c2 cells significantly reduced the miR-150 expression. MIAT inhibition also partly restored the miR-150 levels under Ang II treatment. MiR-150 overexpression could attenuate the Ang II induced upregulation of hypertrophic marker genes and suppress the Ang II induced hypertrophic phenotypes of the cells.

CONCLUSIONS: MIAT is significantly increased in Ang II induced cardiac hypertrophy and contributes to the pathological development. MIAT can suppress miR-150 expression in cardiomyocytes and miR-150 is a downstream effector of MIAT in the development of cardiac hypertrophy.

Key Words:
MIAT, miR-150, Cardiac hypertrophy.

Introduction

Cardiac hypertrophy is an adaptive response of the heart to the increased cardiac load, which is characterized by an enlargement of cardiomyocytes and the addition of contractile proteins[1,2]. Sustained cardiac hypertrophy and maladaptive cardiac remodeling significantly increased the risk of heart failure and cardiac death[3]. The causes of cardiac hypertrophy are quite complex; previous studies[4,5] suggested that diverse factors, including physiological, mechanical, hormonal, and genetic influence are all involved in the regulation.

Long non-coding RNAs (lncRNAs) refers the non-protein-coding RNA transcripts longer than 200 nucleotides[6,7]. Recent studies suggest that several dysregulated lncRNAs are associated with the pathological development of cardiac hypertrophy through transcriptional and post-transcriptional regulation. At transcriptional level, for example, lncRNA H19 is upregulated in pathological cardiac hypertrophy[8]. Both H19 and its encoded miR-675 can inhibit the hypertrophic growth of cardiomyocytes, the effect of which is partly mediated by suppressing the expression of miR-675 target gene CaMKIIdelta[8]. At the post-transcriptional level, lncRNA can function as miRNA sponge and modulate the development of cardiac hypertrophy. For example, lncRNA CHRF can act as an endogenous sponge of miR-489 and increase the expression of miR-489 target gene myeloid differentiation primary response gene 88 (Myd88), thereby promoting cardiac hypertrophy[9]. lncRNA-ROR can also promote cardiac hypertrophy via interacting with miR-133[10]. Myocardial infarction–associated transcript (MIAT), is an lncRNA predominantly expressed in heart and fetal brain tissue. Constant researches showed that dysregulated MIAT is involved in myocardial infarction[11,12]. However, whether this lncRNA has a regulative effect on cardiac hypertrophy is not clear.

Corresponding Author: Peng Wang, MD; e-mail: Pengangood@outlook.com

Functionally, MIAT upregulation can lead to microvascular dysfunction via enhancing endothelial cell proliferation and migration[13]. In both microvascular endothelial cells and lens epithelial cells, MIAT can act as a sponge of miR-150[13,14]. miR-150 is an important miRNA with inhibitive effect on pressure overload-induced cardiac hypertrophy[15] and high glucose-induced cardiomyocyte hypertrophy[16]. Therefore, we hypothesized that MIAT might exert a regulative effect on cardiac hypertrophy via acting as a miR-150 sponge.

Materials and Methods

Animals and Protocols

Animal based study was approved by the Research Committee of Zoucheng People's Hospital. All animal based studies followed the Guide for the Care and Use of Laboratory Animals (US and National Institutes of Health). Eight-week-old male, healthy and specific pathogen-free C57BL/6J mice weighing 19-21 g was purchased from the Experimental Animal Center of the Shandong University. The mice were randomized into three groups (n=10/group): a blank group without any treatment; a sham group only received PBS infusion; an Angiotensin II (Ang II) (Sigma-Aldrich, St. Louis, MO, USA)-infused group. The animals in Ang II group received Ang II dissolved in PBS with 10 μmol/L acetic acid at a dose of 2.5 μg/kg/min using a subcutaneously implanted minipump (model 2002, Alza, Mountain View, CA, USA) for 15 days. The mice were housed in SPF conditions with a 12-h light/12-h dark cycle and with free access to drinking water and food.

Cell Culture and Treatment

Rat heart-derived H9c2 cells were cultured using Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS) at 37°C in a 5% CO_2 incubator. For Ang II treatment, the cells were incubated with 1 μmol/L Ang II or PBS for 48 hours. MIAT siRNA, miR-150 mimics and the scramble negative controls were purchased from Ribobio (Guangzhou, China). The Full length of MIAT cDNA was amplified and inserted into the sites between *BamHI* and *XhoI* of pcDNA3.1 plasmid (Invitrogen, Carlsbad, CA, USA) and the reconstructed MIAT expression plasmids is named as pcDNA3.1-MIAT. H9c2 cells were transfected with 100 nM MIAT siRNA, 100 nM miR-150 mimics or pcDNA3.1-MIAT using Lipofectamine 2000 (Invitrogen) according to manufacturer's instruction.

QRT-PCR Analysis

Total RNA from the tissue and cell samples were extracted using Trizol reagent (Invitrogen) according to manufacturer's instruction. The first strand cDNA were synthesized by reverse transcription using a First Strand Synthesis kit (Invitrogen, Carlsbad, CA, USA). QRT-PCR was performed to detect the expression of MIAT, ANP, BNP, β-MHC using gene specific primers and SYBR® Green qPCR MasterMix (Applied Biosystems, Foster City, CA, USA) in ABI 7500 Real-Time PCR Systems. The primers were:

MIAT, 5'-TTTACTTTAACAGACCAGAA-3' (forward), 5'-CTCCTTTGTTGAATCCAT-30 (reverse);
ANP, 5'-ATCTGATGGATTTCAAGAACC-3' (forward), 5'-CTCTGAGACGGGTTGACTTC-3' (reverse);
BNP, 5'-ACAATCCACGATGCAGAAGCT-3' (forward), 5'-GGGCCTTGGTCCTTTGAGA-3' (reverse);
β-MHC, 5'-CCTCGCAATATCAAGGGAAA-3' (forward), 5'-TACAGGTGCATCAGCTCCAG-3 (reverse).

MiR-150 expression was determined by qRT-PCR using the mirVana qRT-PCR miRNA Detection Kit and Primer Sets from Ambion as well as Taqman® miRNA assays (Applied Biosystems). The relative expression of the RNAs was calculated using the $2^{-\Delta\Delta CT}$ method.

Immunofluorescent Staining and Measurement of Cell Surface Area

Cells on coverslips were fixed with PBS containing 4% paraformaldehyde, permeabilized in PBS containing 0.2% Triton X-100, and then blocked with PBS containing 3% BSA. After that the cells were incubated with primary anti-α-actinin at a dilution of 1:100 in 1% goat serum overnight at 4°C, and then incubated with Alexa Fluor® 594 goat anti-mouse IgG for 1 h at 37°C. The coverslips were mounted onto glass slides with SlowFade Gold antifade reagent with

DAPI. The cell surface area using a quantitative digital image analysis system (Image Pro-Plus version 7.0; Media Cybernetics, Rockville, MD, USA) with a digital camera (Olympus IX-81, Olympus, Tokyo, Japan). 100 cells were randomly selected in three wells of different treatment.

Measurement of [3H]leucine Incorporation and Protein Content Assay

[^{3}H]leucine incorporation was measured according to the method introduced in one previous study[17]. Briefly, Cells were cultured in 24-well plates in serum-free medium for 24 h. After indicated treatment, the cells were pulsed with 1 μCi/mL of [3H]leucine (Amersham Biosciences, Piscataway, NJ, USA) for 4 hours before harvest. After three times washing with PBS, the cells were treated with 5% trichloroacetic acid for 30 min. Finally, cells were solubilized in 500 μL of 1 mol/L NaOH and neutralized using 0.5 mol/L HCl. Then, an aliquot was taken to determine the level of incorporated radioactivity using the Beckman LS 3801 liquid scintillation counter (Beckman, Fullerton, CA, USA). The total protein content per well was measured with a Modified Lowry Protein Assay Kit (Pierce, Rockford, IL, USA).

Statistical Analysis

Data analysis was performed using SPSS18.0 statistical software (SPSS Inc., Chicago, IL, USA). Group comparison was conducted unpaired *t*-tests. A two-tailed $p<0.05$ was considered statistically significant.

Results

MIAT is Significantly Increased in Ang II Induced Cardiac Hypertrophy

Previous studies suggest that MIAT is an lncRNA that is significantly increased in patients with myocardial infarction and with dilated cardiomyopathy[12,18]. In this study, we firstly explored the expression of MIAT in Ang II induced cardiac hypertrophy in a mouse model. The results showed that the hypertrophic cardiac tissues of the mice received 15 d administration of Ang II had significantly increased MIAT expression (Figure 1A). In H9c2 cells, we also confirmed that Ang II treatment induced a significant increase of MIAT expression (Figure 1B). Therefore, we decided to further explore the biological function of MIAT using H9c2 cells as the *in-vitro* model.

Inhibition of MIAT Attenuates Ang II Induced Cardiac Hypertrophy

Cardiac hypertrophy is associated with significantly increased expression of the hypertrophic marker genes and the subsequent enhanced protein synthesis and increased cell size[19]. Therefore, we firstly detected how MIAT suppression during Ang II treatment affected the hypertrophic marker genes, including ANP, BNP and β-MHC. The results showed that MIAT siRNA substantially alleviated Ang II induced upregulation of ANP, BNP and β-MHC in H9c2 cells (Figure 2A). Another common feature of cardiac hypertrophy is the increased cell surface area and the

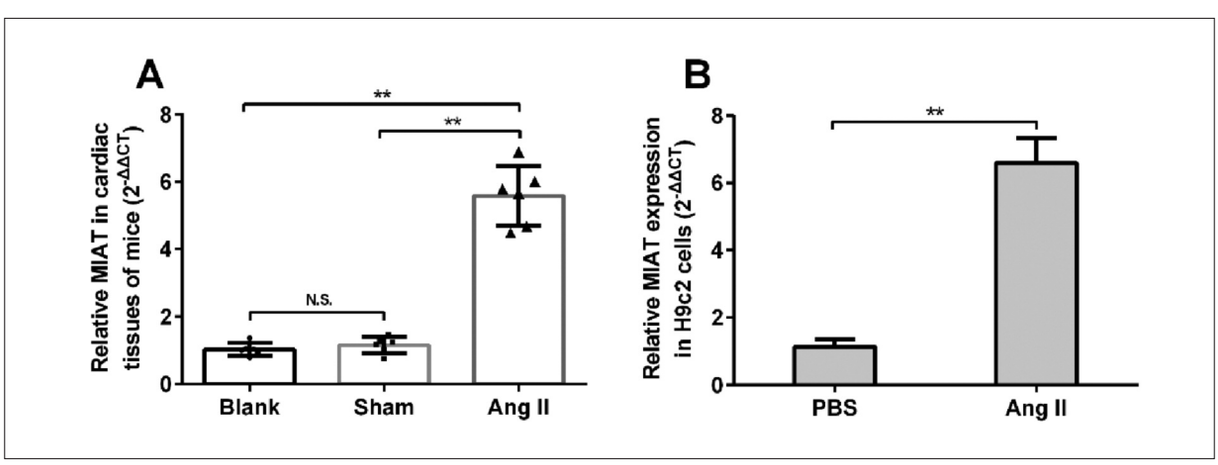

Figure 1. MIAT is significantly increased in Ang II induced cardiac hypertrophy. ***A-B,*** QRT-PCR analysis of MIAT expression in the mouse cardiac tissues of the three groups after indicated treatment ***(A)*** and in H9c2 cells after 48 hours treatment of Ang II ***(B)***. N.S., not significant; $^{**}p < 0.01$.

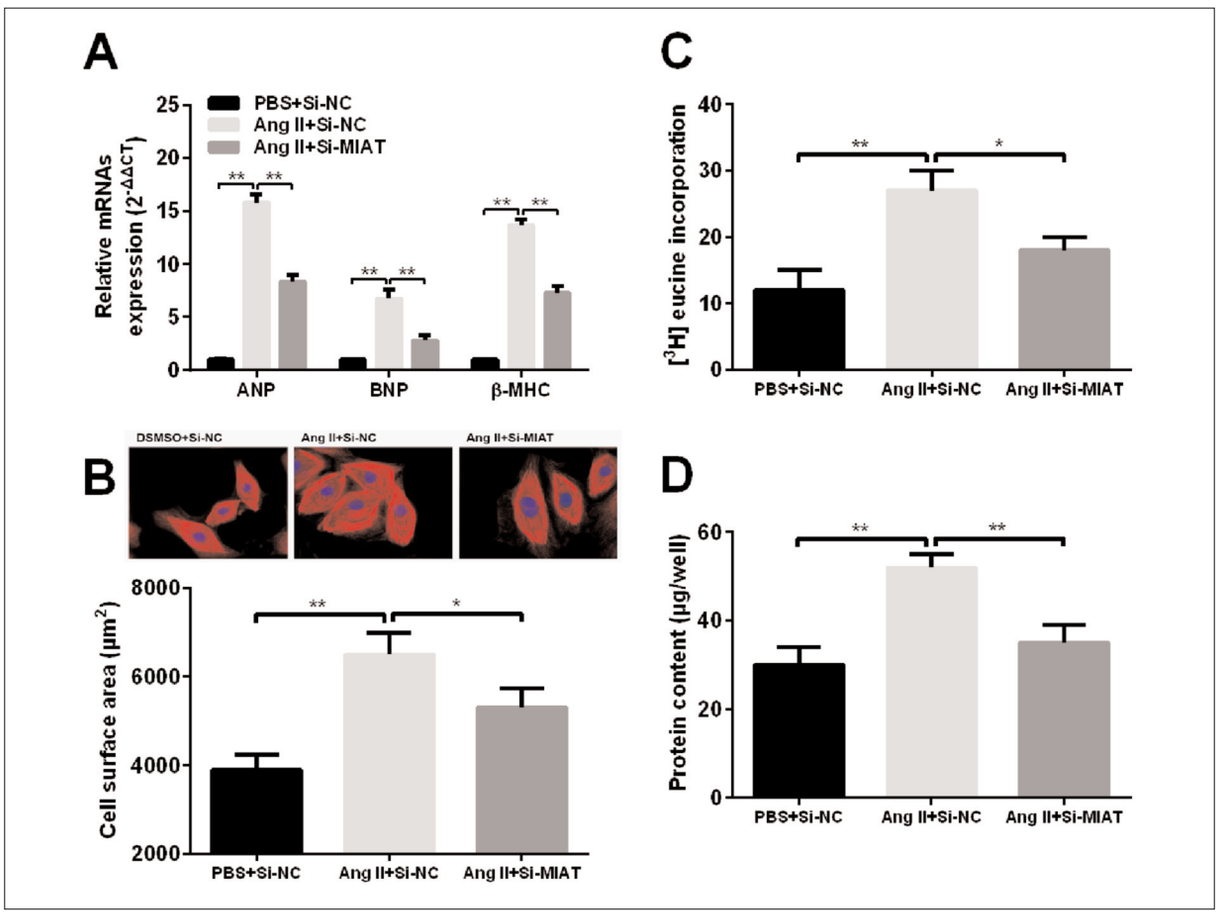

Figure 2. Inhibition of MIAT attenuates Ang II induced cardiac hypertrophy. ***A,*** QRT-PCR analysis of mRNA expression of atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), β-myosin heavy polypeptide (MHC) in H9c2 cells after Ang II treatment with or without MIAT knockdown. ***B-D,*** Immunofluorescent staining of α-actinin and measurement of cell surface area ***(B)***, the rate of protein synthesis ***(C)*** and the total protein content ***(D)*** in the H9c2 cardiomyocytes after Ang II treatment with or without MIAT knockdown. $*p < 0.05$, $**p < 0.01$.

enhanced protein synthesis. In this study, the cell surface area of the H9c2 cells was determined by α-actinin staining (Figure 2B). 48 h treatment with Ang II stimulated a significant increase in the cell surface area. However, MIAT siRNA markedly attenuated the increase (Figure 2B). In addition, we also observed that MIAT siRNA partly abrogated the Ang II induced higher level of [^{3}H]leucine incorporation (Figure 2C) and total protein content (Figure 2D). These results suggest that inhibition of MIAT attenuated Ang II induced cardiac hypertrophy.

MIAT Suppresses miR-150 Expression in H9c2 Cells

Since we confirmed the contribution of MIAT in the development of hypertrophic characteristics, we further investigated the underlying mechanism. Previous studies showed that MIAT could act as a miR-150 sponge in lens epithelial cells and modulate cell proliferation, apoptosis and migration[14]. In fact, miR-150 is an important miRNA with inhibitive effect on pressure overload-induced cardiac hypertrophy[15] and high glucose-induced cardiomyocyte hypertrophy[16]. Bioinformatics analysis showed that MIAT has three possible binding sites with miR-150 (Figure 3A). Therefore, we hypothesized that the pathological effect of MIAT in cardiac hypertrophy might be related to its sponging of miR-150. To test this hypothesis, we firstly overexpressed MIAT in H9c2 cells (Figure 3B). MIAT overexpression significantly reduced miR-150 expression in the cells (Figure 3C). Ang II treatment also induced miR-150 suppression in H9c2 cells (Figure 3D). Notably,

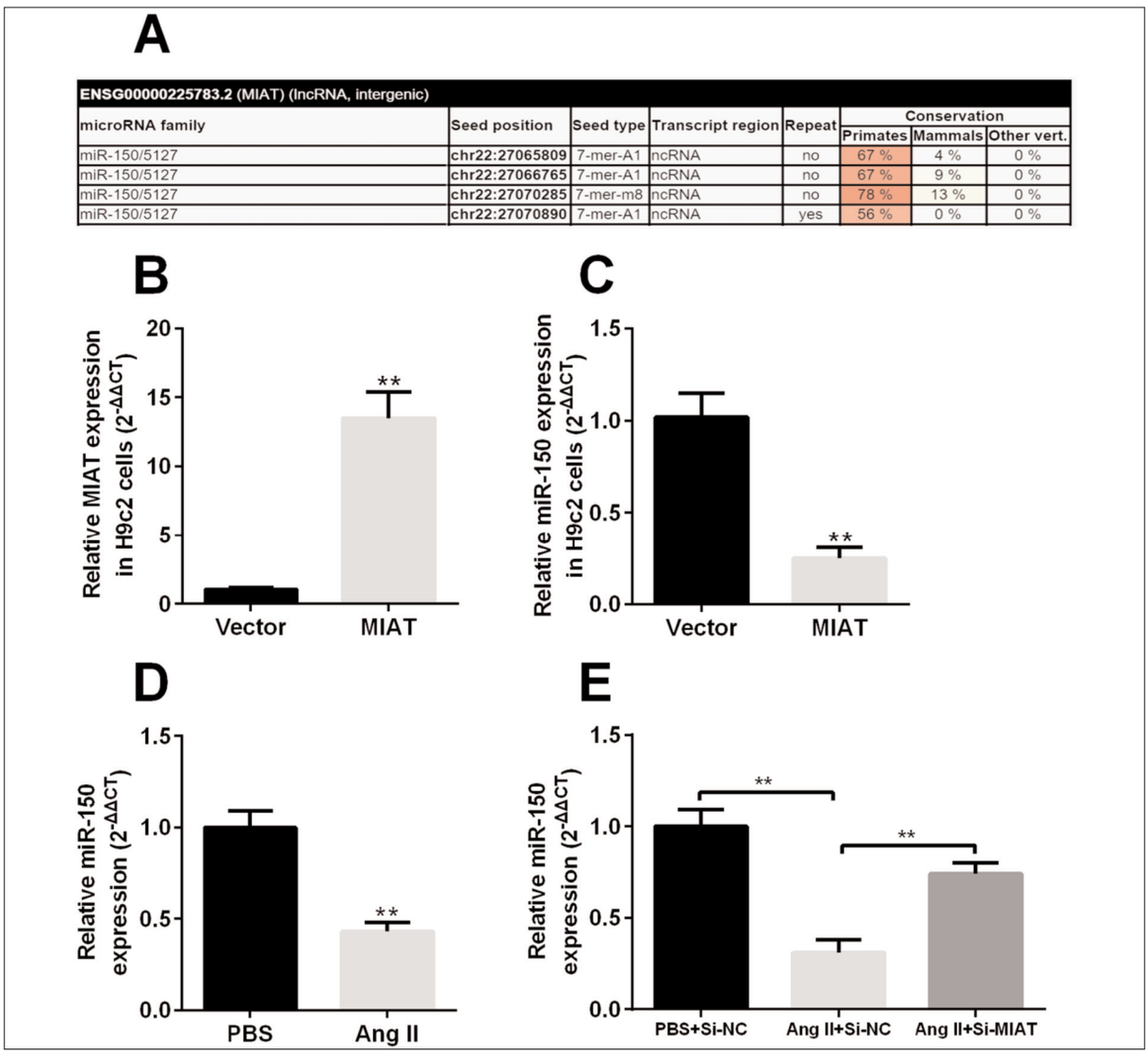

Figure 3. MIAT suppresses miR-150 expression in H9c2 cells. ***A,*** Bioinformatics analysis of the possible binding sites between MIAT and miR-150. ***B-C,*** QRT-PCR analysis of MIAT ***(B)*** and miR-150 ***(C)*** expression in H9c2 cells after MIAT overexpression. ***D-E,*** QRT-PCR analysis of miR-150 expression in H9c2 cells after Ang II treatment ***(D)*** or with MIAT knockdown ***(E)***. $^{**}p < 0.01$.

inhibition of MIAT during Ang II treatment partly restored miR-150 levels (Figure 3E). These results suggest that MIAT can suppress miR-150 expression in H9c2 cells.

MIAT Enhances Cardiac Hypertrophy Partially through Reducing miR-150

Since we verified the regulative effect of MIAT1 on miR-150, we further studied the role of miR-150 in Ang II induced cardiac hypertrophy. MiR-150 overexpression attenuated Ang II induced upregulation of hypertrophic marker genes (Figure 4A), suppressed Ang II induced increase of cell surface area (Figure 4B) and also weakened Ang II induced higher level of [^{3}H]leucine incorporation (Figure 4C) and total protein synthesis (Figure 4D). These results suggest that miR-150 is a downstream effector of MIAT in the development of cardiac hypertrophy.

Discussion

In the past years, emerging evidence showed that lncRNAs might have as either protective or enhancing effect in the development of cardiac

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ENSG00000225783.2 (MIAT) (lncRNA, intergenic)							
microRNA family	Seed position	Seed type	Transcript region	Repeat	Conservation		
					Primates	Mammals	Other vert.
miR-150/5127	chr22:27065809	7-mer-A1	ncRNA	no	67 %	4 %	0 %
miR-150/5127	chr22:27066765	7-mer-A1	ncRNA	no	67 %	9 %	0 %
miR-150/5127	chr22:27070285	7-mer-m8	ncRNA	no	78 %	13 %	0 %
miR-150/5127	chr22:27070890	7-mer-A1	ncRNA	yes	56 %	0 %	0 %

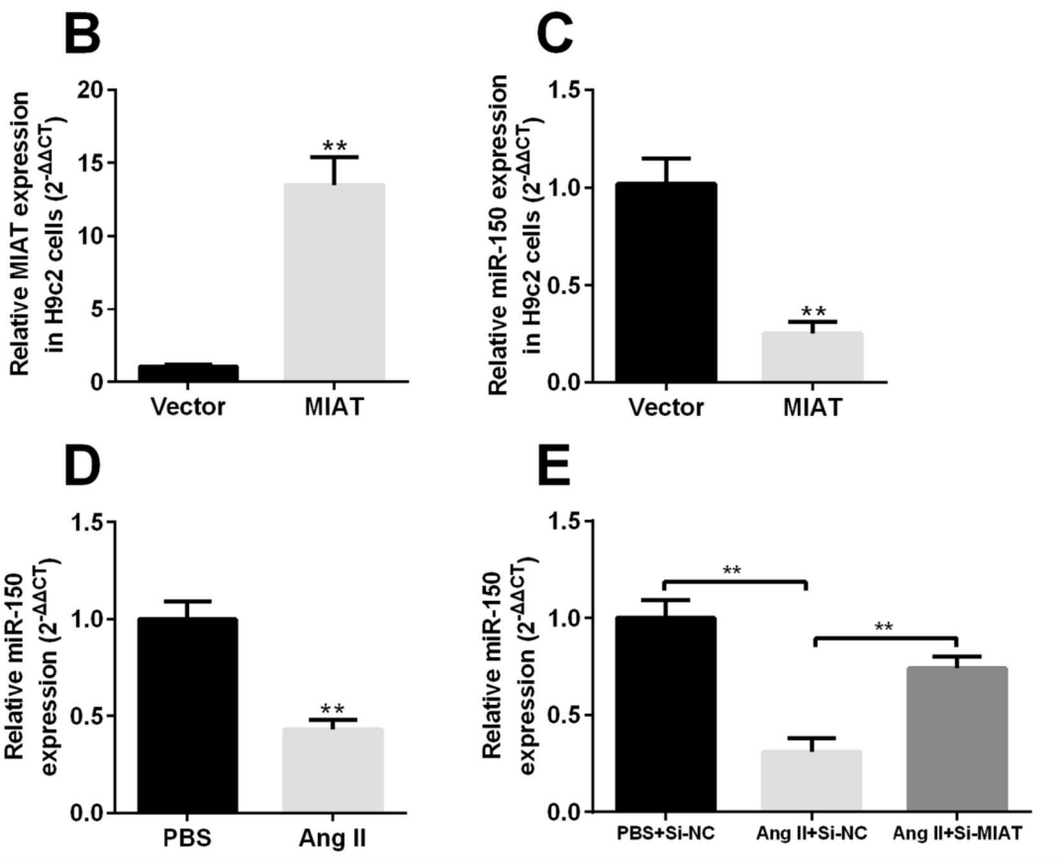

Figure 4. MIAT enhances cardiac hypertrophy partially through reducing miR-150. ***A,*** QRT-PCR analysis of mRNA expression of ANP, BNP, β-MHC in H9c2 cells after Ang II treatment with or without miR-150 overexpression. ***B-D,*** Measurement of cell surface area ***(B)***, the rate of protein synthesis ***(C)*** and the total protein content ***(D)*** in the H9c2 cardiomyocytes after Ang II treatment with or without miR-150 overexpression. $*p < 0.05$, $**p < 0.01$.

hypertrophy. For example, Han et al[20] demonstrated that stress-induced myosin heavy-chain-associated RNA transcripts (Mhrt) repression is essential for cardiomyopathy to develop, while restoring Mhrt to the pre-stress level showed protective effects on the heart from hypertrophy and failure[20]. Both H19 and its encoded miR-675 are upregulated in pathological cardiac hypertrophy. Their upregulation can inhibit the hypertrophic growth of cardiomyocytes, the effect of which is partly mediated by suppressing the expression of miR-675 target gene CaMKI-Idelta[8]. Besides the protective effect, other studies also indicated that some lncRNAs can contribute to the development of cardiac hypertrophy mainly through the competitive endogenous RNA (ceRNA) mechanism, of which lncRNA could interact with miRNA and indirectly interact with mRNAs through competing interactions[21]. For example, lncRNA CHRF can act as an endogenous sponge of miR-489, which reduces miR-489 expression[9]. Via downregulating miR-489, CHRF can upregulate Myd88 expression and promote hypertrophy[9]. Another study

observed that the expression of lncRNA-ROR in hypertrophic heart and cardiomyocytes is elevated dramatically and can suppress miR-133 expfession[10]. Overexpression of miR-133 reduced the elevation of ROR and atennatured ROR induced hypertrophy[10].

The pathological effect of MIAT in myocardial infarction have been reported[11,12]. Vausort et al[12] reported that MIAT is significantly higher in whole blood from patients with non-ST-segment-elevation MI (NSTEMI) than in that from patients with ST-segment-elevation MI (STEMI), suggesting that MIAT is associated with chronic cardiomyopathy. Therefore, in this study, we firstly investigated the association between MIAT and cardiac hypertrophy and we demonstrated that MIAT is significantly increased in Ang II induced cardiac hypertrophy. Knockdown of MIAT can reduce Ang II induced upregulation of hypertrophic markers and alleviated Ang II induced hypertrophic phenotypes in H9c2 cells. Therefore, we decided to further investigate the underlying mechanism. Previous researches found that in both microvascular endothelial cells and lens epithelial cells, MIAT functions as a sponge of miR-150[13,14]. In fact, miR-150 has a well-recognized inhibitive effect on cardiac hypertrophy. Transgenic mice with miR-150 overexpression in the heart were resistant to cardiac hypertrophy and fibrosis through down-regulation of serum response factor (SRF)[15]. In addition, miR-150 mimics can also prevent glucose-induced cardiomyocyte hypertrophy via downregulating p300[22]. Moreover, in transverse aortic constriction (TAC) mouse model, it was observed that miR-150 could also inhibit cardiac fibroblast activation via reducing c-Myb expression[16]. Therefore, we investigated whether the pathological effect of MIAT in cardiac hypertrophy development is via sponging miR-150. In H9c2 cells, we confirmed that MIAT overexpression significantly reduced miR-150 expression, while MIAT inhibition partly restored miR-150 levels under Ang II treatment. Following functional works further verified that miR-150 overexpression could attenuate Ang II induced upregulation of hypertrophic marker genes and suppress Ang II induced hypertrophic phenotypes of the cells. These results confirmed our hypothesis that MIAT could suppress miR-150 expression in cardiomyocytes and miR-150 is a downstream effector of MIAT in the development of cardiac hypertrophy.

Conclusions

MIAT is significantly increased in Ang II induced cardiac hypertrophy and contributes to the pathological development. MIAT can suppress miR-150 expression in cardiomyocytes and miR-150 is a downstream effector of MIAT in the development of cardiac hypertrophy.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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