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Original Article

MiR-495-3p promotes cardiac hypertrophy by targeting Pum2

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Abstract

Pathological cardiac hypertrophy (CH) may lead to heart failure and sudden death. MicroRNAs (miRNAs) have been documented to play crucial parts in CH. The objective of this research was to discuss the potential along with molecule mechanism of miR-495-3p in CH. In vivo CH model was induced by aortic banding (AB) in rats. Cellular hypertrophy in H9c2 rat cardiomyocytes was stimulated by angiotensin II (Ang II) treatment. Haematoxylin and eosin (HE), echocardiography and immunofluorescence staining were used to examine the alterations in cardiac function. The outcomes showed that miR-495-3p expression was high in rat model as well as in Ang II-stimulated cardiomyocytes. Besides, silenced miR-495-3p attenuated CH both in vitro and in vivo. Mechanically, miR-495-3p bound to pumilio RNA binding family member 2 (Pum2) 3'UTR and silenced its expression. Rescue assays further notarized that Pum2 silence abrogated the inhibitory impacts of miR-495-3p inhibitor on CH. In a word, the present research uncovered that miR-495-3p promoted CH by targeting Pum2. Therefore, miR-495-3p may be a novel therapeutic molecule for this disease.

Keywords: Cardiac hypertrophy, MiR-495-3p, Pum2.

1. Introduction

Cardiac hypertrophy (CH) can be divided into physiological and pathological when it is related to normal and damaged cardiac function, respectively [1]. As we all know, pathological CH is featured by enlarged left ventricular diameter along with cardiac dysfunction, which may lead to myocardial infarction, heart failure, and even sudden death [2]. Although many factors have been proven to cause CH, the latent molecular mechanisms have not been elucidated completely [3].

MicroRNAs (miRNAs) pertain to small non-coding RNAs comprising 21-23 nucleotides that control gene expression via combing with the 3'UTR of target mRNAs [4]. A variety of miRNAs have been reported to exert crucial functions in CH [5]. MiR-26a-5p improves CH and dysfunction by binding to ADAM17 [6]. MiR-17-5p induces CH by targeting Mfn2 [7]. MiR-625-5p represses CH via regulating STAT3 and CaMKII expression [8]. As far as we are aware, miR-495-3p is remarkably reduced in myocardial ischemia-reperfusion injury mice [9]. More importantly, it has been proved that miR-495-3p level is elevated in the plasma of hypertrophic cardiomyopathy patients [10], but its role and potential mechanism in CH remains unclear.

Pumilio RNA binding family member 2 (Pum2) is identified as a ribonucleic acid binding protein that manages target mRNA turnover [11]. Pum2 has vital roles in physiological and pathological processes, especially cancer biology [12, 13]. It has been registered to be potentially linked to cardiac fibrosis [14]. Besides, Yuanping Cao et al have provided evidence that Pum2 is up-regulated in the hypoxia/reoxygenation (H/R) stimulated neonatal rat ventricular cardiomyocytes, and plays a baleful role in H/R-induced cardiomyocyte injury by mediating Sirt1 mRNA decay [15]. However, the role of Pum2 in CH remains to be further explored.

In this research, the potential of miR-495-3p in CH in vivo and in vitro was probed. We proved that miR-495-3p promoted CH via targeting Pum2, which might provide novel perspectives for molecular targeted therapy for CH.

2. Materials and methods

2.1. Animal model

All animal procedures were approved by the Experimental Animal Ethics Committee of Tongji University. Male rats were provided by Gempharmatech Co., Ltd (Nanjing, China). A CH model was induced by the aortic banding (AB) method for 28 days following previous depiction [16]. Briefly, pentobarbital sodium (50 mg/kg, Sigma) was used for intraperitoneal injection into male rats for anesthesia. When rats lost the pinching reflex, the left thoracic intercostal site 2-3 was opened to expose the

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aorta, followed by suturing the aorta with a 7-0 silk thread using a 27 or 26 needle. Next, the needle was taken away gently, causing the aorta to contract. Sham rats underwent similar surgery, but did not undergo aortic ligation.

2.2. Cell culture

H9c2 rat cardiomyocytes (ATCC, USA) were cultured in Dulbecco's Modified Eagle's Medium containing 10% fetal bovine serum (FBS; Gibco, USA) and placed at 37°C with 5% CO_2. For in vitro CH model, angiotensin II (Ang II; 1 μM) (Sigma, USA) was implemented to treat cells for 48 h.

2.3. RT-qPCR

Trizol Reagent (Invitrogen, USA) was implemented to extract the total RNA from the heart or cardiomyocytes. Then, M-MLV reverse transcriptase kit (Promega, USA) was implemented for reverse transcription. qPCR was carried out using the SYBR Green PCR master mix (Invitrogen). GAPDH and U6 were worked for negative controls. Relative gene expression was measured by the $2^{-\Delta\Delta Ct}$ method.

2.4. Cell transfection

For silencing miR-495-3p expression in rats, chemically modified antisense oligonucleotides (antagomir) targeting miR-495-3p or the control group were purchased from GenePharma (Shanghai, China), and were injected into rats through tail vein [17]. Besides, cardiomyocytes were planted in 6-well plate to reach around 80% confluence and then transfected with miR-495-3p inhibitor, NC inhibitor, sh-Pum2 or sh-NC (GenPharma) using lipofectamine 3000 reagents (Life Technologies Corporation, USA) for 48 h.

2.5. Hematoxylin and eosin (HE) staining

The hearts were excised, washed, fixed, and embedded in paraffin. Next, the hearts were sliced into sections of 4 μm thickness, followed by staining with hematoxylin and eosin (Beyotime, China) and then observed with an optical microscope (Olympus, Japan).

2.6. Echocardiography detection

Echocardiography was implemented by means of a high-resolution imaging system as described before [18]. In brief, after light general anaesthesia, the rats were treated with echocardiography, and the ejection fraction (EF) was measured.

2.7. Cell surface area detection

Cells after fixation and permeabilization were dyed with α-actinin (Abcam, ab108198). Afterwards, cells were treated with the corresponding antibody, followed by incubation with DAPI. Immunofluorescence was captured under a fluorescence microscope.

2.8. Western blot

Protein from hearts and cardiomyocytes were extracted and then separated by means of 12% SDS-PAGE, followed by shifting onto a PVDF membrane. After sealing, the membrane was probed with antibodies containing atrial natriuretic peptide (ANP, ab181242, Abcam) Brain natriuretic peptide (BNP; ab92500, Abcam), β-myosin heavy chain (β-MHC; ab170867, Abcam), Pum2 (ab92390, Abcam) and GAPDH (ab9485, Abcam) overnight at 4°C. The membrane was added with horseradish peroxidase-conjugated secondary antibodies after washing. Protein was visualized by means of the ECL Western Blotting Substrate (Invitrogen, CA, USA).

2.9. RNA pull-down assay

Biotinylated-Pum2 3'UTR (Bio-Pum2 3'UTR; Thermo Fisher Scientific, Ltd.) were introduced into cardiomyocytes for 48 hours. Then, cells were collected, lysed, and added with beads (Sigma-Aldrich). After washing, the bound RNA was purified, and RT-qPCR was conducted to analyze the enrichment of miR-495-3p.

2.10. Statistical analysis

Data are processed with SPSS17.0 software and presented as mean ± S.D. Student's t-test or one-way ANOVA was used for comparison. P-values less than 0.05 were significant. All experiments were implemented at least thrice.

3. Results

3.1. Antagomir miR-495-3p improves cardiac functions in a rate model of hypertrophic cardiomyopathy

To certify whether miR-495-3p is drawn into CH, we established an AB rat model. We first performed RT-qPCR to detect miR-495-3p expression in the model. In contrast to the sham group, miR-495-3p expression was increased in the model group (Fig. 1A). Then, we silenced miR-495-3p through transfecting antagomir miR-495-3p in the

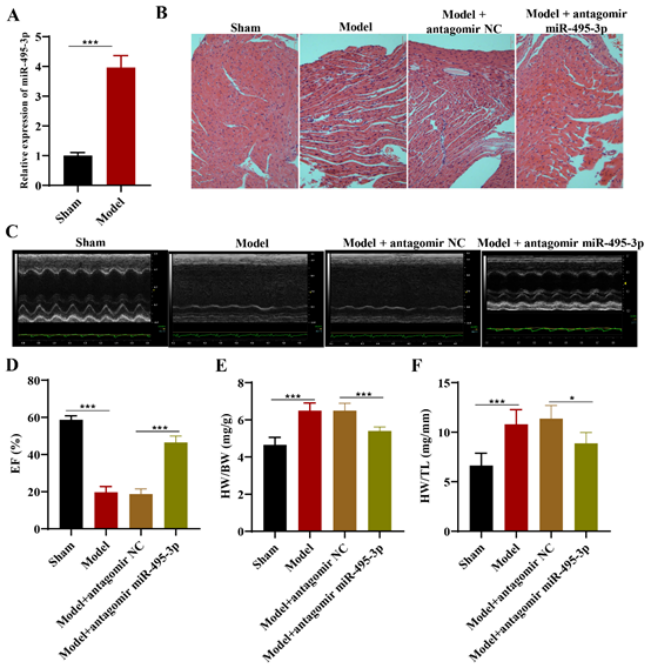

Fig. 1. Antagomir miR-495-3p improves cardiac functions in a mouse model of hypertrophic cardiomyopathy. (A) RT-qPCR detection of miR-495-3p in hearts of sham along with AB-induced CH rat model. (B) HE staining examined the cellular morphology in the sham and AB-induced CH rat model transfected with antagomir miR-495-3p and antagomir NC. (C) Representative echocardiographic images in the sham and AB-induced CH rat model treated with antagomir miR-495-3p and antagomir NC. (D) Cardiac function was evaluated by assessing EF. (E-F) The ratio of heart weight to body weight (HW/BW) and heart weight to tibial length (HW/TL) were calculated. $^{*}P<0.05$, $^{***}P<0.001$.

rats after CH, and this significantly lessened miR-495-3p expression. HE staining indicated that the cardiomyocytes were clearly enlarged in the model group in comparison with the sham group. However, this phenomenon was reversed after treating antagomir miR-495-3p (Fig. 1B). Simultaneously, echocardiography measurements displayed that the heart systolic function was considerably impaired, as indicated by the reduced EF measurements. Treatment with antagomir miR-495-3p greatly improved cardiac systolic function (Fig. 1C-1D). Moreover, we discovered that the enlarged heart weight and cardiomyocyte size in the model group were repressed by miR-495-3p inhibition (Fig. 1E-1F).

3.2. Antagomir miR-495-3p suppresses the expression of hypertrophy biomarkers

Of note, the mRNA and protein expressions of hypertrophy biomarkers containing ANP, BNP and β-MHC were remarkably enhanced in the model group and further lessened after miR-495-3p knockdown (Fig. 2A-2C).

3.3. MiR-495-3p inhibitor rescues Ang II-stimulated cardiomyocyte hypertrophy

An in vitro CH model was built to test whether miR-495-3p promoted CH. RT-qPCR testified that miR-495-3p was elevated in Ang II-stimulated H9c2 cells, and miR-495-3p inhibitor successfully reduced miR-495-3p expression (Fig. 3A). Additionally, we discovered that Ang II treatment amplified cardiomyocyte size and elevated ANP, BNP and β-MHC expression. Meanwhile, transfection of miR-495-3p inhibitor offset the inductive effect caused by Ang II treatment (Fig. 3B-3D).

3.4. MiR-495-3p targets Pum2

Through starBase website (https://starbase.sysu.edu.cn), we predicted Pum2 was targeted by miR-495-3p. We examined the mRNA level of Pum2 was down-regulated in the model group (Fig. 4A). Besides, we found that Pum2 expression was also lower in Ang II-stimulated H9c2 cells than the control group. Interestingly, after miR-495-3p silencing, Pum2 expression was heightened (Fig. 4B-4C). The predictive binding sites of miR-495-3p and Pum2 are shown in Figure 4D. RNA pull-down assay further validated that miR-495-3p combined with Pum2 3'UTR (Fig. 4E).

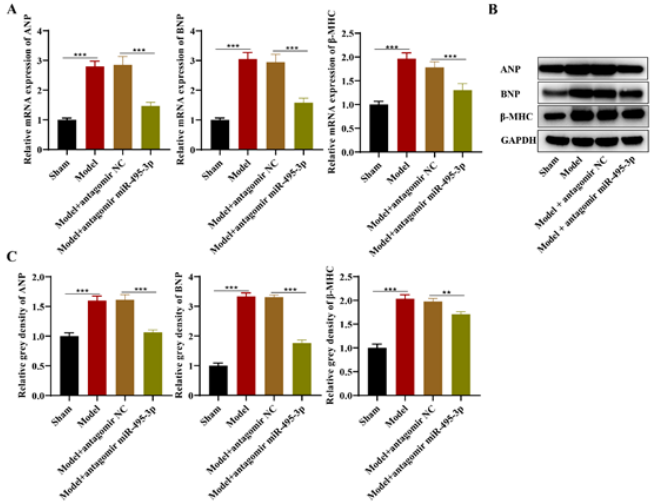

Fig. 2. Antagomir miR-495-3p suppresses the expression of hypertrophy biomarkers. (A) RT-qPCR assessment of ANP, BNP, and β-MHC mRNA levels. (B-C) Western blot analysis of ANP, BNP, and β-MHC protein levels. $^{**}P<0.01$, $^{***}P<0.001$.

3.5. Pum2 silence rescues the impacts of miR-495-3p inhibition in Ang II-stimulated cardiomyocytes

To further assess the impacts of the miR-495-3p/Pum2 axis in CH, a train of rescue assays was arranged. We observed that the reduced cardiomyocyte size along with the lessened expression of ANP, BNP and β-MHC caused by miR-495-3p inhibition was recovered by co-transfection of sh-Pum2 (Fig. 5A-5C).

4. Discussion

MiRNAs take part in complex pathological processes through modulation of cellular activities [19]. Emerging evidence has unveiled the functional potential of miR-495-3p in different kinds of diseases. In terms of tumors, miR-495-3p represses osteosarcoma cell proliferation and motility by down-regulation of CTRP3 [20]. In urinary and reproductive systems, the SNHG14/miR-495-3p/HIPK1 interaction network promotes lipopolysaccharide-induced acute kidney injury [21]. In orthopedic disorders, miR-495-3p is declined in patients with ankylosing spondylitis and can work as a promising molecular marker for the treatment of this disease [22]. According to our awareness, the potential of miR-495-3p in the progression of cardiovascular diseases, especially CH, exists obscurely.

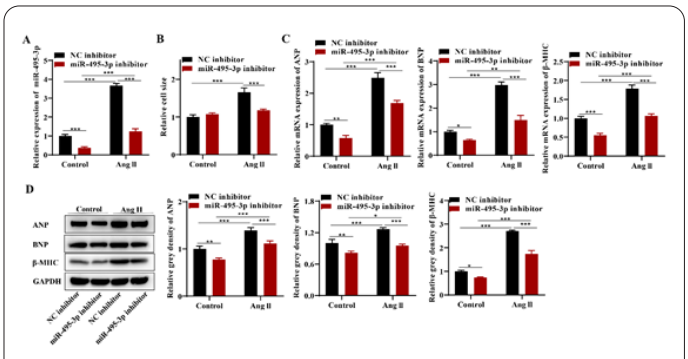

Fig. 3. MiR-495-3p inhibitor rescues Ang II-stimulated cardiomyocyte hypertrophy. (A) RT-qPCR examined miR-495-3p expression in Ang II-stimulated H9c2 upon transfecting NC inhibitor or miR-495-3p inhibitor. (B) The relative cell size was analyzed by immunofluorescence staining in Ang II-stimulated H9c2 upon transfecting NC inhibitor or miR-495-3p inhibitor. (C-D) The mRNA and protein levels of hypertrophy biomarkers were detected using RT-qPCR and western blot in Ang II-stimulated H9c2 upon transfecting NC inhibitor or miR-495-3p inhibitor. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

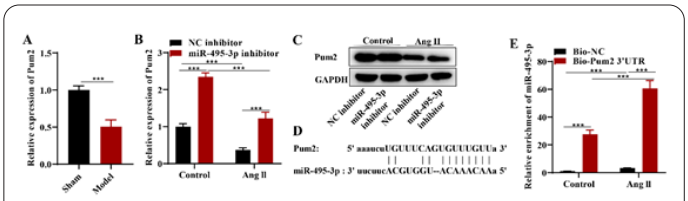

Fig. 4. MiR-495-3p targets Pum2. (A) RT-qPCR analysis of Pum2 expression in hearts of sham and AB-induced CH rat model. (B-C) RT-qPCR and western blot analyses of Pum2 expression in Ang II-stimulated H9c2 upon transfecting NC inhibitor or miR-495-3p inhibitor. (D) Binding sites of Pum2 and miR-495-3p from starBase website. (E) RNA pull-down assay detected the binding of Pum2 and miR-495-3p. $^{***}P<0.001$.

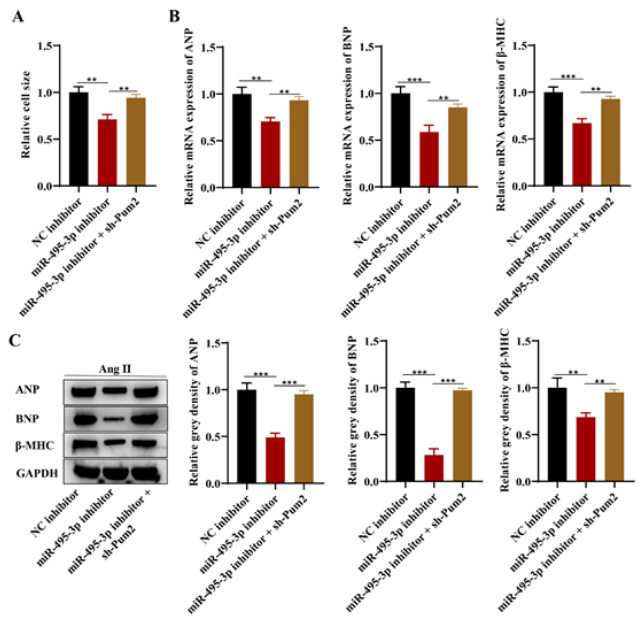

Fig. 5. Pum2 silence rescues the effects of miR-495-3p inhibition in Ang II-stimulated cardiomyocytes. (A) The relative cell size was analyzed by immunofluorescence staining in H9c2 transfected with miR-495-3p inhibitor solely or together with sh-Pum2 prior to Ang II addition. (B-C) The mRNA and protein levels of hypertrophy biomarkers were detected using RT-qPCR and western blot in H9c2 transfected with miR-495-3p inhibitor solely or together with sh-Pum2 prior to Ang II addition. $^{**}P<0.01$, $^{***}P<0.001$.

This research demonstrated that miR-495-3p was up-regulated in the CH model in the rats and Ang II-treated cardiomyocytes. Moreover, silencing of miR-495-3p alleviated CH in vivo and in vitro. It is well-known that miRNAs influence multiple biological processes via binding to and repressing mRNA expression. As reported previously, miR-495-3p directly binds to HMGB1, MYCBP and PDL1 [23-25], and regulates their expression. Herein, we discovered that Pum2 was a direct target of miR-495-3p through bioinformatic analysis. RNA pull-down assay further certified this prediction.

It has been registered that Pum2 functions as a tumor suppressor in osteosarcoma progression [26]. In addition, Jin Wang et al have pointed out that Pum2 is significantly down-regulated by ischemic acute kidney injury [27]. This evidence has mirrored that Pum2 may be a beneficial target for the treatment of several diseases. Our observations were in accordance with the above studies and supported the notion that Pum2 exerted a protective role in CH. Our study clarified that Pum2 was lowly expressed in CH, and was negatively modulated by miR-495-3p. Moreover, we proved that Pum2 silence reversed the repressive influences of miR-495-3p inhibition on CH.

There are several limitations in our present study. Pum2 belongs to a PUF family of RNA-binding proteins, and it can regulate the stability of downstream mRNAs, such as BTG1 and INSM1 [13, 28]. Therefore, our study will further explore the downstream mRNAs of Pum2 in CH. Moreover, we didn't investigate the relationship between other candidate mRNAs and miR-495-3p, and this shortage will be perfected in the future.

5. Conclusion

In conclusion, we discovered that miR-495-3p silence could inhibit CH in vitro and in vivo through binding to and modulating Pum2 expression. Our study elucidated the miR-495-3p/Pum2 axis might be a prospective therapeutic molecule target for CH.

Conflict of interests

The authors declare no competing interests.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

We have received approval from the Experimental Animal Ethics Committee of Tongji University.

Informed consent

Not applicable.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

XY contributed to the study conception and design. Experimental operation, data collection and analysis were performed by YS, WM, XY and WB. The first draft of the manuscript was written by YS and all authors commented on previous versions of the manuscript.

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Not applicable.

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Not applicable.

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