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MiR-140 protects against myocardial ischemia-reperfusion injury by regulating NF-κB pathway

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Abstract. – OBJECTIVE: The aim of this study was to investigate the effect of micro ribonucleic acid (miR)-140 on rats with myocardial ischemia-reperfusion injury (MIRI) through regulating the nuclear factor-κB (NF-κB) pathway.

MATERIALS AND METHODS: A total of 36 Sprague-Dawley rats were randomly divided into three groups, including sham group (n=12), model group (n=12) and miR-140 mimics group (n=12). In sham group, only thoracotomy was performed without ischemia-reperfusion. In model group, the MIRI model was first established, followed by intervention using normal saline. In miR-140 mimics group, the MIRI model was first established as well, followed by intervention using miR-140 mimics. The content of serum creatine kinase (CK) and lactate dehydrogenase (LDH) was detected, and the morphology of myocardial tissues was observed *via* hematoxylin-eosin (HE) staining. Meanwhile, the relative protein expression of NF-κB was determined using Western blotting. Quantitative polymerase chain reaction (qPCR) was conducted to evaluate the expression of miR-140. The content of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) was determined *via* enzyme-linked immunosorbent assay (ELISA). Furthermore, cell apoptosis was detected *via* terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) assay.

RESULTS: The content of serum CK and LDH rose significantly in model group and miR-140 mimics group when compared with sham group ($p<0.05$). However, it declined significantly in miR-140 mimics group compared with model group ($p<0.05$). HE staining results showed that there were no obvious abnormalities in the morphology of myocardial tissues in sham group. However, there were injury and inflammatory infiltration in myocardial tissues in model group. Meanwhile, the structure and morphology of myocardial tissues were improved in miR-140 mimics group compared with those in model group. Western blotting revealed that the relative protein expression of NF-κB was evidently higher in model group and miR-140 mimics group than sham group ($p<0.05$). However, it was remarkably lower in miR-140 mimics group than that in model group ($p<0.05$). QPCR results demonstrated that the relative expression of miR-140 in model group and miR-140 mimics group was obviously lower than sham group ($p<0.05$). However, a markedly higher expression of miR-140 was observed in miR-140 mimics group than model group ($p<0.05$). ELISA results indicated that model group and miR-140 mimics group had remarkably higher content of IL-1β and TNF-α than sham group ($p<0.05$). However, miR-140 mimics group had remarkably lower content of IL-1β and TNF-α than model group ($p<0.05$). TUNEL assay indicated that the apoptosis rate increased obviously in model group and miR-140 mimics group compared with sham group ($p<0.05$). However, it declined significantly in miR-140 mimics group compared with model group ($p<0.05$).

CONCLUSIONS: MiR-140 suppresses inflammation and apoptosis in myocardial tissues of MIRI rats through inhibiting the NF-κB signaling pathway, thereby exerting a cardioprotective effect.

Key Words:
Myocardial ischemia-reperfusion injury (MIRI), MiR-140, NF-κB signaling pathway, Inflammation, Apoptosis.

Introduction

Myocardial infarction is a common critical ischemic cardiovascular disease in clinic. Due to insufficient myocardial blood supply, it often leads to ischemic necrosis of myocardial tissues, seriously threatening the life and health of patients. With the development of society, accelerated pace of life and changes in living habits, the incidence rate of myocardial infarction has increased greatly, showing a younger trend[1,2].

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Currently, many treatment methods have been developed for ischemic heart disease, including interventional surgery and drug therapy. However, the treatment efficiency is still far from satisfactory. Myocardial ischemia-reperfusion injury (MIRI) caused by blood supply recovery in the later stage of ischemic heart disease is a problem that cannot be ignored. As an important pathological process during myocardial infarction, MIRI can induce a variety of pathological reactions, including inflammation and apoptosis. Eventually, this may damage myocardial repair and functional recovery after myocardial infarction[3-5].

As an important regulatory signaling pathway of inflammation, the nuclear factor-κB (NF-κB) pathway is considered to be closely related to the inflammatory response induced by MIRI. Micro ribonucleic acid (miR)-140 is an important member of the miRNA family. MiR-140 is able to regulate downstream signaling pathways, thereby regulating several physiopathological reactions, including inflammation, apoptosis and necrosis[6]. MiR-140 is lowly expressed in myocardial tissues of MIRI rats, confirming that miR-140 is involved in the pathological reaction of MIRI[7,8]. Therefore, the aim of this study was to explore the effect of miR-140 on MIRI rats through regulating the NF-κB pathway.

Materials and Methods

Laboratory Animals

A total of 36 specific pathogen-free Sprague-Dawley (SD) rats aged 1 month old were purchased from Shanghai SLAC Laboratory Animal Co., Ltd. [license No.: SCXK (Shanghai, China) 2014-0003]. The rats were fed with normal food and sterile filtered water every day in the Laboratory Animal Center under 12/12 h light-dark cycle, room temperature and regular humidity. This investigation was approved by the Animal Ethics Committee of Shanxi Yuncheng Central Hospital Animal Center.

Laboratory Reagents and Instruments

MiR-140 mimics (CST, Danvers, MA, USA), anti-NF-κB primary antibody (Abcam, Cambridge, MA, USA) and secondary antibody (Abcam, Cambridge, MA, USA), hematoxylin-eosin (HE) staining kit (Beyotime, Shanghai, China), enzyme-linked immunosorbent assay (ELISA) kit (Beyotime, Shanghai, China), terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) apoptosis kit (Beyotime, Shanghai, China), quantitative polymerase chain reaction (qPCR) kit (Vazyme, Nanjing, China), optical microscope (Leica DMI 4000B/DFC425C, Wetzlar, Germany), and fluorescence qPCR instrument (ABI 7500, Applied Biosystems, Foster City, CA, USA).

Animal Grouping and Treatment

The above 36 SD rats were divided into three groups using a random number table, including sham group (n=12), model group (n=12) and miR-140 mimics group (n=12). All rats were adaptively fed in the Laboratory Animal Center for 7 d before experiments.

In sham group, only thoracotomy was performed without ischemia-reperfusion. In model group, normal saline was first injected *via* the femoral vein at 5 min before modeling. Subsequently, the MIRI model was successfully established *via* myocardial ischemia for 30 min and reperfusion. Next, the wound was sutured. After modeling, normal saline was injected *via* the femoral vein every day, and the rats were fed for 7 d and sampled. In miR-140 mimics group, 3 μM of miR-140 mimics were first injected *via* the femoral vein at 30 min before modeling. Subsequently, the MIRI model was established *via* myocardial ischemia for 30 min and reperfusion. Then, the wound was sutured. After modeling, 3 μM of miR-140 mimics were injected *via* the femoral vein every day, and the rats were fed for 7 d and sampled.

Establishment of MIRI Model

After successful anesthesia *via* intraperitoneal injection of 3% pentobarbital sodium (5 mL/kg), the chest hair was shaved off to expose the skin. After disinfection, the rats were fixed firmly, and the chest was cut open with scissors to expose the heart. Subsequently, the left anterior descending coronary artery was found and ligated at 1/2. The whitening of left anterior wall, weakness in cardiac impulse, ST-segment elevation and T-wave height in electrocardiogram indicated myocardial ischemia. After ischemia for 45 min, the ligation was released to restore the blood supply to the left anterior descending coronary artery. Meanwhile, the conditions of rats were closely observed. After the rats were in stable condition, the wound was sutured layer by layer, and the rats were fed in separate cages.

Sampling

After successful anesthesia, the abdominal aortic blood was drawn from each rat first. Then, heart tissues were directly taken from 6 rats in each group. After washing with normal saline, collected tissues were placed into an Eppendorf

(EP) tube and stored at -80°C for Western blotting and qPCR analysis. Meanwhile, samples were taken through perfusion fixation from the remaining 6 rats in each group. Briefly, the thoracic cavity was cut open to expose the heart, and 400 mL of 4% paraformaldehyde was perfused from the left auricle. Next, heart tissues were taken and fixed in 4% paraformaldehyde solution for subsequent HE staining and TUNEL assay.

Detection of Creatine Kinase (CK) and Lactate Dehydrogenase (LDH)

Collected abdominal aortic blood was first centrifuged in a centrifuge at 1,000 g for 5 min. The content of CK and LDH in the supernatant separated was detected using a full-automatic biochemical analyzer.

HE Staining

Paraffin-embedded tissues were sliced into 5 μm-thick sections, flattened in warm water at 42°C, fished up, baked and prepared into paraffin sections. Subsequently, the sections were soaked and routinely deparaffinized in xylene solution and gradient alcohol. Next, HE staining was performed. The sections were stained with hematoxylin dye for 5 min, placed in pure water for 10 min, color-separated with 95% ethanol for 5 s, transparentized with xylene for 10 s, and sealed with neutral balsam.

Western Blotting

The cryopreserved heart tissues were lysed with lysis buffer and subjected to ice bath for 1 h, followed by centrifugation in a centrifuge at 14,000 g for 10 min. The concentration of extracted protein was quantified using the bicinchoninic acid (BCA) method (Beyotime, Shanghai, China). The absorbance of protein was detected using a microplate reader and the standard curve was plotted, based on which protein concentration was calculated. Subsequently, protein samples were separated *via* sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE), and the position of the Marker protein was observed. The electrophoresis was terminated when the Marker protein reached the bottom of the glass plate in a straight line. Next, proteins were transferred onto polyvinylidene difluoride (PVDF) membranes (Roche, Basel, Switzerland). After sealing with 5% skimmed milk for 1.5 h, the membranes were incubated with the anti-NF-κB primary antibody (1:1,000) overnight. On the next day, the membranes were incubated with corresponding secondary antibody (1:1,000) for 2 h at room temperature. Immunoreactive bands were fully developed in the dark using the chemiluminescent reagent for 1 min.

QRT-PCR

Total RNA in fresh heart tissues was first extracted using TRIzol reagent. Subsequently, extracted RNA was reversely transcribed into complementary deoxyribose nucleic acid (cDNA) using the reverse transcription kit. The qPCR system (20 μL) was designed, and the reaction conditions were as follows: reaction at 53°C for 5 min, pre-denaturation at 95°C for 10 min, denaturation at 95°C for 10 s, and annealing at 62°C for 30 s, for a total of 35 cycles. The ΔCt value was calculated first, and the difference in the expression of target gene was then calculated. Primer sequences used in this study were shown in Table I.

TUNEL Apoptosis Assay

Paraffin-embedded tissues were sliced into 5 μm-thick sections, flattened in warm water at 42°C, fished up, baked and prepared into paraffin sections. Then, the sections were soaked and routinely deparaffinized in xylene solution and gradient alcohol. Subsequently, the sections were added drop-wise with TdT solution for 1 h of reaction in dark and incubated with deionized water for 15 min to terminate the reaction. The endogenous peroxidase was inactivated with hydrogen peroxide added in drops. Next, the working solution was added dropwise for reaction for 1 h, followed by color development *via* DAB solution. Finally, the sections were washed, sealed and observed.

ELISA

Fresh tissues were first smashed into minced tissues. According to the instructions of enzyme-linked immunosorbent assay (ELISA) kit, the samples were loaded and added with standards, biotinylated antibody working solution and enzyme-linked working solution. Next, the plate was fully washed. Absorbance value at 450 nm was finally measured using a micro-plate reader.

Table I. Primer sequences.

Gene	Primer sequence
MiR-140	F: 5'-AGGCGTATTAGCGGCTTAT-3' R: 5'-TTATAGGCAGCAATTGCTA-3'
GAPDH	F: 5'-ACGGCAAGTTCAACGGCACAG-3' R: 5'-GAAGACGCCAGTAGACTCCACGAC-3'

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 20.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Measurement data were expressed as mean ± standard deviation. The *t*-test was used for the data in line with normal distribution and homogeneity of variance, corrected *t*-test for the data in line with normal distribution and heterogeneity of variance, and non-parametric test for the data not in line with normal distribution and homogeneity of variance. Rank sum test was adopted for ranked data, and chi-square test for enumeration data. $p<0.05$ was considered statistically significant.

Results

Content of Serum CK and LDH

As shown in Figure 1, the content of serum CK and LDH rose significantly in model group and miR-140 mimics group compared with sham group ($p<0.05$). However, it declined significantly in miR-140 mimics group compared with model group ($p<0.05$). The differences were all statistically significant.

Myocardial Morphology Observed using HE Staining

In sham group, myocardial tissues had normal morphology, intact structure and orderly arrangement of myocardial fibers. In model group, myocardial tissues had disturbed morphology and disorderly arrangement. Meanwhile, there were evident myocardial injury and massive inflammatory infiltration. In miR-140 mimics group, myocardial tissues were partially damaged still with disturbed morphology, and myocardial injury and inflammatory infiltration were improved compared with those in model group (Figure 2).

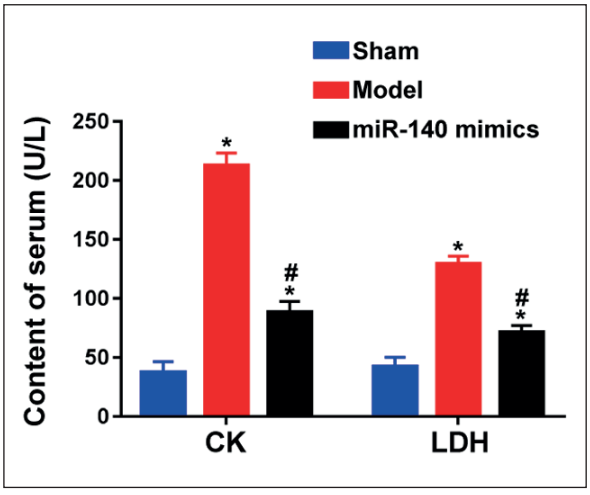

Figure 1. Content of serum CK and LDH in each group. Note: *$p<0.05$ *vs.* sham group, #$p<0.05$ *vs.* model group.

Relative Protein Expression Determined Using Western Blotting

The protein expression of NF-κB was lower in sham group, but higher in model group (Figure 3A). According to the statistical results (Figure 3B), the relative protein expression of NF-κB was evidently higher in model group and miR-140 mimics group than that in sham group ($p<0.05$). However, it was significantly lower in miR-140 mimics group than that in model group ($p<0.05$). There were statistically significant differences.

Relative Expression of MiR-140 Detected by QRT-PCR

The relative expression of miR-140 in model group and miR-140 mimics group was markedly lower than sham group ($p<0.05$). However, a markedly higher expression of miR-140 was observed in miR-140 mimics group than model group ($p<0.05$; Figure 4).

Content of Inflammatory Factors Determined by ELISA

Model group and miR-140 mimics group had remarkably higher content of IL-1β and TNF-α than sham group ($p<0.05$). However, miR-140 mimics group had remarkably lower content of IL-1β and TNF-α than model group ($p<0.05$) (Figure 5). The differences were all statistically significant.

Apoptosis Rate Determined Using TUNEL Assay

As shown in Figure 6, dark brown indicated apoptotic cells. There were fewer apoptotic cells in sham group, but more apoptotic cells in model group. According to the statistical results (Figure 6), the apoptosis rate increased obviously in model group and miR-140 mimics group compared with sham group, with statistically significant differences ($p<0.05$). However, it declined remarkably in miR-140 mimics group compared with model group, with a statistically significant difference ($p<0.05$).

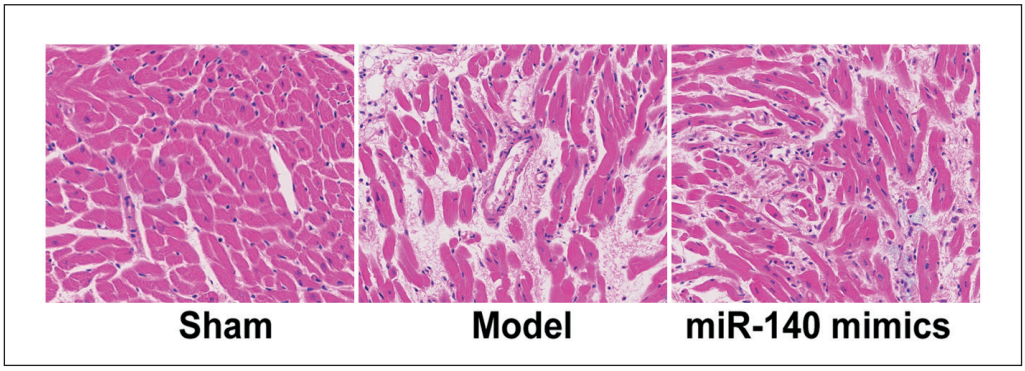

Figure 2. HE staining (magnification: 400×).

Discussion

Myocardial infarction is a clinically common ischemic heart disease, whose morbidity rate is increasing. It is believed that myocardial infarction is a severe cardiovascular disease frequently occurring in the elderly. However, with the development of society, accelerated pace of life and changes in living habits, the incidence of myocardial infarction has shown a younger trend. Cardiac dysfunction or even death due to myocardial infarction occurs in more and more people[9,10]. Therefore, it is extremely important to explore the related pathogenesis and pathological reactions of myocardial infarction. MIRI is one of the important pathological reactions during myocardial infarction. In the early stage of myocardial infarction, insufficient blood supply caused by occlusion of supplying vessels leads to ischemic and hypoxic changes. In the late stage of myocardial infarction, myocardial blood supply is restored due to vascular recanalization and the improvement of compensatory blood supply. As a result, MIRI occurs. MIRI is one of the key pathological processes during myocardial infarction, which leads to ischemia and hypoxia[11-13]. Meanwhile, it can induce inflammation, excessive oxidative stress response, lipid peroxidation and amino acid toxicity. It has been found that inflammation

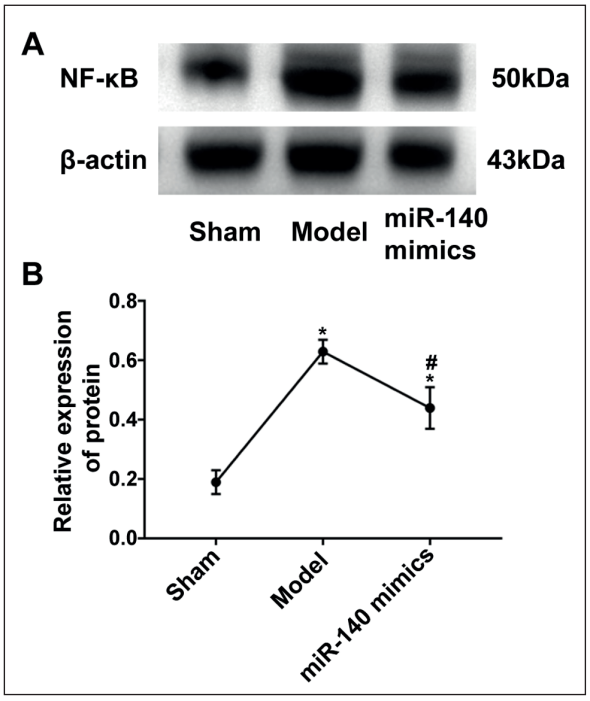

Figure 3. Protein expression detected via Western blotting. Note: (**A**) Western blotting results; (**B**) Relative protein expression in each group. *p<0.05 *vs.* sham group, #p<0.05 *vs.* model group.

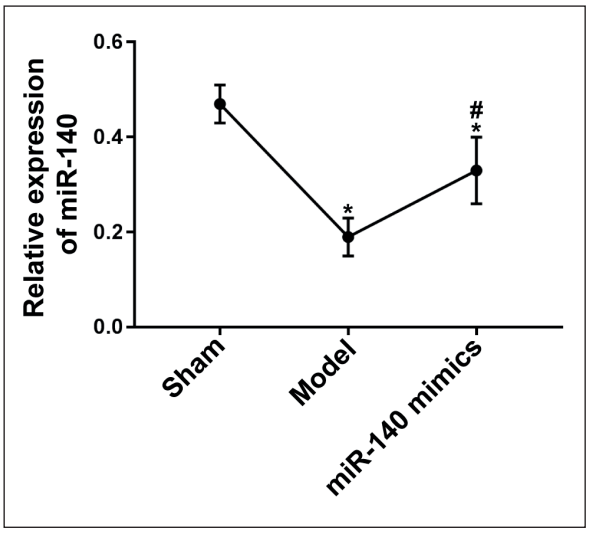

Figure 4. Relative expression of miR-140 in each group. Note: *p<0.05 *vs.* sham group, #p<0.05 *vs.* model group.

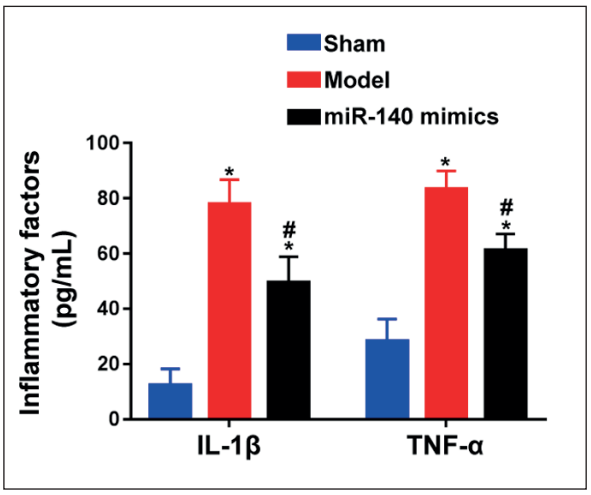

Figure 5. Content of inflammatory factors. Note: *p<0.05 *vs.* sham group, #p<0.05 *vs.* model group.

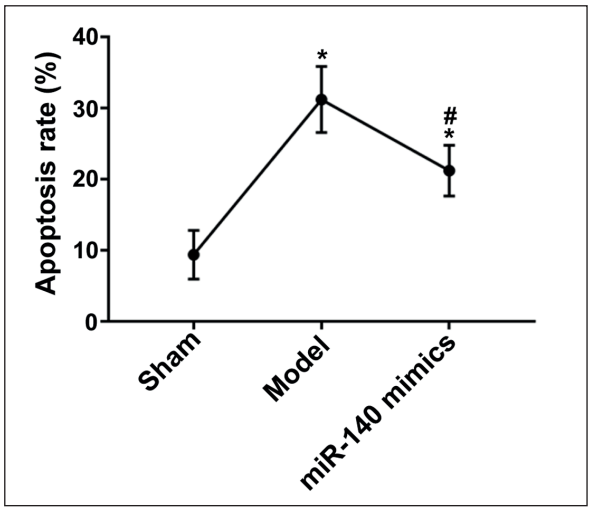

Figure 6. Apoptosis determined using TUNEL assay. Apoptosis rate in each group. *p<0.05 *vs.* sham group, #p<0.05 *vs.* model group.

is one of the important pathological reactions of MIRI. A large number of toxic substances (including cytokines and inflammatory factors) produced by MIRI can activate multiple downstream signaling pathways related to inflammation. Meanwhile, this can also up-regulate the expressions of inflammatory factors, further aggravating inflammatory responses. Then the inflammatory response can in turn activate the signaling pathways and worsen myocardial injury, thus forming an "injury-inflammation" vicious circle. At the same time, inflammation can further cause massive apoptosis and necrosis of myocardial cells. Therefore, a large number of myocardial cells are damaged and myocardial function is affected, eventually aggravating myocardial injury[14,15]. Therefore, MIRI after myocardial infarction can make myocardial injury more serious, harming the repair of myocardial tissues and the recovery of physiological function.

During MIRI, the NF-κB signaling pathway is abnormally activated and involved in the regulation of inflammatory response induced by MIRI. Current studies have confirmed[16,17] that the NF-κB signaling pathway is one of the important signaling pathways closely related to a variety of pathological reactions, including inflammation, apoptosis and necrosis. It affects the degree of inflammation and myocardial tissue repair after MIRI. In this study, it was found that NF-κB was highly expressed in myocardial tissues of MIRI rats. This indicates that the NF-κB signaling pathway is abnormally activated during MIRI, consistent with finding of previous studies. Furthermore, it may be one of the important pathological causes of excessive inflammatory response and massive apoptosis in myocardial tissues of MIRI rats in this study.

As one of the key members of the miRNA family, miR-140 plays an important regulatory role in multiple downstream signaling pathways. It also participates in regulating various physiopathological reactions, such as inflammation, apoptosis, necrosis and cell proliferation, thereby exerting an important biological effect. It has been proved[18-20] that miR-140 has an abnormal expression during MIRI, suggesting its involvement in pathological reactions. The results of this study manifested that the expression of miR-140 declined obviously in myocardial tissues of MIRI rats. After intervention with miR-140 mimics, myocardial morphology and function could be greatly improved. Moreover, NF-κB expression and inflammation in myocardial tissues were significantly reduced in MIRI rats.

Conclusions

In summary, the novelty of this study was that miR-140 suppresses inflammation and apoptosis in myocardial tissues of MIRI rats through inhibiting the NF-κB signaling pathway, thereby exerting a cardioprotective effect.

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Conflict of Interests

The authors declare that they have no conflict of interest.

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