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MicroRNA-338 in MSCs-derived exosomes inhibits cardiomyocyte apoptosis in myocardial infarction

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Abstract. – OBJECTIVE: Myocardial infarction (MI) is caused by myocardial ischemia and hypoxia, which causes irreversible damage to the myocardium and seriously endangers human health. Exosomes are small, monolayer-structured extracellular vesicles that transport proteins, lipids, mRNAs, and miRNAs between cells. Mesenchymal stem cells (MSCs) can secrete a large number of exosomes and play a role in many pathophysiological processes. The purpose of this paper was to investigate the role of exosomal microRNA-338 (miR-338) in MI and its underlying mechanism of action.

MATERIALS AND METHODS: We transfected rat bone marrow-derived MSCs with miR-338 mimic or negative control and extracted exosomes secreted by MSCs. Expression of miR-338 in MSCs, exosomes, and H9c2 cells co-cultured with exosomes was detected by PCR. Then, we treated H9c2 cells with H_2O_2. We transfected miR-338 inhibitor into H9c2 cells co-cultured with exosomes to further study the function of miR-338. Apoptosis of H9c2 cells were observed by Western blot, flow cytometry, and cell staining. We also established a MI rat model to study the function *in vivo* and injected exosomes in the myocardium. Seven days later, we used echocardiography to detect the heart function of rats.

RESULTS: MiR-338 was upregulated in MSCs transfected with miR-338 mimic, exosomes, and H9c2 cells co-cultured with exosomes. When H9c2 cells were co-cultured with exosomes overexpressing miR-338, the expression of Bax was decreased while the expression of Bcl-2 was increased, and the apoptosis rate was also decreased as shown in flow cytometry, and the amount of caspase3 fluorescence was also decreased. Cardiac function was markedly improved after intramyocardial injection of exosomes overexpressing miR-338 in rats. It was demonstrated using computational tools, Western blot, and Luciferase reporter gene experiments that miR-338 could regulate JNK pathway via targeting MAP3K2.

CONCLUSIONS: Exosomal miR-338 can inhibit cardiomyocyte apoptosis and improve cardiac function in rats with myocardial infarction by regulating MAP3K2/JNK signaling pathway.

Key Words:
Myocardial infarction (MI), MicroRNA-338, Mesenchymal stem cells (MSCs), Exosome, MAP3K2.

Introduction

Heart failure (HF) is a chronic heart disease that usually refers to the insufficient blood flow of the heart provided for energy metabolism in the body[1]. Statistics show that the mortality rate of HF in 5 years is higher than that of most malignant tumor diseases[2]. Cardiac remodeling is a hallmark of HF, and an important pathological stimulus that causes cardiac remodeling is MI[3]. MI is generally considered to be an ischemic cardiomyopathy or coronary artery disease, which can cause myocardial apoptosis, inflammation, fibrosis, etc., leading to pathological remodeling of the heart[4]. If the apoptosis of cardiomyocytes can be effectively inhibited in the early stage of MI to improve the structure and function of the damaged myocardium, the probability of progression to HF will be greatly reduced. At present, drugs, interventions, and

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surgery can significantly reduce the mortality of myocardial infarction, but cannot effectively repair the necrotic myocardium[5]. Therefore, there is an urgent need to develop new ways to treat MI.

Stem cells have the ability to self-replicate and, under certain conditions, differentiate into three types of cells in the germ layer, bringing new hope to the treatment of MI[6]. Mesenchymal stem cells (MSC) have attracted much attention due to their easy collection, wide sources and low immunogenicity[7]. Gao et al[8] have found that MSC can differentiate into functional adult cells, such as functional fat cells, neurons, chondrocytes, muscle cells, and fibroblasts. At present, many animal experiments and clinical trials have showed that MSC transplantation after MI can reduce infarct size and improve cardiac function[9]. However, stem cells have problems in the preservation, transportation, and biosafety, in particular, the low survival rate after transplantation limits their clinical application[10]. In recent years, it has been found that stem cell transplantation mainly functions through paracrine, and exosomes play an important biological role in paracrine mechanism[11].

Exosomes are membranous lipid vesicles of 30-150 nm in diameter secreted by cells, which contain a large amount of biological active substances, such as proteins, nucleic acids, and lipids[12]. Exosomes are easy to be preserved without potential toxicity, safety for clinical application, and some biological properties similar to stem cells[13] and they play an important role in the repair of myocardial damage[14]. Mesenchymal stem cells can secrete a large number of exosomes, indicating that the protective effect of stem cells on myocardial injury may be mainly achieved by exosomes. So far, a large number of articles have demonstrated that exosomes function primarily by transmitting non-coding RNAs, especially microRNAs (miRNA).

MiRNAs are short, non-coding RNAs that regulate gene expression at the mRNA level. MiRNAs guide the silencing complex (RISC) to degrade mRNA or hinder translation by base pairing with target mRNA[15]. MSC-derived exosomes contain a variety of miRNAs involved in the regulation of various physiological and pathological processes, such as cell growth, differentiation, apoptosis, and hormone secretion[16]. Zhao et al[17] demonstrated that MSCs-derived exosomal miR-338 can regulate proliferation and apoptosis of cumulus cells. Xin et al[18] believed that MSCs-derived exosomal miR-133b can regulate the growth of nerve cells. So far, a large number of studies have studied the function of miR-338, including tumor formation, autophagy of cardiomyocytes, endothelial cell damage, etc[19]. However, the role of miR-338 in cardiomyocyte apoptosis has not been studied. The aim of this study was to investigate whether miR-338 in MSCs-derived exosomes can inhibit cardiomyocyte apoptosis in MI.

Materials and Methods

MSCs Isolation

The bone marrow of the rat femur and tibia was collected and centrifuged to obtain MSCs. MSCs were cultured in Dulbecco's Modified Eagle's Medium (DMEM; Life Technology, Wuhan, China) containing 10% fetal bovine serum (FBS; Life Technology, Wuhan, China). When 90% of MSCs were fused, they were digested with trypsin containing ethylenediaminetetraacetic acid (EDTA) and passed to the next generation.

MSCs Transfection

MSCs were placed into a 6-well plate. 24 hours later, miR-338 mimic or negative control (RiboBio, Guangzhou, China) was transfected into MSCs using Lipofectamine 2000 (RiboBio, Guangzhou, China) in accordance with the manufacturer's protocols.

Exosomes Isolation and Identification

48 hours after transfection of MSCs, Exosome Isolation Reagent (RiboBio, Guangzhou, China) was used to extract exosomes of the MSCs that transfected with miR-338 mimic or negative control as directed by the instructions. The two groups of MSC culture medium were first collected and centrifuged to remove cells and debris. After that, we added exosome isolation reagent to the supernatant, mixed thoroughly, and put it in a refrigerator at 4°C overnight. After centrifuging the mixture the next day, the total exosomes were obtained. Transmission electron microscopy was used to observe exosomes, and Western blot was used to detect surface markers of exosomes: CD9, CD63, CD81.

H9c2 Cells Culture and Transfection

H9c2 cells were cultured in DMEM containing 10% FBS. The H9c2 cells were placed into a 6-well plate and co-cultured with exosomes secreted by MSCs. Then, the H9c2 cells were

treated with 100 μM H_2O_2 for 4 hours. To further demonstrate the role of miR-338, miR-338 inhibitor was transfected into H9c2 cells using Lipofectamine 2000 in accordance with the protocols.

Rat MI Model

This study was approved by the Animal Ethics Committee of Peking Union Medical College Animal Center. 40 Sprague Dawley (SD) female rats with a body mass of about 200 g were taken, and they were forbidden to drink water 4 h before surgery and fasted 12 h before surgery, among which 30 rats were used to establish the MI model and 10 rats were treated with sham surgery. 10% chloral hydrate was intraperitoneally injected for anesthesia, and the ventilator was used to assist ventilation (breathing frequency: 80 times/min, tidal volume: 8.0 mm, respiratory ratio: 5:4). After the rats were anesthetized, they were placed in the supine position and connected to the ECG. The surgical field was routinely prepared and disinfected. The skin and muscle layer were bluntly separated in the third intercostal space on the left side of the sternum. The chest expander was extended, the heart was exposed and the pericardium was opened, the left anterior descending coronary artery was ligated on the side of the pulmonary conus at the left heart ear root, and the ST segment was significantly elevated on the electrocardiogram. The chest was closed layer by layer, and the air in the chest was pumped before complete suture.

In the ischemic myocardium, 50 μL of exosome overexpressing miR-338 or control exosomes or phosphate-buffered saline (PBS) were injected before the chest was closed. Therefore, the rats were divided into 4 groups: sham group, PBS group, EXO-control group, EXO-338 mimic group.

Echocardiographic Measurement

On day 7 after rat surgery, echocardiography was used to detect cardiac function. Left ventricular end-diastolic diameter (LVD), left ventricular end-systolic diameter (LVS), ejection fraction (EF), and fractional shortening (FS) were detected and counted.

Flow Cytometry

Apoptosis detection kit (KeyGen, Shanghai, China) was utilized to detect the apoptosis rate according to the instructions. After different treatment, H9c2 cells were digested with trypsin without EDTA and stained with Annexin V-fluorescein isothiocyanate (FITC) and propidium iodide (PI). Finally, flow cytometry was used to detect the apoptosis rate.

Western Blot

The total protein was extracted using the radioimmunoprecipitation assay (RIPA) buffer (KeyGen, Shanghai, China) and its concentration was detected using the bicinchoninic acid (BCA) method (KeyGen, Shanghai, China). 20 μg total protein was taken for electrophoresis, and then, transferred to the polyvinylidene difluoride (PVDF; EpiZyme, Shanghai, China). After concentrated gel electrophoresis at 80 V and separation gel electrophoresis at 120 V, the bands were sealed with 5% skim milk for 2 hours. Then, the primary antibodies (CD29, Abcam, Cambridge, MA, USA, Rabbit, 1:1000; CD44, Abcam, Cambridge, MA, USA, Rabbit, 1:1000; CD105, Abcam, Rabbit, Cambridge, MA, USA, 1:1000; CD31, Abcam, Cambridge, MA, USA, Rabbit, 1:1000; CD34, Abcam, Cambridge, MA, USA, Rabbit, 1:1000; CD45, Abcam, Cambridge, MA, USA, Rabbit, 1:1000; CD9, Abcam, Cambridge, MA, USA, Rabbit, 1:1000; CD63, Abcam, Cambridge, MA, USA, Rabbit, 1:1000; CD81, Abcam, Cambridge, MA, USA, Rabbit, 1:1000; Bcl-2, Abcam, Cambridge, MA, USA, Mouse, 1:1000; Bax, Abcam, Cambridge, MA, USA, Mouse, 1:1000; MAP3K2, Abcam, Cambridge, MA, USA, Rabbit, 1:1000; JNK, Abcam, Cambridge, MA, USA, Rabbit, 1:1000; glyceraldehyde 3-phosphate dehydrogenase (GAPDH), ProteinTech, Rosemont, IL, USA, 1:1000) were used to incubate the bands overnight at 4°C. Then, the bands were washed for three times with Tris-Buffered Saline and Tween 20 (TBST) for 5 minutes each time. The bands were then incubated with secondary antibody for 1.5 hours. Finally, Image Lab™ Software was used to expose the bands.

Immunofluorescence

H9c2 cells were plated in 24-well plates, fixed with 4% paraformaldehyde, and then, blocked with 10% goat serum. The appropriate amount of caspase3 primary antibody was added for incubation (Abcam, Cambridge, MA, USA, Rabbit, 1:3000) overnight at 4°C. The fluorescent secondary antibody was added the next day. Then, 4',6-diamidino-2-phenylindole (DAPI; Construction, Nanjing, China) was used to stain the nucleus. Finally, the fluorescence was observed with a fluorescent inverted microscope.

RNA Extraction and Real Time-PCR

TRIzol reagent (MCE, Nanjing, China) was utilized to extract the total RNA of MSCs and H9c2 cells. Exosomal RNA extraction kit (EZ-Bioscience, Shanghai, China) was used for extraction of total RNA from exosomes. The steps were based on the respective instructions for use. NanoDrop™ 8000 was utilized to detect the RNA concentration. Reverse transcription kit (Roche, Basel, Switzerland) was utilized to obtain the cDNA. We used miRNA Universal SYBR qRCR Master Mix (Vazyme, Nanjing, China) to perform PCR, and we used 10 μl of reaction system including 5 μl of SYBR, 0.2 μl of forward primer (10μM, RiboBio, Guangzhou, China), 0.2 μl of reverse primer (10μM, RiboBio, Guangzhou, China), 1 μl of cDNA and 3.6 μl of ddH_2O). Prism 7900 System was utilized to perform PCR. The expression of miR-338 was normalized using U6. All the primers were listed in Table I.

Luciferase Activity Assay

HEK293T cells were placed in a 24-well plate. The plasmids which contained wild-type (WT) or mutant (MUT) 3′-UTR of MAP3K2 were co-transfected with miR-338 mimic or NC into HEK293T cells. 48 hours later, Luciferase reagent was added into the cells in accordance with the instructions and Dual-Glo® Luciferase Assay System was used to detect the activities of Luciferase (Promega, Madison, WI, USA).

Statistical Analysis

Data were expressed as $\chi \pm s$. All data were plotted using GraphPad Prism5 software (La Jolla, CA, USA). The differences between two groups were analyzed by using the Student's *t*-test. Comparison between multiple groups was done using One-way ANOVA test followed by post-hoc test (Least Significant Difference). Test level $\alpha=0.05$.

Results

Identification of MSCs and Exosomes

We first extracted rat bone marrow-derived mesenchymal stem cells. Then, we used Western blot to detect some surface markers (Figure 1A). It was found that the expression of stem cell-specific surface markers CD29, CD44, CD105 increased, while the expression of CD31, CD34, CD45 decreased in MSCs. After different treatments of MSCs, we extracted exosomes secreted by MSCs. It was observed under transmission electron microscope that the exosomes secreted by MSCs were round vesicles with intact membrane structure, which can be scattered or aggregated (Figure 1B). The diameter was in the range of 30 ~ 200 nm. We also used Western blot to detect surface markers of exosomes. As shown in Figure 1C, CD9, CD63, and CD81 were all positive.

The Expression of MiR-338 in MSCs and MSCs-Derived Exosomes Increased After Transfection with MiR-338 Mimic

We first transfected miR-338 mimic or negative control into MSCs. Then, the expression of miR-338 in MSCs was detected by PCR. The expression level of miR-338 was significantly increased after transfection of miR-338 mimic (Figure 2A). At the same time, we collected exosomes secreted by MSCs and extracted total RNA from exosomes. PCR was utilized to measure the expression of miR-338 in exosomes. We found that the expression of miR-338 was significantly increased in exosomes secreted by MSCs transfected with miR-338 mimic (Figure 2B). This showed that miR-338 was successfully loaded into the exosomes. To study the function of miR-338, we co-cultured H9c2 cells with exosomes. The expression of miR-338 was significantly increased in H9c2 cells co-cultured with exosomes overexpressing miR-338 (Figure 2C).

Table I. Real Time-PCR primers.

Gene name	Forward (5′>3′)	Reverse (5′>3′)
miR-338	TGCGGTCCAGCATCAGTGAT	CCAGTGCAGGGTCCGAGGT
U6	CTCGCTTCGGCAGCACA	AACGCTTCACGAATTTGCGT

qRT-PCR, quantitative Reverse Transcription-Polymerase Chain Reaction.

MiR-338 Overexpression Inhibited H_2O_2-Induced Apoptosis in H9c2 Cells

After H9c2 cells were co-cultured with exosomes for 24 hours, they were treated with H_2O_2 (100 μM) for 4 hours. After that, the expression of Bax and Bcl-2 proteins was detected by Western blot (Figure 3A). Compared with the EXO-control group, the expression of Bax in the EXO-338 mimic group was markedly decreased, and the expression of Bcl-2 was markedly increased (Figure 3B and C). Immunofluorescence showed that the caspase3 levels were markedly decreased in H9c2 cells co-cultured with exosomes overexpressing miR-338 (Figure 3D). The apoptotic rate of H9c2 cells induced by H_2O_2 declined in the EXO-338 mimic group compared with the EXO-control group (Figure 3E and 3F). These results indicated that the overexpression of miR-338 can inhibit apoptosis of H9c2 cells.

MiR-338 Inhibitor Reversed the Anti-Apoptotic Effect of Exosomes Overexpressing MiR-338 on H9c2 Cells

To further demonstrate the anti-apoptotic effect of miR-338, we transfected miR-338 inhibitor into H9c2 cells co-cultured with exosomes. We can see from Figure 4A that the treatment of miR-338 inhibitor significantly reduced the expression of miR-338 in H9c2 cells. Then, we treated H9c2 cells with H_2O_2 (100 μM, 4 h). The expression of Bax and Bcl-2 was detected by Western blot (Figure 4B). Compared with the EXO-338 mimic group, the expression of Bax was markedly increased and the expression of Bcl-2 was markedly

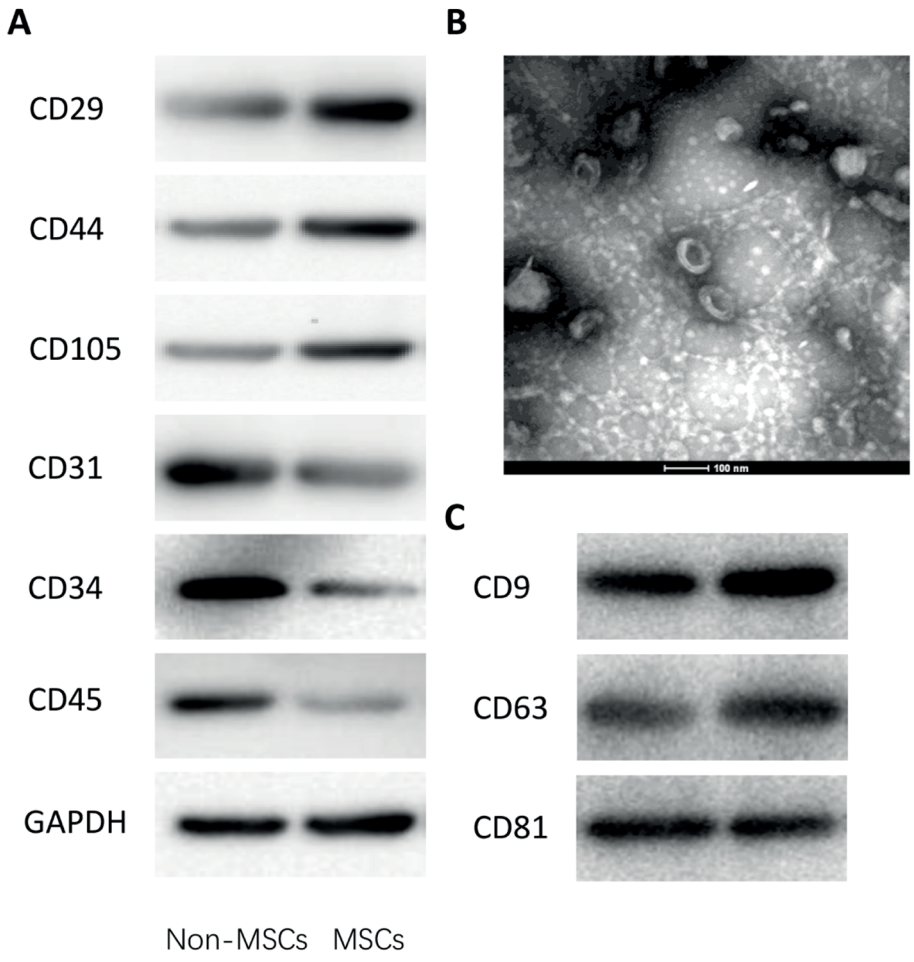

Figure 1. Identification of MSCs and exosomes. **A,** Western blot analysis of the surface markers in MSCs. **B,** Representative TEM image of the exosomes secreted by MSCs (Magnification: 20,000 ×) . **C,** Western blot analysis of the surface markers in exosomes.

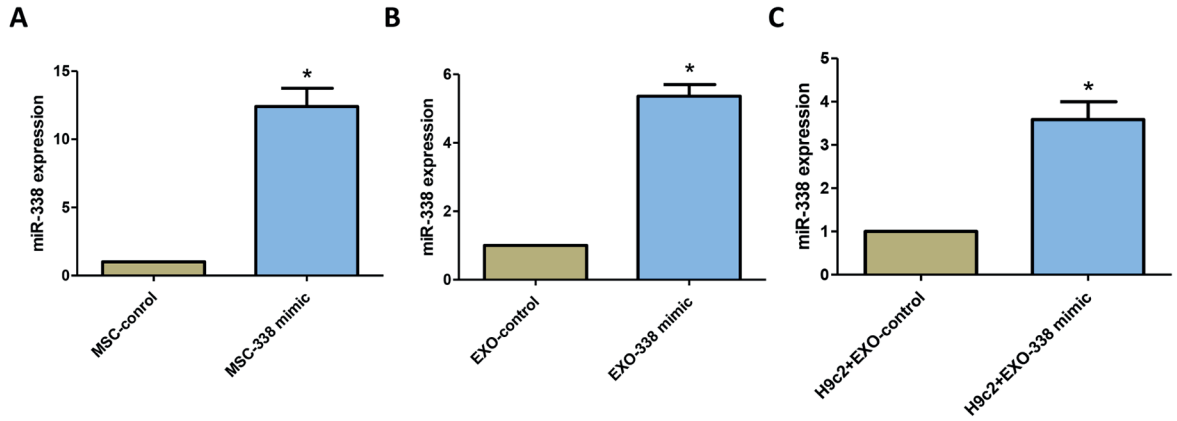

Figure 2. MiR-338 mimic increased the expression of miR-338 in MSCs and MSCs-derived exosomes. **A,** Detection of miR-338 expression in MSCs after transfection ("*" $p<0.05$ *vs.* MSC-control, n = 3). **B,** Detection of miR-338 expression in MSCs-derived exosomes ("*" $p<0.05$ *vs.* EXO-control, n = 3). **C,** Detection of miR-338 expression in H9c2 cells co-cultured with exosomes ("*" $p<0.05$ *vs.* H9c2+EXO-control, n = 3).

decreased in the EXO-338 mimic+inhibitor group (Figure 4C and D). The apoptosis rate of H9c2 cells in the EXO-338 mimic+inhibitor group was also significantly increased (Figure 4E).

Exosomes Overexpressing MiR-338 Improved Cardiac Function in Rats with MI

We generated a rat model of MI to study the function of exosomes that overexpress miR-338. Cardiac function of myocardial infarction rats was measured by echocardiography 7 days after intramyocardial injection of exosomes (Figure 5A). We measured left ventricular end-systolic diameter (LVS) and left ventricular end-diastolic diameter (LVD) (Figure 5B and 5C), and calculated left ventricular ejection fraction (EF) and fractional shortening (FS) (Figure 5D and 5E). Compared with the EXO-control group, the LVS and LVD in the EXO-338 mimic group were greatly reduced, and the EF and FS were greatly increased. These results indicated that exosomes overexpressing miR-338 can significantly improve cardiac function in rats.

MiR-338 Inhibited Cardiomyocyte Apoptosis by Targeting MAP3K2

To further explore the mechanism of action of miR-338 against cardiomyocyte apoptosis, we predicted the target of miR-338 using the TargetScan database and the StarBase database. It was predicted that MAP3K2 had a binding site to miR-338 (Figure 6A). MAP3K2 is a member of the MAPK pathway which contains four major branch pathways (ERK, JNK, p38, ERK5). Western blot analysis showed that the expression of MAP3K2 and JNK was markedly decreased in H9c2 cells co-cultured with exosomes overexpressing miR-338 (Figure 6B-6D). When H9c2 cells were transfected with miR-338 inhibitor, the expression of MAP3K2 and JNK was reversed (Figure 6E-6G). MiR-338 overexpression greatly inhibited Luciferase activity in WT group, but failed in mutant (MUT) group (Figure 6H). These indicated that miR-338 may inhibit cardiomyocyte apoptosis by regulating the MAP3K2/JNK pathway.

Discussion

About 17 million people worldwide die from cardiovascular disease each year, of which acute myocardial infarction accounts for more than 50%, and the incidence of myocardial infarction is increasing year by year[20]. Traditional treatments (drug therapy, intervention, bypass surgery) can significantly reduce mortality, but cannot repair necrotic myocardium. In recent years, stem cells have received increasing attention due to their strong proliferation and differentiation potential. Currently, in many diseases, MSCs are considered as potential therapeutic methods, and the studies in MSCs are mostly concentrated in bone marrow mesenchymal stem cells[21]. So, this paper selected bone marrow-derived MSCs.

Due to lack of oxygen, ischemia, lack of nutrition, etc., apoptosis or necrosis occurs within

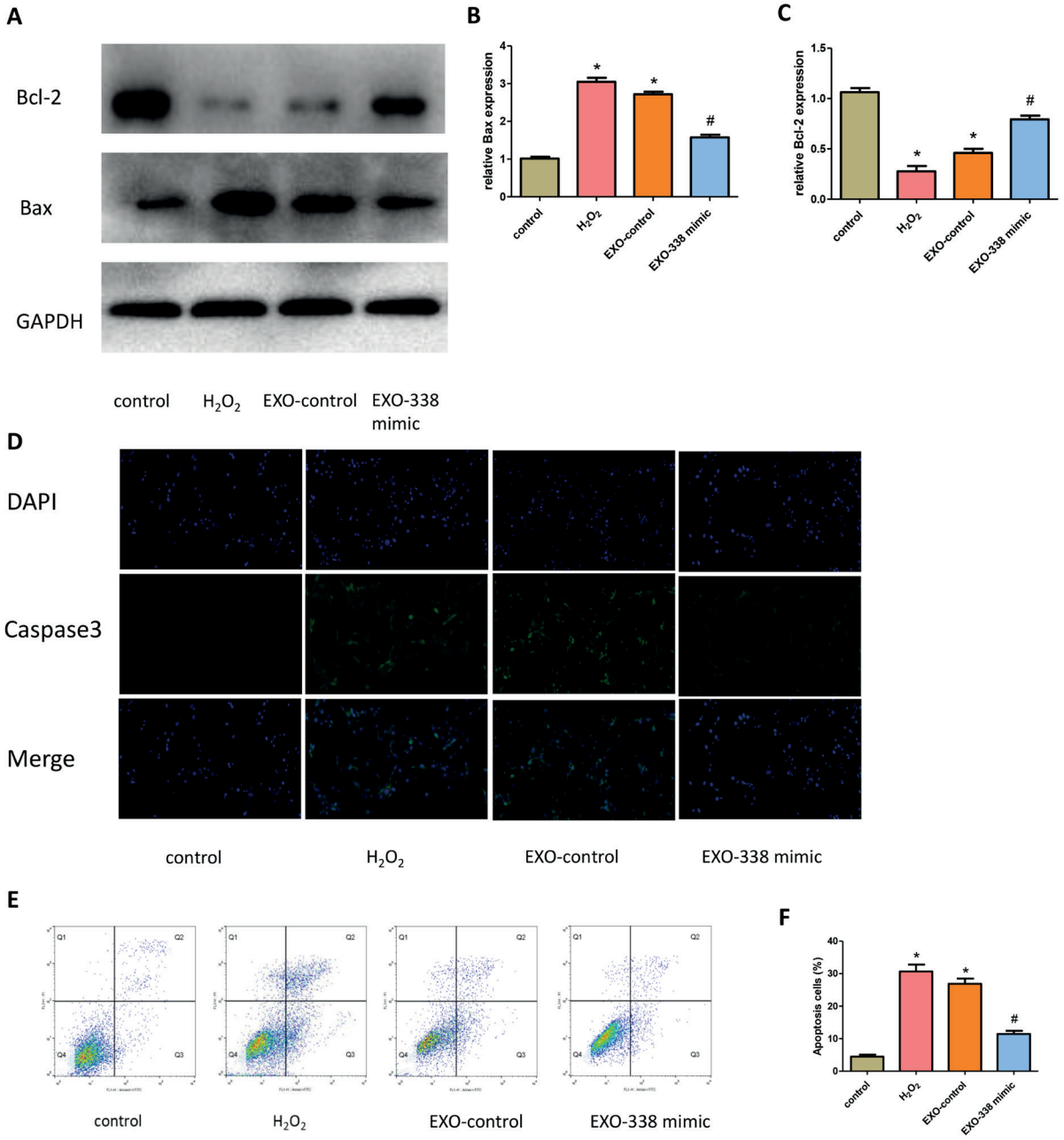

Figure 3. MiR-338 overexpression inhibited H_2O_2-induced apoptosis. **A,** Western blot analysis of the Bax and Bcl-2 in H9c2 cells treated with H_2O_2. **B,** Statistical results of protein level of Bax ("$_*$" $p<0.05$ *vs.* control, "$_\#$" $p<0.05$ *vs.* EXO-control, n=3). **C,** Statistical results of protein level of Bcl-2 ("$_*$" $p<0.05$ *vs.* control, "$_\#$" $p<0.05$ *vs.* EXO-control, n=3). **D,** Representative images of Immunofluorescence (Magnification: 100 ×). **E,** The representative images of flow cytometry using Annexin V-FITC and PI staining. **F,** Statistical analysis of apoptosis rate detected by flow cytometry ("$_*$" $p<0.05$ *vs.* control, "$_\#$" $p<0.05$ *vs.* EXO-control, n=3).

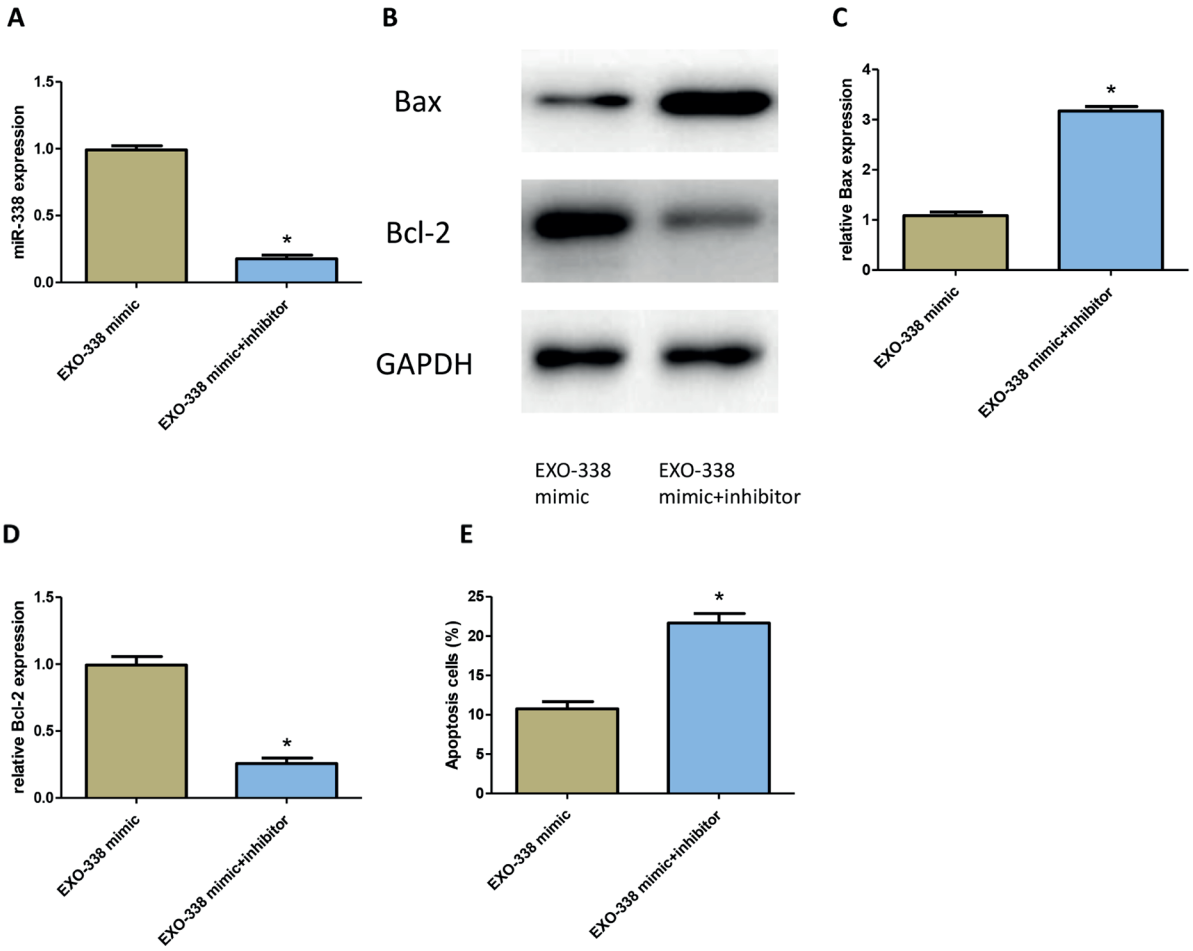

Figure 4. MiR-338 inhibitor reversed the anti-apoptotic effect of exosomes overexpressing miR-338. **A,** Detection of miR-338 expression in H9c2 cells co-cultured with exosomes and transfected with miR-338 inhibitor ("*" $p<0.05$ *vs.* EXO-338 mimic, n = 3). **B,** Western blot analysis of the Bax and Bcl-2 in H9c2 cells co-cultured with exosomes and transfected with miR-338 inhibitor. **C,** Statistical results of protein level of Bax ("*" $p<0.05$ *vs.* EXO-338 mimic, n = 3). **D,** Statistical results of protein level of Bcl-2 ("*" $p<0.05$ *vs.* EXO-338 mimic, n = 3). **E,** Statistical analysis of apoptosis rate detected by flow cytometry ("*" $p<0.05$ *vs.* EXO-338 mimic, n = 3).

24 h after stem cell transplantation, and the low survival rate limits its clinical application[22]. In addition, the differentiation efficiency of MSC into cardiomyocytes is very low. Li et al[23] showed that stem cell transplantation improves left ventricular remodeling and cardiac function primarily through paracrine effects. Balbi and Bollini[24] have found that conditioned medium from stem cells can reduce the infarct size of ischemia/reperfusion (I/R) injury. By paracrine, stem cells can promote the survival of the host myocardium and angiogenesis, mobilize autologous stem cells, regulate immune responses, and inhibit fibrosis, thereby improving cardiac function. Among them, exosomes may be important mediators for the function of MSCs. Exosomes carry substances, such as soluble proteins, lipids, mRNA, and miRNA, and can be transmitted to recipient cells to mediate cell-to-cell communication. The exosomal membrane protects its contents from nucleases in the blood and the immune system. Therefore, MSC-derived exosomes have broader application prospects than MSCs.

In the present study, we overexpressed miR-338 in MSCs and found that the secreted exosomes also overexpressed miR-338 and could be taken up by cardiomyocytes, thereby increasing the expression of miR-338 in cardiomyocytes.

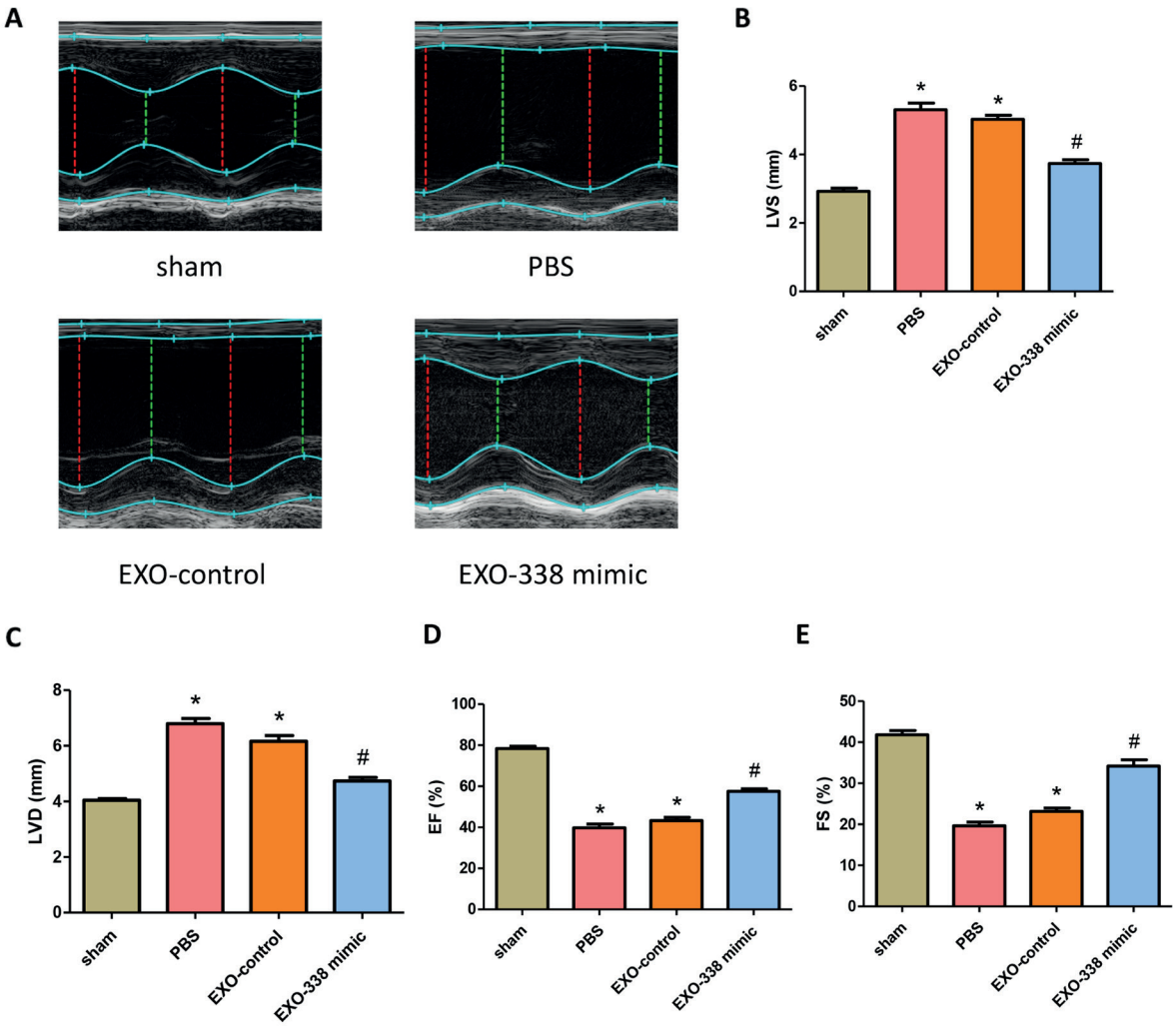

Figure 5. Exosomes overexpressing miR-338 improved cardiac function in MI rats. **A,** Representative photographs of rats echocardiography. **B**-**E**, Exosomes overexpressing miR-338 improved LV function (EF, FS, LVS, and LVD) measured by echocardiography ("$_{*}$" $p<0.05$ *vs.* sham, "$_{\#}$" $p<0.05$ *vs.* EXO-control, n=6).

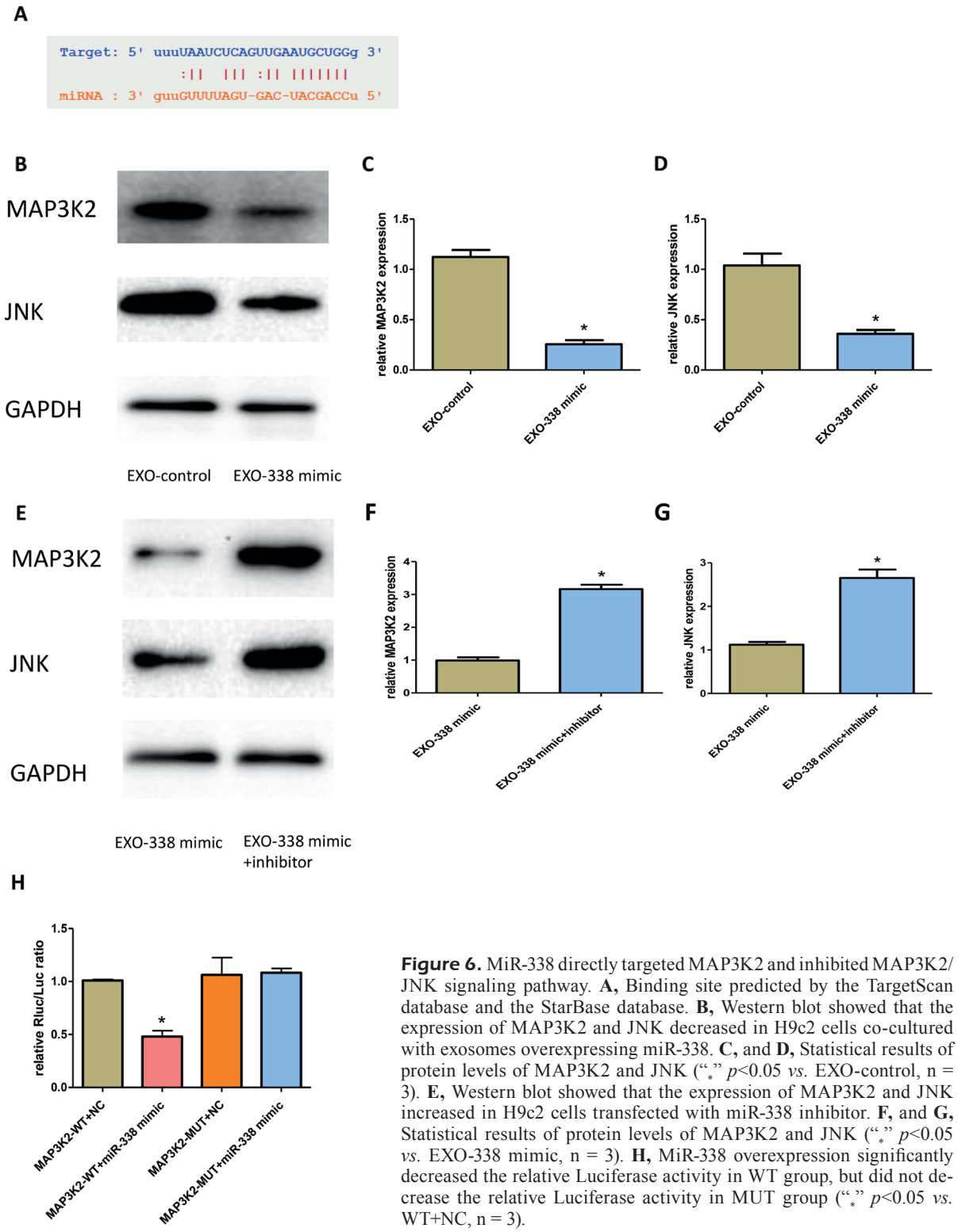

Figure 6. MiR-338 directly targeted MAP3K2 and inhibited MAP3K2/JNK signaling pathway. **A,** Binding site predicted by the TargetScan database and the StarBase database. **B,** Western blot showed that the expression of MAP3K2 and JNK decreased in H9c2 cells co-cultured with exosomes overexpressing miR-338. **C,** and **D,** Statistical results of protein levels of MAP3K2 and JNK ("*" $p<0.05$ *vs.* EXO-control, n = 3). **E,** Western blot showed that the expression of MAP3K2 and JNK increased in H9c2 cells transfected with miR-338 inhibitor. **F,** and **G,** Statistical results of protein levels of MAP3K2 and JNK ("*" $p<0.05$ *vs.* EXO-338 mimic, n = 3). **H,** MiR-338 overexpression significantly decreased the relative Luciferase activity in WT group, but did not decrease the relative Luciferase activity in MUT group ("*" $p<0.05$ *vs.* WT+NC, n = 3).

Moreover, we found that overexpression of miR-338 greatly inhibited cardiomyocyte apoptosis, thereby improving cardiac function in rats with MI. At the same time, we found that miR-338 exerts anti-apoptotic effects by targeting MAP3K2, thereby regulating the JNK signaling pathway.

Conclusions

Briefly, exosomal miR-338 can inhibit cardiomyocyte apoptosis and improve cardiac function in rats with myocardial infarction by regulating MAP3K2/JNK signaling pathway.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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