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LncRNA MALAT1 knockdown alleviates oxygen-glucose deprivation and reperfusion induced cardiomyocyte apoptotic death by regulating miR-122

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ABSTRACT

Background: Metastasis associated lung adenocarcinoma transcript 1 (MALAT1) has been reported to be critical in the onset and progression of acute myocardial ischemia (AMI). This study attempted to reveal the biological function of MALAT1 in AMI.

Methods: Expression of MALAT1 in H9c2 cells was silenced by shRNA-mediated transfection, following which cells were suffered from oxygen-glucose deprivation and reperfusion (OGD/R). CCK-8, flow cytometry and western blot were carried out to evaluate the effects of MALAT1 against OGD/R injury. Further, the correlation between MALAT1, miR-122 and AKT/GSK-3β/β-catenin signaling was studied to decode the underlying mechanisms.

Results: MALAT1 expression was highly expressed following OGD/R. Suppression of MALAT1 attenuated OGD/R-induced cardiomyocyte apoptosis, as evidenced by the increase of cell viability and the decrease of apoptosis rate. Besides that, miR-122 was found to be positive regulated by MALAT1. The protective effects of MALAT1 knockdown were flattened by miR-122 overexpression. Furthermore, AKT/GSK-3β/β-catenin signaling was activated by MALAT1 knockdown. The effects of MALAT1 knockdown on the signaling were flattened when miR-122 was overexpressed.

Conclusion: Our finding revealed protective effects of MALAT1 knockdown on OGD/R induced cardiomyocyte apoptosis. MALAT1 exerted its function possibly through regulating AKT/GSK-3β/β-catenin signaling through up-regulating miR-122.

1. Introduction

Acute myocardial ischemia (AMI) is one of the main diseases threating human life worldwide (GBD2015, 2016). Severe and sustained myocardial ischemia trigger cell death and irreversible loss of cardiomyocytes, which lead to the myocardial contractile dysfunction and even heart failure and sudden death (Tepekoylu et al., 2017; Wit, 2017). Cell death, i.e., apoptosis, necrosis and autophagy, are the final arbiters of cardiomyocytes following AMI (Gottlieb, 2011; Zhan and Zhang, 2018). Reperfusion therapy is the most common used strategy for AMI treatment by decreasing the quantities of necrosis. However, reperfusion cannot recover cardiomyocyte injury but lead to a further cardiomyocyte apoptotic death (Hausenloy and Yellon, 2013; Rentrop and Feit, 2015). Thereby, improving the tolerance of cardiomyocytes to ischemia and reperfusion injury and blocking irreversible cell death appear to ameliorate the symptoms of AMI and arrest the progression of this disease.

Long non-coding RNAs (lncRNAs) are a class of RNA molecules with length of 200–100,000 nt. In earlier studies, lncRNAs are ignored by scientists and has been regarded as meaningless transcription fragments. But, recent studies revealed the over-expanding roles of lncRNAs in regulating gene expression and numerous cellular biological processes. A growing number of lncRNAs has been considered as potential bio-markers and therapeutic targets for AMI, like KCNQ1OT1 (Li et al., 2017a), Mirt1 (Li et al., 2017b) and HOTAIR (Gao et al., 2017). Metastasis associated lung adenocarcinoma transcript 1 (MALAT1) is an lncRNA of over 8000 nt and locates on chromosome 11q13.1. In 2003, MALAT1 was firstly identified since its high expression predicted the metastasis and survival of non-small cell lung cancer (Ji et al., 2003). From then on, the correlation between MALAT1 and human diseases has gained considering attentions (Zhang et al., 2017a). Among patients with AMI, the single nucleotide polymorphisms (SNP) of MALAT1 participates in regulating lipid levels (Li et al., 2019) and risk factors of coronary artery disease (Hu et al., 2019). MALAT1 also participates in remodeling of electrophysiological/ion channel in cardiomyocytes during arrhythmia (Zhu et al., 2018). Moreover, several literatures have

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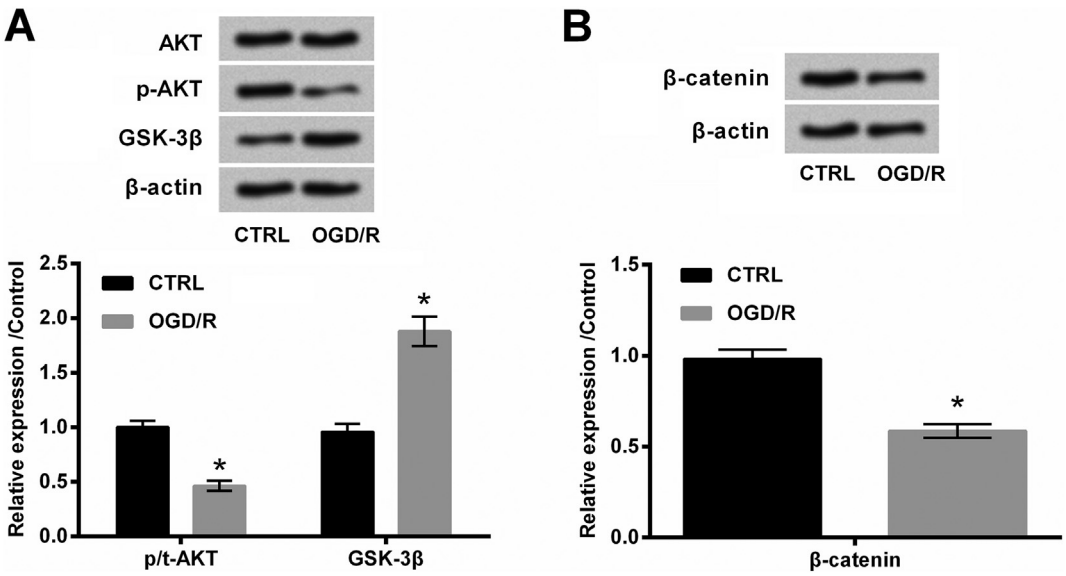

Fig. 1. AKT/GSK-3β/β-catenin signaling was restrained by OGD/R. H9c2 cells were suffered from OGD/R. Expression of (A) AKT, GSK-3β and (B) β-catenin was determined by western blot. *$P < 0.05$ compared with control group. CTRL: control..

reported that manipulating the expression of MALAT1 regulated the initiation and progression of AMI (Hu et al., 2018; Zhao et al., 2017). However, the role of MALAT1 in AMI has not been fully revealed at least its function in an oxygen-glucose deprivation and reperfusion (OGD/R) model is largely unknown.

In this study, an OGD/R injury model was constructed to enlarge our understanding of MALAT1 in AMI. Besides that, the correlation between MALAT1 and microRNA (miR)-122 was studied. miR-122 has previously revealed as a contributor of cardiomyocyte death during AMI (Cortez-Dias et al., 2016; Yao et al., 2019; Zhang et al., 2017b). Moreover, MALAT1 expression was negatively correlated with miR-122 in plasma. And miR-122 could inhibit the expression of MALAT1 in gastric cancer cells (Xia et al., 2016). Furthermore, miR-122 was suggested to be a potential biomarker for AMI (Yao et al., 2015b). The revealed correction between these two will further explain MALAT1'-function in AMI.

2. Materials and methods

2.1. OGD/R model

The primary cardiomyocytes were isolated from 3-day-old neonatal Wistar rats (purchased from the Experimental Animal Centre of Yangzhou University). Both primary cardiomyocytes and H9c2 cells (ATCC, Manassas, VA) were cultured in DMEM medium (ATCC). Fetal bovine serum (FBS, Gibco, Grand Island, NY) was added to a final concentration of 10% to make complete growth medium. Culture conditions are 37 °C, 5% CO_2.

OGD/R model was constructed by culturing primary cardiomyocytes and H9c2 cells in glucose-free medium in an atmosphere with 2% O_2 for 6 h. The cells were then return into the normal medium and atmosphere for 24 h.

2.2. Transfection

sh-MALAT1 for expression of MALAT1 specific shRNA was constructed by placing the MALAT1 shRNA into BLOCK-iT™ U6 vector (Invitrogen, Carlsbad, CA). The non-targeting sequence was used as its control. miR-122 mimic and the negative control (mimic NC) were purchased from GenePharma (Shanghai, China). Lipofectamine 3000 (Invitrogen, Carlsbad, CA) was used in transfection, and the process was lasted for 48 h.

2.3. CCK-8 assay

The transfected cells in 96-well plates (2000 wells/well) were used for testing cell viability, following OGD/R. 10 μL reagent from Enhanced Cell Counting Kit-8 (Beyotime, Shanghai, China) was added each well and the sample was incubated for 1 h at 37 °C. Optical density (OD) of samples was analyzed by a microplate reader (Bio-Rad, Hercules, CA) at 450 nm.

2.4. Apoptosis assay

The transfected cells were suffered from OGD/R, after which cells were collected for testing apoptosis by using an Annexin V-FITC Apoptosis Detection Kit (Beyotime). The percentage of apoptotic cells in total cells was measured by a flow cytometer (Beckman Coulter, Fullerton, CA).

2.5. qRT-PCR

Total RNAs were extracted by Trizol reagent (Invitrogen). The purity of the extracts was verified by measuring the OD values at 260 and 280 nm. PrimeScript™ RT reagent Kit and TB Green™ Premix Ex Taq™ II (Takara, Dalian, China) were used to measure relative MALAT1 expression. miRNAs were extracted by using miRNeasy Mini Kit (Qiagen, Hilden, Germany). Mir-X™ miRNA First-Strand Synthesis Kit together with Mir-X™ miRNA qRT-PCR TB Green™ Kit (Takara) were used to measure relative miR-122 expression. β-actin and U6 served as internal controls.

2.6. Western blot

Proteins were extracted by using RIPA buffer (Beyotime). The proteins were immunobloted with the rabbit monoclonal anti-Bcl-2 (No. ab32124), anti-Bax (No. ab32503), anti-caspase-3 (No. ab13847), anti-activated caspase-3 (No. ab2302), anti-AKT (No. ab8805), anti-GSK-3β (No. ab93926), anti-β-catenin (No. ab32572), anti-β-actin (No. ab115777) and rabbit polyclonal anti-AKT (phospho T308, No. ab38449) antibodies (all from Abcam, Cambridge, MA). Goat Anti-Rabbit IgG (Abcam) was used as the secondary antibody. The target

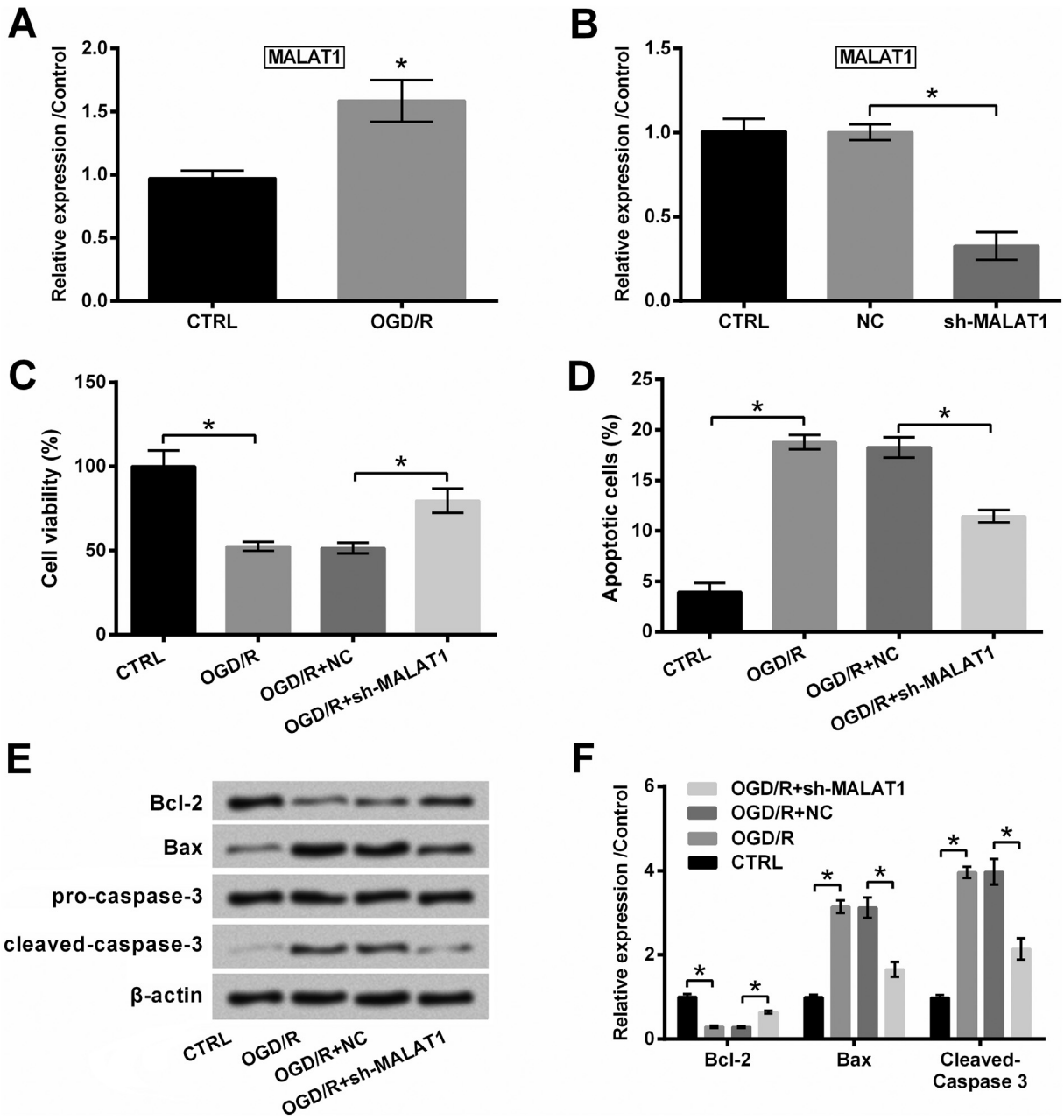

Fig. 2. OGD/R induced apoptotic death was prevented by MALAT1 overexpression in H9c2 cells. (A) MALAT1 expression in H9c2 cells was tested by qRT-PCR, following OGD/R. (B) MALAT1 expression was tested by qRT-PCR, following transfection with pc-MALAT1 or pcDNA3.1. The transfected cells were suffered from OGD/R, after which (C) cell viability, (D) apoptosis, and (E, F) expression of proteins associated with apoptosis was respectively determined by CCK-8 assay, flow cytometry and western blot. $*P < 0.05$ compared with indicated group. CTRL: control.

bands were developed by using the BeyoECL Moon (Beyotime). Intensity of bands was quantified by using Image Lab™ Software (Bio-Rad).

2.7. Statistics

Data presented as mean ± SD and statistical results presented as asterisks. Statistical difference was set at $P < 0.05$. SPSS 19.0 software (Chicago, IL) was used for calculating statistical difference. Student *t*-test and ANOVA followed by Duncan procedure were conducted to compare the difference between two or more groups.

3. Results

3.1. AKT/GSK-3β/β-catenin signaling was restrained by OGD/R

AKT/GSK-3β/β-catenin signaling is an intracellular signaling that contributes to cell apoptosis (Dai et al., 2017; He et al., 2019). The activation of AKT/GSK-3β/β-catenin signaling in response to OGD/R was investigated in this study. Results displayed that, the phosphorylation level of AKT was decreased by OGD/R ($P < 0.05$, Fig. 1A). Meanwhile, GSK-3β was up-regulated while β-catenin was down-regulated by OGD/R ($P < 0.05$, Fig. 1A-B).

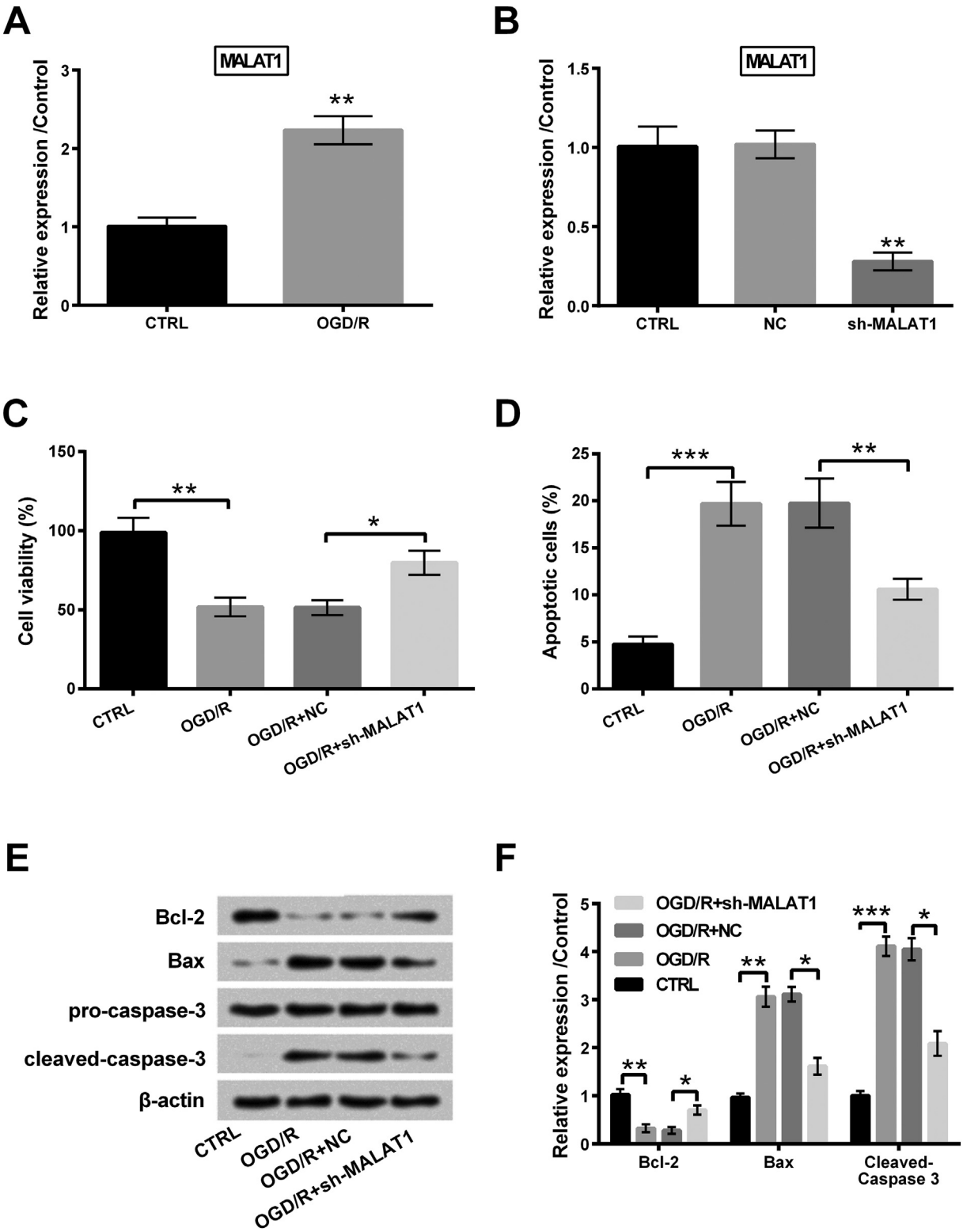

Fig. 3. OGD/R induced apoptotic death was prevented by MALAT1 overexpression in primary cardiomyocytes. (A) MALAT1 expression in primary cardiomyocytes was tested by qRT-PCR. (B) MALAT1 expression was tested by qRT-PCR, following transfection with pc-MALAT1 or pcDNA3.1. The transfected cells were suffered from OGD/R, after which (C) cell viability, (D) apoptosis, and (E, F) expression of proteins associated with apoptosis was respectively determined by CCK-8 assay, flow cytometry and western blot. $*P < 0.05$, $**P < 0.01$ or $***P < 0.001$ compared with indicated group. CTRL: control.

3.2. OGD/R induced apoptotic death was prevented by MALAT1 knockdown in H9c2 cells

By using qRT-PCR, MALAT1 expression was found to be up-regulated by OGD/R ($P < 0.05$, Fig. 2A). We next investigated whether suppressing MALAT1 expression could implicate in OGD/R-induced apoptosis. To this end, the expression of MALAt1 in H9c2 cells was knocked down by transfection with MALAT1 specific shRNA (sh-MALAT1). Transfection efficiency was shown in Fig. 2B. As a result, OGD/R-induced cell viability loss, as the viability was reduced in OGD/

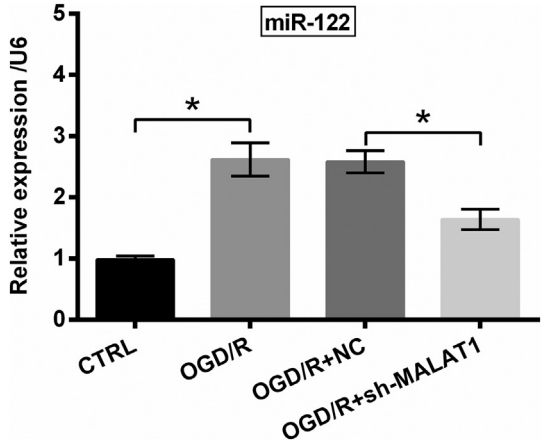

Fig. 4. MALAT1 functioned as a miR-122 sponge in H9c2 cells. (A) miR-122 expression was increased by OGD/R and then inhibited by sh-MALAT1. The specific binding sites of miR-122 and MALAT1 were miR-122 3'-GUUUGUGG UAACAGUGUGAGGU-5'; lncMALAT1 5'- UGAAAAUAUUGUCAAGAGUUUCAG -3'. *$P < 0.05$ compared with indicated group. CTRL: control.

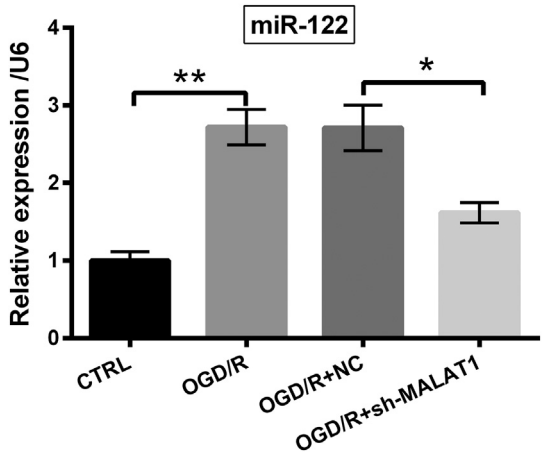

Fig. 5. miR-122 expression was inhibited by sh-MALAT1. miR-122 expression was increased by OGD/R and then inhibited by sh-MALAT1 in primary cardiomyocytes. *$P < 0.05$ or **$P < 0.01$ compared with indicated group. CTRL: control.

R group when compared to control group ($P < 0.05$). Transfection of cells with sh-MALAT1 significantly attenuated the viability loss ($P < 0.05$, Fig. 2C). As compared to control group, apoptotic cell rate was increased ($P < 0.01$). Meanwhile, apoptosis was attenuated by sh-MALAT1 ($P < 0.05$, Fig. 2D). To be specific, cell viability was increased, apoptosis was repressed. Expression of Bcl-2 was repressed ($P < 0.05$) while expression of Bax and cleaved-caspase-3 was promoted ($P < 0.05$). While the expression of proteins associated with apoptosis was recovered ($P < 0.05$, Fig. 2E-F).

3.3. OGD/R induced apoptotic death was prevented by MALAT1 knockdown in primary cardiomyocytes

MALAT2 expression was observed to be up-regulated as well by OGD/R in primary cardiomyocytes ($P < 0.05$, Fig. 3A). Then MALAT1 expression in primary cardiomyocytes was knocked down by transfection with sh-MALAT1 ($P < 0.05$, Fig. 3B). As a next step, viability was repressed induced by OGD/R ($P < 0.01$) and attenuated by sh-MALAT1 in primary cardiomyocytes ($P < 0.05$, Fig. 3C). While apoptotic cell rate was increased by OGD/R ($P < 0.001$) and recovered by sh-MALAT1 ($P < 0.01$, Fig. 3D). Expression of Bcl-2 was down-regulated by OGD/R ($P < 0.01$) and increased by sh-MALAT1 ($P < 0.05$). However, expression of Bax and cleaved-caspase-3 was up-regulated by OGD/R ($P < 0.01$ or $P < 0.001$) and repressed by sh-MALAT1 ($P < 0.05$, Fig. 3E-F).

3.4. MALAT1 knockdown inhibited miR-122 expression in H9c2 cells

The downstream gene of MALAT1 was explored to explain the protective function of MALAT1 against OGD/R injury. Data from Fig. 4A showed that, miR-122 expression was increased by OGD/R ($P < 0.05$), however sh-MALAT1 inhibited miR-122 expression induced by OGD/R ($P < 0.05$). Moreover, the specific binding sites of miR-122 and MALAT1 were displayed.

3.5. MALAT1 knockdown inhibited miR-122 expression in primary cardiomyocytes

The function of MALAT1 in primary cardiomyocytes was investigated. Data in Fig. 5 displayed that, miR-122 expression in primary cardiomyocytes was also increased by OGD/R ($P < 0.01$) and repressed by sh-MALAT1 ($P < 0.05$).

3.6. MALAT1 knockdown prevented OGD/R induced apoptotic death via miR-122 in H9c2 cells

Next, whether the up-regulated miR-122 by MALAT1 participated in MALAT1'function was studies. To this end, miR-122 expression was up-regulated by mimic transfection. The efficiency of transfection was shown in Fig. 6A. As a result, MALAT1 knockdown could not that significantly protected H9c2 cells against OGD/R injury when miR-122 was overexpressed. To be specific, the effects of sh-MALAT1 on viability loss ($P < 0.05$, Fig. 6B) and apoptosis ($P < 0.05$, Fig. 5C-E) made by OGD/R were attenuated by miR-122 mimic.

3.7. MALAT1 knockdown prevented OGD/R induced apoptotic death via miR-122 in primary cardiomyocytes

Similarly, the regulation of miR-122 in primary cardiomyocytes was explored. After miR-122 expression was up-regulated by mimic transfection in primary cardiomyocytes ($P < 0.05$, Fig. 7A), viability was decreased by miR-122 mimic ($P < 0.05$, Fig. 7B). And apoptosis and expression of apoptosis-associated proteins were attenuated by miR-122 mimic in primary cardiomyocytes ($P < 0.05$ or $P < 0.01$, Fig. 7C-E).

3.8. MALAT1 knockdown activated AKT/GSK-3β/β-catenin signaling via miR-122 in H9c2 cells

Finally, the roles of MALAT1 and miR-122 in the AKT/GSK-3β/β-catenin signaling were studied. Fig. 8A-B revealed that, the down-regulation of p-AKT and β-catenin as well as the up-regulation of GSK-3β made by OGD/R was attenuated by sh-MALAT1 ($P < 0.05$). However, the effects of sh-MALAT1 on these alterations were flattened when miR-122 mimic was transfected ($P < 0.05$).

3.9. MALAT1 knockdown activated AKT/GSK-3β/β-catenin signaling via miR-122 in primary cardiomyocytes

The similar results were displayed in primary cardiomyocytes. Fig. 9A-B displayed that, the down-regulated of p-AKT and β-catenin as well as up-regulation of GSK-3β made by OGD/R was OGD/R was reversed by sh-MALAT1 ($P < 0.05$ or $P < .01$). And the effects were diminished by miR-122 mimic ($P < 0.05$ or $P < 0.01$).

4. Discussion

Studies in both animal models of ischemia and ischemia/reperfusion

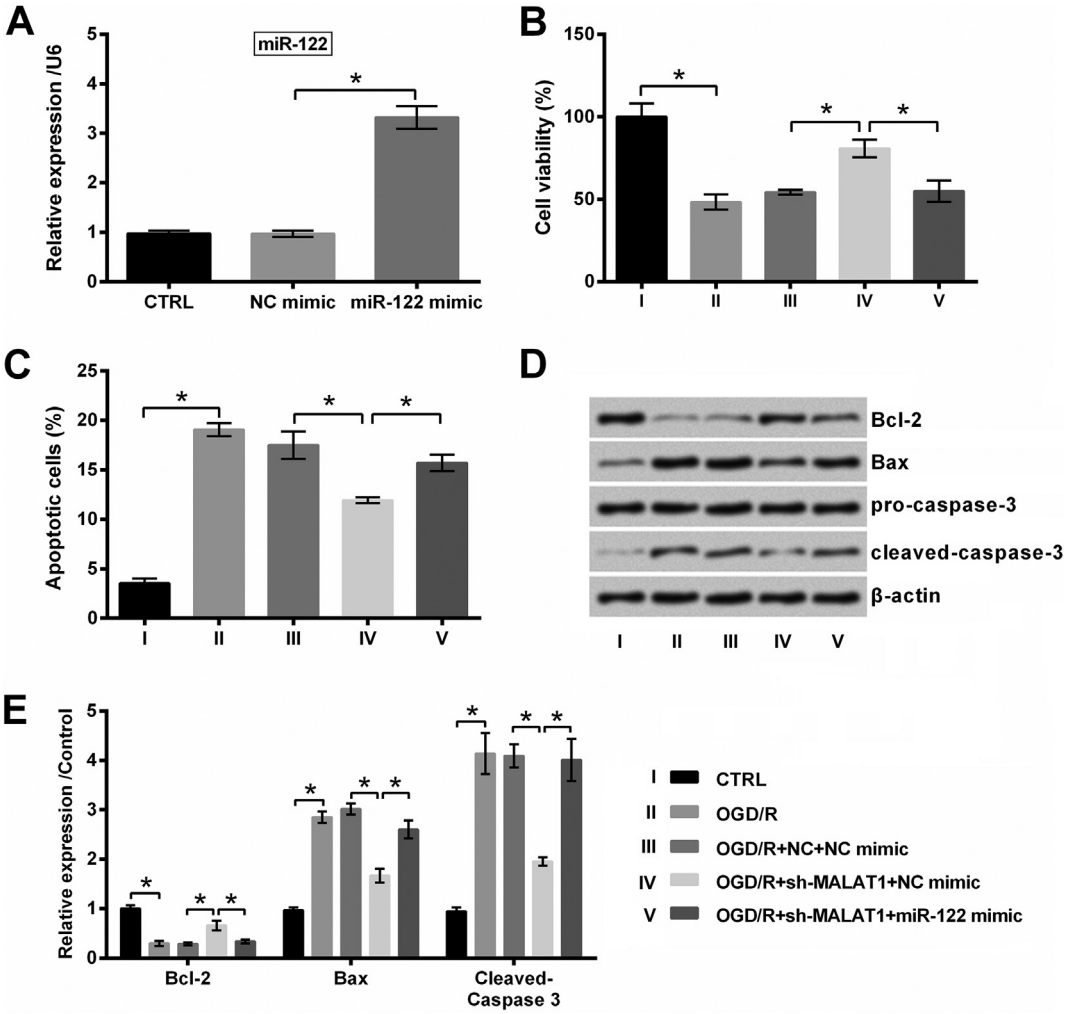

Fig. 6. MALAT1 overexpression prevented OGD/R induced apoptotic death via miR-122 in H9c2 cells. (A) miR-122 expression was tested by qRT-PCR, after H9c2 cells were transfected with miR-122 mimic or mimic NC. H9c2 cells were co-transfected with pc-MALAT1 and miR-122 mimic, and then suffered from OGD/R. (B) Cell viability, (C) apoptosis, and (D, E) expression of proteins associated with apoptosis were respectively assessed by CCK-8 assay, flow cytometry and western blot. $^{*}P < 0.05$ compared with indicated group. CTRL: control.

demonstrate apoptosis in the infarct zone and the immediate peri-infarct penumbra (Abbate et al., 2006). A sustained increase in apoptotic rate ultimately leads to clinically relevant loss in cell number and ultimately heart failure. Inhibition of apoptosis can significantly decrease infarct size (Yao et al., 2015a). The objective of the present work is to explore the functional role of MALAT1 in cardiomyocyte apoptotic death made by ischemia/reperfusion. Results revealed that MALAT1 expression was highly expressed following OGD/R. Suppression of MALAT1 by shRNA-mediated transfection attenuated OGD/R-induced cardiomyocyte apoptosis, as evidenced by the increase of cell viability and the decrease of apoptosis rate. Besides that, miR-122 was found to be positive regulated by MALAT1. The protective effects of MALAT1 knockdown were flattened by miR-122 overexpression. Furthermore, we revealed that AKT/GSK-3β/β-catenin signaling was involved in the regulation of MALAT1/miR-122.

Studies have focused on investigating the role of MALAT1 in the onset and progression of AMI. As reported by Vausort et al., MALAT1 expression was highly expressed in patients with myocardial ischemia than in healthy volunteers (Vausort et al., 2014). The elevated expression of MALAT1 was also confirmed in a cell model of AML (Yao et al., 2019). Functional experiments illustrated the MALAT1 knockdown repressed myocardial apoptosis in a mouse model of AMI (Hu et al., 2018). Besides, MALAT1 overexpression was able to abrogate cardioprotective effects of Fentanyl in a cell model of AMI made by hypoxia-reoxygenation (Zhao et al., 2017). The findings of this study were consistent with these former studies, confirming the cardioprotective effects of MALAT1 knockdown in controlling cardiomyocyte apoptosis. This study revealed the role of MALAT1 in a cell model of AMI made by OGD/R, which increased our understanding of MALAT1. However, the findings of several studies demonstrated a conflicting function of MALAT1 during cardiomyocyte injury. As reported by Yao et al., knockdown of MALAT1 enhanced cardiomyocyte injury made by hypoxia (Yao et al., 2019). Likewise, MALAT1 could protect cardiomyocytes against isoproterenol-induced apoptosis (Guo et al., 2019). The confusing function of MALAT1 may result from the different stimulations used in experimental system. More efforts are required to interpret the complexity of MALAT1.

Recently, overwhelming experimental evidences suggested that lncRNAs exert theirs function through influencing the expression of miRNAs (Rotini et al., 2018). In the aspect of AMI, MALAT1 knockdown attenuated myocardial apoptosis through acting as miR-320 sponge (Hu et al., 2018). Apart from miR-320, other miRNAs are also reported to be the downstream effectors of MALAT1 in regulating myocardial apoptosis, like miR-145 (Zhao et al., 2017), miR-200a-3p (Sun and Zhang, 2019) and miR-558. Herein, we illustrated miR-122 as such downstream gene of MALAT1 (Guo et al., 2019). miR-122 is a sensitive biomarker in AMI. Its expression is massively increased in patients with AMI and circulating level of miR-122 is considered as a diagnostic

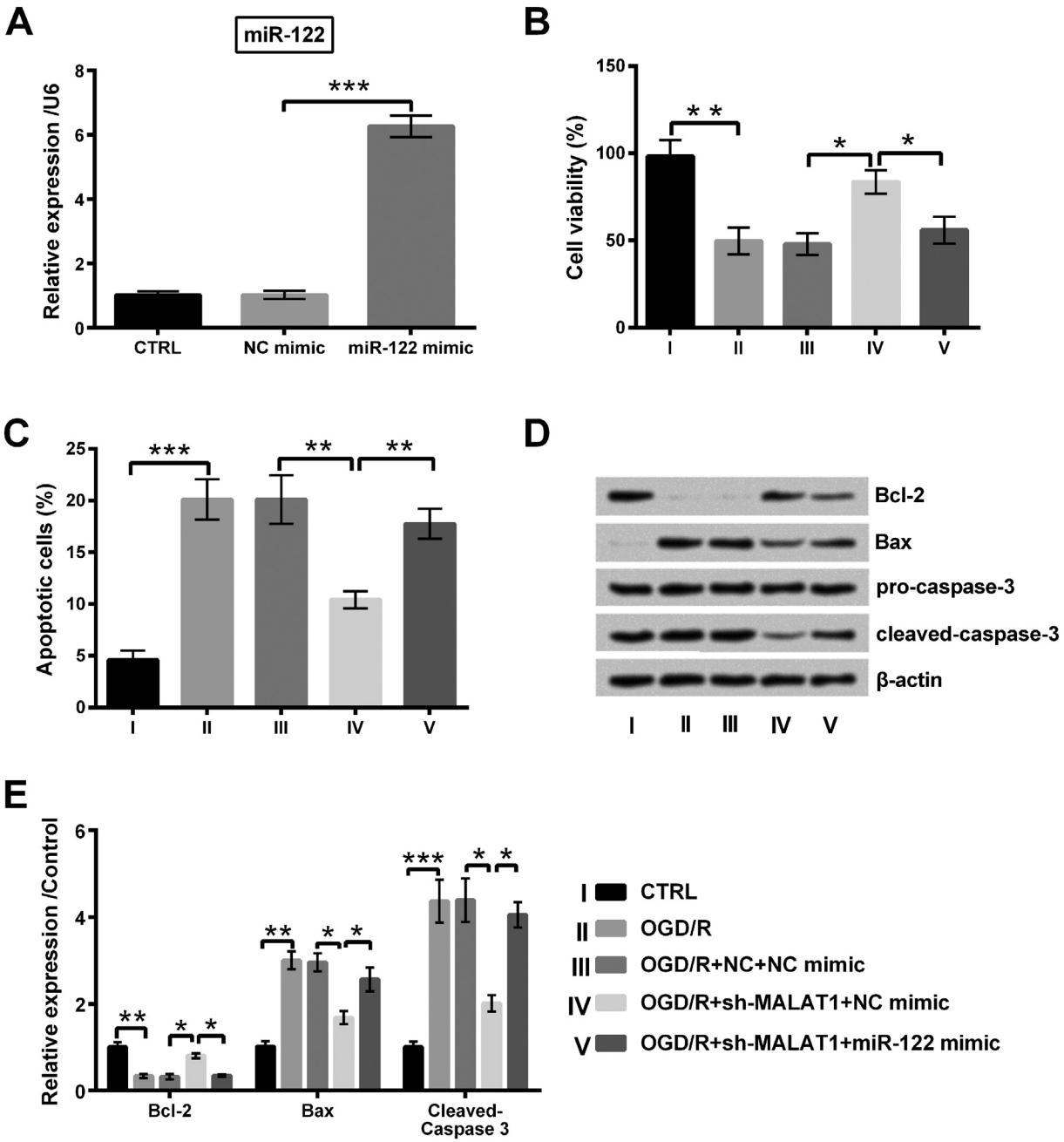

Fig. 7. MALAT1 overexpression prevented OGD/R induced apoptotic death via miR-122 in primary cardiomyocytes. (A) miR-122 expression was tested by qRT-PCR, after H9c2 cells were transfected with miR-122 mimic or mimic NC. H9c2 cells were co-transfected with pc-MALAT1 and miR-122 mimic, and then suffered from OGD/R. (B) Cell viability, (C) apoptosis, and (D, E) expression of proteins associated with apoptosis were respectively assessed by CCK-8 assay, flow cytometry and western blot. $^{*}P < 0.05$, $^{**}P < 0.01$ or $^{***}P < 0.001$ compared with indicated group. CTRL: control.

accuracy for this disease (Yao et al., 2015b). More recently, studies revealed the cardioprotective effects of miR-122 knockdown on hypoxia-induced apoptosis (Zhang et al., 2017b). Data from our study showing that MALAT1 knockdown prevented OGD/R induced cardiomyocyte apoptosis through down-regulating miR-122.

It is well-known that activation of PI3K/AKT signaling not only promotes cell survival but also prevents cell death during myocardial ischemia/reperfusion (Wang et al., 2015). Thereby, activation of PI3K/AKT has been considered as a promising strategy for treating AMI. Wnt/β-catenin is also a dominating pathway in cardiogenesis and cardiac repair (Duan et al., 2012). Interruption of Wnt/β-catenin signaling impairs epicardial expansion, epithelial–mesenchymal transition and leads to a rapid decline in cardiac function (Duan et al., 2012). There exists an interesting crosstalk between these two pathways. GSK-3β is a key member of Wnt/β-catenin pathway that can be phosphorylated by the activated form of AKT. GSK-3β activation through phosphorylation can further mediate the degradation of β-catenin. In the current study, AKT/GSK-3β/β-catenin signaling was found to be activated by MALAT1 knockdown. Besides that the effects of MALAT1 knockdown on the signaling were flattened when miR-122 was overexpressed. Based on these findings, we preliminary conclude that MALAT1 exerted its function in H9c2 cells and primary cardiomyocytes. And MALATT1 regulated AKT/GSK-3β/β-catenin signaling through a miR-122-dependent fashion.

To conclude, OGD/R induced apoptosis in H9c2 cells and primary cardiomyocytes. And our findings revealed the protective effects of

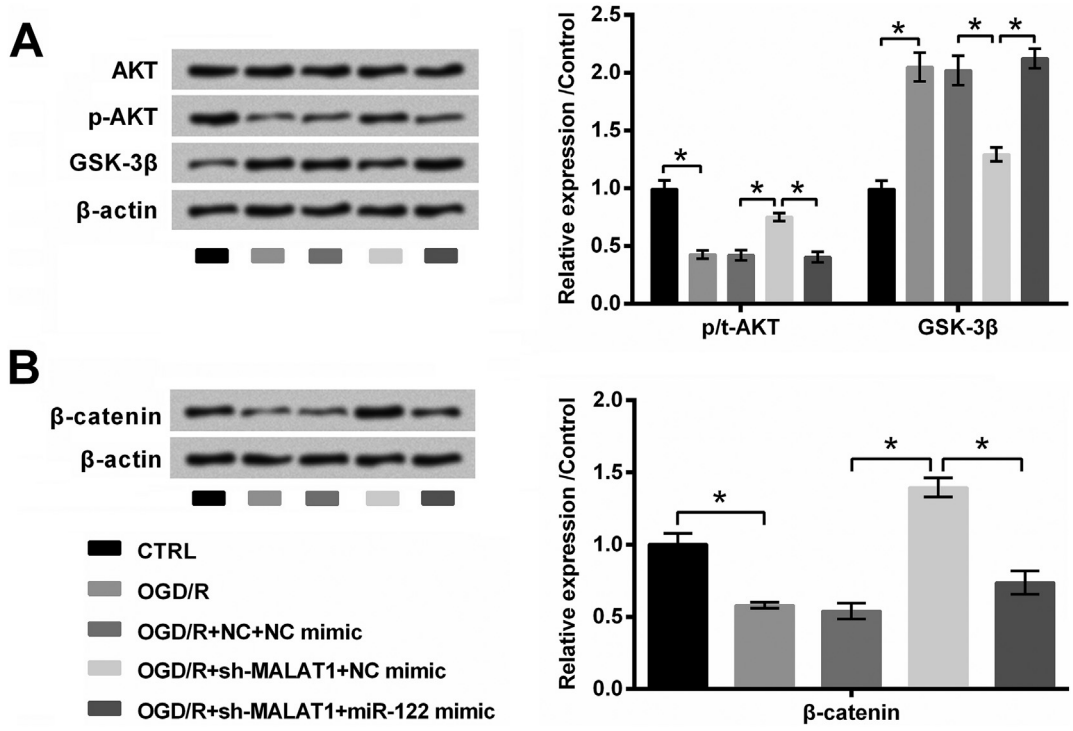

Fig. 8. MALAT1 overexpression activated AKT/GSK-3β/β-catenin signaling via miR-122 in H9c2 cells. H9c2 cells were co-transfected with pc-MALAT1 and miR-122 mimic, and then suffered from OGD/R. Expression of (A) AKT, GSK-3β and (B) β-catenin was determined by western blot. $^{*}P < 0.05$ compared with indicated group. CTRL: control.

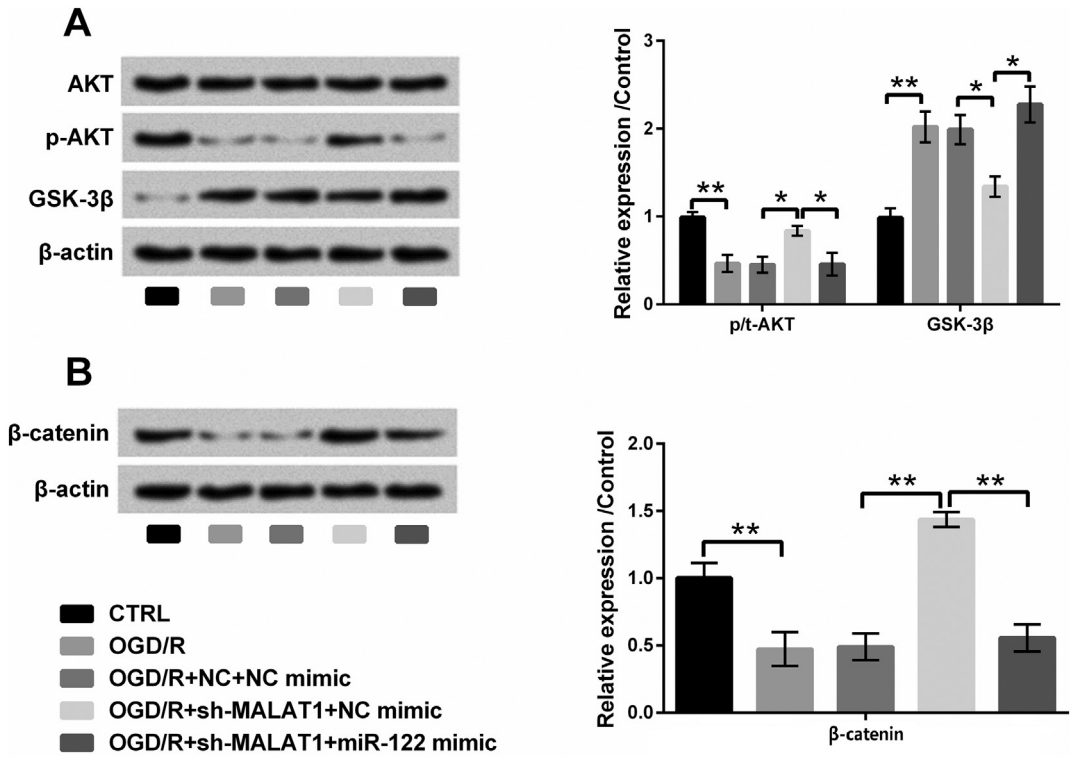

Fig. 9. MALAT1 overexpression activated AKT/GSK-3β/β-catenin signaling via miR-122 in primary cardiomyocytes. Primary cardiomyocytes were co-transfected with pc-MALAT1 and miR-122 mimic, and then suffered from OGD/R. Expression of (A) AKT, GSK-3β and (B) β-catenin was determined by western blot. $^{*}P < 0.05$ or $^{**}P < 0.01$ compared with indicated group. CTRL: control.

MALAT1 knockdown on apoptosis. MALAT1 exerted its function possibly through regulating AKT/GSK-3β/β-catenin signaling via up-regulating miR-122. To conclude, our finding revealed protective effects of MALAT1 knockdown on OGD/R induced cardiomyocyte apoptosis. MALAT1 exerted its function possibly.

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None.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

Authors declare that there is no conflict of interests.

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