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Long noncoding RNA XIST regulates cardiomyocyte apoptosis by targeting miR-873-5p/MCL1 axis

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Abstract. – OBJECTIVE: The purpose of this study was to investigate the expression of miR-873-5p and long non-coding RNA X-inactive specific transcript (lncRNA-XIST) in myocardial infarction (MI), the interaction mechanism and the effect of target gene MCL1 on apoptosis in H9c2 cells.

MATERIALS AND METHODS: quantitative Real Time-Polymerase Chain Reaction (qRT-PCR) was used to detect and compare the expressions of miR-873-5p and lncRNA XIST in 8 myocardial infarction rats and 8 normal rats tissues, respectively, and the correlation between the expressions of miR-873-5p and lncRNA XIST in the myocardial tissues was explored. Next, qRT-PCR and Western blot were used to detect the effects of upregulation of miR-873-5p and downregulation of lncRNA XIST, as well as the impacts of their interactions on the expression level of MCL1 in H9c2 cells and the apoptosis of cells.

RESULTS: It was found that the downregulation of miR-873-5p protected the heart against apoptosis after AMI, and lncRNA XIST inhibited apoptosis in H9c2 cells after hypoxia. Besides, inhibiting lncRNA XIST could upregulate miR-873-5p and downregulate MCL1, thus increasing apoptosis in the H9c2 cells after hypoxia.

CONCLUSIONS: LncRNA XIST can regulate cardiomyocyte apoptosis by targeting miR-873-5p.

Key Words:
LncRNA XIST, MiR-873-5P, MCL1, Myocardial infarction, Apoptosis.

Introduction

At present, acute myocardial infarction (AMI), a kind of emergency and severe disease, makes people's life, health, and quality of life severely affected due to its high incidence[1]. It belongs to the coronary artery myocardial necrosis caused by a persistent acute ischemia, hypoxia[2]. Generally, the symptoms will be durable and clinically severe retrosternal pain, and patients at rest or those of nitrate medications can still not fully relieve the pain symptoms. It is often accompanied by increased serum myocardial enzymes and progressive electrocardiogram changes, and usually can be complicated by shock, arrhythmia, and heart failure, seriously threatening the patient's life[3]. This disease in Europe and the United States is the most common. About 1.5 million people in the United States suffer from myocardial infarction every year[4]. The incidence of MI in China has been on the rise year by year, and the incidence has reached more than 2 million[5].

MicroRNA is a kind of new recently discovered endogenous non-protein coding short single-stranded RNA, with about 18 to 25 nucleotides. It can pass the specificity of base pairing and target of messenger RNA (mRNA) region (3' UTR), and the target gene mRNA degradation or inhibiting will affect the transcription translation process, so as to give play to the important function of regulating gene expression[6]. At present, a large number of studies have shown that microRNAs in normal tissue and myocardial infarction tissue express differences, diagnosis, and prognosis judgement of tumor biological marker[7]. Currently, the relationship between the imbalance of microRNAs and ischemic heart disease is a hot topic in recent studies. Some authors[8] have confirmed that miR-873-5p has roles in many clinical diseases, such as cancer, heart diseases, so this study aims to research the relationship between ischemic heart diseases and miR-873-5p.

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With the development of a new generation of gene detection technology, a large number of long non-coding RNAs (lncRNAs) have been found in the human genome[9]. LncRNAs are a kind of RNA molecules transcribed by RNA polymerase II alternative splicing, and the length is between 200 nt to 100 KB, lacking open reading frame. Currently, Jathar et al[10] have showed that lncRNA is involved in a variety of biological processes of physiological pathology of diseases and has a variety of biological functions, such as interfering transcription, post-transcriptional regulation, chromatin modification, cell cycle regulation, epigenetic regulation, and immune surveillance, etc. Abnormal lncRNA expression is closely related to a variety of human diseases, including tumors, cardiovascular and cerebrovascular diseases, and degenerative neuropathy, which may become specific molecular markers for disease diagnosis and treatment[11]. LncRNA X-inactive specific transcript (XIST) have an important effect in X chromosome inactivation, and it is also involved in numerous aspects of metastasis, apoptosis, autophagy, and so on. In this study, we aim to research the relationship of XIST and heart diseases[12]. It can interact with the miRNA to regulate disease development, which not only contributes to the understanding of non-coding RNA regulation network, but also to disease diagnosis and treatment[13]. At present, the specific regulatory mechanisms between miRNA and lncRNA are mainly as follows: (1) lncRNA is a precursor that can produce mature miRNA, so miRNA expression is directly affected; (2) lncRNA inhibits the regulation of miRNA on target genes by competitively binding miRNA to the binding site of target mRNA; (3) lncRNA, as competing endogenous RNA (ceRNA), exerts a "molecular sponge" to inhibit the expression of miRNA. Currently, ceRNA is one of the hotspots in heart diseases, and many lncRNAs can be regulated as ceRNA[14].

The present study investigated the expression of miR-873-5p in ischemia/hypoxia (I/H) model *in vitro* of MI using the H9c2 cell line. In addition, the effects of lncRNA XIST down-expression on cellular apoptosis was investigated. In order to explore the molecular mechanisms underlying the effects of lncRNA XIST and miR-873-5p during I/H pathogenesis, MCL2 expression was examined. The aim of the present study was to investigate whether the signaling pathway of lncRNA XIST regulates cardiomyocytes apoptosis by targeting miR-873-5p/MCL1 axis in the pathogenesis of MI. Findings of this study may provide a basis for the development of new therapeutic approaches of this disease.

Materials and Methods

Cell Culture

H9c2 cells (Cell Culture Center, Shanghai, China) were cultured in Dulbecco's Modified Eagle's Medium (DMEM, Life Technology, Wuhan, China) supplemented with 10% fetal bovine serum (FBS, Life Technology, Wuhan, China). The cells were cultured in a 37°C, 5% CO_2 incubator. The cells were observed with an inverted microscope every day, and the culture medium was changed every 2 days. Warm cell culture medium, 0.25% trypsin, and phosphate-buffered saline (PBS; Life Technology, Wuhan, China) were placed in a constant temperature water bath box at 37°C, and the old culture medium was discarded. The 25 cm^2 culture bottle was added to PBS buffer solution (1 mL) for washing twice, and then, 4 mL of fresh culture medium was added to complete the liquid exchange. After the cells become round and float up, 3 mL of fresh culture solution was added to terminate digestion, transferred to a sterile centrifuge tube, and centrifuged for 5 min at 1000 r/min. Then, the supernatant was discarded, and the original medium was replaced with 2 to 3 mL of fresh culture medium. The cells were resuspended in liquid and transferred to a new sterile culture bottle in a ratio of 1:2-1:3. After 75% alcohol disinfection culture bottle, the cells were placed in incubator for further culture.

Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

Mung bean sized heart tissues were placed in a mortar, cut up, and added with liquid nitrogen to make them brittle and hard. Thereafter, these tissues were ground into powder and 1 mL TRIzol Reagent (Thermo Fisher Scientific, Waltham, MA, USA) was added. Similarly, the method of cell extraction: culture solution was aspirated and removed from the culture plate, and then, 1 mL of pre-cooled PBS solution was added and washed twice. Next, total RNA was extracted, diluted with RNA-free water (Thermo Fisher Scientific, Waltham, MA, USA), and the concentration was measured. Complementary deoxyribose nucleic acid (cDNA) was obtained by reverse transcription and amplified by fluo-

rescence quantitative PCR. Finally, the relative expression level of the target gene in each sample was detected. The sequences of qRT-PCR used in the present study were as follows: glyceraldehyde 3-phosphate dehydrogenase (GAPDH) forward primer, 5'-GGAGCGAGATCCCTCCAAAAT-3' and reverse primer, 5'-GGCTGTTGTCATACTTCTCATGG-3'; lncRNA-XIST forward primer, 5'-ACGCTGCATGTGTCCTTAG-3' and reverse primer, 5'-GAGCCTCTTATAAGCTGTTTG-3; MCL1 forward primer, 5'-AAAGGCGGCTGCATAAGTC-3' and reverse primer, 5'-TGGCGGTATAGGTCGTCCTC-3; miR-873-5p forward primer, 5'-GCAGGAACUUGUGAGUCUCCU-3' and reverse primer, 5'-GAGACUCACA AGUUCCUGCUU-3.

Western Blot

The concentration of the extracted protein was determined by the bicinchoninic acid (BCA) method (Camilo Biological, Nanjing, China). Then, the gel of 10% was prepared and protein samples were put on after the gel was completely solidified. The pre-stained protein marker was taken as the standard sample of protein molecular weight. After the dye was concentrated into a line (about 30 minutes), the voltage was increased to 120 V until the phenol blue dye reached the bottom of the separating glue. After that, the power was disconnected, and the gel in the region of the target protein was cut under 300 mA constant current and 90 min of conversion. Subsequently, a polyvinylidene difluoride (PVDF; Thermo Fisher Scientific, Waltham, MA, USA) membrane was incubated in 5% skim milk at room temperature for 2 h, followed by incubation with specific antibodies (MCL1, Abcam, Cambridge, MA, USA, Rabbit, 1:3000, Bcl-2, Abcam, Cambridge, MA, USA, Mouse, 1:2000, Bax, Abcam, Cambridge, MA, USA, Mouse, 1:2000, AMPK, Abcam, Cambridge, MA, USA, Rabbit, 1:3000, p-AMPK, Abcam, Cambridge, MA, USA, Rabbit, 1:3000, and GAPDH, ProteinTech, Rosemont, IL, USA, 1:5000) were incubated overnight at 4°C. Next day, the membrane was washed with Tris Buffered Saline-Tween (TBST) and incubated with the corresponding secondary antibody (goat anti-rabbit IgG antibody, Yifei Xue Biotechnology, Nanjing, China, 1:3000) at 37°C for 1.5 h, followed by TBST washing. Finally, enhanced chemiluminescence (ECL) solution (Thermo Fisher Scientific, Waltham, MA, USA) was prepared with 1:1 configuration for later use, and Image J software (NIH, Bethesda, MD, USA) was used for gray analysis of the target strip.

Flow Cytometry

First, the supernatant was moved to the centrifuge tube, and the cells were washed with PBS. Then, the cells were digested by trypsin without EDTA (ethylenediaminetetraacetic acid) and washed with PBS, and 500 binding buffers were added to suspension cells. Thereafter 5 Annexin V-FITC (Kaiji, Nanjing, China) and Propidium Iodide (PI; Kaiji, Nanjing, China) were added and mixed. The reaction was conducted at room temperature in the dark for 15 minutes, and flow cytometry (Becton Dickinson, Heidelberg, Germany) was used for detection.

Luciferase Reporter Analysis

MiR-873-5p overexpression was co-transfected with reporter gene plasmids: 293T culture was performed on 24-well plates. 48 h later, lentivirus containing miR-873-5p mimics was used for infection [4×10^5 cells with 20 μL virus (10^9 TU/mL, Kaiji, Nanjing, China) and polybrene (final concentration 5 mg/ml, Kaiji, Nanjing, China)], Finally, Luciferase activity was detected on day 5.

Statistical Analysis

All data were processed by Statistical Product and Service Solutions (SPSS) 17.0 statistical analysis software (SPSS Inc., Chicago, IL, USA). The data obtained were expressed by mean ± SD (standard deviation). Comparison between multiple groups was done using One-way ANOVA test, followed by post-hoc test (Least Significant Difference). $p<0.05$ was considered statistically significant.

Results

Downregulation of MiR-873-5p Protects the Heart Against Apoptosis after AMI

qRT-PCR was used to detect the expression of miRNA-873-5p in 8 collected myocardial infarction tissues and 8 normal tissues, and the differences were statistically significant (Figure 1A). Compared with that in the control group, the expression of miR-873-5p was significantly increased in hypoxia group (Figure 1B). Besides, compared with that in hypoxia group, the expression of miR-873-5p in the miR-873-5p mimics group was remarkably increased (Fig-

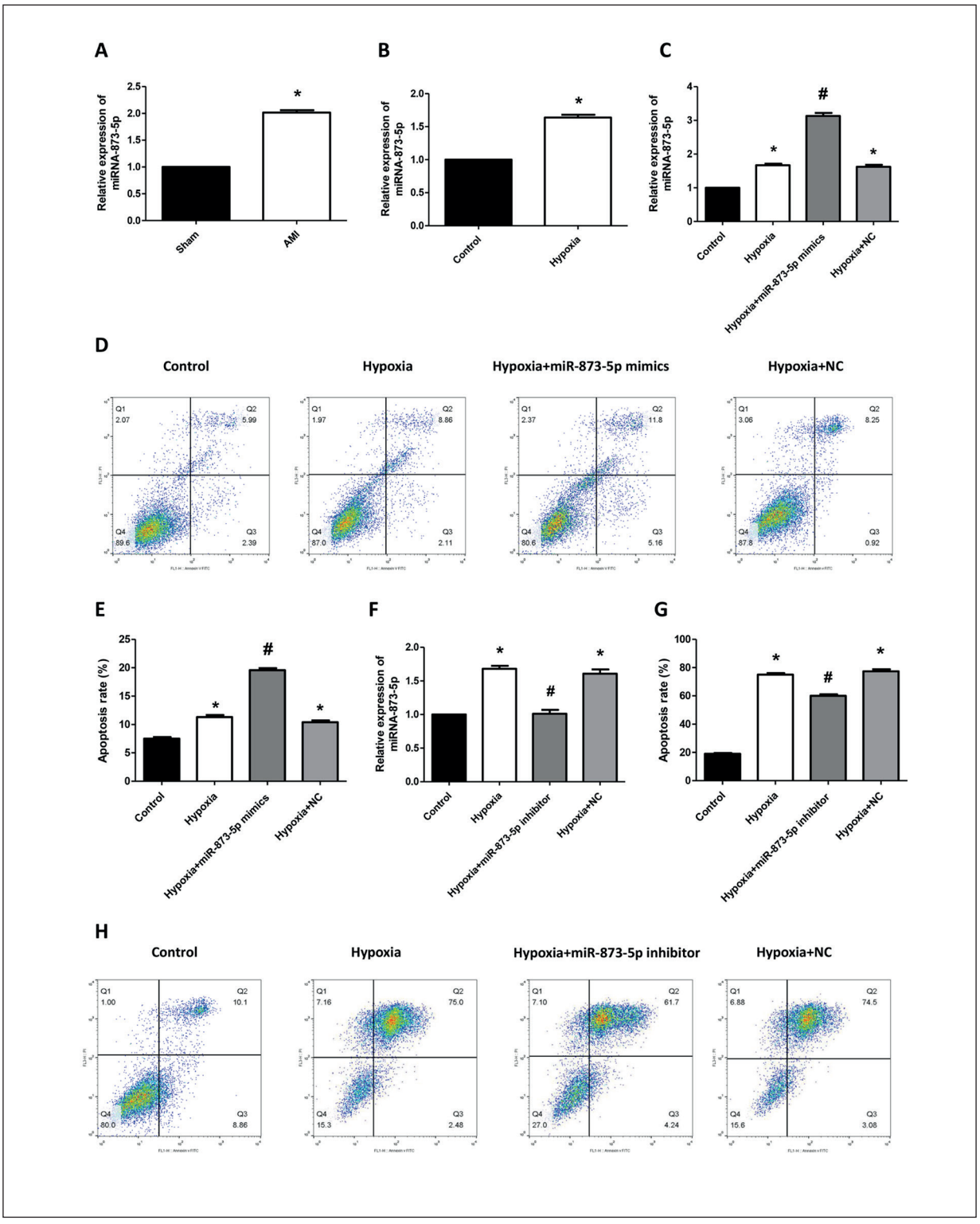

Figure 1. Downregulation of miR-873-5p protects the heart against apoptosis after AMI. **A,** RT-qPCR is used to detect miRNA-873-5p expression in tissues. **B,** The expression of miRNA-873-5p in the cells is assessed by RT-qPCR. **C,** RT-qPCR is used to detect the expression of miRNA-873-5p mimics on miRNA-873-5p. **D,** Flow cytometry examines apoptosis. **E,** Apoptosis analysis. **F,** RT-qPCR is used to detect the effect of miR-873-5p inhibitor on miRNA-873-5p expression. **G,** Apoptosis analysis. **H,** Apoptosis is examined by flow cytometry. ("*" indicates statistical difference from the control/sham group $p<0.05$ and "#" indicates statistical difference from the hypoxia group $p<0.05$).

ure 1C). The apoptosis rate of the miR-873-5p mimic group was dramatically increased by flow cytometry (Figure 1D and 1E), while the apoptosis rate of the miR-873-5p inhibitor group was dramatically decreased (Figure 1F). In addition, the apoptosis rate of miR-873-5p inhibitor group was significantly lower than that of hypoxia group, and no evident difference in the apoptosis rate was found between NC group and hypoxia group (Figure 1G and 1H).

LncRNA XIST Inhibits Apoptosis in H9c2 Cells After Hypoxia

qRT-PCR was adopted to detect the expression of lncRNA XIST in the heart tissues, and the results showed that the expression of lncRNA XIST in the AMI group was dramatically lower than that in the sham group (Figure 2A). The result was same in the H9c2 cells: the expression of lncRNA XIST decreased in the hypoxia group (Figure 2B). Then, siRNA XIST was utilized to knock down the expression of lncRNA XIST, and the results confirmed that the expression of lncRNA XIST in the siRNA group was lower than that in the hypoxic group (Figure 2C). Moreover, flow cytometry also showed that apoptosis rate was significantly increased in the siRNA group (Figure 2D and 2E).

MiR-873-5p Targets MCL1 to Increase Apoptosis After Hypoxia in H9c2 Cells

The miRNA-873-5p target genes were predicted by online miRNA target gene prediction tools, and MCL1 was predicted to be the target gene of miRNA-873-5p. After transfection of H9c2 cells with miRNA-873-5p mimics for 48 h, the cells were collected. With GAPDH as the internal reference, the relative expression of MCL1 was detected to observe the changes after transfection. The results showed that miRNA mimics could inhibit the expression of MCL1, and the difference was statistically significant (Figure 3A-3C). In addition, Luciferase activity analysis showed that, the Luciferase activity in the over-expressed miR-873-5p group transfected with pGL3-MCL1 3'-UTR-wild type was decreased, while no significant difference in the Luciferase activity was detected between the over-expressed miR-873-5p group transfected with pGL3-MCL1 3'-UTR-mutantion type and control group (Figure 3D).

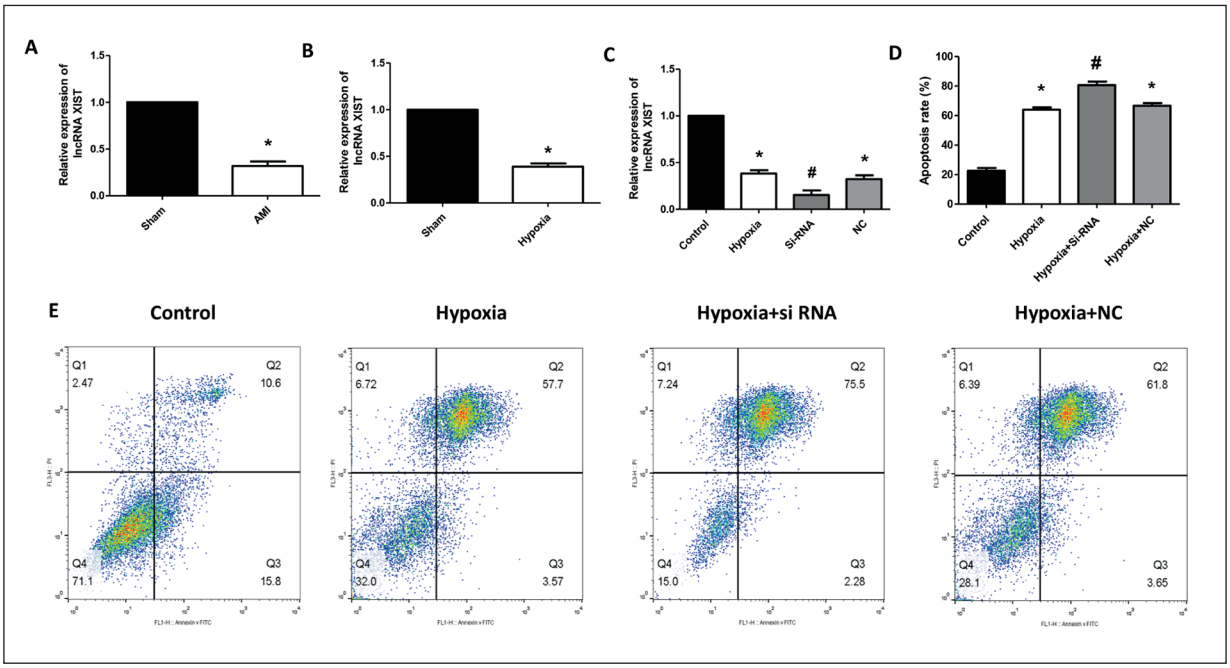

Figure 2. LncRNA XIST inhibits apoptosis in H9c2 cells after hypoxia. **A,** RT-qPCR is used to detect lncRNA XIST expression in tissues. **B,** RT-qPCR is used to detect lncRNA XIST expression in cells. **C,** RT-qPCR is used to detect the effect of siRNA-XIST on lncRNA XIST expression. **D,** Apoptosis analysis. **E,** Apoptosis is examined by flow cytometry. ("*" indicates statistical difference from the control group $p<0.05$ and "#" indicates statistical difference from the hypoxia group $p<0.05$).

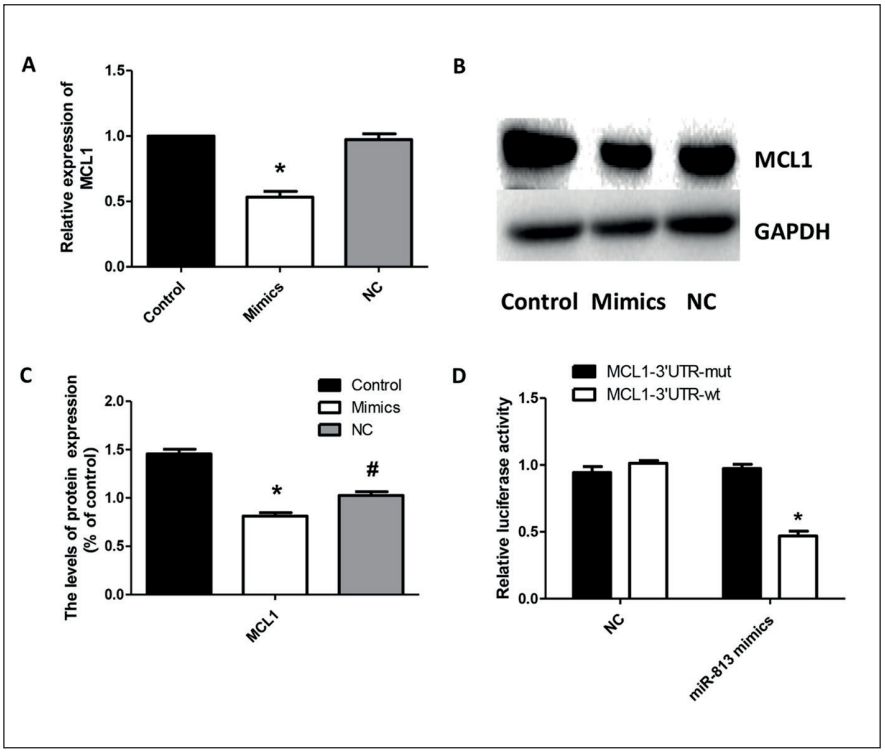

Figure 3. MiR-873-5p targets MCL1 to increase apoptosis after hypoxia in H9c2 cells. **A,** RT-qPCR detects MCL1 expression. **B,** Western blotting detects MCL1 expression. **C,** Protein expression analysis. **D,** Luciferase activity analysis. ("*" indicates statistical difference from the control group $p<0.05$ and "#" indicates statistical difference from the Mimics group $p<0.05$).

Inhibited XIST Upregulated MiR-873-5p and Downregulated MCL1 Increased Apoptosis in the H9c2 Cells After Hypoxia

After H9c2 cells were co-transfected with miR-873-5p-inhibitor and siRNA-XIST, the cells were collected 48 h later, GAPDH was used as internal reference, and MCL1 expression was detected by qRT-PCR and Western blot, respectively, to observe the changes after transfection. It was found that compared with the control group, miR-873-5p inhibitor increased MCL1 expression, with a statistically significant difference. Compared with the inhibitor group, miR-873-5p inhibitor + siRNA XIST inhibited MCL1 expression, with a statistically significant difference, indicating that siRNA-XIST can reverse the function of miR-873-5p inhibitor to increase MCL1 expression (Figure 4A-4C). Flow cytometry showed that the apoptosis rate in the miR-873-5p inhibitor + siRNA-XIST group was dramatically increased compared with the inhibitor group (Figure 4D and 4E). Thereafter, Bcl-2 and Bax proteins were detected *via* Western blot, and it was discovered that compared with that in inhibitor group, the expression of Bcl-2 was decreased in the miR-873-5p inhibitor + siRNA-XIST group (Figure 4F and 4G). All these results demonstrate that inhibiting XIST can upregulated miR-873-5p and downregulate MCL1, thus increasing apoptosis in the H9c2 cells after hypoxia.

MiR-873-5p May Through AMPK Pathway to Regulate Apoptosis

To find the pathway of miR-873-5p regulating H9c2 apoptosis, many articles were searched, and it was found that the AMPK/p-AMPK may play the role in the progress. So, miR-873-5p mimics and inhibitor were applied to research the pathway participating in the apoptosis progress. The protein expression of p-AMPK was significantly decreased in the mimics group compared with that in hypoxia group, and the expression of AMPK showed no significant difference (Figure 5A and B). H9c2 cells were treated with miR-873-5p inhibitor. Next, AMPK and p-AMPK expressions were detected by Western blot (Figure 5C and D), and the results showed that the expression of p-AMPK was increased compared with that in the hypoxia group. All above results confirm that miR-873-5p can regulate apoptosis through the AMPK pathway.

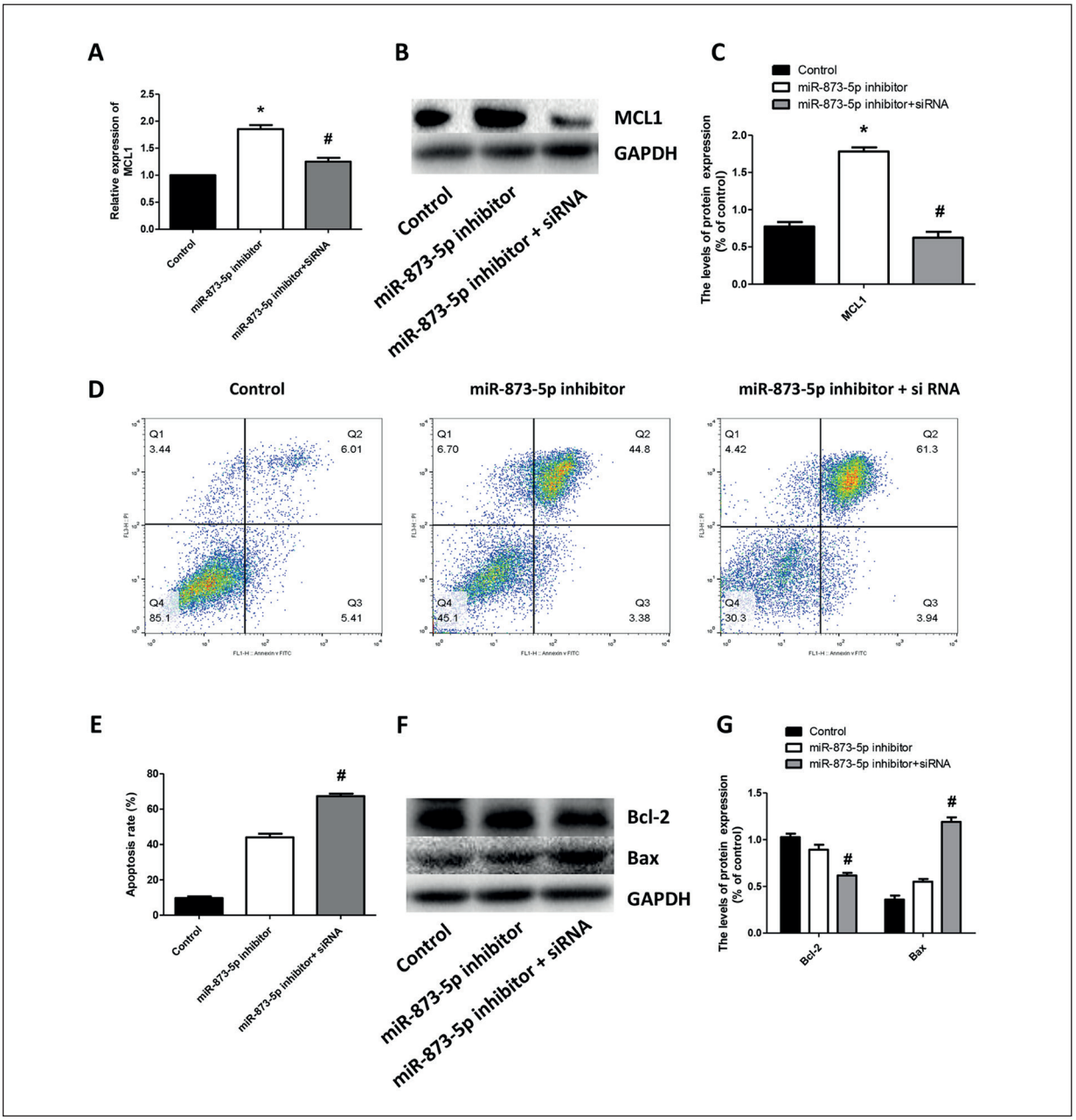

Figure 4. Inhibited XIST upregulates miR-873-5p and down-regulates MCL1, thus increasing apoptosis in the H9c2 cells after hypoxia. **A,** qRT-PCR detects MCL1 expression. **B,** Western blotting detects MCL1 expression. **C,** Protein expression analysis. **D,** Apoptosis is detected by flow cytometry. **E,** Apoptosis analysis. **F,** Western blot is used to detect Bcl-2 and Bax expressions. **G,** Protein expression analysis. ("*" indicates statistical difference from the control group $p<0.05$ and "#" indicates statistical difference from the miR-873-5p inhibitor group $p<0.05$).

Discussion

Jiang et al[15] showed that the miRNA and lncRNA mutual regulation in the development of cardiovascular diseases plays an important role. LncRNA has become a new direction as it can interact with the miRNA regulation function, further deepening the understanding of non-coding RNA regulation network. LncRNAs are competing endogenous RNAs (ceRNAs) containing miRNA response elements (MERs), which can inhibit the regulation of miRNAs on downstream genes by competitively binding miRNA sites. Therefore, it has been proved

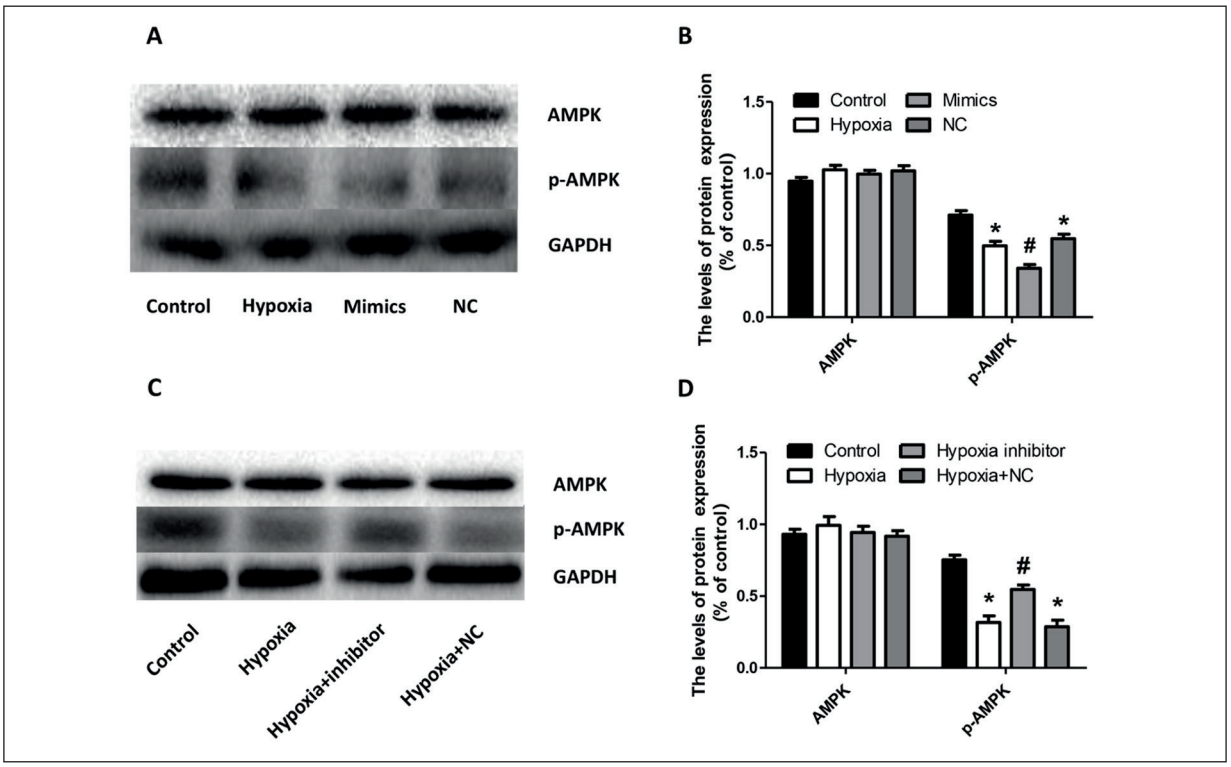

Figure 5. MiR-873-5p may regulate apoptosis through AMPK pathway. **A,** Western blot is used to detect the effect of mimics on the expression of AMPK and p-AMPK. **B,** Protein expression analysis. **C,** Western blot detection of inhibitor effects on AMPK and p-AMPK expression. **D,** Protein expression analysis. ("*" indicates statistical difference from the control group $p<0.05$ and "#" indicates statistical difference from the hypoxia group $p<0.05$).

that miR-873-5p with lncRNA XIST exist in cardiovascular regulation[16], and the relationship between them has been validated at a cellular level. In the H9c2 cells, miR-873-5p was upregulated, while lncRNA XIST expression was reduced. Besides, lncRNA XIST showed a positive effect when downregulating miR-873-5p. Similarly, when siRNA XIST expression was downregulated, the expression of miR-873-5p was increased. The above findings show that when one of the two expressions changes, the other expression will change contrary to its trend. The mechanism of mutual regulation between miR-873-5p and lncRNA XIST is also likely to be realized through competitive endogenous inhibition. It was also demonstrated that inhibiting XIST could upregulate miR-873-5p and downregulate MCL1, increased apoptosis in the H9c2 cells after hypoxia. MCL1 is distributed on the mitochondrial membrane and directly binds to Bak protein to block apoptosis[17]. In addition, it has been reported[18] that MCL1 also regulates the process of cell differentiation and cycle. To further investigate the molecular mechanisms underlying the involvement of miR-873-5p in the pathogenesis of PD, the effects of miR-873-5p on the AMPK/p-AMPK signaling pathway were examined. This is a process that is critical for the regulation of cell growth and survival. LncRNA and miRNA also have a complicated relationship, and lncRNA can be used as ceRNA miRNA[19]. Therefore, in this study, the role of miRNA-873-5p with lncRNA XIST regulation in the apoptosis of myocardial cells after MI was investigated, so as to reveal more progress mechanism and improve the mechanism of occurrence and development of MI, thus providing effective way for prevention and treatment of MI.

Conclusions

The interaction between miR-873-5p and lncRNA XIST regulates the expression of MCL1 in myocardial cells after MI, thereby affecting the apoptosis of myocardial cells, making miR-873-5p and lncRNA XIST potential targets for the treatment of myocardial infarction.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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