



Long non-coding RNA SENCR alleviates hypoxia/reoxygenation-induced cardiomyocyte apoptosis and inflammatory response by sponging miR-1

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Background: Myocardial cell apoptosis is one of the main reasons for the occurrence of acute myocardial infarction (AMI). The role of smooth muscle and endothelial cell enriched migration/differentiation-associated lncRNA (SENCR) in the cardiomyocyte apoptosis induced by hypoxia/reoxygenation (H/R) injury and its potential mechanism were investigated in this study to provide a novel biomarker for the development of AMI.

Methods: The expression levels of SENCR in the serum of AMI patients and non-AMI patients with chest pain (control) were detected by qRT-PCR. The function of SENCR in the cardiomyocyte apoptosis and inflammatory response induced by H/R injury was evaluated by MTT, cell apoptosis, and ELISA assay, respectively. The mechanism underlying the function of SENCR was investigated with the luciferase reporter assay.

Results: SENCR was significantly downregulated in AMI compared with the control volunteers, which showed negative correlations with the cardiac troponin I (cTnI) and creatine kinase-MB (CK-MB) level of patients. The H/R injury-induced cell apoptosis and inflammatory response in cardiomyocytes, which were attenuated by the overexpression of SENCR. The expression of miR-1 was suppressed by the overexpression of SENCR, while the overexpression of miR-1 could alleviate the cell apoptosis, enhance cell viability, and attenuate inflammatory response in cardiomyocyte. SENCR reversed H/R-induced myocardial cell injury by regulating the expression of miR-1.

Conclusions: SENCR was correlated with the clinicopathological features of patients and was revealed to alleviate the cardiomyocyte apoptosis and inflammatory response induced by H/R injury via sponging miR-1.

Keywords: Smooth muscle and endothelial cell enriched migration/differentiation-associated lncRNA (SENCR); hypoxia/reoxygenation injury (H/R injury); acute myocardial infarction (AMI); miR-1

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Introduction

Acute myocardial infarction (AMI) is one of the most common cardiovascular diseases (1). AMI was considered as a leading cause of morbidity and mortality around the world and was particularly prevalent in elderly patients (2).

Hypoxia/reoxygenation (H/R) injury could exert irreversible damage to microenvironment homeostasis, leading to myocardial cell apoptosis, which were major reasons for the occurrence of AMI (3). The early diagnosis and timely therapy could repair ischemic myocardium, therefore reduce

mortality and improve the clinical outcome (4). Thus, the identification of myocardial cell apoptosis-related markers could improve the treatment and management of AMI.

Long noncoding RNAs (lncRNAs) with a length of over 200 nucleotides have been demonstrated to regulate gene expression and to have various biological functions in human diseases, such as cancers, cardiovascular diseases, and neurodegenerative diseases (5-8). Nowadays, the role of relevant lncRNAs in the physical and pathological processes of cardiovascular disease, including AMI, has attracted special attention. For example, lncRNA MALAT1 was found to be upregulated in AMI, of which the knockdown could attenuate myocardial apoptosis (9). Smooth muscle and endothelial cell enriched migration/differentiation-associated lncRNA (SENCR) is a lncRNA located on chromosome 11 and enriched in vascular (10). Previously, SENCR was revealed to inhibit the proliferation and migration of human aortic-vascular smooth muscle cells, which are key regulatory links of atherosclerosis, via regulating the miR-4731-5p/FOXO3a pathway (11). AMI is one of the main clinical manifestations of atherosclerosis, therefore, it was speculated that SENCR may be involved in the occurrence and development of AMI.

lncRNAs could interact with specific microRNA to affect the translation of microRNAs, which is involved in the biological process of human diseases. Recently, circulating miR-1 has been revealed to be upregulated and to have significant diagnostic and prognostic value in AMI (12). Another study also presented that the overexpression of circulating miR-1 can predict the occurrence of larger infarct size and more myocardial necrosis (13). The role of SENCR in AMI was studied in this study and its potential molecular mechanism among SENCR and circulating miR-1 was also declared. We presented the following article in accordance with the MDAR reporting checklist (available at <http://dx.doi.org/10.21037/cdt-20-1037>).

Methods

This study had obtained approval from the Ethics Committee of Changle People's Hospital (approval No. 2017089) and followed ICMJE guidelines. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from all participants.

Patients

A total of 73 AMI patients and 77 volunteers without AMI but

with chest pain were included in this study during 2017–2019. The inclusion criteria of AMI patients were as follows based on the 2012 European Society of Cardiology (ESC)/American Heart Association (AHA)/American College of Cardiology (ACC) guidelines (14): (I) the level of cTnI >0.1 ng/mL or the level of CK-MB doubled; (II) persistent chest pain >20 min; (III) pathological Q wave; (IV) significant changes in ST-segment T wave or new left bundle branch block; (V) imaging evidence for the abnormal ventricular wall motion or loss of viable heart muscle; (VI) completed clinical data. Patients with the history of heart disease or malignant tumor and patients who received surgery were excluded. The control volunteers were non-AMI patients with chest pain who were hospitalized during the same period with a similar composition of gender and age and had no coronary artery stenosis in the same catheterization laboratory. Serum samples were collected from each participant and centrifuged to obtain the supernatant for the following analyses.

Cell culture and transfection

The cardiomyocyte H9C2 cells (Serial: GNR 5) were obtained from the Cell Bank of the Chinese Academy of Science and cultured in DMEM medium with 10% FBS at 37 °C and 5% CO₂. The H/R injury cell model was conducted in a hypoxic incubator (95% N₂ and 5% CO₂) for 2 h, and then incubated in the fresh medium for 4 h with 75% N₂, 20% O₂, and 5% CO₂.

The sequence of SENCR was cloned into pcDNA3.1 and transfected into H9C2 cells with the Lipofection 2000 reagent for 48 h. miR-1 mimic and corresponding negative control (miR-NC) were also transfected into H9C2 cells with the help of Lipofection 2000 reagent. The H/R injury cells need to be treated with H/R after cell transfection.

Quantitative real-time polymerase chain reaction (qRT-PCR)

The TRIzol (Invitrogen, USA) was used to isolate total RNA from collected samples and cultured cells. cDNA was generated with extracted RNA by using a reverse transcription kit (Fermentas, Thermo Fisher Scientific, Inc.). The expression of SENCR and miR-1 was detected by qRT-PCR with SYBR Green kit (Thermo Fisher Scientific, Inc.), and β-actin and U6 were used as the reference genes. PCR was conducted with following conditions: 95 °C for 10 min, 40 cycles of 95 °C for 10 s and 60 °C for 45 s, then 95 °C for 15 s, 60 °C for 1 min, 95 °C for 15 s and 60 °C for

15 s. The results were calculated by the $2^{-\Delta\Delta Ct}$ method.

Enzyme-linked immunosorbent assay (ELISA)

The ELISA assay was performed on 96-well plates. The protein concentrations of IL-1 β , TNF- α , and IL-6 in serum samples were detected by ELISA kit (R&D System) according to the instructions. The absorbance at 450 nm was measured by an ELISA plate reader (Biotrak GE, USA), and the concentration was obtained by comparison to the standard curve. The analyses were performed in triplicate.

Dual-luciferase reporter assay

The binding sites between SENCR and circulating miR-1 were predicted online with the help of an online tool (<http://www.rna-society.org>). The 3'UTR of SENCR containing the binding sites was cloned into pGLO vector to establish a wild-type SENCR reporter vector (WT-SENCR). While the mutant-type SENCR reporter vector (MT-SENCR) was generated by site mutation. The WT-SENCR or MT-SENCR vectors were co-transfected with miR-1 mimics or miR-NC into cultured cells for 48 h. The Dual-Luciferase Reporter Assay kit (Promega) was employed to evaluate the luciferase activity of SENCR with Renilla luciferase activity as the reference.

Cell viability assessment

Cell viability was assessed by the MTT assay. Briefly, cells were seeded into 96-well plates supplied with culture medium and incubated for 24 h at 37 °C. Then, the MTT solution was added to each well and continued incubating for 4 h. After that, 100 μ L DMSO was added, and OD 490 nm was detected with a microplate reader to evaluate the viability of cells.

Cell apoptosis detection

Cells were seeded into the 6-well plates and incubated for 24 h at 37 °C. Cells were collected and washed with cold PBS solution twice. Annexin V-FITC and propidium iodide (PI) were added according to the instructions. After incubation in the dark for 15 min, the apoptosis ratio of the cells was detected by the FACSCanto II flow cytometry (BD Biosciences).

Statistical analysis

All data are represented as mean \pm standard deviation

(SD) obtained from independent triplicate experiments. Data analyses were performed with the help of SPSS 20.0 software (SPSS, Inc., USA) and GraphPad (GraphPad Software, Inc., USA). The Student's *t*-test was employed to estimate the differences between two groups, and the one-way ANOVA followed by the Turkey *post-hoc* was to evaluate the differences among multiple groups. The correlation between SENCR and the level of cTnI and CK-MB of patients was evaluated by the Pearson's correlation analysis. The value of $P < 0.05$ was statistically significant.

Results

The baseline characteristics of patients

The clinical features of the study subjects were summarized in *Table 1*. The significant difference was found in the level of cTnI and CK-MB between the control volunteers and AMI patients ($P < 0.001$). While other characteristics, including age, gender, total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), serum creatinine (Scr), systolic blood pressure (SBP), and diastolic blood pressure (DBP), showed insignificant differences between the control group and the AMI group ($P > 0.05$).

The expression of SENCR in AMI and its correlation with patients' characteristics

Compared with the expression in the serum of the control volunteers, SENCR showed a significantly lower expression in the serum of AMI patients ($P < 0.001$, *Figure 1A*). The levels of cTnI ($r = -0.692$) and CK-MB ($r = -0.714$) of patients were negatively correlated with the expression of SENCR ($P < 0.001$, *Figure 1B,C*).

Effect of SENCR on the H/R injury-induced cell apoptosis and inflammation

After the treatment of H/R injury, the expression level of SENCR significantly decreased in H9C2 cells, compared with that in untreated cells ($P < 0.001$, *Figure 2A*). Whereas the transfection of pcDNA-SENCR alleviated the downregulation of SENCR in H/R injury cells ($P < 0.01$, *Figure 2A*). H/R injury dramatically inhibited cell viability and promoted cell apoptosis rate, which was reversed by the overexpression of SENCR ($P < 0.01$, $P < 0.001$, *Figure 2B,C*).

Table 1 Baseline characteristics of the study subjects

Parameters	Control group	AMI group	P value
Age, years	60.03±6.13	59.58±7.67	0.691
Gender (male/female)	45/32	39/34	0.536
TC (mmol/L)	4.84±0.99	5.11±1.15	0.136
HDL (mmol/L)	1.42±0.28	1.38±0.27	0.381
LDL (mmol/L)	2.15±0.28	2.04±0.48	0.116
TG (mmol/L)	1.52±0.36	1.59±0.37	0.236
Scr (mmol/L)	79.89±12.24	78.92±14.51	0.669
SBP (mmHg)	127.34±12.36	126.71±14.30	0.774
DBP (mmHg)	80.75±10.32	81.95±11.69	0.508
cTnl (pg/mL)	0.05±0.03	3.67±3.32	<0.001
CK-MB (IU/L)	14.79±7.00	136.92±44.33	<0.001

TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; Scr, serum creatinine; SBP, systolic blood pressure; DBP, diastolic blood pressure; cTnl, cardiac troponin I; CK-MB, creatinine kinase-MB.

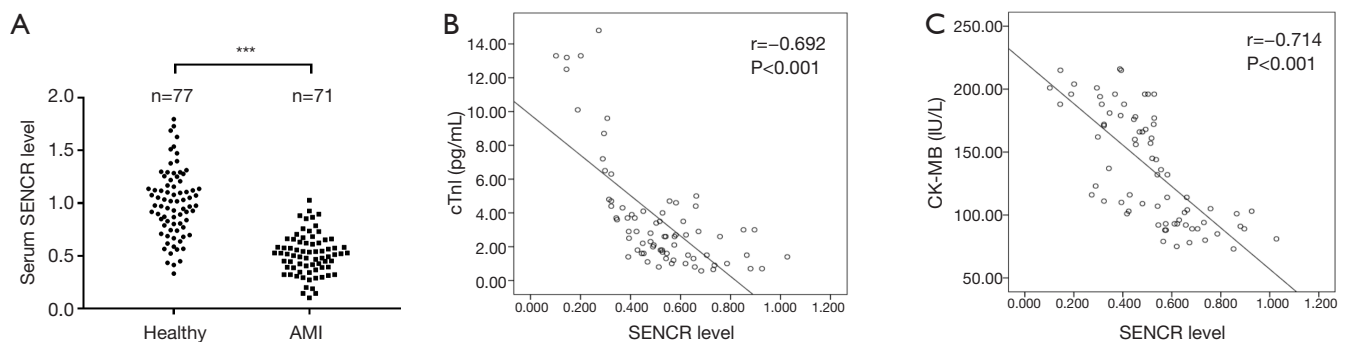


Figure 1 The expression of SENCR in the serum of AMI patients and non-AMI patients with chest pain (control) and its correlation with the clinical features of patients. (A) SENCR was downregulated in AMI patients compares with that of the controls. ***, $P<0.001$. (B) SENCR was negatively correlated with the cTnl level of AMI patients. $r=-0.692$, $P<0.001$. (C) SENCR was negatively correlated with the CK-MB level of AMI patients. $r=-0.714$, $P<0.001$. AMI, acute myocardial infarction; cTnl, cardiac troponin I.

Furthermore, the protein concentrations of pro-inflammatory cytokines (IL-1 β , TNF- α , and IL-6) were evaluated after the H/R injury and the overexpression of SENCR. The protein concentration of IL-1 β , TNF- α , and IL-6 significantly increased after the treatment of H/R injury ($P<0.001$, Figure 2D,E,F). The overexpression of SENCR by the transfection of pcDNA-SENCR reduced the increased concentration of pro-inflammatory cytokines induced by H/R injury ($P<0.01$, $P<0.001$, Figure 2D,E,F).

SENCR targets miR-1 in cardiomyocyte

It was predicted that SENCR could bind to miR-1, and the binding sites were shown in Figure 3A. The relative luciferase activity of WT-SENCR was suppressed by the overexpression of miR-1 compared with the NC group ($P<0.001$, Figure 3B). While no significant effects of miR-1 expression were found in the luciferase activity of MT-SENCR ($P>0.05$, Figure 3B). Additionally, miR-1 was found to be upregulated in H/R injury cardiomyocytes, which was inhibited

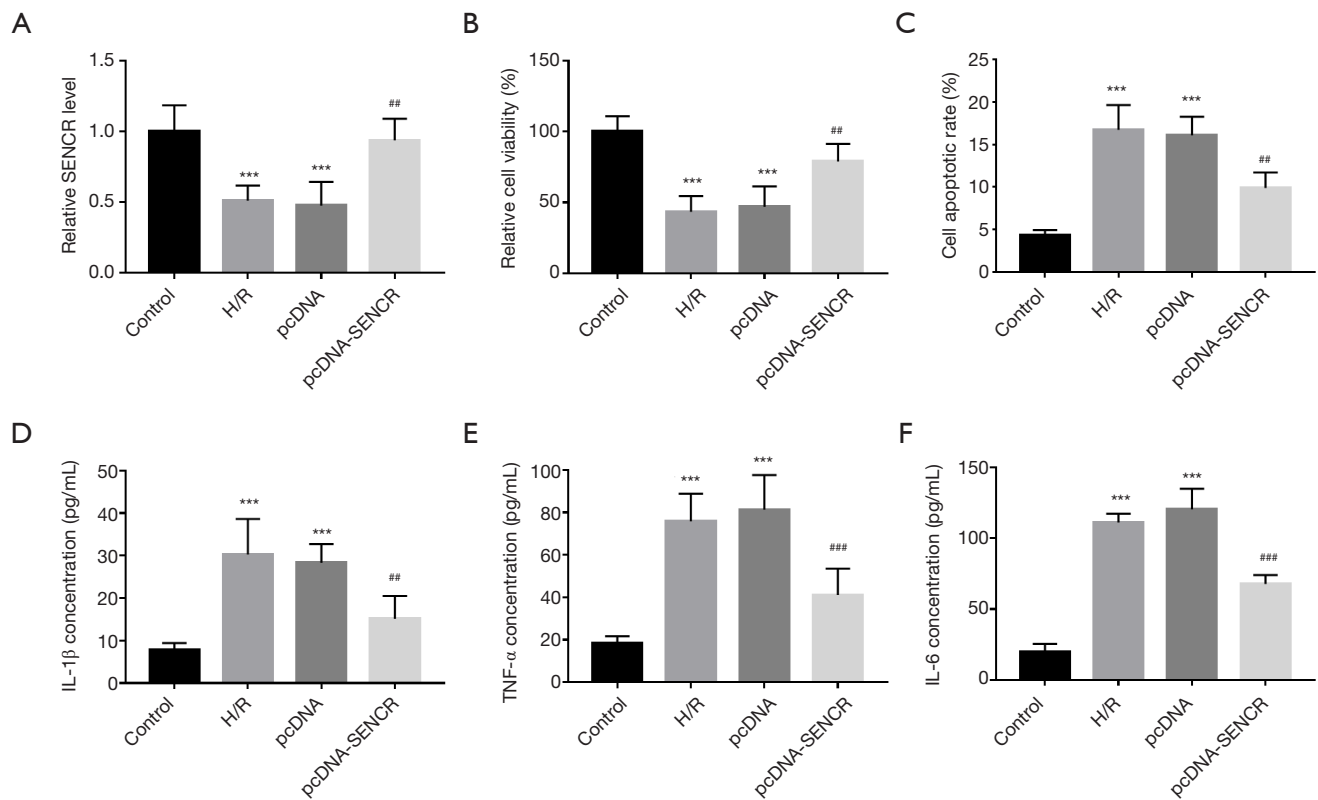


Figure 2 Effect of SENCR on cell apoptosis and inflammation induced by H/R injury. (A) SENCR was significantly downregulated in H/R injury cardiomyocyte and upregulated after the transfection of pcDNA-SENCR. (B) The treatment of H/R injury significantly inhibited cell viability, which was reversed by the overexpression of SENCR. (C) The treatment of H/R injury significantly enhanced cell apoptosis rate, which was alleviated by the overexpression of SENCR. (D,E,F) The protein concentration of pro-inflammatory cytokines dramatically increased in the H/R injury group and decreased in the SENCR overexpression group. ***, $P < 0.001$ relative to the control group; ##, $P < 0.01$; ###, $P < 0.001$ relative to the H/R injury group. H/R, hypoxia/reoxygenation.

by the overexpression of SENCR ($P < 0.001$, Figure 3C).

SENCR inhibited H/R injury-induced cell apoptosis and inflammation by sponging miR-1

The transfection of pcDNA-SENCR significantly inhibited the expression of miR-1 compared with that in cells transfected with pcDNA alone. While the co-transfection of pcDNA-SENCR and miR-1 mimic reversed the knockdown of miR-1 by the overexpression of SENCR ($P < 0.001$, Figure 4A). The upregulation of miR-1 by the co-transfection notably reduced cell viability and enhanced cell apoptosis of cardiomyocytes ($P < 0.01$, Figure 4B,C). Similarly, the protein concentrations of pro-inflammatory cytokines were suppressed by the overexpression of SENCR, which was attenuated by the upregulation of miR-1 ($P < 0.001$, Figure 4D).

Discussion

AMI is the myocardial injury by emergency occlusion of coronary arteries, which seriously threaten human life and health. Although the diagnosis and treatment of AMI have developed in the past decades, the incidence rate and mortality rate were still increasing worldwide. The early detection and intervention are necessary to reduce myocardial damage and improve the prognosis of patients. cTnI and CK-MB are two common diagnostic markers in the clinic, however, these indicators are vulnerable to heart failure, malignant tumor, renal insufficiency, infection, and other kinds of diseases, which decrease the accuracy of diagnosis (15,16). Therefore, it is of great importance to explore novel diagnostic and prognostic indicators. Previous studies have reported a number of lncRNAs that play vital

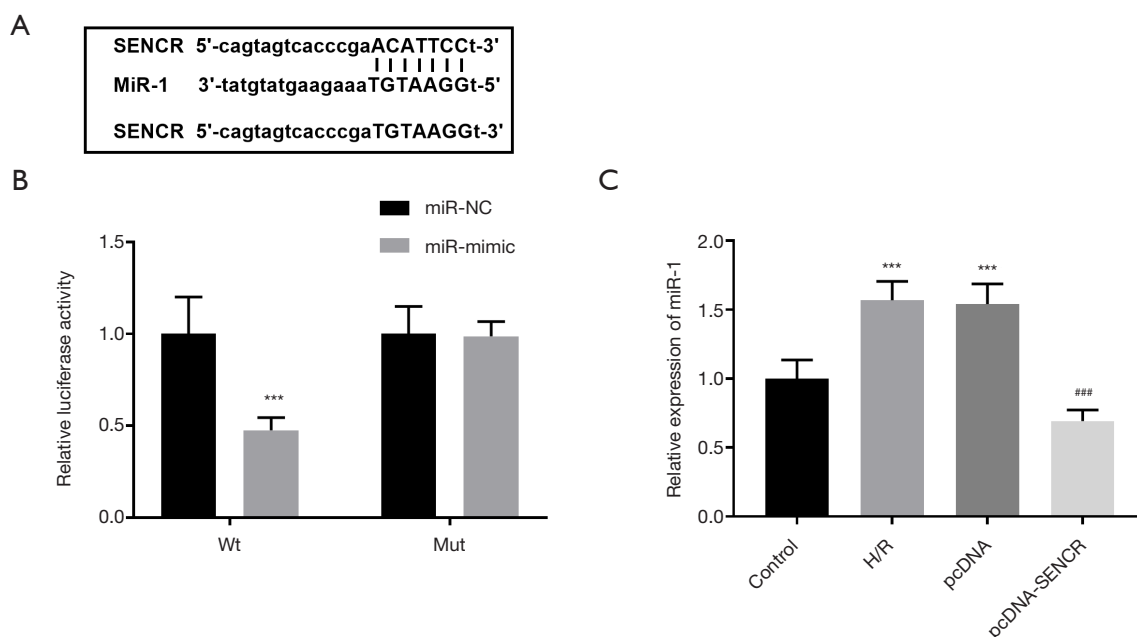


Figure 3 SENCR targets miR-1 in cardiomyocytes. (A) Binding sites between SENCR and miR-1. (B) miR-1 significantly suppressed the relative luciferase of Wt-SENCR. ***, $P < 0.001$. (C) miR-1 was significantly upregulated in the H/R injury group, which was suppressed by the overexpression of SENCR. ***, $P < 0.001$ relative to the control group. ###, $P < 0.001$ relative to H/R injury group. H/R, hypoxia/reoxygenation; Wt, wild type.

roles in the occurrence and development of various human diseases, especially heart diseases. For example, lncRNA-Safe served as a key regulator of cardiac fibrosis, which could be a novel target for anti-fibrotic therapy (17). The knockdown of lncRNA Meg3 in cardiac fibroblasts could improve diastolic performance and inhibit cardiac fibrosis (18).

SENCR is a vascular cell-enriched lncRNA, which has been demonstrated to regulate the differentiation, proliferation, and migration of smooth muscle cells and is associated with the remodeling of vascular (10,19,20). Previous studies reported the functional role of SENCR in atherosclerosis, which is the basis of AMI, indicating its potential role in AMI (10,21). The significant downregulation of was found in the serum of AMI patients, compared with the control volunteers in this study. The downregulation of SENCR was negatively correlated with the cTnI and CK-MB of patients, which are two main diagnostic markers for AMI, indicating that SENCR may be involved in the disease development of AMI (22).

Cardiomyocyte apoptosis is one of the most important events during AMI, which was always caused by myocardial ischemia and subsequent myocardial hypoxia (23). Here, the H/R injury cardiomyocyte cell model was established, and a significant increase was found in the cell apoptosis rate of

the cardiomyocyte. While the overexpression of SENCR could suppress cell apoptosis and enhanced cell viability. Meanwhile, the H/R injury increased the concentration of pro-inflammation cytokines, including IL-1 β , TNF- α , and IL-6, indicating the presence of the inflammatory response in H/R injury cardiomyocyte cells. The inflammatory response of cardiomyocytes was also reversed by the overexpression of SENCR. These results suggested that SENCR could protect cardiomyocytes from the H/R injury.

miR-1 was reported to specific expressed in the myocardium and involved in the differentiation of cardiac progenitor cells (24). Recently, the diagnostic and prognostic value of miR-1 in AMI has been disclosed, and the involvement of miR-1 in the pathological process of AMI has also been demonstrated (25,26). It was found that miR-1 could alleviate the cell apoptosis and enhanced cell viability induced by the overexpression of SENCR. The overexpression of miR-1 also suppressed the inflammatory response of cardiomyocytes with high expression of SENCR, suggesting that miR-1 participated in the function of SENCR. miR-1 was also demonstrated to bind with SENCR, which inhibited the expression of miR-1. Therefore, the potential molecular mechanism underlying the biological function of SENCR was revealed to be a result of

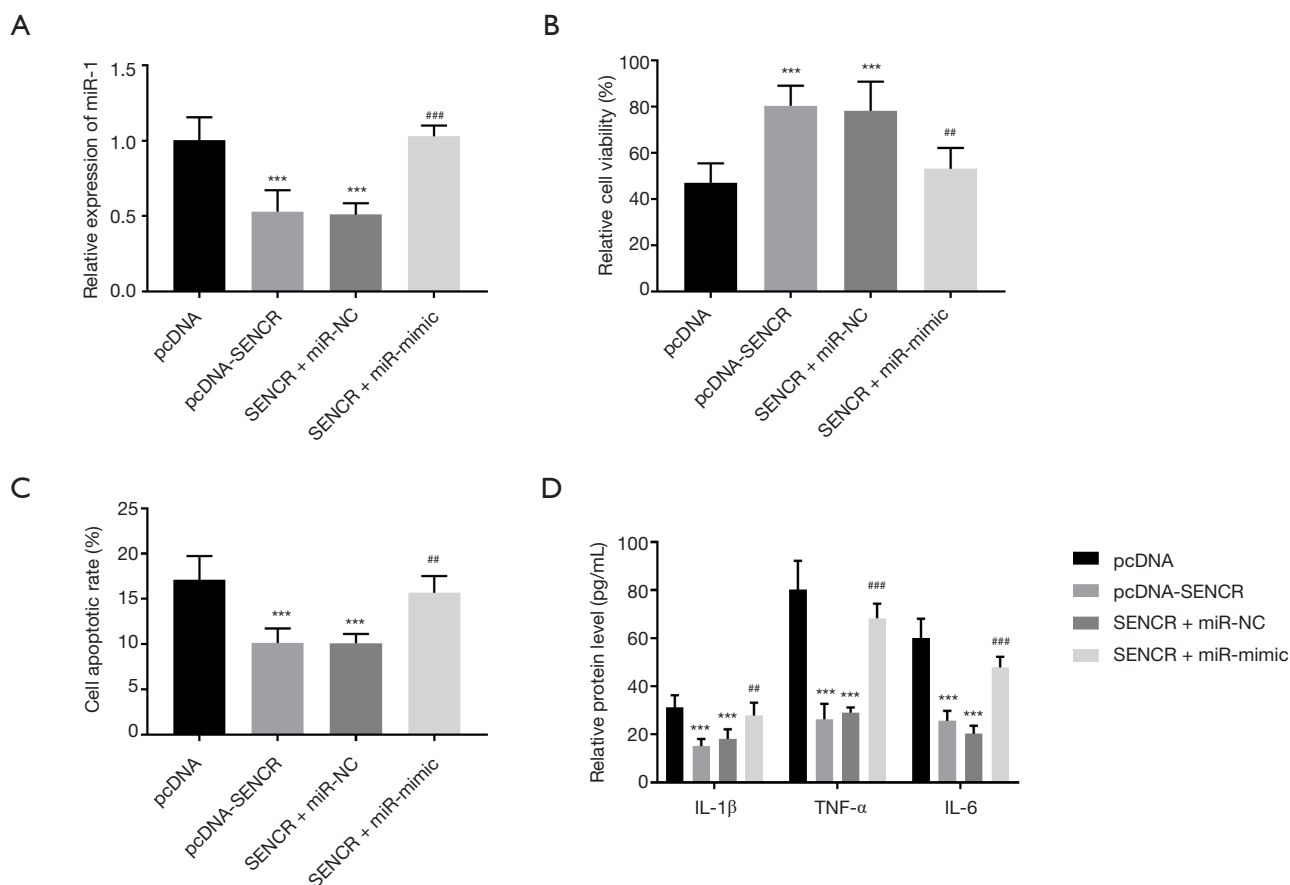


Figure 4 Effect of miR-1 on cell apoptosis and inflammation induced by SENCN overexpression. (A) The overexpression of SENCN significantly suppressed the expression of miR-1, which was reversed by the transfection of miR-1 mimic. (B) The overexpression of SENCN significantly promoted cell viability, which was reversed by the upregulation of miR-1. (C) The cell apoptosis rate increased by transfection of pcDNA-SENCN, which was attenuated by the upregulation of miR-1. (D) The protein levels of IL-1 β , TNF- α , and IL-6 significantly decreased in the presence of SENCN overexpression, which was reversed by the upregulation of miR-1. ***, $P < 0.001$ relative to the control group. **, $P < 0.01$; ***, $P < 0.001$ relative to the pcDNA-SENCN group.

sponging miR-1.

In summary, SENCN was downregulated in AMI and negatively correlated with the cTnI and CK-MB of patients. SENCN could alleviate cardiomyocyte apoptosis and inflammation induced by H/R injury by sponging miR-1.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/cdt-20-1037>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study had obtained approval from the Ethics Committee of Changde People's Hospital (approval No. 2017089). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from all participants.

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