Long Non-Coding RNA SNHG8 Plays a Key Role in Myocardial Infarction Through Affecting Hypoxia-Induced Cardiomyocyte Injury

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Background: The objective of the study was to explore the role of long non-coding RNA SNHG8 (lncRNA SNHG8) in myocardial infarction (MI) and the related mechanism of action.

Material/Methods: In vitro model of MI was established by hypoxia induction in cardiomyocyte line H9c2 cells. H9c2 cells were transfected with control-plasmid, SNHG8-plasmid, control-shRNA and SNHG8-shRNA. Quantitative real-time polymerase chain reaction (qRT-PCR) assay was performed to measure transfection efficiency. Creatine kinase-muscle/brain (CK-MB) release, cardiac troponin 1 (cTnI) release and mitochondria viability were detected by using related detection kits. MTT (3-(4,5-dimethylthiazol-2-yl)-3,5-diphenyltetrazolium bromide) assay was used to detect cell viability and flow cytometry analysis was used to detect cell apoptosis. Western blot assay was performed to measure protein expression of cleaved-Caspase3, p-p65 and p65. Enzyme-linked immunosorbent assay (ELISA) and qRT-PCR assay were performed to detect expression of interleukin (IL)-1β, tumor necrosis factor (TNF)-α and IL-6.

Results: LncRNA SNHG8 was overexpressed in hypoxia-induced cardiomyocytes. SNHG8-plasmid increased lncRNA SNHG8 expression, CK-MB release, cTnI release, and mitochondria viability in hypoxia-induced H9c2 cells. In addition, SNHG8-plasmid reduced cell viability, induced cell apoptosis, and increased expression of cleaved-caspase3, IL-1β, TNF-α, IL-6, and p-p65 in hypoxia-induced H9c2 cells, while the effects of SNHG8-shRNA were opposite.

Conclusions: We demonstrated that lncRNA SNHG8 affected myocardial infarction by affecting hypoxia-induced cardiomyocyte injury via regulation of the NF-κB pathway.

MeSH Keywords: Myocardial Infarction • NF-kappa B • RNA, Long Noncoding

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Myocardial infarction (MI) refers to ischemic necrosis of the myocardium. Clinically, there are severe and long-lasting sternum pains, accompanied by increased serum myocardial enzyme activity, and progressive electrocardiogram changes, which can be complicated by arrhythmia, shock, or heart failure and ultimately threaten life [1–3]. At present, MI pathogenesis is not fully understood, but aging, overwork, overeating, and smoking are major pathogenic factors [4]. MI is most common in Europe and the United States, with about 1.5 million people suffering from it each year in the United States. China has shown a clear upward trend in recent years, with at least 500,000 new cases each year and a current incidence of at least 2 million [5,6]. The primary objective of treatment of MI is clearance of the blocked coronary artery and restoration of function of ischemic and hypoxic myocardium [7]. Treatment is usually done by dilating the coronary arteries and removing the pathogenic blockages. In addition, reduction of cardiac load, such as oxygen absorption, absolute bedrest, and avoidance of emotional fluctuations is also conducive to recovery of patients. MI is known to be harmful, but there is no effective treatment for it so far. Therefore, new, safe, and more effective treatments for MI are desperately needed. Previous reports have used an in vitro model of MI created by inducing hypoxia in cardiomyocytes to study the related mechanism of MI, and we used hypoxia-induced a similar model to further study MI [8,9].

Long non-coding RNAs (lncRNAs) are usually defined as RNA molecules longer than 200 nucleotides and that lack biological functions [10,11]. To date, lncRNAs have been shown to play an extensive regulatory role in life activities and have been implicated in various diseases, such as cervical, gastric, and esophageal cancers; Parkinson’s disease; and myocarditis and MI [12–14]. LncRNA SNHG8, known as a novel small nucleolar guide RNA, is located on 4q26 [15]. LncRNA SNHG8 has been well studied in various types of cancers, including cervical, gastric and colorectal cancers and esophageal squamous cell carcinomas [16–20]. A recent study indicated that lncRNA SNHG8 was significantly overexpressed in patients with MIMI, and found that lncRNA SNHG8 was a risk factor for acute MI, but the specific mechanism of action still needed further study [21].

In this study, we explored whether lncRNA SNHG8 played an important role in hypoxia-induced myocardial cell injury in vitro, and further studied its molecular mechanism. Our results provide more theoretical basis and new strategies for treatment of MI.

Material and Methods

Cell culture

Rat cardiomyocyte line H9c2 cells were purchased from the American Type Culture Collection (ATCC, Manassas, Virginia, United States). The cells were cultured in DMEM medium (Gibco, United States) containing 10% fetal bovine serum (FBS, Gibco), 1% penicillin/streptomycin and incubated in 5% CO₂ at 37°C.

Establishment of in vitro MI model

We established an in vitro MI model by inducing hypoxia in cardiomyocytes. Briefly, rat cardiomyocyte line H9c2 cells were cultured under hypoxic conditions (94% N₂, 5% CO₂, and 1% O₂) for 48 h [22].

Cell transfection assay

Hypoxia-induced cardiomyocytes were seeded at a concentration of 5×10⁴ cells/mL in six-well plates and incubated overnight. According to the instructions, control-plasmid or SNHG8-plasmid (GenePharma, Shanghai, China), control-shRNA (CATAGCGGTGTAGTAAAGCATAATA) or SNHG8-shRNA (ATTACGATGGATGATGGAAACATA) (GenePharma, Shanghai, China) were transfected into hypoxia-induced cardiomyocytes using Lipofectamine 2000 reagent (Invitrogen, United States). After transfection for 48 h, we collected the cells for further experiments. Cell transfection efficiency was detected through quantitative real-time polymerase chain reaction (qRT-PCR) assay.

RNA extraction and qRT-PCR

Total RNA was isolated from cells using an RNA isolation kit (Invitrogen, United States), and then reverse transcribed into first-strand cDNA by using the cDNA Synthesis Kit (Invitrogen) following the manufacturer’s protocol. All the reactions were performed to quantify miRNA expression of relative genes using a Prism 7000 Real-Time PCR system with SYBR qPCR Master Mix (Vazyme, Nanjing) in accordance with the manufacturer’s instruction. Amplification conditions included the following steps: 5 min at 95 °C followed by 40 cycles of 95°C for 10 sec and 60°C for 30 sec. GAPDH was used as the internal control. Relative expression of lncRNA SNHG8, IL-1β, TNF-α, and IL-6 mRNA were calculated by 2⁻DDCq method [23]. All primers were provided by Sangon Biotech (Shanghai, China) and primer sequences were listed as follows:

| Primer Name | Forward Sequence | Reverse Sequence |
|-------------|-----------------|-----------------|
| lncRNA SNHG8 forward | 5’-AAGTTTACAAGCATGCGCGG-3’ | 5’-TGAGTGATACTGCCTGCCTG-3’ |
| IL-1β forward | 5’-TGTGAAATGCCACCTTTTGA-3’ | 5’-TGTGAAATGCCACCTTTTGA-3’ |
| TNF-α forward | 5’-GAACGTGCAGAACAGGCACT-3’ | 5’-GAACGTGCAGAACAGGCACT-3’ |
To study the effect of high expression of lncRNA SNHG8 on cell injury in hypoxia-induced cardiomyocytes

Protein expression levels of cleaved-Caspase3, p-p65 and p65 in cells were investigated with Western blot analysis. Briefly, we extracted the protein using a total protein extraction kit (Beyotime, Shanghai, China), and determined protein concentrations using a BCA protein kit (Pierce, United States). The total protein extracted was resolved with SDS-PAGE using a 10% polyacrylamide gel under reduced conditions, and then transferred to polyvinylidene difluoride membranes. The membranes were blocked with 5% nonfat milk PBS Tween (PBST) solution at room temperature for 1 h. Afterwards, we incubated cleaved-Caspase3 (cat. no. ab2302; 1: 1,000; Abcam), p-p65 (cat. no. 3033; 1: 1,000; Cell Signaling Technology, Inc.) and p65 (cat. no. 8242; 1: 1,000; Cell Signaling Technology, Inc.) or GAPDH (cat. no. 5174; 1: 1,000; Cell Signaling Technology, Inc.) at 4°C overnight. Afterwards, the membranes were washed three times with PBST and incubated with horseradish peroxidase-conjugated secondary antibody (cat. no. 7074; 1: 2,000; Cell Signaling Technology, Inc.) at room temperature for 1 h. Protein bands were detected by enhanced chemiluminescent reagent (ECL Advance Western Blotting Detection Kit; GE Healthcare Life Sciences) according to the protocol and protein levels were quantified with Image J software. In addition, we calculated the value of Pp65/p65.

Detection of CK-MB release, cTnl release and mitochondria viability

To explore the role of lncRNA SNHG8 in cellular damage of hypoxia-induced cardiomyocytes, CK-MB release, cTnl release, and mitochondria viability were detected by the CK-MB Detection Kit, cTnl Detection Kit (ReLIA, California, United States) and mitochondria activity assay kit (fiancheng Bioengineering Institute, China), respectively, after the cells were transfected for 48 h.

Results

Hypoxia induced lncRNA SNHG8 accumulation in H9c2 cells

For preliminary assessment of the role of lncRNA SNHG8 in MI, we detected expression of lncRNA SNHG8 in H9c2 cells. As shown in Figure 1, expression of lncRNA SNHG8 was upregulated in hypoxia-induced H9c2 cells significantly compared with the control group.

Effects of high expression of lncRNA SNHG8 on cell injury in hypoxia-induced cardiomyocytes

To study the effect of high expression of lncRNA SNHG8 on cell injury, control-plasmid or SNHG8-plasmid was transfected into hypoxia-induced cardiomyocytes. After transfection,
**Figure 1.** Expression of lncRNA SNHG8 in hypoxia-induced cardiomyocytes. mRNA expression of lncRNA SNHG8 in hypoxia-induced cardiomyocytes was detected by qRT-PCR analysis. Control: cells without any treatment; Hypoxia: H9c2 cells were cultured under hypoxic conditions (94% N₂, 5% CO₂, and 1% O₂) for 48 h. ** P<0.01 vs. Control group.

**Figure 2.** Effects of SNHG8-plasmid on cell injury in hypoxia-induced cardiomyocytes. (A) Transfection efficiency was evaluated by qRT-PCR assay. (B) Release of CK-MB was measured by using a CK-MB Detection Kit. (C) Release of cTnI was measured by using a cTnI Detection Kit. (D) A mitochondrial activity assay kit was used to detect mitochondrial viability of hypoxia-induced cardiomyocytes. Control: cells without any treatment; plasmid-control: H9c2 cells were transfected with control-plasmid for 48 h; SNHG8-plasmid: H9c2 cells were transfected with control-plasmid for 48 h; SNHG8-plasmid: H9c2 cells were transfected with SNHG8-plasmid for 48 h; Hypoxia: H9c2 cells were cultured under hypoxic conditions (94% N₂, 5% CO₂, and 1% O₂) for 48 h; Hypoxia+control-plasmid: H9c2 cells were transfected with control-plasmid for 48 h under hypoxic conditions; Hypoxia+SNHG8-plasmid: H9c2 cells were transfected with SNHG8-plasmid for 48 h under hypoxic conditions. ** P<0.01 vs. control-plasmid; ** P<0.01 vs. Control group; & & & P<0.5, 0.01 vs. Hypoxia+control-plasmid.
the cells were separated into four groups: control, hypoxia, hypoxia+control-plasmid and hypoxia+SNHG8-plasmid group. Transfection efficiency was evaluated by qRT-PCR assay. Compared with the control-plasmid group, expression of lncRNA SNHG8 was dramatically increased after cells were transfected with SNHG8-plasmid (Figure 2A). In comparison with the control group, hypoxia significantly induced release of creatine kinase isoenzyme-MB (CK-MB) and cardiac troponin I (cTnI), while SNHG8-plasmid further promoted release of CK-MB and cTnI (Figures 2B, 2C). Meanwhile, we detected viability of mitochondria in H9c2 cells. The results showed that hypoxia reduced mitochondrial viability remarkably compared to the control group, and SNHG8-plasmid further reduced mitochondrial viability (Figure 2D).

### Effects of high expression of lncRNA SNHG8 on cell viability and apoptosis of hypoxia-induced cardiomyocytes

To assess whether lncRNA SNHG8 interfered with cell viability and apoptosis of hypoxia-induced cardiomyocytes, cell viability, apoptosis, and cleaved-Caspase3 protein expression were measured following transfection. Compared with the control group, hypoxia markedly reduced the cell viability of cardiomyocytes (Figure 3A), induced cell apoptosis (Figure 3B, 3C), and promoted cleaved-Caspase3 protein expression (Figure 3D, 3E), while SNHG8-plasmid deepened these effects.

**Effect of high expression of lncRNA SNHG8 on secretion of inflammatory factors in hypoxia-induced cardiomyocytes**

To study the mechanism of lncRNA SNHG8 in cardiomyocytes, expression of related inflammatory factors was detected. As shown in Figure 4A–4C, in contrast with the control group, hypoxia markedly increased secretion of TNF-α, L-1β, and IL-6, while SNHG8-plasmid further induced secretion of TNF-α, L-1β and IL-6. Similarly, hypoxia increased mRNA expression of TNF-α, L-1β and IL-6 remarkably compared with the control group, and all these effects were further improved by SNHG8-plasmid (Figure 4D–4F).

**Effects of knockdown of lncRNA SNHG8 on cell damage in hypoxia-induced cardiomyocytes**

Rat cardiomyocyte line H9c2 cells were transfected with control-shRNA or SNHG8-shRNA in anoxic condition and the cells were

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Figure 3. Effects of SNHG8-plasmid on the cell viability and apoptosis in hypoxia-induced cardiomyocytes. (A) Cell viability in hypoxia-induced cardiomyocytes following transfection was measured by MTT assay. (B, C) Flow cytometry analysis was used to determine the apoptotic rate of hypoxia-induced cardiomyocytes. (D, E) Western blotting analysis was performed to detect relative expression of cleaved-Caspase3 protein. Control: cells without any treatment; Hypoxia: H9c2 cells were cultured under hypoxic conditions (94% N₂, 5% CO₂, and 1% O₂) for 48 h; Hypoxia+control-plasmid: H9c2 cells were transfected with control-plasmid for 48 h under hypoxic conditions; Hypoxia+SNHG8-plasmid: H9c2 cells were transfected with SNHG8-plasmid for 48 h under hypoxic conditions. **P<0.01 vs. Control group; * & P<0.5, 0.01 vs. hypoxia+control-plasmid.
Figure 4. Effects of up-regulating lncRNA SNHG8 on the secretion of inflammatory factors in hypoxia-induced cardiomyocytes. (A–C) Secretion of IL-1β, TNF-α, and IL-6 in transfected hypoxia-induced cardiomyocytes were measured by ELISA. (D–F) Relative expression levels of IL-1β, TNF-α, and IL-6 in transfected hypoxia-induced cardiomyocytes were determined by qRT-PCR analysis. Control: cells without any treatment; Hypoxia: H9c2 cells were cultured under hypoxic conditions (94% N₂, 5% CO₂, and 1% O₂) for 48 h; Hypoxia+control-plasmid: H9c2 cells were transfected with control-plasmid for 48 h under hypoxic conditions; Hypoxia+SNHG8-plasmid: H9c2 cells were transfected with SNHG8-plasmid for 48 h under hypoxic conditions.

**P<0.01** vs. Control group; **#** & **##** P<0.5, 0.01 vs. Hypoxia+control-plasmid.
separated into four groups: control, hypoxia, hypoxia+control-shRNA group, and hypoxia+SNHG8-shRNA group. Results of transfection efficiency detection showed that the expression of lncRNA SNHG8 was lower in the SNHG8-shRNA group than that in the control-shRNA group (Figure 5A). In contrast with the control group, hypoxia significantly increased release of CK-MB and cTnI, while SNHG8-shRNA significantly reduced release of CK-MB and cTnI (Figure 5B, 5C). As shown in Figure 5D, hypoxia remarkably reduced mitochondrial viability compared with the control group, while SNHG8-shRNA improved mitochondrial viability.

In addition, cell viability, apoptosis, and cleaved-Caspase expression were detected after transfection. Compared with the control group, hypoxia reduced cell activity of cardiomyocytes (Figure 6A), induced cell apoptosis (Figure 6B, C), and promoted cleaved-Caspase3 protein expression (Figures 6D, 6E), while SNHG8-shRNA reversed these effects.

Effects of knockdown of lncRNA SNHG8 on secretion of inflammatory factors in hypoxia-induced cardiomyocytes

As shown in Figure 7A–7C, hypoxia markedly promoted secretion of TNF-α, L-1β, and IL-6, while SNHG8-shRNA decreased secretion of TNF-α, L-1β, and IL-6. Similarly, hypoxia significantly increased mRNA expression of TNF-α, L-1β, and IL-6, while SNHG8-shRNA decreased mRNA expression levels of TNF-α, L-1β, and IL-6 (Figure 7D–7F).

Effects of lncRNA SNHG8 on NF-κB signal pathway in hypoxia-induced cardiomyocytes

To investigate the signal pathway underlying the role of lncRNA SNHG8 in hypoxia-induced cardiomyocytes, we detected expression of p-p65 and p65 in H9c2 cells using Western blot assay. The results showed that hypoxia increased p-p65 protein expression and p-p65/p65 ratio remarkably in comparison with
the control group, and SNHG8-plasmid further increased protein expression of p-p65 and p-p65/p65 ratio (Figure 8A, 8B). SNHG8-shRNA markedly decreased expression of p-p65 protein and p-p65/p65 ratio (Figure 8C, 8D).

Discussion

Coronary heart disease (CHD) is a cardiovascular disease with high incidence. Data indicate that the rate of CHD in China continues to increase every year, and it is being seen in younger and younger patients [24]. MI is a type of CHD that involves myocardial necrosis and often results in malignant arrhythmia, heart failure, other serious complications, or even sudden death [25,26]. In previous studies, we developed an in vitro MI model by inducing hypoxia in cardiomyocytes. Studies show that lncRNA SNHG8 is highly expressed in patients with MI. Rat cardiomyocyte line H9c2 cells were cultured under oxygen-deficit conditions for 48 h in one study. We found that expression of lncRNA SNHG8 was obviously higher in hypoxia-induced H9c2 cells which is consistent with previous research. To further study mechanism of action of lncRNA SNHG8, we up-regulated and down-regulated lncRNA SNHG8 by transfection.

Creatine kinase, also known as phosphocreatine or creatine phosphokinase, is an important enzyme found in a variety of tissues and cells. It consists of three isozyme forms: CK-BB, CK-MM, and CK-MB. CK-MB accounts for 20% of the total creatine kinase in the myocardial tissues. In addition, CK-MB is specific for myocardial tissues, and CK-MB level can be considered an important clinical indicator for diagnosis of MI [27,28]. Cardiac troponin (cTn) is mainly present in myocardial myocardial fibroblasts, including three subunits: troponin I, troponin T, and troponin C. It is an important functional protein that maintains myocardial fiber contraction and relaxation. Cardiac troponin I (cTnI) has myocardial specificity and is diagnostic for myocardium. Combined with CK-MB, it can improve specificity of diagnosis of MI. Mitochondrial dysfunction and resulting oxidative stress also are closely related to myocardial ischemia-reperfusion injury [29–31].

In this study, we found that overexpression of lncRNA SNHG8 increased CCK-MB release, cTnI release, and mitochondria viability. Upregulation of lncRNA SNHG8 also reduced cell viability, induced cell apoptosis, and increased the expression of cleaved-Caspase3, while downregulation of lncRNA SNHG8 had the opposite effect. In addition, we found that lncRNA SNHG8...
Figure 7. Effects of down-regulating lncRNA SNHG8 on the secretion of inflammatory factors in hypoxia-induced cardiomyocytes. (A–C) secretion of IL-1β, TNF-α and IL-6 in transfected hypoxia-induced cardiomyocytes were detected by ELISA. (D–F) mRNA expression levels of IL-1β, TNF-α and IL-6 in transfected hypoxia-induced cardiomyocytes were measured by qRT-PCR analysis. Control: cells without any treatment; Hypoxia: H9c2 cells were cultured under hypoxic conditions (94% N₂, 5% CO₂, and 1% O₂) for 48 h; Hypoxia+control-shRNA: H9c2 cells were transfected with control-shRNA for 48 h under hypoxic conditions; Hypoxia+SNHG8-shRNA: H9c2 cells were transfected with SNHG8-shRNA for 48 h under hypoxic conditions. ** P<0.01 vs. Control group; && P<0.01 vs. Hypoxia+control-shRNA.
upregulation further promoted L-1β, TNF-α and IL-6 expression, while hypoxia-induced L-1β, TNF-α and IL-6 expression was significantly reduced by lncRNA SNHG8 downregulation.

Several protein kinase pathways were activated in myocardial ischemia and hypoxia [32]. Some studies indicate that pro-inflammatory cytokine levels are elevated in an NF-κB activation-dependent manner during myocardial damage [33]. During treatment of ischemic myocardium, the NF-κB pathway is crucial to preventing myocardial cell death [34]. But the relationship between IncRNA SNHG8 and the NF-κB pathway remains unclear. Therefore, we analyzed whether the NF-κB pathway was involved in regulation of IncRNA SNHG8 in hypoxia-induced myocardial cell injury. Results indicated that IncRNA SNHG8 up-regulation further enhanced the NF-κB signal pathway activation in hypoxia-induced cardiomyocytes, while IncRNA SNHG8 downregulation inhibited NF-κB signal pathway activation.

In other words, SNHG8 played a significant role in myocardial cell injury caused by hypoxia, knockdown of SNHG8 played a protective role in the myocardial cell injury caused by hypoxia, and overexpression of SNHG8 promoted myocardial cell injury caused by hypoxia.

**Conclusions**

We found that IncRNA SNHG8 affected MI by promoting hypoxia-induced cardiomyocyte injury via regulation of the NF-κB signaling pathway. These findings suggest that SNHG8 may be an effective target for treatment of MI, which could translate into new opportunities for clinical therapies for MI.

**Conflict of interests**

None.
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