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Original Article

Long noncoding RNA MALAT1 modulates sepsis-induced cardiac inflammation through the miR-150-5p/NF-κB axis

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Abstract: Background: Accumulating evidence shows that long noncoding RNAs (lncRNAs) and microRNAs (miRNAs) are involved in the sepsis inflammatory response. However, the involvement of lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)/miR-150-5p axis in sepsis has not been reported. Methods: Lipopolysaccharide (LPS)-treated H9c2 cells were used to establish a sepsis cell model *in vitro*. The expressions of MALAT1 and miR-150-5p were monitored using a quantitative reverse transcription polymerase chain reaction (qRT-PCR). An ELISA assay was perfor med to detect the levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). The protein expression of NF-κB was determined by western blot. A luciferase reporter assay was introduced to verify the relationship between MALAT1/miR-150-5p. An RNA immunoprecipitation (RIP) assay and an RNA pull-down assay were carried out to detect the abundance of MALAT1. Results: MALAT1 was highly expressed, but miR-150-5p was downregulated in LPS-mediated H9c2 cells. Meanwhile, LPS significantly promoted the expressions of IL-6, TNF-α, and NF-κB. MALAT1 depletion attenuated the effect of LPS on the expressions of the inflammatory factors and the NF-κB signaling pathway, which was consistent with that of miR-150-5p overexpression. MALAT1 interacted with miR-150-5p. In addition, the rescue-of-function experiments also indicated that the loss of miR-150-5p undermined the effect of MALAT1 downregulation on H9c2 cells with LPS treatment. Conclusion: We first demonstrated that MALAT1 depletion is responsible for the sepsis inflammatory response by inhibiting the expressions of IL-6 and TNF-α and the NF-κB signaling pathway by upregulating miR-150-5p.

Keywords: lncRNA MALAT1, miR-150-5p, sepsis, inflammatory response

Introduction

Sepsis, a severe systemic inflammatory response to infection, has a high morbidity and mortality worldwide [1, 2]. More than 40% of sepsis patients have cardiac dysfunction, and the condition has a mortality rate of up to 70% [3]. Although many advances have been made to understand the mechanisms of sepsis [4, 5], the functional roles of additional sepsis biomarkers are pending further elucidation.

It is increasingly evident that long noncoding RNAs (lncRNAs) could function as master regulators for gene expression as well as cell signaling pathways in many cancers [6]. Moreover, lncRNAs have been reported to be aberrantly expressed in sepsis [7]. Wu et al. [8] showed that the lncRNA HOX transcript antisense RNA (HOTAIR) is increased in the cardiomyocytes of lipopolysaccharide (LPS)-induced sepsis mice. Also, it has also been shown that the overexpression of HOTAIR could promote tumor necrosis factor-α (TNF-α) production in the circulation by activating the NF-κB signaling pathway. Also, the silencing of HOTAIR preserves LPS-induced myocardial dysfunction in septic mice. Recently, Huang et al. [9] found that lncRNA nuclear-enriched abundant transcript 1 (NEAT1) is more highly expressed in sepsis patients than in healthy controls. Moreover, lncRNA NEAT1 has also been observed to be positively correlated with interleukin-6 (IL-6). Those data indicated the involvement of lncRNAs in regulating the sepsis inflammatory response. The metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) has been shown to be upregulated in a cecal ligation and puncture

(CLP)-induced sepsis model [10]. It has also been shown that MALAT1 aggravates cardiac inflammation and dysfunction in sepsis by interacting with the miR-125b and p38 MAPK/NF-κB pathways. In another study, MALAT1 upregulation induced cardiomyocyte death and enhanced the TNF-α level in response to the LPS stimulation [11]. Although many investigations about MALAT1 in sepsis have been reported, the roles of MALAT1 are not completely understood.

MicroRNAs (miRNAs) in blood could be biomarkers for monitoring the evolution of sepsis [12-14]. miR-150-5p has been reported to be significantly reduced in sepsis patients [15]. Moreover, Ma et al. also provided evidence that miR-150 could predict the survival of sepsis patients [16]. Their findings also proved that miR-150 suppresses LPS-induced inflammatory factors such as NF-κB1, IL-6, TNF-α, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin, and promotes apoptosis in human umbilical vein endothelial cells. Many studies have demonstrated that miR-150-5p is required for the inflammatory responses of various diseases [17, 18]. However, little known is about how miR-150-5p could be implicated in the inflammatory response of sepsis by interacting with MALAT1.

In this study, we sought to explore whether MALAT1 could regulate inflammatory factors such as IL-6, TNF-α, and the NF-κB signaling pathway in sepsis by sponging miR-150-5p.

Materials and methods

Reagent and cell transfection

H9c2 cardiomyocyte was obtained from the American Type Culture Collection (Manassas, VA, USA) and cultured in complete Dulbecco's modified Eagle's medium (Thermo Fisher Scientific, Waltham, MA, USA), supplemented with 10% fetal bovine serum (Thermo Fisher Scientific), penicillin (100 U/mL) and streptomycin (100 mg/mL). Cells were maintained at 37°C in a humidified incubator containing 5% CO_2. For the LPS treatment, cells (70% confluence in six-well plates) were treated with LPS dissolved in phosphate-buffered saline (0.5 μg/mL) for 12 h. The cells were (70% confluence at 6-well plates) introduced with small interfering RNA for MALAT1 (sh-MALAT1), negative interfering RNA (Scramble), an miR-150-5p mimic (miR-150-5p), a negative control mimic (NC), an miR-150-5p inhibitor (anti-miR-150), and a negative control inhibitor (anti-NC) using Liposome3000 (Thermo Fisher Scientific). Then the cells were cultured for an additional 48 hours before being subjected to LPS treatment and then used for following experiments.

Luciferase reporter assay

MALAT1 fragments containing the wild-type (MALAT1-wt) or mutated (MALAT1-mut) binding sites of miR-150-5p were cloned into the pmirGLO Dual-Luciferase miRNA Target Expression Vector (Promega, Madison, WI, USA). For the association between miR-150-5p and MALAT1, H9c2 cells were co-transfected with miR-150-5p mimic or NC and MALAT1-wt or MALAT1-mut using Lipofectamine 3000. Then the luciferase activity was measured using the Dual Luciferase Reporter Assay System (Promega) according to the manufacturer's instructions.

RNA immunoprecipitation (RIP) and RNA pull down assays

An RIP assay was performed using an EZ-Magna RIP kit (Millipore, Billerica, MA, USA) according to the manufacturer's instructions. Cells were lysed in a complete RIP lysis buffer, and then 100 μL of cell extracts were incubated with the RIP buffer containing magnetic beads conjugated with human anti-Ago2 antibody (Abcam, Cambridge, MA, USA), and a negative control normal mouse IgG (Abcam). Samples were treated with proteinase K, and then immunoprecipitated RNAs were isolated, and the purified RNAs were subjected to qRT-PCR analysis. For the RNA pulldown assay, probes for miR-150-5p were biotinylated (Qingke, Guangzhou, China) and then transfected into the cells. After 48 h, the cells were harvested and lysed. The samples were incubated with Dynabeads M-280 Streptavidin (Solarbio, Beijing, China). The bound RNAs were analyzed by qRT-PCR.

qRT-PCR assay

Total RNA was isolated from the cells using Trizol reagent (Invitrogen, Carlsbad, CA, USA), and reverse transcribed into complementary DNA (cDNA) using the TaqMan MicroRNA Reverse Transcription Kit (Biosystems, Foster City,

CA, USA) or the Primer Script RT reagent kit (TaKaRa, Dalian, China). qRT-PCR was performed using a SYBR Green PCR Master Mix (Biosystems) in line with the manufacturer's instructions. Relative expressions of MALAT1 and miR-150-5p were calculated using the $2^{-\Delta\Delta Ct}$ method, normalized to GAPDH or U6 small nuclear RNA, respectively. The primers used were: MALAT1-F: 5'-ATGCGAGTTGTTCTCCGTCT-3'; MALAT1-R: 5'-TATCTGCGGTTT-CCTCAAGC-3'; GAPDH-F: 5'-AGAAGGCTGGGGCTCATTTG-3'; GAPDH-R: 5'-AGGGGCCATCCACAGTCTTC-3'; U6-F: 5'-CTCGCTTCGGCAGCACA-3'; U6-R: 5'-AACGCTTCACGAATTTGCGT-3'; miR-150-5p-F, 5'-ACACTCCAGCTGGGTCTCCCAACCCTTGTACCA-3'; miR-150-5p-R, 5'-CTCAACTGGTGTCGTGGA-3'.

ELISA assay

The protein expressions of IL-6 and TNF-α were examined using ELISA kits (Solarbio, Beijing, China) according to the manufacturer's protocols.

Western blot assay

The proteins were separated using sodium dodecyl sulfate polyacrylamide gel electrophoresis and transferred onto polyvinylidene fluoride membranes (Millipore, Billerica, MA, USA). The membranes were blocked with 5% non-fat milk dissolved in Tris-buffered saline with 0.1% Tween 20 buffer and then incubated at 4°C overnight with primary antibodies against NF-κB and GAPDH (Abcam, Cambridge, MA, USA). Then, the membranes were incubated with a horseradish peroxidase-conjugated secondary antibody (Abcam) for 1 h. After that, the protein signals were visualized using enhanced chemiluminescence (Beyotime). Densitometry values were normalized to levels of GAPDH and analyzed by ImageJ software (Media Cybernetics, Rockville, MD, USA).

Statistical analysis

The data are presented as the mean ± standard deviation (SD). The statistical analyses in this study were carried out using SPSS 18.0 software (SPSS, Inc., Chicago, IL, USA). The differences were measured using Student's *t* test or a one-way ANOVA. *P* values less than 0.05 were considered be statistically significant.

Results

The effect of LPS on the expressions of MALAT1, miR-150-5p, the inflammatory factors, and NF-κB in H9c2 cells

First, we examined the expressions of MALAT1 and miR-150-5p in the H9c2 cells' response to LPS. As displayed in **Figure 1A** and **1B**, the level of MALAT1 was upregulated, but miR-150-5p was decreased in LPS-mediated H9c2 cells. Then, the inflammatory factors IL-6 and TNF-α were also measured. We found that LPS significantly promoted the expressions of IL-6 and TNF-α (**Figure 1C** and **1D**). Additionally, the effect of LPS on the NF-κB signaling pathway was evaluated. Compared with the control group, the relative expression of p-NF-κB/NF-κB was notably increased in the LPS group (**Figure 1E**). The data suggest that MALAT1 and miR-150-5p may play important roles in the LPS-mediated cardiac inflammation.

The loss of MALAT1 is involved in the LPS-mediated inflammation and NF-κB signaling pathway

To further explore the role of MALAT1 in LPS-mediated inflammation and the NF-κB signaling pathway, we downregulated the expression of MALAT1 using sh-MALAT1. The transfection efficiency results showed that the introduction of sh-MALAT1 distinctly inhibited the LPS-mediated promotion of MALAT1 (**Figure 2A**). Subsequently, we also showed that MALAT1 depletion attenuated the effect of LPS on the levels of IL-6 and TNF-α (**Figure 2B** and **2C**), suggesting that the inflammatory reaction in sepsis was relieved by the silencing of MALAT1. In addition, the LPS-mediated promotion of the NF-κB signaling pathway was also abated by MALAT1 downregulation (**Figure 2D**).

Overexpression of miR-150-5p abates the effect of LPS on inflammation and the NF-κB signaling pathway

The gain-of-function experiment was also performed to evaluate the function of miR-150-5p. The introduction of the miR-150-5p mimic upregulated the expression of miR-150-5p in LPS-treated cells (**Figure 3A**). As expected, the ectopic expression of miR-150-5p rescued the LPS-mediated enhancement of IL-6 and TNF-α (**Figure 3B** and **3C**). More interestingly, we then

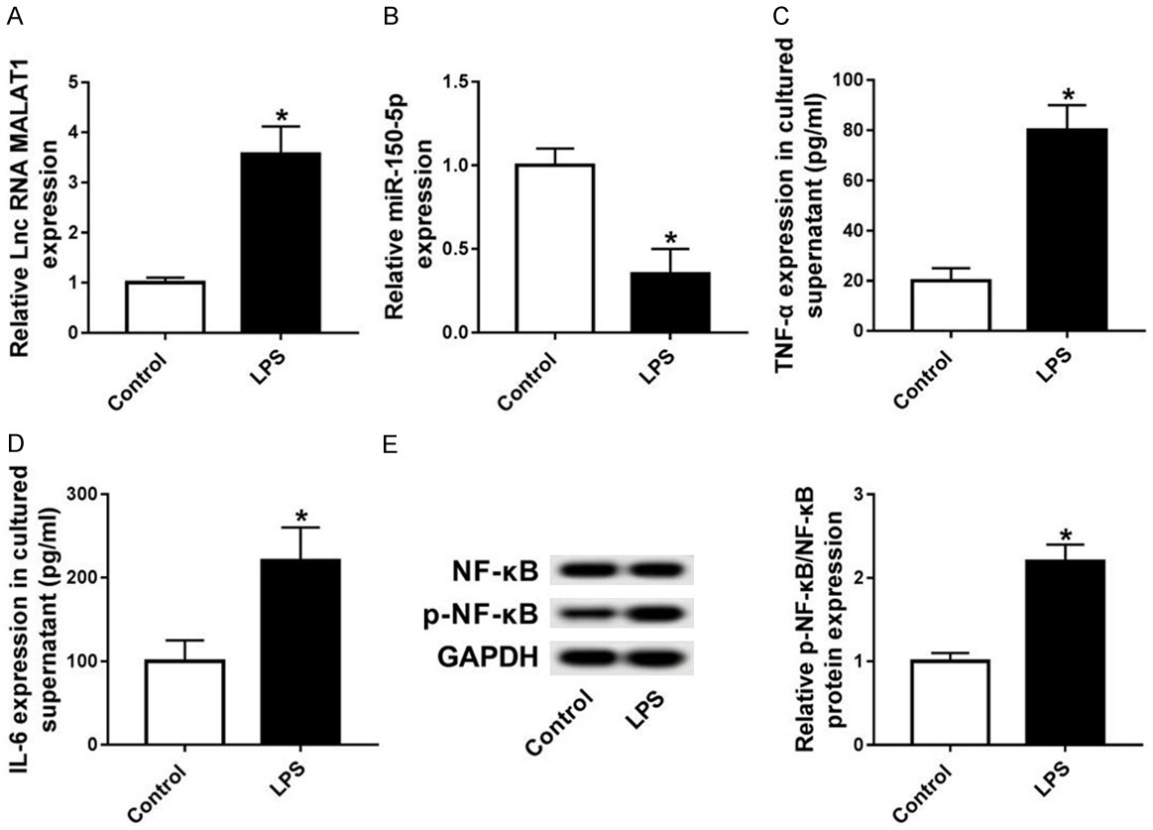

Figure 1. The effect of LPS on H9c2 cells. A and B. A qRT-PCR assay was performed to measure the levels of MALAT1 and miR-150-5p in LPS-treated H9c2 cells. C and D. An ELISA assay was used the detect the expressions of IL-6 and TNF-α. E. Western blot was carried out to examine the protein expression of NF-κB. *$P < 0.05$.

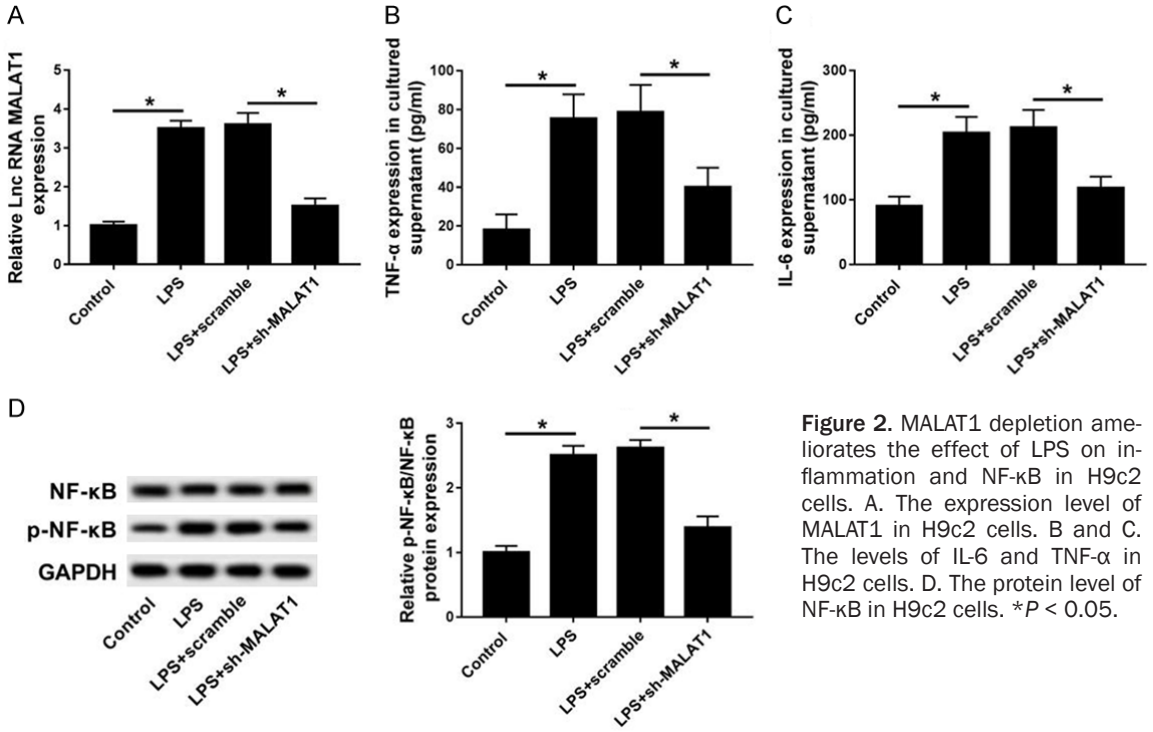

Figure 2. MALAT1 depletion ameliorates the effect of LPS on inflammation and NF-κB in H9c2 cells. A. The expression level of MALAT1 in H9c2 cells. B and C. The levels of IL-6 and TNF-α in H9c2 cells. D. The protein level of NF-κB in H9c2 cells. *$P < 0.05$.

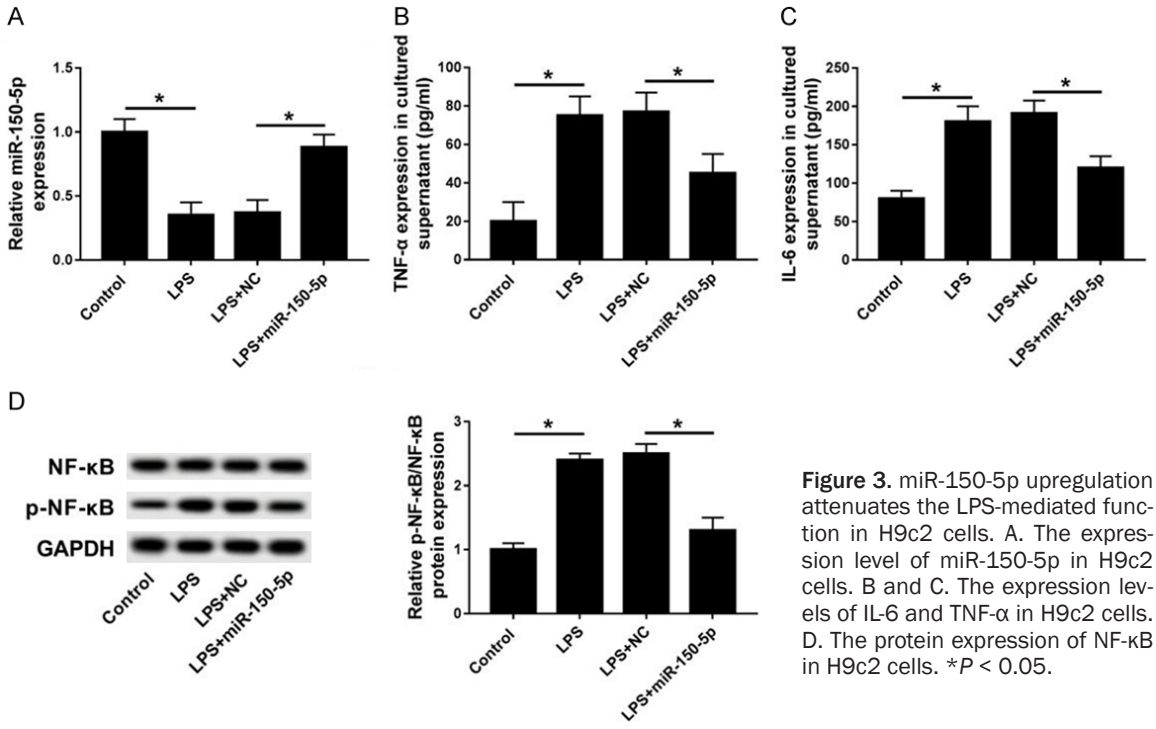

Figure 3. miR-150-5p upregulation attenuates the LPS-mediated function in H9c2 cells. A. The expression level of miR-150-5p in H9c2 cells. B and C. The expression levels of IL-6 and TNF-α in H9c2 cells. D. The protein expression of NF-κB in H9c2 cells. *$P < 0.05$.

demonstrated that upregulation of miR-150-5p weakened the effect of LPS on the expression of NF-κB. Our results indicated that the effect of miR-150-5p overexpression on the LPS-induced inflammation and the NF-κB signaling pathway was similar to the pathway involved in the silencing of MALAT1. Therefore, we thought that miR-150-5p may be associated with the function of MALAT1 in LPS-treated H9c2 cells.

miR-150-5p is interacted with MALAT1

It is well known that lncRNAs could be competing with endogenous RNAs for miRNAs. As shown in **Figure 4A**, we found that miR-150-5p contained binding sites with MALAT1. Moreover, the luciferase reporter assay data indicated that the luciferase activity was suppressed in cells transfected with the miR-150-5p mimic in the MALAT1-wt group, but it showed no obvious change in the MALAT1-mut group (**Figure 4B**). The RIP assay further indicated that the enrichment of MALAT1 was strongly increased in the miR-150-5p group relative to that of the NC group using antibodies against Ago2 (**Figure 4C**). Meanwhile, the abundance of MALAT1 was higher in the Bio-miR-150-5p group than it was in the Bio-NC group (**Figure 4D**), further demonstrating that MALAT1 was interacting with miR-150-5p. In addition, we also showed that the enhanced expression of MALAT1 inhibited the expression of miR-150-5p, but the shRNA-mediated knockdown of MALAT1 enhanced the expression of miR-150-5p (**Figure 4E**).

MALAT1 is implicated in inflammatory factor modulation and the NF-κB signaling pathway by interacting with miR-150-5p

Finally, the rescue-of-function experiment was carried out to analyze whether MALAT1 regulates LPS-induced cardiac inflammation by sponging miR-150-5p. As shown in **Figure 5A**, the introduction of anti-miR-150-5p abated the MALAT1 downregulation-mediated increase of miR-150-5p expression. Moreover, miR-150-5p suppression rescued the MALAT1 inhibition-mediated decrease of IL-6 and TNF-α expressions (**Figure 5B** and **5C**). More importantly, our results further indicated that the loss of MALAT1 blocked the NF-κB signaling pathway, which was undermined by miR-150-5p ablation (**Figure 5D**). All those data implied that MALAT1 could induce the inflammatory response and activate the NF-κB signaling pathway by interacting with miR-150-5p.

Discussion

MALAT1 has been reported to be involved in the regulation of the physiological and pathological processes in various diseases [19, 20].

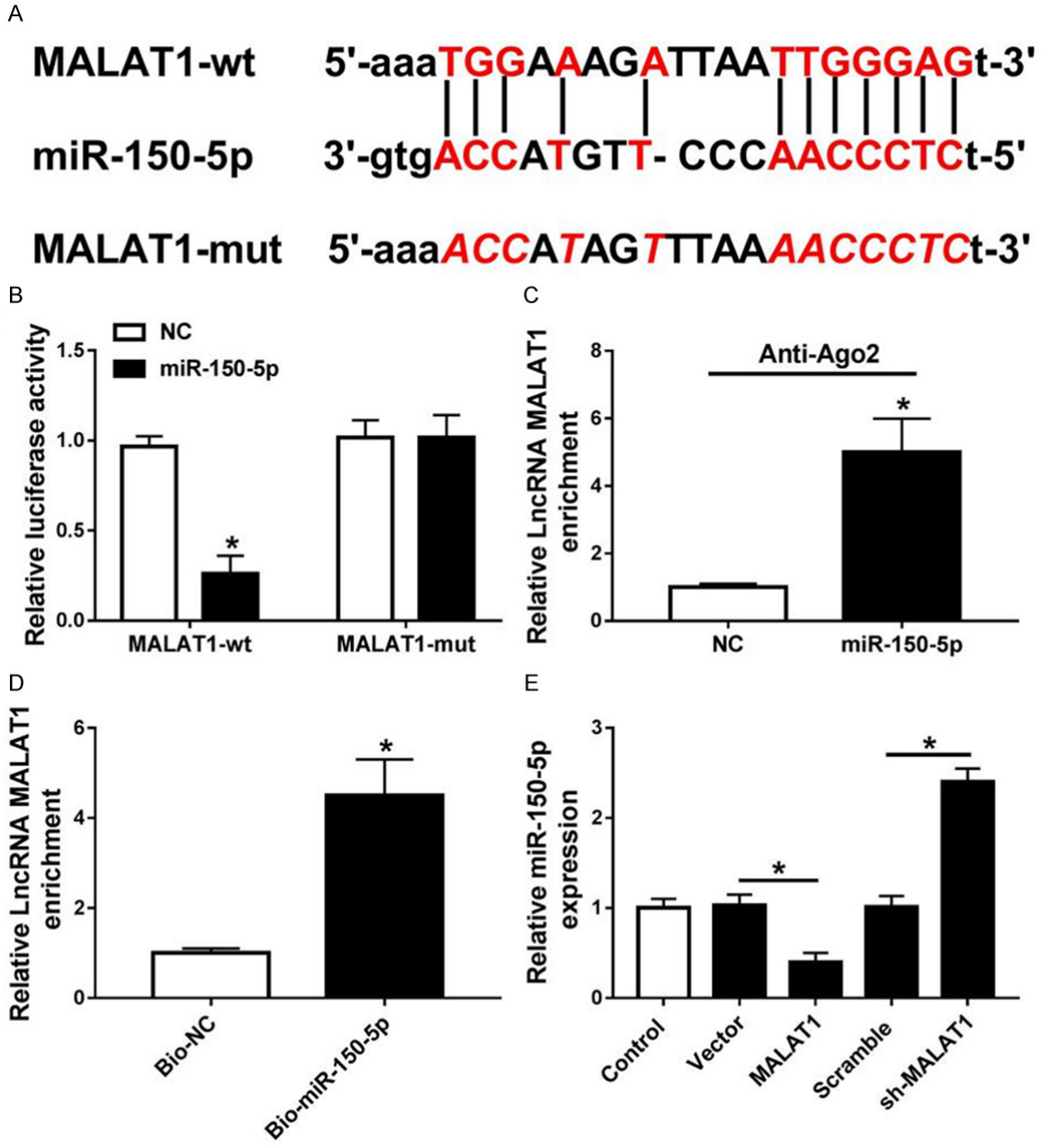

Figure 4. miR-150-5p is regulated by MALAT1. A. The binding sites between MALAT1 and miR-150-5p were predicted by starBase 2.0, and the luciferase reporter plasmids containing the wild-type (wt) or mutated (mut) MALAT1 binding sites of miR-150-5p were established. B. The luciferase activity was examined in H9c2 cells co-transfected with MALAT1-wt or MALAT1-mut luciferase reporter plasmids and miR-150-5p mimic or the negative control mimic. C. An RIP assay was performed to analyze the abundance of MALAT1. D. The MALAT1 enrichment was determined in H9c2 cells transfected with Bio-NC or Bio- miR-150-5p. E. The expression of miR-150-5p in cells introduced with the MALAT1 overexpression plasmid, the pcDNA3.0 vector, sh-MALAT1, or Scramble. *$P < 0.05$.

For example, MALAT1 could be an oncogenic lncRNA that enhances the cell proliferation and metastasis of osteosarcoma through the PI3K/AKT signaling pathway [21]. Moreover, MALAT1 also promotes the proliferation and metastasis of gallbladder carcinoma and activates the ERK/MAPK pathway [22]. In acute myocardial infarction, the silencing of MALAT1 could abate myocardial apoptosis by inhibiting phosphatase and the tensin homolog deleted on chromosome 10 expression by sponging miR-320 [23]. It is understood that sepsis-induced or-

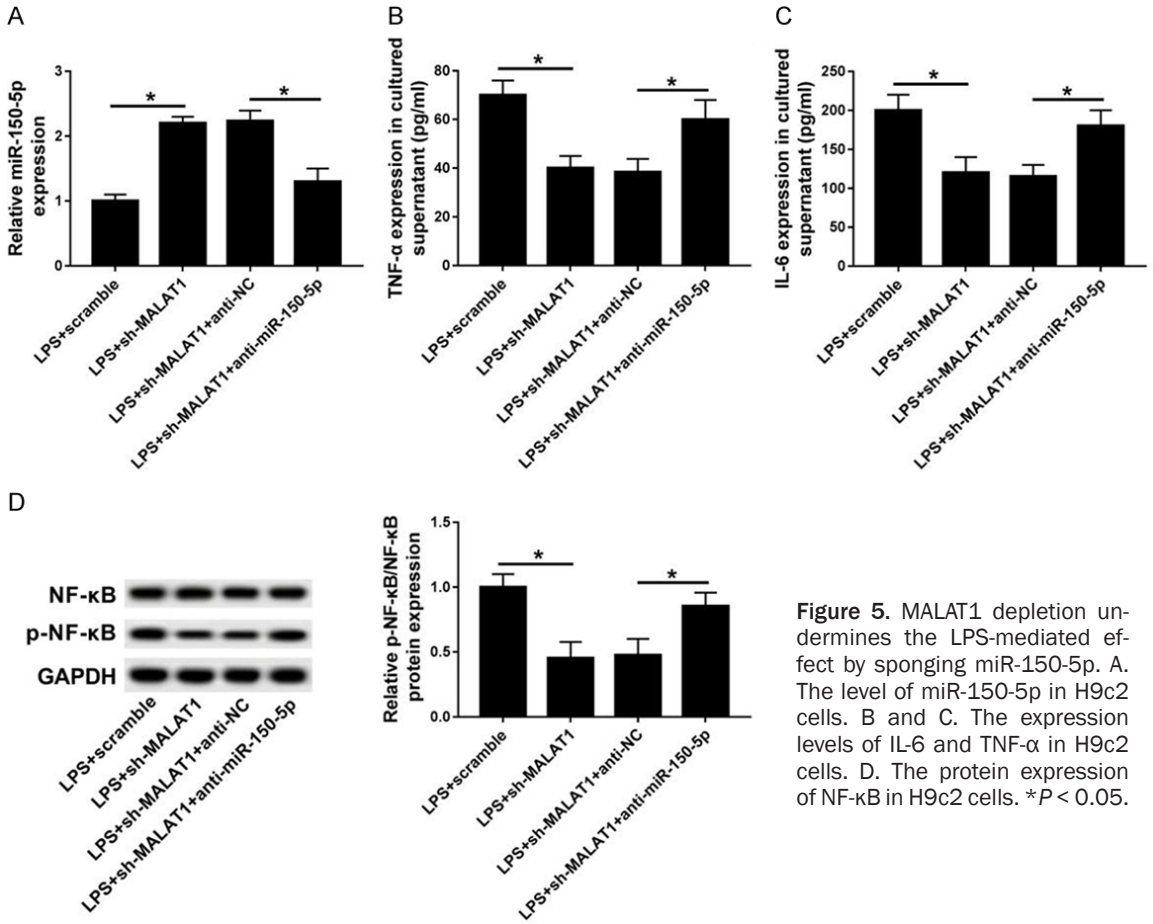

Figure 5. MALAT1 depletion undermines the LPS-mediated effect by sponging miR-150-5p. A. The level of miR-150-5p in H9c2 cells. B and C. The expression levels of IL-6 and TNF-α in H9c2 cells. D. The protein expression of NF-κB in H9c2 cells. *$P < 0.05$.

gan dysfunction and lethality are related to initial inflammatory and later anti-inflammatory responses. Meanwhile, sepsis survivors succumb later to persistent, recurrent, and secondary infections. Many studies about sepsis-induced alterations in cellular immune function have been done. In a previous study, researchers found that cats with sepsis have significantly greater plasma TNF activity and detectable concentrations of IL-6 compared to healthy cats [24]. Recently, it was found that MALAT1 is associated with the immune response [25, 26]. Zhao et al. showed that MALAT1 is elevated in LPS-activated macrophages and that the knockdown of MALAT1 enhances the LPS-induced expression of TNF-α and IL-6 [27]. However, Puthanveetil et al. found that the loss of MALAT1 showed a significant reduction in IL-6 and TNF-α mRNA in endothelial cells [28]. In LPS-induced cardiac sepsis in a mice model and in an *in vitro* cardiomyocyte model, MALAT1 is upregulated, and the knockdown of MALAT1 reduces LPS-induced TNF-α production [11]. Consistently, our data also provide evidence that MALAT1 is upregulated in LPS-mediated H9c2 cells. Moreover, the sh-MALAT1-mediated silence of MALAT1 attenuates the effect of LPS on the expressions of TNF-α and IL-6. More importantly, the downregulation of MALAT1 also abates the LPS-induced activating of the NF-κB pathway. Those findings further suggest the involvement of MALAT1 in the immune response during sepsis.

LncRNAs have been found to serve as miRNA sponges [29, 30]. For the first time, we first disclosed that miR-150-5p interacts with MALAT1 in H9c2 cells, suggesting that miR-150-5p may be responsible for the function of MALAT1. Xue et al. [17] demonstrated that miR-150 is downregulated in the lungs of cigarette smoke-exposed (CSE) mice in contrast to control mice under normal air. In addition, the upregulation of miR-150 decreased the induction of IL-6, TNF-α, and IL-8 expressions and NF-κB transcriptional activity in BEAS-2B cells by CSE. MiR-150 is also associated with the develop-

ment of neuropathic pain. An increase of miR-150 can reduce the expressions of inflammatory cytokines such as COX-2, IL-6, and TNF-α in chronic sciatic nerve injury rats [18]. An earlier study reported on the important role of miR-150-5p in sepsis [16]. The study's data indicated that miR-150 could be a prognostic molecule for predicting the survival of sepsis patients. Also, miR-150 inhibits the LPS-induced inflammatory factors TNF-α and IL-6 and blocks apoptosis by negatively regulating the expression of NF-κB1 in human umbilical vein endothelial cells. In our study, a low level of miR-150 was observed in LPS-mediated H9c2 cells. More interestingly, we found that the restoration of miR-150 attenuated the effect of LPS on the expressions of TNF-α, IL-6, and NF-κB, which was consistent with the data of the loss-of-function of MALAT1. Additionally, the depletion of miR-150-5p abated the effect of MALAT1 knockdown on the effect of the expression of TNF-α, IL-6, and NF-κB. As expected, our data lend credence to our hypothesis that MALAT1 may be implicated in the inflammatory response by negatively regulating the expression of miR-150-5p.

There are some limitations to our study. For example, we only explored the roles of MALAT1 and miR-150-5p in *in vitro* experiments. Their functions should be confirmed in *in vivo* experiments. Moreover, whether the MALAT1/miR-150-5p axis can influence the other cell biological processes in LPS-mediated H9c2 cells also need to be further investigated.

Taken together, our study for the first time demonstrated that the MALAT1/miR-150-5p axis may be a mechanism of cardiomyocyte inflammatory response after LPS stimulation, which may participate in the development of sepsis. In addition, our data provided the theoretical basis for a therapeutic target to treat sepsis.

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Disclosure of conflict of interest

None.

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