Effect of lncRNA-MIAT on kidney injury in sepsis rats *via* regulating miR-29a expression

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Abstract. – OBJECTIVE: The long non-coding ribonucleic acid (lncRNA)-myocardial infarction associated transcript (MIAT) has been demonstrated to serve as a key regulator in various physiological and pathological processes. This study aims to explore whether lncRNA-MIAT regulates the expression of micro RNA (miR)-29a to affect kidney's injury in sepsis rats.

MATERIALS AND METHODS: A total of 30 healthy male Sprague-Dawley (SD) rats were randomly divided into experimental group and control group. Rats in the experimental group were injected with lipopolysaccharide (LPS) through the tail vein to prepare the model of sepsis-induced kidney injury, while those in the control group with the equal volume of normal saline. After the levels of serum creatinine (SCr) and blood urea nitrogen (BUN) in rats were determined to ascertain successful modeling, fluorescence quantitative Real-time polymerase chain reaction (qRT-PCR) was performed to measure the expression levels of the lncRNA-MIAT and miR-29a messenger RNAs (mRNAs) in renal tissues. The normal rat kidney epithelial (NRK-52E) cell line was cultured *in vitro*, and the model was established *in vitro via* LPS to study the influences of lncRNA-MIAT and miR-29a on the kidney injury in sepsis rats. Moreover, cell apoptosis was detected using Western blotting.

RESULTS: According to the results of the rat in vivo experiment and NRK-52E cell line *in vitro* experiment, the model of kidney injury was established successfully, and compared with the control group, experiment group had significantly raised SCr and BUN levels (*p*<0.01) and a remarkably increased lincRNA-MIAT gene expression level (*p*<0.01), but a substantially decreased miR-29a gene expression level (*p*<0.01). Additionally, when the expression of lncRNA-MIAT was up-regulated, the expression of miR-29a was prominently decreased (*p*<0.01), but that of the cell apoptosis gene cysteine-aspartic proteases (Caspase)-8 protein was remarkably increased (*p*<0.01). However, the expression of Caspase-8 protein was significantly lowered (*p*<0.01) once the expression of miR-29a was up-regulated.

CONCLUSIONS: LncRNA-MIAT may bind to miR-29a to participate in sepsis-related kidney injury.

Key Words:
LncRNA-MIAT, MiR-29a, Rats, Kidney injury, Sepsis.

Introduction

Sepsis is a clinical disease that is commonly caused by a primary bacterial infection, where the minority is caused by fungal or viral infection. Severe sepsis patients will suffer from multiple organ dysfunction syndrome (MODS) and multiple organ failure (MOF), and 1 out of 23 inpatient has sepsis. Moreover, sepsis is one of the sixth most common diseases and those costing most in hospitalization[1,2]. It tends to be one of the main causes of acute kidney injury in severe cases, and the degree of sepsis-caused kidney injury is positively correlated with the risk of death[3]. Therefore, it is of great significance to study the influence of sepsis on kidney injury and its mechanism.

Long non-coding ribonucleic acids (LncRNAs), belonging to ncRNAs, are a class of RNAs measuring more than 200 nt in length and without the function of coding proteins. They participate in the incidence and development of various diseases in animals and play crucial roles in cell physiological and pathological processes[4,5]. Li et al[6] found that lncRNA-myocardial infarction associated transcript (MIAT) may be involved in the vascular inflammatory response. Micro RNAs (MiRNAs) are single-stranded non-coding small RNAs coded by endogenous genes and take part in the regulation of the post-transcriptional gene expression. The results of the research showed that the expression level of miR-29a is changed in kidney injury[7]. Besides, some lncRNAs have

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been confirmed to interact with miR-29a[8,9]. LncRNAs competitively bind to miR-29a-3p, thereby promoting the proliferation, migration and invasion of cancer (gastric cancer) cells[6], and they may negatively regulate the expression of miR-29a to affect the development of fibrotic hypertrophic cardiomyopathy (HCM)[10]. However, there have not been related works on lncRNA-MIAT and miR-29a in sepsis-induced kidney injury yet. In the present study, the regulatory effect of lncRNA-MIAT on miR-29a was analyzed to explore their roles in kidney injury.

Materials and Methods

Main Materials

Sprague-Dawley (SD) rats, pentobarbital sodium (Shanghai Longsheng Chemical Co., Ltd., Shanghai, China), SYBR Green Real-Time (RT) Master Mix kit (TaKaRa, Otsu, Shiga, Japan), normal rat kidney epithelial (NRK-52E) cell line (Shanghai Cell Bank of Chinese Academy of Sciences, Shanghai, China), Dulbecco's modified Eagle's medium (DMEM), Opti-minimal essential medium (EME) and fetal bovine serum (FBS) (Gibco, Rockville, MD, USA), lipopolysaccharide (LPS) and dimethyl sulfoxide (DMSO) (Sigma-Aldrich, St. Louis, MO, USA), Lipofectamine 2000 and TRIzol (Invitrogen, Carlsbad, CA, USA), miRNA reverse transcription kit (Applied Biosystems, Foster City, CA, USA), cysteine-aspartic proteases (Caspase)-8 and β-actin antibodies (Abcam, Cambridge, MA, USA), luciferase reporter assay system (Promega, Madison, WI, USA) and bioluminescence plate reader (Modulus ™ Promega, Madison, WI, USA).

Experimental Methods

Establishment of the Rat Model of Kidney Injury

This study was approved by the Animal Ethics Committee of The Affiliated Suzhou Hospital of Nanjing Medical University Animal Center. A total of 30 healthy male SD rats weighing 180-200 g were randomly divided into experiment group (n=15) and control group (n=15). The rat model of kidney injury was established according to the experimental method used in a previous study[11]. Before modeling, rats in experiment group were subjected to food and water fasting for 8 h, each of whom was anesthetized by intraperitoneal injection of 0.75% pentobarbital sodium. Next, they were fixed in the supine position and injected with 10 mg/kg LPS *via* the tail vein to prepare the model of sepsis-induced kidney injury, while those in control group were injected with the equal volume of normal saline. After 24 h, blood and renal tissues were collected.

Establishment of the NRK-52E Cell Model of Injury

The NRK-52E cell line was cultured using the DMEM containing 10% FBS in an incubator containing 5% CO_2 at 37°C. When covering 90% of the dish bottom, the cells were rinsed with phosphate-buffered saline (PBS) for twice, and then they were digested using 0.25% trypsin and sub-cultured at the density of 1:3. Cell modeling was based on the methods of previous researchers[12]. In the experiment group, the NRK-52E cells were treated with 1 μg/mL LPS for 24 h, while those in the control group were given the equal concentration of DMSO for 24 h of treatment.

Serum and Tissue Collection

At 24 h after modeling, blood was extracted from the eyeball of the rats and centrifuged to collect the supernatant serum. Then, the levels of serum creatinine (SCr) and blood urea nitrogen (BUN) were measured using a multi-functional biochemical analyzer. After the rats were executed, the renal tissues were quickly taken out, some of which were fixed in formalin and the others of which were frozen in liquid nitrogen for later use.

Cell Transfection

The cells in the logarithmic growth phase were seeded into a 24-well plate at the density of 1×10^6 cells/mL. After that, they were transfected with pc deoxyribonucleic acid (DNA) 3-MIAT and miR-29a using the Lipofectamine 2000. The plasmid was diluted in 250 μL serum-free Opti-MEM to be at the final concentration of 50 nM and mixed evenly, followed by 5 min of incubation at room temperature. Besides, 5 μL Lipofectamine 2000 was diluted using an equal volume of serum-free Opti-MEM, and after mixing evenly, the mixture was incubated at room temperature for 5 min. The two mixtures were mixed together, incubated at room temperature for 20 min, and then added into a culture dish. Finally, they were cultured in an incubator containing 5% CO_2 at 37°C for 6-8 h, and continued to be cultured for 48 h after the medium was replaced with a complete medium, followed by a collection of cells.

RNA Extraction and Quantitative RT Polymerase Chain Reaction (qRT-PCR)

The sequence of lncRNA-MIAT was obtained from the NCBI database website (http://www.ncbi.nlm.nih.gov/), and the primers were designed using the Primier 6.0 software and synthesized by Sangon Biotech (Shanghai, China) Co., Ltd. The specific sequences of the lncRNA-MIAT and miR-29a primers are listed in Table I. Total RNAs were extracted using the TRIzol reagent, and their concentration was determined with the NanoDrop spectrophotometer. All the PCR primers were provided by Invitrogen (Carlsbad, CA, USA). The miRNA RT kit was used to synthesize miR-29a from 5 ng total RNAs into complementary DNAs (cDNAs), while the lncRNA-MIAT was synthesized from the total RNAs into cDNAs using the random primers from the RT Master Mix kit. The qRT-PCR was performed using the SYBR Green RT-PCR Master Mix and ABI 7500 sequence detection system according to the manufacturer's scheme. The transcription level was evaluated using the cycle threshold (Ct). The target level standardized as an endogenous reference was obtained by the $2^{-\Delta\Delta Ct}$ method. U6 and GAPDH served as the internal control.

Western Blotting

Total proteins were extracted from the tissues and cultured cell lines, and the concentration of the proteins was determined *via* bicinchoninic acid (BCA) protein assay (Pierce, Rockford, IL, USA). The protein was separated through 8% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and then transferred onto a polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA). The membrane was sealed in tris buffered saline (TBS) with 5% skim milk powder and 0.1% Tween-20 and added with the Caspase-8 primary antibody for slight shaking and incubation at 4°C overnight. After reaction with the primary antibody, the horseradish peroxidase (HRP)-labeled secondary antibody was used for incubation. Finally, the proteins were treated *via* enhanced chemiluminescence (ECL) reagent for exposure and detection, with the β-actin detected in the same Western blotting band as a reference.

Luciferase Determination

After 48 h of transfection, the transfected NRK-52E cells were harvested. The activity of luciferase in the transfected cells was measured using the luciferase reporter detection system combined with the bioluminescent plate reader. Each experiment was conducted with 3 parallel controls set, and independently repeated for 3 times.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 20.0 software (IBM, Armonk, NY, USA) was applied to statistically process data. The data in different treatment groups were expressed as mean ± standard deviation ($\overline{\chi}$±s), and inter-group comparison was subjected to the independent-samples *t*-test. $p<0.05$ suggested that the difference was statistically significant.

Results

Renal Histopathology in Rats

According to the results of HE staining, the control group had no significant histopathological changes, while experiment group manifested evident basal layer thickening and inflammatory cell infiltration (Figure 1).

Detection of Rat SCr and BUN After Modeling via LPS

After the rats were treated with LPS in experiment group, the serum of the rats in both groups

Table I. Sequences of lncRNA-MIAT and miR-29a primers detected.

Name	Sequence
LncRNA-MIAT F	5'-ACCAGCAACGGAGTAGTGTG-3'
LncRNA-MIAT R	5'-CACAGCCCGGAATGAAGAGT-3'
MiR-29a F	5'-TAGCACCATTTGAAATCAGTTT-3'
MiR-29a R	5'-TGCGTGTCGTGGAGTC-3'
GAPDH F	5'-AGGTCGGTGTGAACGGATTTG-3'
GAPDH R	5'-TGTAGACCATGTAGTTGAGGTCA-3'
U6 F	5'-CTCGCTTCGGC AGCACA-3'
U6 R	5'-AACGCTTCACGAATTT GCGT-3'

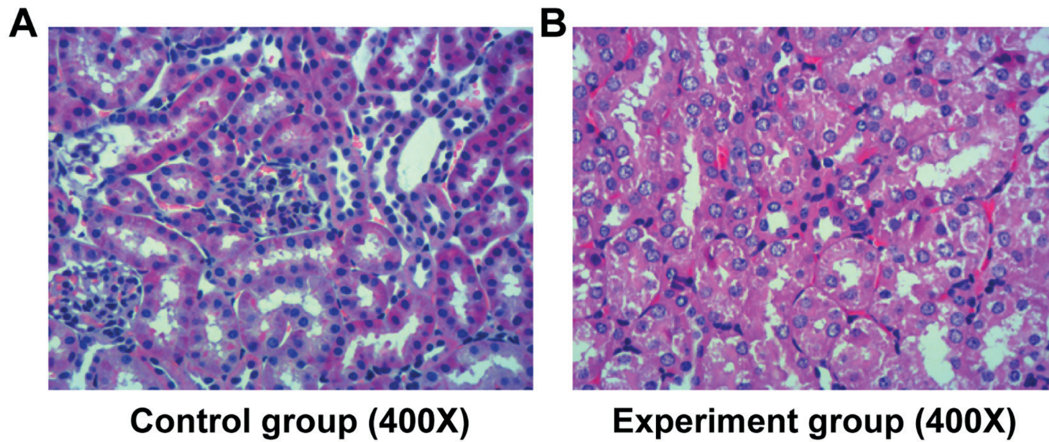

Figure 1. HE staining results of the rat renal tissues in experiment and control groups. **A,** The renal tissue sections of the rats in control group are normal in morphology. **B,** At 24 h after injection of LPS, the renal tissue sections of rats show basal layer thickening and inflammatory cell infiltration (magnification: 400×).

was collected, and the results revealed that the experiment group had significantly higher levels of SCr and BUN than the control group ($p<0.01$) (Figure 2).

Expressions of lncRNA-MIAT and miR-29a in Rat Renal Tissues and In Vitro Cells

According to the results of the qRT-PCR, after being treated with LPS for 24 h, the rats in experiment group had a significantly higher expression level of lncRNA-MIAT in renal tissues than control group, but the expression level of miR-29a was remarkably lower than that in control group ($p<0.01$) (Figure 3). After the NRK-52E cells cultured *in vitro* were treated with LPS for 24 h, the expression trends of lncRNA-MIAT and miR-29a were similar to the findings of the *in vivo* experiment, namely, compared with control group, experiment group had a substantially raised expression level of lncRNA-MIAT ($p<0.01$), but a significantly lowered expression level of miR-29a ($p<0.01$) (Figure 4).

Relationship Between lncRNA-MIAT and miR-29a Verified via the Luciferase Reporter System

To detect the regulatory relationship between lncRNA-MIAT and miR-29a, the cells were transfected with the wild-type and mutant lncRNA-MIAT plasmids separately in combination with miR-29a mimics. According to the results, miR-29a mimics could inhibit the luciferase activity of the wild-type lncRNA-MIAT ($p<0.05$), whereas that of the mutant lncRNA-MIAT was not significantly repressed ($p>0.05$) (Figure 5).

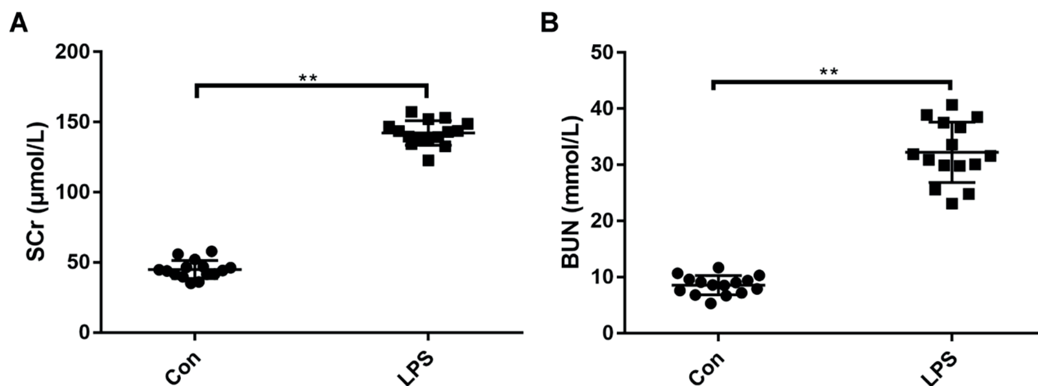

Figure 2. Levels of rat serum SCr and BUN in experiment and control groups after 24 h of treatment with LPS. **A,** The level of rat serum BUN in experiment group is significantly higher than that in control group ($p<0.01$). **B,** The level of rat serum SCr in experiment group is prominently higher than that in control group ($p<0.01$).

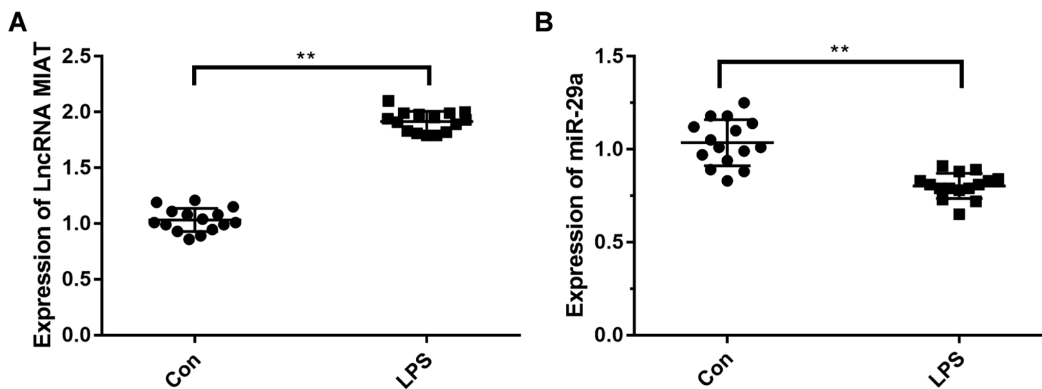

Figure 3. Expression levels of lncRNA-MIAT and miR-29a in the rat renal tissues of the two groups after 24 h of treatment with LPS **A,** In comparison with control group, experiment group has a significantly raised expression level of lncRNA-MIAT ($p<0.01$). **B,** Compared with control group, experiment group exhibits a substantially reduced expression level of miR-29a ($p<0.01$).

Influences of lncRNA-MIAT and miR-29a on NRK-52E Cell Apoptosis

The NRK-52E cells were transfected with the wild-type and mutant lncRNA-MIAT plasmids separately combined with miR-29a mimics, and after the cells were treated with LPS for 24 h, the expression of the cell Caspase-8 protein was detected. The results showed that the apoptosis of the NRK-52E cells treated with LPS was significantly up-regulated, and the apoptosis degree of the NRK-52E cells transfected with the wild-type lncRNA-MIAT was prominently higher than those in other treatment groups ($p<0.05$). Besides, there was no significant difference in the apoptosis degree of all the cells treated with miR-29a between experiment group and control group ($p>0.05$), and the cell apoptosis degree in the wild-type lncRNA-MIAT and miR-29a mimics co-transfection group was remarkably higher than that in the mutant lncRNA-MIAT and miR-29a mimics co-transfection group ($p<0.05$) (Figure 6).

Discussion

Severe sepsis will cause MODS and MOF, including kidney injury, with a relatively high mortality rate in patients, but current studies on the molecular mechanism of sepsis-induced kidney injury remain superficial. Therefore, the molecular mechanism of sepsis-induced kidney injury was studied to search for effective molecular targets

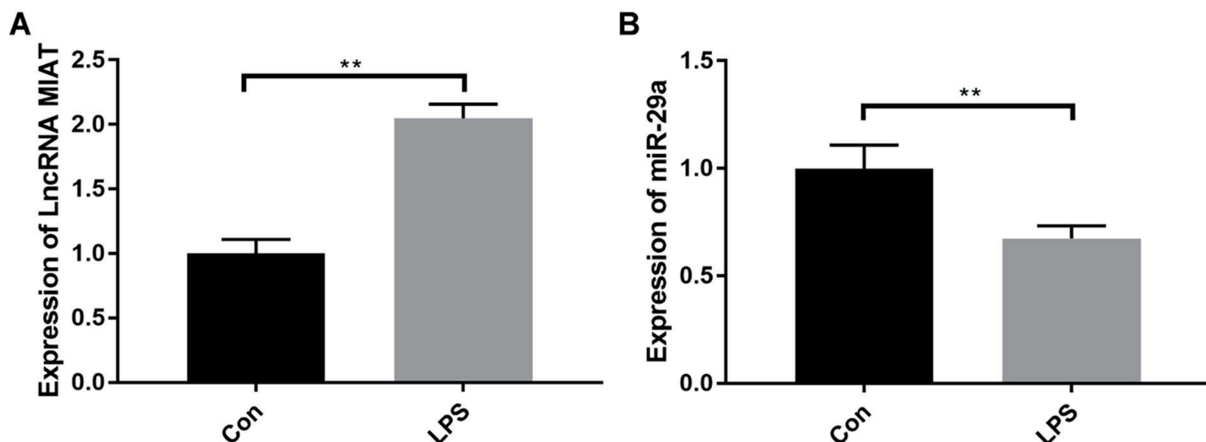

Figure 4. Expression levels of lncRNA-MIAT and miR-29a in the two groups of NRK-52E cells after 24 h of treatment with LPS **A,** In comparison with control group, experiment group has a significantly raised expression level of lncRNA-MIAT ($p<0.01$). **B,** Compared with control group, experiment group exhibits a substantially reduced expression level of miR-29a ($p<0.01$).

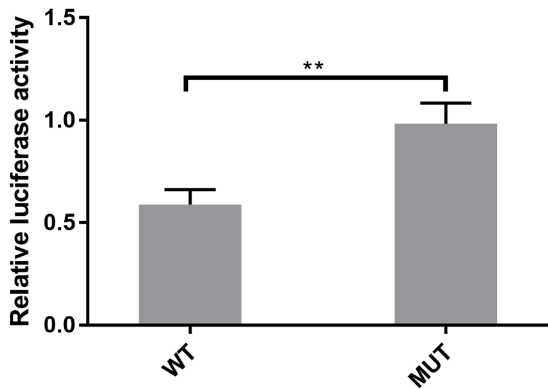

Figure 5. Action relationship between the wild-type and mutant lncRNA-MIATs in miR-29a mimics. The relative luciferase activity of the wild-type lncRNA-MIAT is significantly lower than that of the mutant lncRNA-MIAT ($p<0.01$).

and provide a theoretical basis for the pathogenesis and treatment of this disease. Scholars[13-16] have used LPS to establish the rat model of sepsis-induced kidney injury. In this study, the rats were injected with LPS, and the serological test indicated significant increases in the levels of SCr and BUN. Moreover, the histopathological results of the renal tissue sections revealed that experiment group had evident basal layer thickening and inflammatory cell infiltration. These results suggest that the rat model of kidney injury was established successfully with the LPS method, which are consistent with the findings of the previous research. LncRNAs play important roles in the cell physiological and pathological processes, and more and more researchers have been paying attention to their roles in human diseases in recent years[5,17,18]. They target miRNAs to modulate the expression of the downstream gene, accelerating the progression of the related diseases[19-21]. Li et al[6] suggested that lncRNA-MIAT may participate in the inflammatory response of vascular endothelial cells and promote inflammations as well. In this experiment, the expression of lncRNA-MIAT in the rat renal tissues and NRK-52E cells of both control group and experiment group was detected *via* the qRT-PCR, and the results showed that experiment group had a significantly raised lncRNA-MIAT expression. The possible cause is that in the LPS-induced

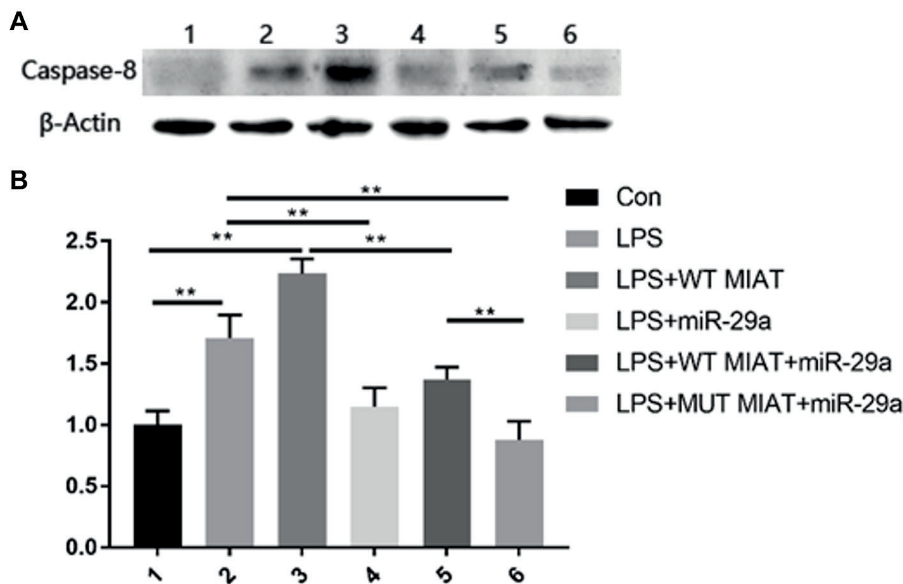

Figure 6. Expression of NRK-52E cell apoptosis factor Caspase-8 under different treatments. **A,** Expression of NRK-52E cell apoptosis factor Caspase-8 under different treatments according to Western blotting detection **B,** Relative quantification graph of Caspase-8 expression, which reveals that after induction with LPA, the expression level of the cell apoptosis factor is significantly higher than that in control group ($p<0.01$), and the apoptosis factor in the cells transfected with the wild-type lncRNA-MIAT is substantially higher that in non-transfected cells ($p<0.01$). Additionally, miR-29a can significantly reduce the LPS-induced cell apoptosis ($p<0.01$), and the apoptosis degree of the LPS-induced cells subjected to the combined action of wild-type lncRNA-MIAT and miR-29a is higher than that caused by the joint action of the mutant lncRNA-MIAT and miR-29a ($p<0.01$). 1: NRK-52E cells cultured normally. 2: NRK-52E cells induced with LPS for 24 h. 3: NRK-52E cells induced with LPS for 24 h after transfection with the wild-type lncRNA-MIAT. 4: NRK-52E cells induced with LPS for 24 h after transfection with miR-29a. 5: NRK-52E cells induced with LPS for 24 h after co-transfection with the wild-type lncRNA-MIAT and miR-29a. 6: NRK-52E cells induced with LPS for 24 h after co-transfection with the mutant lncRNA-MIAT and miR-29a.

kidney injury, lncRNA-MIAT, as an important regulator, takes part in the inflammatory responses in renal tissues and cells, promoting the progression of kidney injury.

MiRNAs are involved in the regulation of the post-transcriptional gene expression, and they have varying expression profiles in different pathological progressions of various diseases and differ in the expression level changes in multiple inflammatory diseases[22-24]. According to the findings of Huo et al[7], the expression level of miR-29a is changed in the process of kidney injury. Additionally, miR-29a has been proved to be capable of resisting apoptosis, and it, recognized as a potent anti-apoptosis factor, inhibits the expression of the target gene to exert the anti-apoptosis effect[24,25]. In terms of kidney injury, miR-29a can protect renal tubular epithelial cells from irreversible damage caused by renal ischemia-reperfusion, alleviate their apoptosis and protect renal tissues and functions[22]. The results of the present study revealed that the levels of the rat serum SCr and BUN were negatively proportional to the expression of miR-29a in renal tissues. This suggests that LPS can induce kidney injury in rats, raising the levels of serum SCr and BUN. However, the expression of miR-29a that can lower the degree of apoptosis and protect renal tissues and functions exhibited a down-regulated trend. The expression of miR-29a in NRK-52E cells was similar to the result above, which is probably related to the expression of the above-mentioned lncRNA-MIAT.

Hence, the interaction between lncRNA-MIAT and miR-29a-3p in the process of kidney injury was further investigated. The research results showed that lncRNA-MIAT is highly expressed in gastric cancer tissues and gastric mucosal cell lines[6] and competitively binds to miR-29a-3p to up-regulate the transcription level of HDAC4 and promote the proliferation, migration and invasion of gastric cancer cells. In the pathogenesis of HCM fibrosis[10], lncRNA-MIAT accelerates the progression of this disease through negatively regulating the expression of miR-29a. According to the findings in this study, lncRNA-MIAT regulated the expression of miR-29a in a negative manner. The Western blotting results displayed that up-regulating the expression of lncRNA-MIAT significantly promoted the LPS-induced NRK-52E cell apoptosis, possibly because with the proinflammatory effect, lncRNA-MIAT aggravates the cell apoptosis. On the contrary, the up-regulation of miR-29a markedly lowered such cell apoptosis, and the possible cause is that miR-29a exerts the anti-apoptosis effect to protect the cells. The apoptosis degree of the cells co-transfected with lncRNA-MIAT and miR-29a was higher than that of the cells transfected with miR-29a alone, which suggests that the mutant lncRNA-MIAT suppresses or binds to miR-29a, while the cells transfected with the mutant lncRNA-MIAT and miR-29a together exhibited a lower degree of apoptosis than those co-transfected with the wild-type lncRNA-MIAT and miR-29a, which further suggests that lncRNA-MIAT probably affects the process of kidney injury through the competitive binding to miR-29a. However, more in-depth research still needs to be done for more specific mechanisms of action of lncRNA-MIAT and miR-29a in the process of kidney injury and their influences on the repair of kidney injury.

Conclusions

We observed the mechanism of action by which lncRNA-MIAT may bind to miR-29a to worsen LPS-induced kidney injury, providing effective approaches for the clinical prevention and treatment of kidney injury and a theoretical basis for the related research.

Conflict of Interests

The Authors declare that they have no conflict of interests.

References

1) Bellomo R, Kellum JA, Ronco C, Wald R, Martensson J, Maiden M, Bagshaw SM, Glassford NJ, Lankadeva Y, Vaara ST, Schneider A. Acute kidney injury in sepsis. Intensive Care Med 2017; 43: 816-828.
2) Li JM, Zhang H, Zuo YJ. MicroRNA-218 alleviates sepsis inflammation by negatively regulating VOPP1 via JAK/STAT pathway. Eur Rev Med Pharmacol Sci 2018; 22: 5620-5626.
3) Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D, Honore PM, Joannes-Boyau O, Joannidis M, Korhonen AM, Lavrentieva A, Mehta RL, Palevsky P, Roessler E, Ronco C, Uchino S, Vazquez JA, Vidal AE, Webb S, Kellum JA. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015; 41: 1411-1423.
4) Jin Y, Cui Z, Li X, Jin X, Peng J. Upregulation of long non-coding RNA PlncRNA-1 promotes proliferation and induces epithelial-mesenchymal transition in prostate cancer. Oncotarget 2017; 8: 26090-26099.

5) Peng WX, Koirala P, Mo YY. LncRNA-mediated regulation of cell signaling in cancer. Oncogene 2017; 36: 5661-5667.
6) Li Y, Wang K, Wei Y, Yao Q, Zhang Q, Qu H, Zhu G. lncRNA-MIAT regulates cell biological behaviors in gastric cancer through a mechanism involving the miR-29a-3p/HDAC4 axis. Oncol Rep 2017; 38: 3465-3472.
7) Huo R, Dai M, Fan Y, Zhou JZ, Li L, Zu J. [Predictive value of miRNA-29a and miRNA-10a-5p for 28-day mortality in patients with sepsis-induced acute kidney injury]. Nan Fang Yi Ke Da Xue Xue Bao 2017; 37: 646-651.
8) Bernardo BC, Gao XM, Tham YK, Kiriazis H, Winbanks CE, Ooi JY, Boey EJ, Obad S, Kauppinen S, Gregorevic P, Du XJ, Lin RC, McMullen JR. Silencing of miR-34a attenuates cardiac dysfunction in a setting of moderate, but not severe, hypertrophic cardiomyopathy. PLoS One 2014; 9: e90337.
9) He H, Wang N, Yi X, Tang C, Wang D. Long non-coding RNA H19 regulates E2F1 expression by competitively sponging endogenous miR-29a-3p in clear cell renal cell carcinoma. Cell Biosci 2017; 7: 65.
10) Zhou J, Zhou Y, Wang CX. LncRNA-MIAT regulates fibrosis in hypertrophic cardiomyopathy (HCM) by mediating the expression of miR-29a-3p. J Cell Biochem 2018 Dec 11. doi: 10.1002/jcb.28001. [Epub ahead of print]
11) Gupta A, Rhodes GJ, Berg DT, Gerlitz B, Molitoris BA, Grinnell BW. Activated protein C ameliorates LPS-induced acute kidney injury and downregulates renal INOS and angiotensin 2. Am J Physiol Renal Physiol 2007; 293: F245-F254.
12) Jung JH, Ha JY, Min KR, Shibata F, Nakagawa H, Kang SS, Chang IM, Kim Y. Reynosin from Sassurea lappa as inhibitor on CINC-1 induction in LPS-stimulated NRK-52E cells. Planta Med 1998; 64: 454-455.
13) Li Y, Xiong W, Yang J, Zhong J, Zhang L, Zheng J, Liu H, Zhang Q, Ouyang X, Lei L, Yu X. Attenuation of inflammation by emodin in lipopolysaccharide-induced acute kidney injury via inhibition of toll-like receptor 2 signal pathway. Iran J Kidney Dis 2015; 9: 202-208.
14) Wang JT, Jiao P, Zhou Y, Liu Q. protective effect of dihydromyricetin against lipopolysaccharide-induced acute kidney injury in a rat model. Med Sci Monit 2016; 22: 454-459.
15) Han M, Li Y, Liu M, Li Y, Cong B. Renal neutrophil gelatinase associated lipocalin expression in lipopolysaccharide-induced acute kidney injury in the rat. BMC Nephrol 2012; 13: 25.
16) Cao HJ, Yu DM, Zhang TZ, Zhou J, Chen KY, Ge J, Pei L. Protective effect of penehyclidine hydrochloride on lipopolysaccharide-induced acute kidney injury in rat. Genet Mol Res 2015; 14: 9334-9342.
17) Moran VA, Perera RJ, Khalil AM. Emerging functional and mechanistic paradigms of mammalian long non-coding RNAs. Nucleic Acids Res 2012; 40: 6391-6400.
18) Liu D, Li Y, Luo G, Xiao X, Tao D, Wu X, Wang M, Huang C, Wang L, Zeng F, Jiang G. LncRNA SPRY4-IT1 sponges miR-101-3p to promote proliferation and metastasis of bladder cancer cells through up-regulating EZH2. Cancer Lett 2017; 388: 281-291.
19) Shao S, Tian J, Zhang H, Wang S. LncRNA myocardial infarction-associated transcript promotes cell proliferation and inhibits cell apoptosis by targeting miR-330-5p in epithelial ovarian cancer cells. Arch Med Sci 2018; 14: 1263-1270.
20) Li Q, Pang L, Yang W, Liu X, Su G, Dong Y. long non-coding rna of myocardial infarction associated transcript (LncRNA-MIAT) promotes diabetic retinopathy by upregulating transforming growth factor-beta1 (TGF-beta1) signaling. Med Sci Monit 2018; 24: 9497-9503.
21) Xiang Y, Huang Y, Sun H, Pan Y, Wu M, Zhang J. Deregulation of miR-520d-3p promotes hepatocellular carcinoma development via lncRNA MIAT regulation and EPHA2 signaling activation. Biomed Pharmacother 2019; 109: 1630-1639.
22) Lin X, Zhou X, Liu D, Yun L, Zhang L, Chen X, Chai Q, Li L. MicroRNA-29 regulates high-glucose-induced apoptosis in human retinal pigment epithelial cells through PTEN. In Vitro Cell Dev Biol Anim 2016; 52: 419-426.
23) Chen J, Liu X, Chen X, Guo Z, Liu J, Hao J, Zhang J. Real-time monitoring of miRNA function in pancreatic cell lines using recombinant AAV-based miRNA Asensors. PLoS One 2013; 8: e66315.
24) Hu W, Dooley J, Chung SS, Chandramohan D, Cimmino L, Mukherjee S, Mason CE, de Strooper B, Liston A, Park CY. miR-29a maintains mouse hematopoietic stem cell self-renewal by regulating Dnmt3a. Blood 2015; 125: 2206-2216.
25) Matsumoto Y, Itami S, Kuroda M, Yoshizato K, Kawada N, Murakami Y. MiR-29a assists in preventing the activation of human stellate cells and promotes recovery from liver fibrosis in mice. Mol Ther 2016; 24: 1848-1859..