MEDICAL SCIENCE MONITOR

LAB/IN VITRO RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2020; 26: e921822
DOI: 10.12659/MSM.921822

Received: 2019.11.30
Accepted: 2020.01.07
Available online: 2020.02.05
Published: 2020.03.29

Long Noncoding RNA DANCR Suppressed Lipopolysaccharide-Induced Septic Acute Kidney Injury by Regulating miR-214 in HK-2 Cells

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: This research was supported by the National Natural Science Foundation of China (grant number: 81571946)

Background: Acute kidney injury (AKI) is one of the most important causes of death in sepsis patients. Here, we first measured the level of DANCR (differentiation antagonizing nonprotein coding RNA) expression in AKI, and the potential mechanism was further elucidated.

Material/Methods: We used qRT-PCR to examine the level of DANCR in patient blood serum samples and in HK-2 cells. In addition, DANCR overexpression was established using lentiviral transfection in HK-2 cells. Subsequently, Cell Counting Kit-8 (CCK-8) assay and flow cytometry were applied to evaluate the role of DANCR in HK-2 cells treated with lipopolysaccharide (LPS). Enzyme linked immunosorbent assay (ELISA), western blot and recovery experiments were performed to elucidate the further mechanism.

Results: We found that DANCR was decreased in the serum of AKI patients and HK-2 cells treated with LPS. Additionally, DANCR promoted cell viability and suppressed cell apoptosis and cytokine production in LPS-treated HK-2 cells. Bioinformatics analysis showed that DANCR served as a sponge for miR-214. Furthermore, DANCR inhibited the expression of Krüppel-like factor 6 (KLF6).

Conclusions: Our study suggests that AKI development could be alleviated by sponging miR-214 and regulating KLF6 expression, which provides a novel potential mechanism involved in the diagnosis and treatment of sepsis-induced AKI patients.

MeSH Keywords: Acute Kidney Injury • MicroRNAs • RNA, Long Noncoding • Sepsis

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/921822

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Background

Sepsis is a systemic inflammatory response syndrome caused by infectious factors that can lead to organ dysfunction and/or circulatory disorders in severe cases [1]. It is a common complication of severe trauma, burns, shock, infection and major surgery [2]. It has been reported that more than 30% of the mortality in intensive care units is related to sepsis-induced AKI [3]. Hence, improving the prevention and treatment of AKI in patients with sepsis is of great significance.

Long noncoding RNAs (lncRNAs), greater than 200 nucleotides in length, have been verified to modulate diverse cellular processes, including the cell cycle, autophagy and apoptosis [4]. Notably, accumulated evidence has revealed that lncRNAs are involved in sepsis-induced AKI development. For example, TapSAKI was observed to promote HK-2 cell apoptosis and the inflammatory response in sepsis-induced AKI [5], and HOTAIR may accelerate kidney injury induced by urine-derived sepsis [6]. As a novel lncRNA, DANCR (differentiation antagonizing nonprotein coding RNA) was first to be reported to repress cell differentiation [7] and has been confirmed to act as an important role in cancers and orthopedic disorders [8,9]. However, the molecular function of DANCR in other diseases has yet to be fully explored.

MicroRNAs (miRNAs) belongs to noncoding single-stranded RNAs which are involved in many physiological processes like cell proliferation, apoptosis and migration [10]. Research on the role of miR-214 in AKI discovered that miR-214 could exacerbate kidney damage and inflammation in the development of AKI [11,12]. Hence, we attempted to evaluate DANCR expression level in AKI, and the hidden mechanism was further elucidated.

Material and Methods

Sample collection

Between December 2016 and December 2017, 20 patients (18 to 60 years old) diagnosed with sepsis-induced AKI at The Second Hospital of Tianjin Medical University were recruited in this study. During the same period, 20 healthy volunteers were enrolled as controls. The characteristics of the participants enrolled in the study are shown in Table 1. The diagnostic criteria for sepsis were according to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM), and the criteria for AKI were based on the Acute Kidney Injury Network (AKIN) classification. Patients were included if they 1) were over 50 years old; 2) conformed to the diagnostic criteria of ACCP/SCCM; and 3) conformed to the diagnostic criteria of AKIN. The patients were excluded if they 1) were diagnosed with sepsis; 2) had concurrent viral myocarditis; 3) had concurrent severe hepatitis or cirrhosis; 4) did not have complete clinical records; or 5) had poor adherence. All participants signed informed consent, and this study was approved by the ethics committee of Tianjin Medical University. The 5 mL serum samples from the participants were centrifuged at 12 000 g for 3 minutes, and the supernatant was frozen at –80°C immediately for further analysis.

Cell culture and transfection

The human renal tubular epithelial cell line HK-2 (obtained from the Cell Bank of the Chinese Academy) was cultured in Dulbecco's modified Eagle's medium/nutrient mixture F-12 (1: 1, Gibco, Carlsbad, CA, USA) containing 10% fetal bovine serum and 1% penicillin/streptomycin with humidified air and 5% CO_2 at 37°C. Until approximately 60% confluence, HK-2 cells were treated with 100 ng/mL lipopolysaccharide (LPS) for 24 hours to mimic inflammation. Cells were transfected with DANCR mimic, miR-214 mimic or the corresponding controls mixed with Lipofectamine 2000 reagent according to the manufacturer's protocols.

Table 1. Baseline characteristics of case (patients with sepsis-induced AKI) and control (healthy individuals) group.

Baseline characteristics	AKI	Control	*P* value
Age (years)	65.25±7.21	64.78±6.54	0.725
Gender			
Male	12	11	0.749
Female	8	9	
Body mass (kg/m^2)	26.23±7.56	25.98±9.24	0.695
BUN (mmol/L)	10.25±1.56	5.23±1.78	0.012*
Cr (μmol/L)	260.23±20.56	46.75±16.13	0.006*

* $P<0.05$.

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Cell viability

HK-2 cells (1×10^3 cells/well) with different transfections were seeded in 96-well plates and cultured for 0, 24, 48, 72, and 96 hours. Then 10 μL of Cell Counting Kit-8 (CCK-8) solution was then added to the cells for 3 hours of incubation. The absorbance at 450 nm (OD450) was calculated using a Microplate Reader.

Cell apoptosis

The cells were suspended in the binding buffer, placed in ice-cold 70% ethanol, and stained with FITC/Annexin V and propidium iodide (PI) in the dark at room temperature for 15 minutes. Apoptosis detection was immediately performed using a FACScan (Beckman Coulter, Fullerton, CA, USA) and analyzed using CellQuest software.

Enzyme linked immunosorbent assay (ELISA)

The concentrations of inflammatory cytokines (tumor necrosis factor [TNF]-α, monocyte chemoattractant protein [MCP] MCP-1, interleukin [IL]-1β, and IL-6) in the serum of all participants were determined using an enzyme linked immunosorbent assay (ELISA) kit. A microplate reader was used to read the absorbance at 450 nm.

Real-time quantitative PCR analysis

Total RNA was isolated from the serum of participants and HK-2 cells using TRIzol reagent (Invitrogen). Complementary DNA (cDNA) synthesis was conducted using the TaqMan MicroRNA reverse transcription kit (Applied Biosystems) for miR-214 and the OneStep PrimeScript cDNA kit (Qiagen) for DANCR and Krüppel-like factor 6 (KLF6). The relative expression was analyzed by using the $2^{-\Delta\Delta CT}$ method and normalized to GAPDH or U6 expression. The primers were as follows:
DANCR forward 5'-CCTATCCCTTTCTCTA-3' and
reverse 5'-ACTTCTGCAAAAACGTGCTG-3';
miR-214 forward 5'-AACGAGACGACGACAGAC-3' and
reverse 5'- CTTGGAGTAGGTCATTGGGT-3';
lnc-NC 5'-UGGACAACAUGGGCUCU-3';
miR-432 mimic: 5'-AUCGAGACUACGUCUGAC-3';
KLF6 forward 5'-TCAAATGCTATCCCCTTTCC-3' and
reverse 5'- CCAGGGCTAGGAAGTAGGAG-3';
U6 forward 5'-GCTCGCTTCGGCAGCACA-3' and
reverse 5'-GAGGTA TTCGCA CCAGAG GA-3'; and
GAPDH forward 5'-ACCACA GTCCATGCCATCCAC-3' and
reverse 5'-TCCACCACCCTGTTGCTGTA-3'.

Western blotting analysis

Proteins were extracted from cultured HK-2 cells by RIPA buffer (Sigma-Aldrich; Merck KGaA). After blocking with 5% skimmed milk, the membrane was incubated with the primary antibody anti-KLF6 (1: 1000, Santa Cruz, sc-365633) at 4°C overnight, and then incubated with anti-rabbit horseradish peroxidase-conjugated secondary antibody and detection using an enhanced chemiluminescence detection system.

Luciferase reporter assay

The sequence of DANCR containing wild-type (WT) or mutant (Mut) miR-214 binding sites was constructed by Genomeditech (Shanghai, China) and inserted into the pGL3 Basic vector. Cells were seeded into 24-well plates and co-transfected with the luciferase reporter constructs, miR-630 mimics, and Renilla luciferase construct (Promega) and incubated for 24 hours. The relative luciferase activities were measured using the Dual-Luciferase Reporter System (Promega).

Statistical analysis

All measurement data were expressed as the mean±standard deviation. Differences were calculated with Student's *t*-test or one-way ANOVA. Pearson's correlation analysis was used to evaluate the expression correlation. All statistical analyses were calculated using SPSS 17.0 software and GraphPad Prism 6. $P<0.05$ indicated a statistically significant difference.

Results

The level of DANCR was decreased in the serum of AKI patients and HK-2 cells

To evaluate the role of DANCR in sepsis-induced AKI, we initially measured DANCR expression levels in 20 patients and healthy volunteers using RT-qPCR. The results demonstrated that DANCR expression was remarkably lower in serum of patients than healthy controls (Figure 1A). We observed that the concentrations of inflammatory cytokines (TNF-α, MCP-1, IL-1β, and IL-6) in patients were significantly increased (Figure 1B). In addition, the DANCR level was notably decreased in HK-2 cells treated with LPS (Figure 1C).

DANCR promoted cell viability and suppressed cell apoptosis and cytokine production in LPS-treated HK-2 cells

Subsequently, we explored the role of DANCR in LPS-treated HK-2 cells. First, we established a DANCR overexpression model in LPS-treated HK-2 cells by transfection (Figure 2A). The CCK-8 assay showed that DANCR overexpression significantly reduced the proliferation of LPS-treated HK-2 cells (Figure 2B). In addition, flow cytometry analysis demonstrated that the cell apoptosis rate was lower in LPS-treated HK-2 cells after transfection

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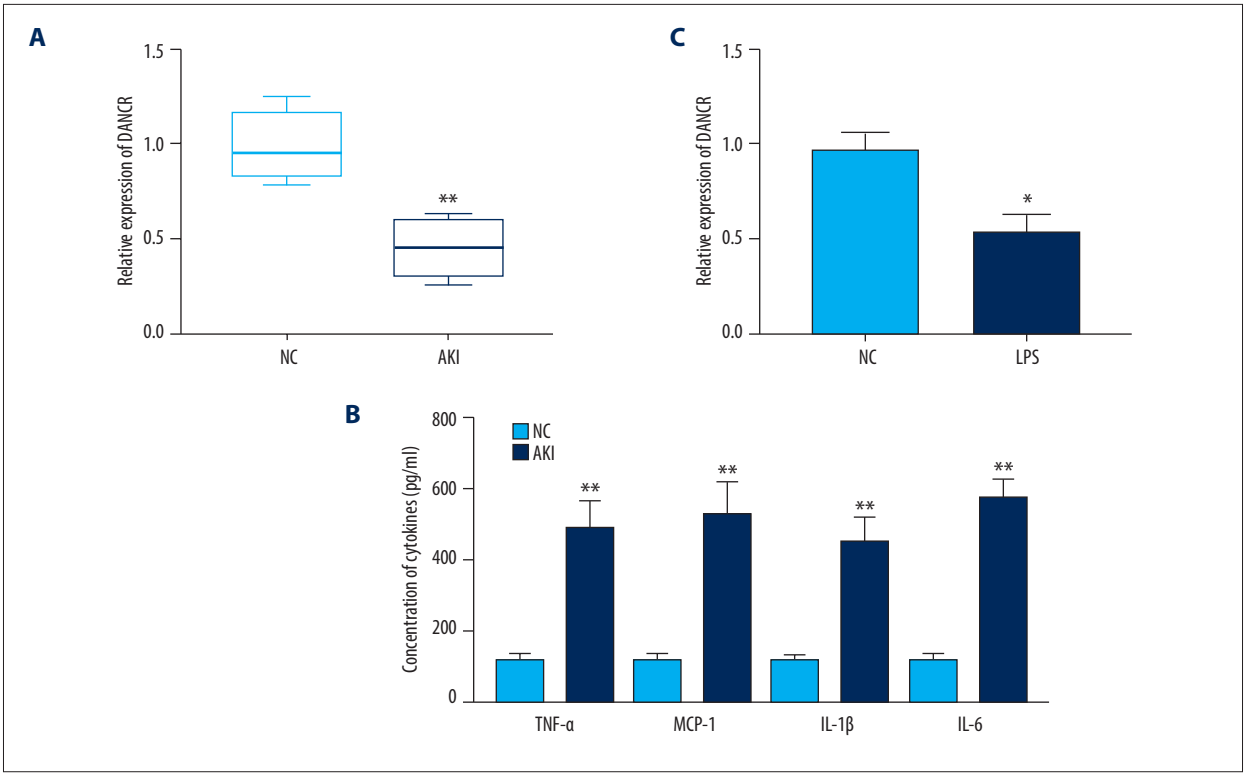

Figure 1. The level of DANCR was decreased in the serum of AKI patients and HK-2 cells. (**A**) The DANCR level was obviously lower in the serum of patients than healthy controls. (**B**) The concentrations of cytokines (TNF-α, MCP-1, IL-1β, and IL-6) in patients were significantly higher. (**C**) The expression of DANCR was notably decreased in HK-2 cells treated with LPS. * $P<0.05$, ** $P<0.01$ compared to the control group. DANCR – differentiation antagonizing nonprotein coding RNA; AKI – acute kidney injury; TNF – tumor necrosis factor, IL – interleukin; MCP – monocyte chemoattractant protein.

with DANCR mimic (Figure 2C). Furthermore, DANCR overexpression obviously reduced the expression of related cytokines (Figure 2D).

DANCR served as a sponge for miR-214

Given that lncRNAs serve as molecular sponges for miRNAs in many diseases [4], we used starBase v2.0 to predict the candidate target miRNAs binding with DANCR [13]. As shown in Figure 3A, miR-214 was observed to have a potential binding site with DANCR. A luciferase reporter assay verified the binding with decreased fluorescence in cells transfected with the miR-214 mimic and DANCR wild type construct (Figure 3B). In addition, the miR-214 expression level was significantly upregulated in patient sera and LPS-treated HK-2 cells (Figure 3C). Under LPS-stimulated conditions, DANCR overexpression significantly decreased miR-214 levels in HK-2 cells, which was reversed by the miR-214 mimic (Figure 3D). The CCK-8 assay revealed that the miR-214 mimic reversed the effect of DANCR overexpression on the proliferation of HK-2 cells treated with LPS at 96 hours (Figure 3E). In addition, the miR-214 mimic increased the apoptosis rate of LPS-treated HK-2 cells transfected with the DANCR mimic (Figure 3F). As expected, the miR-214 mimic obviously promoted cytokine production in cells transfected with the DANCR mimic (Figure 3G).

DANCR could suppress KLF6 expression

KLF6 has been verified to take part in the inflammation occurrence [14,15]. Thus, we explored the effect of DANCR on the expression of KLF6 in LPS-treated HK-2 cells. We noticed that KLF6 expression was significantly elevated in the serum of patients and LPS-treated HK-2 cells (Figure 4A). After transfection with DANCR, the expression level of KLF6 was downregulated significantly in LPS-treated HK-2 cells, which was rescued by the miR-214 mimic (Figure 4B).

Discussion

Acute kidney injury (AKI) is a common critical disease in the clinic, and its main characteristics are acute decline in renal function caused by various etiologies [16]. Previous research has shown that more than 50% of sepsis patients often develop AKI as a complication during treatment [17]. So far, accumulating evidence has revealed that abnormally expressed noncoding

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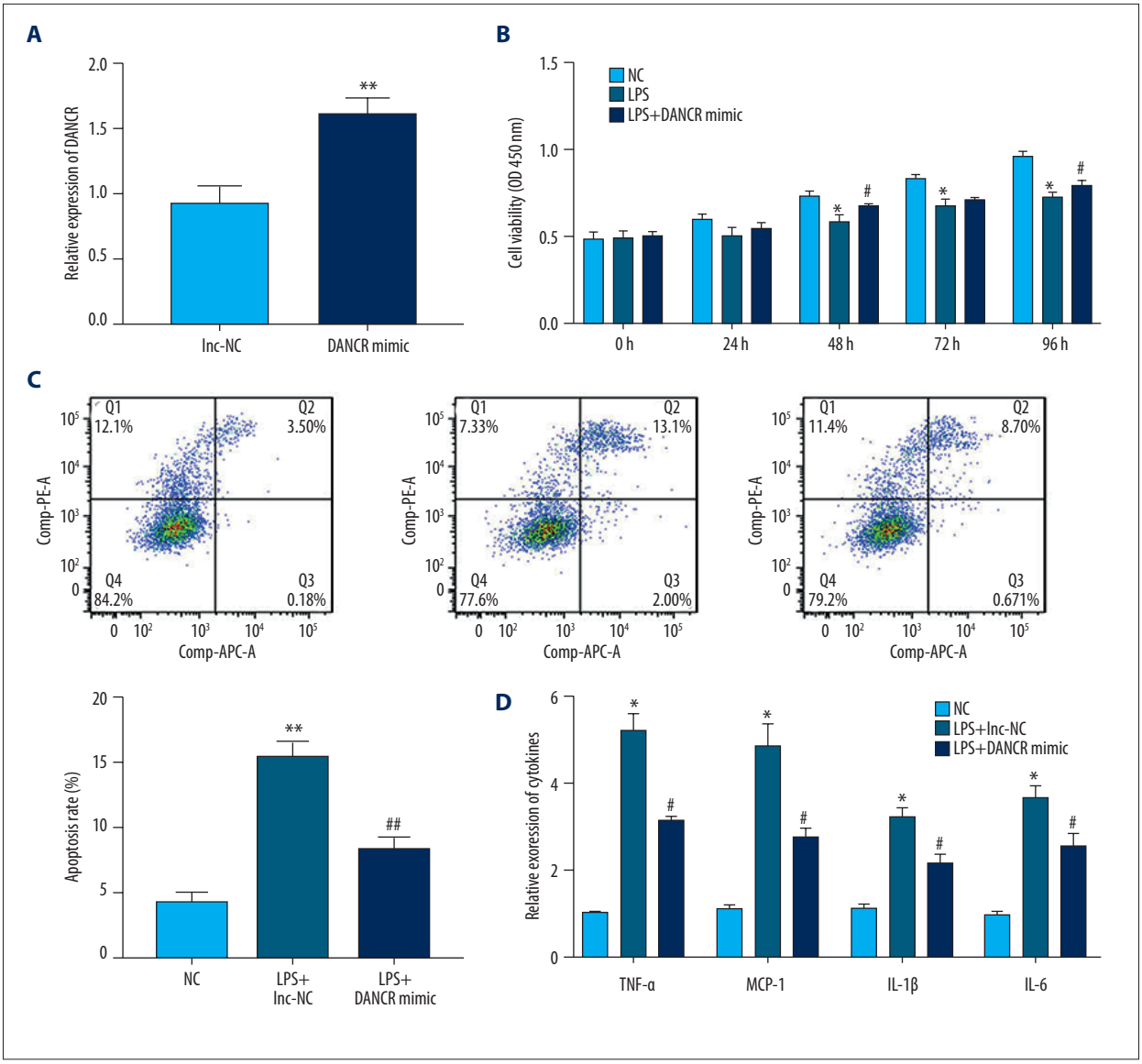

Figure 2. DANCR promoted cell viability and suppressed cell apoptosis and cytokine production in LPS-treated HK-2 cells. (**A**) DANCR overexpression was established in LPS-treated HK-2 cells. (**B**) DANCR overexpression significantly reduced the proliferation of LPS-treated HK-2 cells. (**C**) Flow cytometry analysis demonstrated that the cell apoptosis rate was lower in LPS-treated HK-2 cells after transfection with DANCR mimic. (**D**) DANCR overexpression obviously reduced the expression of related cytokines (TNF-α, MCP-1, IL-1β, and IL-6). * $P<0.05$ compared to the control group; # $P<0.05$ compared to the LPS group; ** $P<0.01$ compared to the control group; ## $P<0.01$ compared to the LPS group. DANCR – differentiation antagonizing nonprotein coding RNA; LPS – lipopolysaccharide; TNF – tumor necrosis factor, IL – interleukin; MCP – monocyte chemoattractant protein.

RNAs are closely related to the development of AKI [18]. As a novel lncRNA, DANCR has been observed to regulate the inflammatory phenotype of breast cancer cells in breast cancer progression [19]. DANCR also regulates the proliferation and apoptosis of chondrocytes in osteoarthritis [20]. Here, we initially found that the level of DANCR expression was notably downregulated in the serum of patients and HK-2 cells treated with LPS. Then, we observed that DANCR promoted cell viability and inhibited cell apoptosis and inflammatory cytokine production in LPS-treated HK-2 cells. These data implied that DANCR may repress the biological behavior of HK-2 cells under LPS-stimulated conditions.

It is accepted that lncRNAs may exert their regulatory function in gene expression by sponging miRNAs [21]. Bioinformatics analysis showed that DANCR could functionally act as a sponge for miR-214. Some studies have reported that miR-214 silencing attenuated inflammation progression and suppressed

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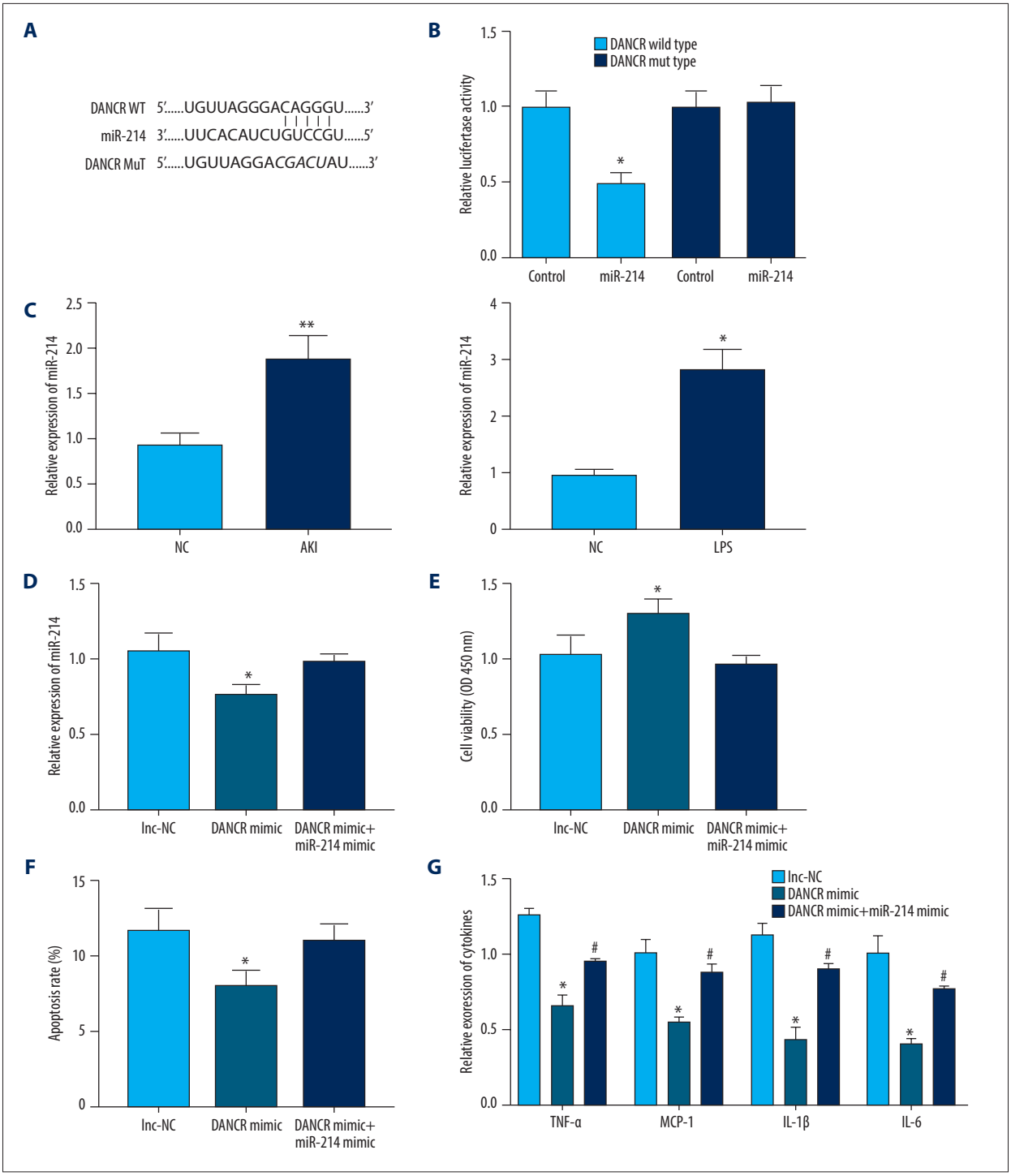

Figure 3. DANCR served as a sponge for miR-214. (**A**) Bioinformatics analysis showed that miR-214 has a potential binding site with DANCR. (**B**) Luciferase reporter assay revealed that miR-214 overexpression repressed the luciferase activity of only of the DANCR wild type construct in HK-2 cells. (**C**) The miR-214 level was significantly upregulated in patient sera and LPS-treated HK-2 cells. (**D**) DANCR overexpression significantly decreased miR-214 levels in HK-2 cells, which was reversed by the miR-214 mimic. (**E**) miR-214 mimic could reverse the effect of DANCR overexpression on the proliferation of HK-2 cells treated with LPS at 96 hours. (**F**) miR-214 mimic increased the apoptosis rate of LPS-treated HK-2 cells transfected with DANCR mimic. (**G**) The miR-214 mimic obviously promoted cytokine production in cells transfected with the DANCR mimic. * $P<0.05$ compared to the control group; # $P<0.05$ compared to the LPS group; ** $P<0.01$ compared to the control group. DANCR – differentiation antagonizing nonprotein coding RNA; LPS – lipopolysaccharide.

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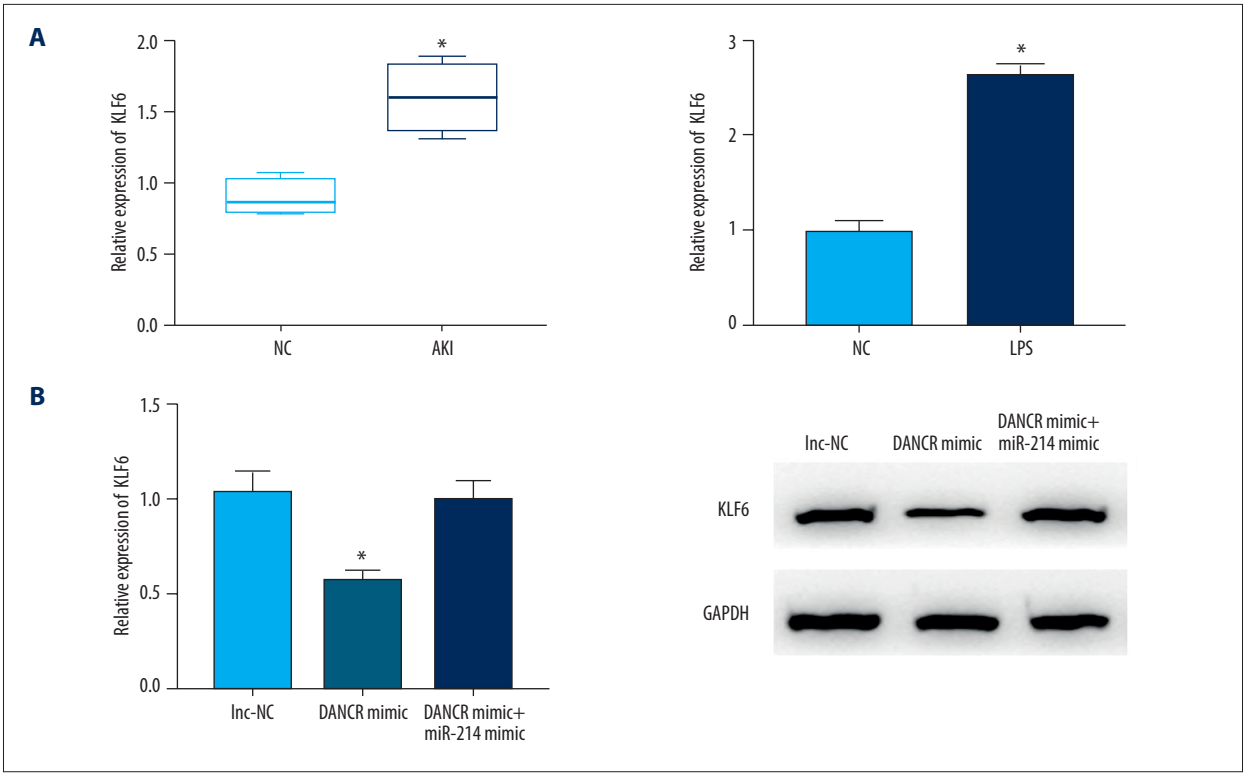

Figure 4. DANCR could suppress KLF6 expression. (**A**) KLF6 expression was significantly upregulated in the serum of patients and LPS-treated HK-2 cells. (**B**) DANCR overexpression downregulated the expression level of KLF6 in cells, which was reversed by the miR-214 mimic. * *P*<0.05 compared to the control group. DANCR – differentiation antagonizing nonprotein coding RNA; KLF6 – Krüppel-like factor 6; LPS – lipopolysaccharide.

the secretion of proinflammatory cytokines in some diseases [22,23]. Similarly, we observed that the miR-214 expression level was significantly upregulated in the blood serum of patients and LPS-treated HK-2 cells. In addition, miR-214 could rescue the suppressive effect of DANCR overexpression on the proliferation of HK-2 cells and increase cell apoptosis and cytokine production.

Krüppel-like factors (KLFs) are highly conserved zinc-finger proteins that regulate the cellular transcription machinery [24]. In light of the evidence that KLF6 promotes proinflammatory gene expression in kidney diseases [25], we investigated the effect of DANCR on this molecule. After transfection with DANCR, the level of KLF6 expression was remarkably downregulated in HK-2 cells treated with LPS. miR-214 reversed the inhibitory effect of DANCR on KLF6 expression. These data implied that DANCR may suppress KLF6 expression in LPS-induced septic AKI.

Conclusions

Overall, we first identified and confirmed that DANCR was downregulated in AKI. DANCR overexpression could alleviate AKI development by sponging miR-214 and inhibiting KLF6 expression, which provides a novel potential mechanism involved in the diagnosis and treatment of sepsis-induced AKI.

Conflict of interest

None.

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