Abstract. Long non-coding RNA (lncRNA) is considered a crucial modulator of the initiation and progression of several diseases. However, the roles of lncRNA in sepsis have yet to be fully elucidated. Thus, the aim of the present study was to investigate the effects of the lncRNA GDP-mannose 4,6-dehydratase antisense 1 (GMDS-AS1) and its target in order to understand its role in the pathogenesis of sepsis. An in vitro sepsis model was established by lipopolysaccharide (LPS) induction. Reverse transcription-quantitative PCR analysis was applied to detect the expression of inflammatory cytokines and the levels of GMDS-AS1, microRNA (miR)-96-5p and caspase-2 (CASP2). Flow cytometry was used to quantify the rate of apoptosis. In addition, the interaction between miR-96-5p and CASP2 was verified using a luciferase reporter assay. Western blot analysis was performed to assess the protein levels of CASP2 following alterations in GMDS-AS1 and miR-96-5p expression using transfection. The levels of interleukin (IL)-6, tumor necrosis factor-α and IL-1β were increased by LPS treatment in THP-1 cells, whereas miR-96-5p expression was downregulated. miR-96-5p overexpression inhibited LPS-induced inflammatory responses and apoptosis. In addition, GMDS-AS1 expression increased, and upregulation of GMDS-AS1 inhibited, the expression of miR-96-5p in the in vitro sepsis model. Moreover, CASP2 was confirmed to be a direct target of miR-96-5p. Therefore, the lncRNA GMDS-AS1 regulated inflammatory responses and apoptosis by modulating CASP2 and sponging miR-96-5p in LPS-induced THP-1 cells. In summary, the findings of the present study demonstrated that lncRNA GMDS-AS1 could promote the development of sepsis by targeting miR-96-5p/CASP2, indicating that the GMDS-AS1/miR-96-5p/CASP2 axis may be a new therapeutic target and potential research direction for sepsis therapy.

Introduction

Sepsis is a life-threatening systemic inflammatory response syndrome, which may be accompanied by multiple organ failure and septic shock in severe cases (1,2). Sepsis is a dominant cause of mortality worldwide, particularly in intensive care units, with a higher mortality rate compared with that of breast and lung cancer (3). In recent years, research had demonstrated that dysregulation of gene expression and dysfunction of the immune system are closely associated with the pathogenesis and pathophysiology of sepsis, in addition to pathogens and endotoxins (4-6). Furthermore, sepsis induces the excessive release of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α, as well as immunosuppression and tissue injury, thereby promoting susceptibility to secondary infections, these inflammatory cytokines contribute to aggressive immunopathology, including sepsis (7,8).

Long non-coding RNA (lncRNA) is a large class of non-protein-coding transcripts that are >200 nucleotides in length (9). It has been demonstrated that lncRNA plays various roles in numerous biological processes, such as cell proliferation, apoptosis, inflammatory and immune responses (10). Aberrant expression of lncRNA has been implicated in several inflammatory and immune diseases, including sepsis (11-13). For example, lncRNA H19 functions as a competitive endogenous (ce)RNA of microRNA (miRNA/miR)-874 to regulate the progression of sepsis, both in septic patients and in animal models of sepsis (14). The lncRNA HOX transcript antisense RNA accelerates the secretion of TNF-α in mice with lipopolysaccharide (LPS)-induced sepsis (15). The lncRNA GDP-mannose 4,6-dehydratase antisense 1 (GMDS-AS1) is a novel functional lncRNA that has only been studied in lung adenocarcinoma, in which it was found to inhibit cell proliferation and induce apoptosis by targeting the miR-96-5p/CYLD axis (16). However, few studies have investigated the role of GMDS-AS1 and its mechanism of action in the progression of sepsis.
In the present study, the expression of GMDS-AS1 was examined in LPS-induced THP-1 cells. The effects of GMDS-AS1 on the production of inflammatory factors and cell apoptosis were investigated. The study explored whether GMDS-AS1 functioned as a ceRNA to regulate the expression of caspase-2 (CASP2) by sponging mir-96-5p in LPS-induced THP-1 cells. The findings may contribute to the diagnosis and treatment of sepsis in the clinical setting.

**Materials and methods**

**Cell culture and treatment.** The human monocytic leukemia THP-1 cell line was obtained from the American Type Culture Collection and cultured in RPMI 1640 medium (MilliporeSigma) supplemented with 10% FBS (HyClone; Cytiva) at 37°C in a humidified atmosphere containing 5% CO₂. To mimic sepsis in vitro, THP-1 cells were stimulated with 1 µg/ml LPS (Sigma-Aldrich; Merck KGaA) for 24 h at 37°C.

**Cell transfection.** For the overexpression of GMDS-AS1 and mir-96-5p, the pcDNA3.1 vector containing full-length GMDS-AS1 (pcDNA-GMDS-AS1) and empty vector (pcDNA-NC), mir-96-5p mimics (5'-UUUGGCAACAGCA CAUUUUUGCUCAAAAAUGUGCUAGGCAAAUU-3') and miR-NC (cat. no. 4464061) were all designed and synthesized by Thermo Fisher Scientific, Inc. In addition, the cells that were not transfected with the plasmid were used as the control group. Following stimulation with 1 µg/ml LPS for 24 h at 37°C, THP-1 cells were transfected with pcDNA-GMDS-AS1 or/and mir-96-5p mimic using Lipofectamine® 2000 (Invitrogen; Thermo Fisher Scientific, Inc.) at a concentration of 50 ng/ml. Following transfection for 48 h at 37°C, the transfection efficiency was detected by reverse transcription-quantitative PCR (RT-qPCR).

**RT-qPCR analysis.** Total RNA was extracted from cells using TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.). The quality of the RNA was assessed using a NanoDrop 2000 spectrophotometer (Nanodrop Technologies; Thermo Fisher Scientific, Inc.) at 260 and 280 nm, according to the manufacturer's protocol. RT was performed using PrimeScript RT Master Mix (Takara Bio, Inc.) at 50°C for 45 min. qPCR was then performed with SYBR Premix EX Taq™ II (Takara Bio, Inc.) on an ABI PRISM 7300 detection system (Thermo Fisher Scientific, Inc.) with the following thermocycling conditions: Initial denaturation at 95°C for 30 sec, followed by 22 cycles at 95°C for 30 sec and 72°C for 30 sec. The results are presented using the 2^ΔΔCq method (17). U6 was used as an internal control of mir-96-5p and GAPDH served as the internal reference of IL-6, TNF-α, IL-β, GMDS-AS1 and CASP2. The following primer sequences were used: IL-6, forward 5'-GGA GAC TTTGCGCTTGTA AAA-3' and reverse, 5'-CTGGGT GCTT TCCCTACA TACT-3' and TNF-α, forward, 5'-AGCCGATGG GTGTGACCT-3' and reverse, 5'-TGA GGTGTTGTC CCCC CTTCT-3'; and IL-β, forward 5'-TGTTGCAGCAT CTA TGTC-3' and reverse, 5'-GGGAACATCAC ACAC CACTAGCA- and GMDS-AS1, forward 5'-AATGCTGTTT GAAGCC AGCTA-3' and reverse, 5'-TGGGTTCA AAGGT GTTGCAT-3', and CASP2, forward 5'-GCAA ACCTCA GGGAAACATT- and reverse, 5'-TGTCGGATA CGTTTCA GCA-3'; and GAPDH, forward 5'-CTGG GTCTAC ACTTG AGC-3' and reverse, 5'-AAGTGGTCTTG A GGGAATGTC-3'; and U6, forward 5'-CTCG CTTCCGC AGCA CACA-3' and reverse, 5'-AACGC TTTCA GAAATTC-3'.

**Luciferase reporter assay.** The wild-type and mutant CASP2 3'-untranslated region (UTR) fragments, including putative mir-96-5p-binding sites, were synthesized and cloned into the pGL3 vector (Promega Corporation). THP-1 cells were co-transfected with the wild-type and mutant constructs and miRNA (miR-NC; cat. no. 4464061 or miR-96-5p mimic (5'-UUUGGCAACAGCA CAUUUUUGCUCAAAAAUGUGCUAGGCAAAUU-3') and miR-NC (cat. no. 4464061) were all designed and synthesized by Thermo Fisher Scientific, Inc.) using Lipofectamine® 2000 (Invitrogen; Thermo Fisher Scientific, Inc.) at a concentration of 50 ng/ml. Following transfection for 48 h at 37°C, the transfection efficiency was detected by reverse transcription-quantitative PCR (RT-qPCR).

**Western blot analysis.** Cells were lysed using RIPA lysis buffer (Beiyotime Institute of Biotechnology), and the concentration of the proteins extracted from the cells was detected using a BCA Protein Assay kit (Beijing Dingguo Changsheng Biotechnology Co., Ltd.). A total of 20 µg protein samples were separated on 10% gels using SDS-PAGE and transferred onto PVDF membranes. After being blocked using 5% non-fat milk at room temperature for 1 h, the membranes were incubated with anti-caspase-2 primary antibody (1:500; cat. no. ab32021; Abcam) and anti-GAPDH primary antibody (1:2,500; cat. no. ab9485; Abcam) at 4°C overnight. The membranes were then incubated with a goat anti-rabbit secondary antibody (1:5,000; cat. no. ab6721; Abcam) for 1 h at room temperature. Proteins bands were visualized using an ECL reagent (Invtrogen; Thermo Fisher Scientific, Inc.) and analyzed with Image J software (version 3.0; National Institutes of Health).

**Bioinformatics analysis.** The Targets can Data Base (version 7.2; targetscan.org/vert_72/) was used to screen the target genes of miR-96-5p. P(CT) (probability of preferentially conserved targeting) was used to evaluate the conservative targeting probability of all highly conservative miRNA families.

**Statistical analysis.** SPSS 23.0 software (IBM Corp.) and GraphPad Prism 6 (GraphPad Software, Inc.) were used for statistical analysis.
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statistical analysis. The data are presented as the mean ± SD. Two-tailed Student's t-tests (unpaired) were used to compare the differences between two groups. Comparisons among multiple groups were performed with one-way ANOVA followed by Tukey's or Dunnett's post hoc test. P<0.05 was considered to indicate a statistically significant difference. All experiments were performed in triplicate.

Results

miR-96-5p is downregulated in an in vitro model of LPS-induced sepsis. An in vitro sepsis model was first established using LPS treatment of THP-1 cells, and the expression levels of IL-1β, IL-6, and TNF-α were detected. As shown in Fig. 1A, a significant increase in the secretion of IL-1β, IL-6, and TNF-α was observed following LPS stimulation. Additionally, miR-96-5p expression in THP-1 cells significantly decreased following induction with LPS (Fig. 1B). These results indicated that the septic cell model was successfully constructed and that miR-96-5p may be associated with the pathophysiology of sepsis.

miR-96-5p overexpression decreases LPS-induced inflammatory cytokine production and apoptosis. To explore the biological role of miR-96-5p in sepsis, a miR-96-5p mimic was transfected into THP-1 cells to upregulate miR-96-5p expression, and transfection efficiency was verified by RT-qPCR. The expression levels of miR-96-5p were significantly increased in the miR-96-5p mimic group compared with the control and miR-NC groups, demonstrating efficient transfection (Fig. 1C).

THP-1 cells were stimulated by LPS and transfected with miR-96-5p mimic or miR-NC (Fig. 2A), and the effects of miR-96-5p overexpression on the inflammatory responses and apoptosis of THP-1 cells were determined. As shown in Fig. 2B, LPS treatment significantly increased the mRNA expression of IL-6, TNF-α, and IL-1β, whereas miR-96-5p mimic decreased the levels of these inflammatory cytokines. Moreover, flow cytometry revealed a significantly increased rate of apoptosis in LPS-stimulated cells, whereas the opposite results were observed in miR-96-5p-overexpressing cells (Fig. 2C). These results suggested a protective role for miR-96-5p in LPS-induced THP-1 cells.

GMDS-AS1 is highly expressed and regulates miR-96-5p expression in LPS-induced THP-1 cells. RT-qPCR showed that the expression levels of GMDS-AS1 and mir-96-5p were significantly increased after co-transfection (Fig. 3A-B). The GMDS-AS1 level was then examined in THP-1 cells following LPS stimulation. As shown in Fig. 3C, the expression of GMDS-AS1 significantly increased following LPS stimulation. A GMDS-AS1 overexpression vector was transfected into THP-1 cells, and the transfection efficiency was verified by RT-qPCR. The expression levels of GMDS-AS1 were significantly increased in the pcDNA-GMDS-AS1 group compared with those in the control and pcDNA-NC groups, suggesting that the transfection was efficient (Fig. 3D). After transfection with pcDNA-GMDS-AS1 in THP-1 cells, miR-96-5p expression was significantly downregulated compared with that in the control and pcDNA-NC groups (Fig. 3E). These data indicated that GMDS-AS1 exerted a regulatory effect on miR-96-5p expression in LPS-induced THP-1 cells.
CASP2 is the target gene of miR-96-5p. To investigate the target gene of miR-96-5p in LPS-induced THP-1 cells, bioinformatics analysis was performed using TargetScan (www.targetscan.com). CASP2 was identified as one of the targets of miR-96-5p and the binding sequence is shown in Fig. 4A. Luciferase reporter assays demonstrated that the luciferase activity of the wild-type CASP2 construct was significantly inhibited by the miR-96-5p mimic, whereas that of the mutated CASP2 was not (Fig. 4B). In addition, the mRNA expression level of CASP2 significantly decreased after overexpression of miR-96-5p (Fig. 4C). Furthermore, LPS exposure significantly increased the expression of CASP2 (Fig. 4D). These findings confirmed the interaction between CASP2 and miR-96-5p in LPS-stimulated THP-1 cells.

GMDS-AS1/miR-96-5p affects inflammatory responses and apoptosis by modulating CASP2 expression. The subsequent experiments investigated how the GMDS-AS1/miR-96-5p axis might regulate inflammatory responses and apoptosis by CASP2. CASP2 and miR-96-5p mimic were transfected into THP-1 cells, and transfection efficiency was verified by RT-qPCR. The expression of CASP2 was significantly increased in the pcDNA-CASP2 group compared with that in the control and pcDNA-NC groups, demonstrating that the transfection was efficient (Fig. 5A). Moreover, the expression of CASP2 and miR-96-5p was maintained following co-transfection with miR-96-5p mimic and pcDNA-CASP2 (Fig. 5B).

THP-1 cells were stimulated by LPS, then co-transfected with pcDNA-GMDS-AS1 or pcDNA-NC and miR-96-5p or miR-NC. As shown in Fig. 5C, western blotting results revealed that following LPS stimulation, GMDS-AS1 overexpression significantly increased the protein levels of CASP2 compared with the control and pcDNA-NC groups; however, miR-96-5p mimic transfection significantly inhibited the CASP2 levels compared with pcDNA-GMDS-AS1 + miR-NC. Moreover, GMDS-AS1 increased, whereas miR-96-5p decreased, the levels of IL-6, TNF-α and IL-1β, indicating that CASP2 overexpression accelerated the production of inflammatory factors while downregulation of CASP2 exerted the opposite effects (Fig. 5D). In addition, the apoptosis rate significantly increased following GMDS-AS1 overexpression. However, this increase was inhibited by transfection with the miR-96-5p mimic (Fig. 5E). Thus, it may be concluded that the GMDS-AS1/miR-96-5p/CASP2 axis regulates the levels of inflammatory cytokines and apoptosis in THP-1 cells following LPS exposure.

Discussion

Severe sepsis is a life-threatening medical emergency (18). Although a standardized approach and new strategies for sepsis treatment have gradually developed, the pathogenesis of sepsis has yet to be fully elucidated (19,20). In the present study, the expression level of miR-96-5p and effects of miR-96-5p overexpression on inflammatory cytokine production and apoptosis were investigated in LPS-induced THP-1 cells. Moreover, the mechanism through which GMDS-AS1 regulates miR-96-5p and CASP2 to affect inflammatory responses and apoptosis.

miRNA participates in a variety of cellular processes, such as cell proliferation, metastasis and apoptosis (21,22). The dysregulation of miRNA contributes to the occurrence and development of multiple diseases, including sepsis (23-25).

miR-96-5p has been reported to be involved in several cancer
types. For example, Ress et al. (26) reported that miR-96-5p affected the proliferation of colorectal cancer (CRC) cells and was associated with poor survival of patients with CRC. Furthermore, miR-96-5p accelerated ovarian cancer cell proliferation and migration by targeting Caveolae1 (27). In addition, a previous study revealed that miR-96-5p expression....
Figure 5. Continued.
was significantly downregulated in clinical samples from patients with sepsis (28). In the present study, the expression level of miR-96-5p was decreased in an LPS-induced THP-1 cell model, which is consistent with previous reports (29,30). Moreover, upregulation of miR-96-5p inhibited the secretion of inflammatory factors, including IL-6, TNF-α and IL-1β, as well as apoptosis.

A previous study have reported that lncRNAs may act as ceRNAs that bind to sites similar to the 3'-UTR region of mRNA to regulate biological processes (31). In this regard, in the present study, the expression of GMDS-AS1 was detected in THP-1 cells exposed to LPS, revealing higher expression of GMDS-AS1 compared with that in untreated THP-1 cells. Subsequent experiments revealed that GMDS-AS1 overexpression inhibited miR-96-5p expression, highlighting the regulatory effect of GMDS-AS1 on miR-96-5p. In addition, the target gene of miR-96-5p was also examined in order to further elucidate the mechanisms underlying sepsis. Through bioinformatics analysis, CASP2 was predicted as the target gene of miR-96-5p in sepsis, and a luciferase reporter assay verified the association between miR-96-5p and CASP2. The subsequent experiments also demonstrated that CASP2 expression was altered in LPS-treated cells and was negatively modulated by miR-96-5p.

Excessive inflammatory responses and cell apoptosis are two major characteristics of sepsis (32,33). Anti-inflammatory and anti-apoptosis strategies have been considered as effective approaches for relieving or treating sepsis (34,35). Previous studies demonstrated that certain lncRNAs and miRNAs play regulatory roles in inflammatory responses and apoptosis to slow down the development of sepsis (36,37). Yong et al (38) demonstrated that the lncRNA metastasis-associated lung adenocarcinoma transcript 1 decreased the expression of breast cancer susceptibility gene 1 and recruited zeste homolog 2 to promote skeletal muscle cell apoptosis and inflammatory response in sepsis. Lu et al (39) reported that sepsis-induced kidney injury associated transcript 1 (SIKIAT1) was highly expressed both in sepsis patients and an LPS-treated sepsis cell model. SIKIAT1 silencing repressed cell apoptosis, whereas its overexpression promoted apoptosis by regulating the miR-96/forkhead box A1 axis (39). In the present study, upregulation of GMDS-AS1 increased the CASP2 level and this effect was reversed by miR-96-5p overexpression. The protein levels of IL-6, TNF-α and IL-1β and cell apoptosis were increased after GMDS-AS1 overexpression and decreased after treatment with miR-96-5p mimic, suggesting that GMDS-AS1 and miR-96-5p jointly regulate the inflammatory response and cell apoptosis by targeting CASP2.

In summary, the present study uncovered the significance of the lncRNA GMDS-AS1 in sepsis. GMDS-AS1 was demonstrated to facilitate inflammatory responses and cell apoptosis...
by targeting miR-96-5p/CASP2 in LPS-induced THP-1 cells. This ceRNA mechanism may provide novel evidence and a new research direction for the clinical treatment of sepsis.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LJ and JL designed the experiments. LJ was involved in the collection, interpretation and analysis of the data and wrote the manuscript. JL designed the study and was involved in data collection, analysis and interpretation, as well as preparation of the manuscript. LJ and JL confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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