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ORIGINAL RESEARCH

LncRNA PCED1B-AS1 Inhibits Sepsis-Induced Acute Kidney Injury by Promoting Transformation of Macrophages from M1 to M2 Type via Regulating the miR-361-3p/SOCS1 Axis

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Purpose: A common complication observed in septic patients under intensive care is acute kidney injury (AKI), which is characterized by acute onset and strong inflammation, resulting in poor clinical outcomes for patients. This study aims to explore the expression status of PCED1B-AS1 in sepsis-induced AKI and to preliminarily investigate the molecular mechanism by which PCED1B-AS1 affects AKI.

Patients and Methods: This study included 105 healthy individuals and 220 patients with sepsis (110 patients with AKI and 110 non-AKI patients). The levels of PCED1B-AS1 were examined by RT-qPCR. Macrophage polarization was induced by LPS treatment of RAW264.7 cells, and an in vitro renal injury model was established using HK-2 cells. Cell proliferation ability was evaluated by CCK-8 assay, apoptosis was detected by flow cytometry, and the levels of inflammatory factors were assessed using ELISA kits. The dual-luciferase assay was used to verify the interrelationship among the PCED1B-AS1/miR-361-3p/SOCS1 axis.

Results: PCED1B-AS1 was downregulated in sepsis patients without AKI and further reduced in AKI patients. PCED1B-AS1 could differentiate healthy individuals from non-AKI sepsis patients and identify AKI patients. Additionally, low PCED1B-AS1 expression correlated with poor AKI prognosis. Overexpression of PCED1B-AS1 promoted the polarization of M1 macrophages to M2 by regulating the miR-361-3p/SOCS1 axis, thereby inhibiting apoptosis and inflammatory responses in HK-2 cells.

Conclusion: PCED1B-AS1 may serve as a potential diagnostic and prognostic marker and inhibit sepsis-induced AKI by promoting transformation of macrophages from M1 to M2 type via regulating the miR-361-3p/SOCS1 axis.

Keywords: PCED1B-AS1, miR-361-3p, macrophage polarization, diagnosis, prognosis

Introduction

Sepsis is a life-threatening condition characterized by organ dysfunction, stemming from an improperly regulated host reaction to infectious agents, and is associated with an exceptionally high rate of mortality.[1] A common complication observed in septic patients under intensive care is acute kidney injury (AKI).[1] The pathophysiological basis underlying sepsis-induced AKI is intricate, encompassing a multitude of factors including modifications in renal hemodynamics, endothelial cell dysfunction, and heightened inflammatory responses.[2,3] Regrettably, sepsis-induced AKI carries a very poor prognosis. Additionally, the death rate among sepsis patients with AKI is estimated to be three to five times higher than in non-AKI.[4] The prevention of sepsis-induced AKI presents significant challenges, as the majority of patients typically initiate treatment only upon the manifestation of overt clinical signs.[5] Consequently, early identification is crucial, enabling the initiation of supportive therapies and the mitigation of disease progression in affected individuals.

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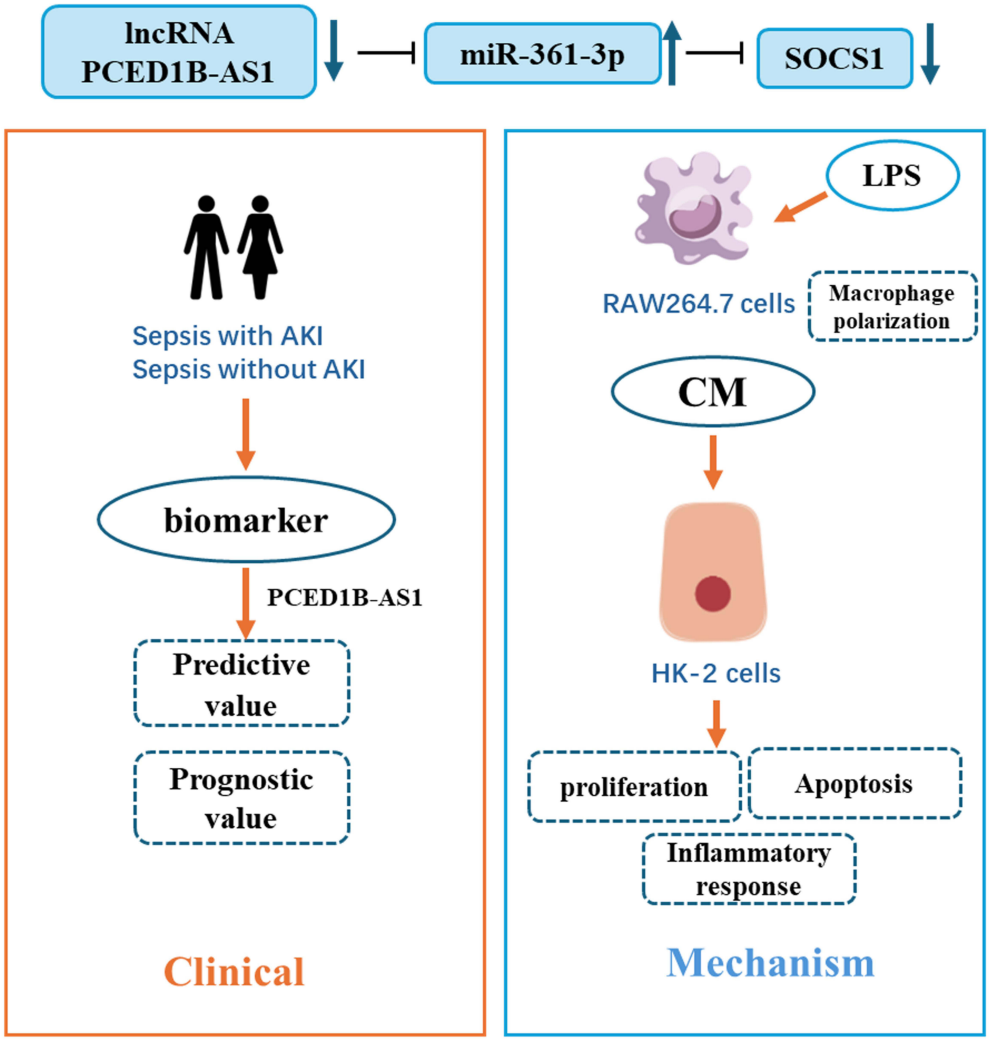
Graphical Abstract



PCED1B-AS1 may serve as a potential diagnostic and prognostic marker and inhibit sepsis-induced AKI by promoting transformation of macrophages from M1 to M2 type via regulating the miR-361-3p/SOCS1 axis

Evidence is mounting to suggest that while long noncoding RNAs (lncRNAs) lack the capacity for protein translation, they are involved in regulating the generation of proteins, consequently impacting disease states.[6,7] Extensive studies have demonstrated that lncRNA expression is often aberrant in diverse diseases, particularly relevant to conditions like sepsis-induced AKI.[8,9] Findings from previous studies indicate that PCED1B-AS1 plays a role in the advancement of various types of cancer, such as osteosarcoma,[10] gastric cancer,[11] and colorectal cancer.[12] PCED1B-AS1 could function as a biological indicator relevant to pulpitis pain.[13] Moreover, PCED1B-AS1 is dysregulated in diabetic retinopathy and regulates the function of retinal vascular endothelial cells.[14] In a study conducted by Zheng Liming et al, potential markers for diagnosing sepsis were screened, among which it was found that PCED1B-AS1 was downregulated in patients with sepsis.[15] However, it is not yet fully established if PCED1B-AS1 displays aberrant expression patterns during sepsis-induced AKI, nor has its precise regulatory mechanism been delineated.

Functionally, lncRNA has been demonstrated to serve as a microRNA (miRNA) competitive endogenous RNA (ceRNA), which helps alleviate the inhibitory impact of miRNA targeting downstream genes.[16] miR-361-3p is

abnormally expressed in various diseases and is involved in regulating the progression of these diseases, such as Alzheimer's disease,[17] acute myeloid leukemia,[18] and multiple cancers.[19,20] Furthermore, a point of significance is that the overexpression of miR-361-3p intensifies cardiac injury resulting from sepsis.[21] Consequently, we hypothesize that miR-361-3p holds a significant function in the development of AKI associated with sepsis.

The Suppressor of Cytokine Signaling (SOCS) family comprises key negative regulators of cytokine-mediated signaling pathways.[22] Specifically, SOCS1 contributes to peripheral T cell tolerance through suppression of aberrant T cell activation triggered by inflammatory cytokines.[23] Evidence indicates that SOCS1 peptidomimetics confer protection in pathological glomerular lesions associated with MsPGN by diminishing macrophage infiltration and restraining their polarization toward the M1 phenotype.[24] Furthermore, SOCS1 has been implicated as a critical modulator of inflammatory factors under physiological conditions.[25] Previous investigations also establish SOCS1 as a metabolic reprogramming regulator that mitigates excessive inflammation and preserves organ function in sepsis.[26] Bioinformatics analysis conducted in this study reveals potential binding sites between SOCS1 and miR-361-3p, implying a regulatory role of miR-361-3p in SOCS1 expression.

This study intends to explore the expression status of PCED1B-AS1 in sepsis-induced AKI. Through preliminary in vitro studies, we also aim to gain initial insights into the molecular mechanisms by which PCED1B-AS1 affects AKI. Moreover, this study evaluated the potential regulatory role of PCED1B-AS1 on the miR-361-3p/SOCS1 axis and its subsequent effects on the occurrence and advancement of sepsis-induced AKI.

Materials and Methods

Study Subjects

This study adheres to the Declaration of Helsinki, and the participants have been fully informed of the purpose of the trial. Approval of the investigational protocol was granted by the Institutional Review Board of Affiliated Hospital of Youjiang Medical University for Nationalities, with written consent obtained from all individuals participating in the study. The number of patients included in this study was determined based on the power analysis conducted by GPower software. With the given parameters of effect size f = 0.25, $\alpha = 0.05$, and power = 0.8, the minimum total sample size calculated was 153. A total of 110 patients with sepsis-induced AKI and 110 sepsis patients without AKI (non-AKI) were enrolled from the ICU at Affiliated Hospital of Youjiang Medical University for Nationalities. Furthermore, 105 healthy volunteers, participating in standard physical examinations, were incorporated into the Control group. Patient enrollment criteria for sepsis adhered to The Third International Consensus Definitions for Sepsis and Septic Shock.[27] All patients were admitted to the ICU within 24 hours of symptom onset. The diagnosis of AKI was established in accordance with the Improving Global Outcomes (KDIGO) guidelines.[28] In addition, this study excluded patients with chronic renal insufficiency or those who had undergone kidney transplantation, patients who had used nephrotoxic drugs, and patients with other complications, including but not limited to those with infectious diseases and autoimmune diseases.

Venous blood samples were drawn from all participants and then stood for 30 minutes before being centrifuged at a specific speed for 10 minutes to separate the serum. The isolated serum specimens were subsequently stored at −80°C for preservation prior to subsequent laboratory analysis. A 28-day post-admission follow-up period was conducted for patients diagnosed with AKI, during which their mortality outcomes were documented. Subsequently, the collected follow-up data underwent analysis via Kaplan-Meier analysis and Cox regression analysis.

Cell Culture and Treatment

The RAW264.7 mouse macrophage cells (ATCC, USA) were grown in DMEM (Life Technologies). Separately, human HK-2 proximal tubular epithelial cells, provided by BeNa Culture Collection, were cultured using DMEM/F12 medium (Life Technologies). A standard supplementation of 10% FBS was added to both media. Cells were incubated at 37°C under a CO_2 environment. For the induction of macrophage polarization, RAW264.7 cells were exposed to 10 μg/mL LPS for 24 h. Additionally, the medium conditioned (CM) from the macrophages was collected and used to expose HK-2 cells for 24 h.

Cell Transfection

To facilitate PCED1B-AS1 overexpression, the corresponding expression plasmid (oe-PCED1B-AS1) was generated by GenePharma. The empty vector was used as the negative control (oe-NC). Separately, for miR-361-3p overexpression, miR-361-3p mimic was sourced from GenePharma, with a mimic NC acting as its respective negative control. Transfection of all these agents into the cellular environment was accomplished using the Lipofectamine 3000 (Invitrogen).

qRT-PCR

The extraction of total RNA was performed with the aid of Trizol (Takara, Dalian, China). Reverse transcription was carried out using the PrimeScript™ RT Master Mix (Takara). Following this, qPCR was executed with the Power SYBR Green PCR Master Mix (Applied Biosystems, CA, USA). GAPDH acted as the reference gene for mRNA analysis, and U6 was chosen as the reference for miRNA assessment. Normalization of the Ct values was done using the $2^{-\Delta\Delta Ct}$ formula to determine relative expression levels. The primer sequences are shown in Supplementary Table 1.

CCK-8

Upon completion of treatment or transfection, cells were harvested and reseeded into 96-well plates. Following incubation for various time points, 10 μL of the CCK-8 reagent (Medchemexpress, NJ, USA) was dispensed into each well. The plates were incubated for a further 4 hours thereafter. Finally, cell viability measurements were performed at 450 nm using a standard microplate reader.

Flow Cytometry

Cell apoptosis was assessed utilizing the Annexin V, FITC Apoptosis Detection Kit, obtained from Dojindo (Kumamoto, Japan). In brief, HK-2 cells were resuspended and cultured within 6-well plates. Subsequently, the cells were labeled with FITC-conjugated Annexin V and propidium iodide. The extent of apoptosis was then quantified via flow cytometric analysis, performed using equipment from BD Biosciences (San Jose, CA, USA).

ELISA

The concentrations of several cytokines, specifically tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), interleukin 1 beta (IL-1β), interleukin 10 (IL-10), and transforming growth factor-β (TGF-β), were determined via ELISA using kits supplied by RD (Minneapolis, MN, USA) (Supplementary Table 2). All measurements were standardized to picograms per milliliter (pg/mL).

Western Blot

Proteins were extracted with RIPA lysis buffer (Beyotime), and their concentrations were measured employing a bicinchoninic acid protein assay kit (Beyotime). Separation was carried out using 10% SDS-PAGE, and proteins were subsequently electro-transferred to PVDF membranes. Blocking was conducted with 5% non-fat milk. Primary antibody incubation took place at 4 °C overnight. This was followed by incubation with an HRP-labeled goat anti-rabbit secondary antibody at 37 °C for 1 h. Blots were visualized with ECL detection reagent (Millipore) and analyzed quantitatively with ImageJ software. Protein expression was normalized relative to β-actin. The catalog numbers of antibodies are listed in Supplementary Table 2.

Dual-Luciferase Reporter Assay

To identify putative interaction sites, the StarBase platform was employed for predicting the binding interfaces between miR-361-3p and PCED1B-AS1, and between miR-361-3p and SOCS1 3'UTR. The PCED1B-AS1 sequence containing miR-361-3p binding sites and a corresponding mutant version were separately cloned into the pGL3 plasmid (Promega), resulting in the construction of wt-PCED1B-AS1, mut-PCED1B-AS1 vectors. The generation of the wt-SOCS1 and mut-SOCS1 vectors followed the same methodology. The vectors were co-transfected into HK-2 cells alongside either miR-361-3p mimic/inhibitor or the corresponding mimic/inhibitor NC, utilizing Lipofectamine 3000. Following a 48-hour incubation post-transfection, luciferase activity for each vector was assessed using the Dual-Luciferase Reporter Assay System (Promega).

Cecal Ligation and Puncture (CLP)

The CLP technique was employed to establish a sepsis model. Adult male Sprague-Dawley rats (n = 10, weight range 220–250 g) were obtained from Vital River Co. Ltd (Beijing, China). Following anesthesia induced by intraperitoneal administration of 10% chloral hydrate, a midline abdominal incision was performed. The mesentery and cecum were carefully dissected. The ileocecal valve was then ligated, and the cecal tip was perforated twice with a sterile needle. After extrusion of fecal content, the cecum was repositioned into the abdominal cavity. In the sham-operated group, only dissection of the mesentery and cecum was performed before suturing the incision, with all other steps matching the sepsis group. After 24 hours, rats were anesthetized using 3% pentobarbital and euthanized. Kidney tissues were harvested and cryopreserved in liquid nitrogen for subsequent analysis.

Statistical Analysis

The dataset was summarized using mean values ± standard deviation (SD), and subsequent statistical analysis was carried out with the aid of GraphPad Prism 9.0 and SPSS 26.0. Within the clinical analysis, the ROC curve was used to evaluate the diagnostic significance of PCED1B-AS1. Survival data derived from follow-up studies were evaluated using the Kaplan-Meier method and Cox regression analysis. Regarding the in vitro experiment of the study, cell culture experiments were performed in triplicate, each involving three parallel technical replicates. The determination of statistical differences between two experimental groups relied on the *t*-test, while comparisons in multiple groups were executed using ANOVA.

Results

Patient Baseline Characteristics

The analysis revealed no significant disparities in age or gender among the healthy controls, the non-AKI cohort, and the AKI cohort ($P>0.05$). In comparison to the healthy control group, sepsis patients with non-AKI displayed significantly increased CRP and NGAL levels and a corresponding decrease in eGFR ($P<0.001$). On the other hand, when compared to both the healthy control and non-AKI groups, AKI patients showed significant increases in CRP, Scr, BUN, and NGAL levels, along with decreased eGFR levels ($P<0.001$). Additionally, it was observed that AKI patients had markedly greater SOFA and APACHE II scores than non-AKI patients ($P<0.001$) (Table 1).

Table 1 Comparison of Baseline Data

	Healthy (n=105)	Non-AKI (n=110)	AKI (n=110)
Age (years)	49.22±10.95	50.33±10.14	52.11±10.43
Gender (male, n)	57	66	63
CRP (ng/mL)	2.54±0.29	64.84±16.39 [a]	92.77±24.78 [a,b]
Scr (mmol/L)	58.91±15.59	63.79±15.05	165.20±17.21 [a,b]
BUN (mmol/L)	4.60±0.72	4.83±0.91	19.15±5.34 [a,b]
eGFR (mL/min per 1.73 m^2)	97.95±7.08	66.58±7.76 [a]	47.68±6.14 [a,b]
NGAL (ng/mL)	5.09±1.34	59.18±6.77 [a]	258.27±31.92 [a,b]
SOFA	/	4.58±2.48	18.31±3.82 [b]
APACHE II	/	11.53±2.48	18.31±3.82 [b]

Notes: [a]$P < 0.05$ in relative to healthy individuals; [b]$P < 0.05$ in relative to non-AKI patients.
Abbreviations: AKI, acute kidney injury; CRP, C-reactive protein; Scr, serum creatinine; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration; NGAL, neutrophil gelatinase-associated lipocalin; SOFA, sequential organ failure assessment; APACHE II, acute physiology and chronic health evaluation.

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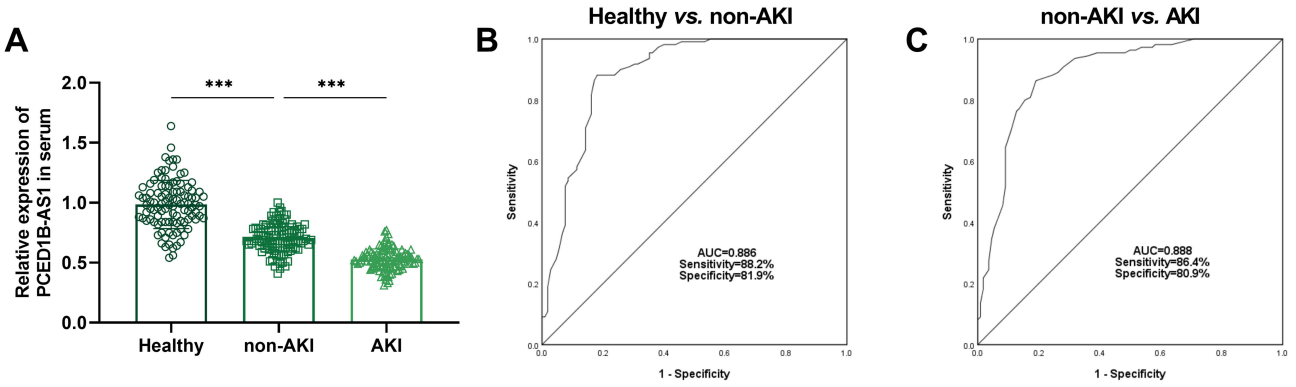

Figure 1 The expression level of PCED1B-AS1 and its diagnostic role. ***P<0.001. The expression level of PCED1B-AS1 in the serum of healthy individuals and sepsis patients with non-AKI and AKI (**A**). PCED1B-AS1 could differentiate healthy individuals from non-AKI sepsis patients (**B**) and identify AKI patients (**C**).

The Expression Level of PCED1B-AS1 in Serum and Its Diagnostic Role

A significant reduction in PCED1B-AS1 expression level in serum was noted when comparing the non-AKI group to the healthy controls (95% CI=0.233 to 0.325, P<0.001). This downregulation was more pronounced among AKI patients, whose expression levels were markedly lower than those in the non-AKI sepsis group (95% CI=0.133 to 0.224, P<0.001, Figure 1A). Moreover, significantly reduced levels of PCED1B-AS1 in serum could effectively separate the group of sepsis patients without AKI from the healthy control group (AUC=0.886, sensitivity=88.2%, specificity=81.9%, 95% CI=0.840 to 0.932) (Figure 1B). In a similar capacity, PCED1B-AS1 also demonstrated utility in identifying AKI cases from non-AKI patients (AUC=0.888, sensitivity=86.4%, specificity=80.9%, 95% CI=0.843 to 0.932) (Figure 1C).

The Expression Level of PCED1B-AS1 Was Associated with the Prognosis of Sepsis-Induced AKI Patients

Based on the average serum PCED1B-AS1 level of sepsis patients without AKI as the cut-off point, sepsis patients without AKI were divided into a high-expression group and a low-expression group. The Kaplan-Meier curve showed that the 28-day survival rate of sepsis patients with low expression of PCED1B-AS1 was lower than that of the high-expression group (Log Rank P=0.041, Figure 2A). Patients with AKI were categorized into low- and high-expression groups based on the average serum PCED1B-AS1 expression level within this patient subset. The findings indicated a significant association between the levels of PCED1B-AS1 and the values of Scr, eGFR, and NGAL, as well as the calculated scores for SOFA and APACHE II, and there was no correlation between CRP levels and PCED1B-AS1 levels (Table 2). Moreover, a poorer clinical outcome was noted among patients classified into the low-expression group in sepsis-induced AKI patients (Log Rank P=0.017, Figure 2B). In addition, results from multivariate Cox regression analysis pointed towards PCED1B-AS1 potentially serving as an independent determinant of prognosis in septic individuals with AKI (HR = 0.354, 95% CI = 0.147 to 0.856, P=0.021) (Figure 2C).

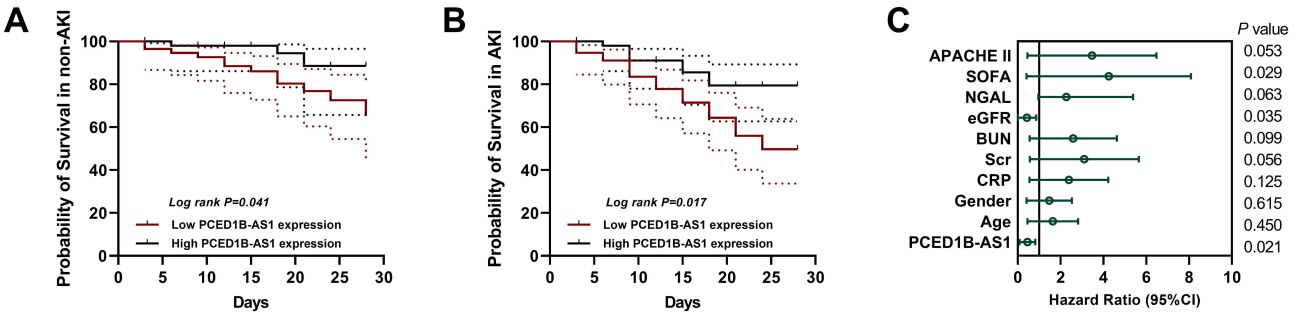

Figure 2 The expression level of PCED1B-AS1 was associated with the prognosis of sepsis-induced AKI patients. The downregulation of serum PCED1B-AS1 was closely related to poor prognosis in sepsis patients with non-AKI (**A**). The downregulation of serum PCED1B-AS1 was closely related to poor prognosis in patients with sepsis-induced AKI (**B**), and it was an independent prognostic indicator (**C**).

Table 2 The Correlation Between the Expression of PCED1B-AS1 and Clinical Indicators

	Patients (n=110)	PCED1B-AS1 Expression		P Value
		Low	High	
Age (years)				0.881
<52	49	25	24	
≥52	61	32	29	
Gender				0.364
Female	47	22	25	
Male	63	35	28	
CRP (ng/mL)				0.129
<92	54	24	30	
≥92	56	33	23	
Scr (mmol/L)				0.034
<165	57	24	33	
≥165	53	33	20	
BUN (mmol/L)				0.059
<19	52	22	30	
≥19	58	35	23	
eGFR (mL/min per 1.73 m^2)				0.022
<47	54	34	20	
≥47	56	23	33	
NGAL (ng/mL)				0.038
<258	51	21	30	
≥258	59	36	23	
SOFA				0.009
<8	67	28	39	
≥8	43	29	14	
APACHE II				0.024
<18	50	20	30	
≥18	60	37	23	

Abbreviations: AKI, acute kidney injury; CRP, C-reactive protein; Scr, serum creatinine; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration; NGAL, neutrophil gelatinase-associated lipocalin; SOFA, sequential organ failure assessment; APACHE II, acute physiology and chronic health evaluation.

The Expression Level of miR-361-3p and Its Relationship with PCED1B-AS1

Elevated expression of miR-361-3p in serum was observed in non-AKI sepsis patients relative to healthy controls (95% CI=−0.489 to −0.357, $P<0.001$). Furthermore, AKI patients exhibited even higher levels of miR-361-3p compared to non-AKI patients (95% CI=−0.477 to −0.347, $P<0.001$, Figure 3A). Correlation analysis demonstrated a significant

negative association between PCED1B-AS1 expression levels and miR-361-3p levels within the AKI patient group (r= −0.783, 95% CI=−0.846 to −0.698, *P*<0.001, Figure 3B). Dual-luciferase reporter assays showed that increased miR-361-3p expression was associated with diminished luciferase activity originating from wt-PCED1B-AS1 (95% CI=0.209 to 0.751, *P*<0.001), while miR-361-3p inhibition was associated with augmented luciferase activity from the same construct (95% CI=−0.814 to −0.272, *P*<0.001, Figure 3C).

Overexpression of PCED1B-AS1 Promoted M2 Polarization of LPS-Treated Macrophages

The expression of PCED1B-AS1 was significantly downregulated in RAW264.7 cells treated with LPS (95% CI=0.303 to 0.664, *P*<0.001), however, its expression level was significantly restored after transfection with the overexpression vector of PCED1B-AS1 (95% CI=−0.474 to −0.113, *P*<0.01, Figure 4A). Meanwhile, LPS stimulation led to a significant upregulation of miR-361-3p in RAW264.7 cells (95% CI=−0.826 to −0.287, *P*<0.001), while overexpression of PCED1B-AS1 effectively inhibited the expression of miR-361-3p (95% CI=0.194 to 0.733, *P*<0.001). Notably,

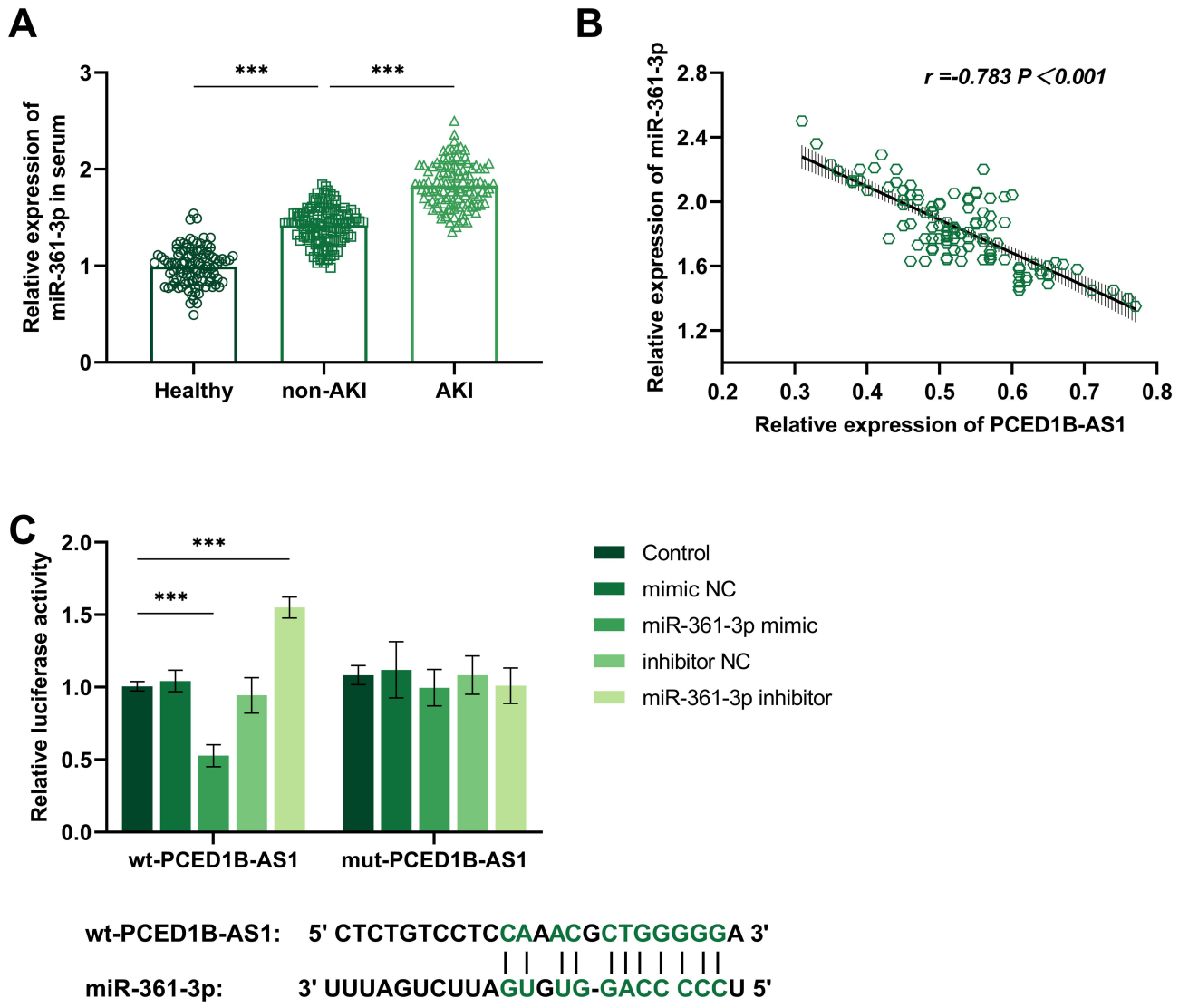

Figure 3 The expression level of miR-361-3p and its relationship with PCED1B-AS1. ****P*<0.001. The expression level of miR-361-3p in the serum of healthy individuals and sepsis patients with non-AKI and AKI (**A**). The expression levels of PCED1B-AS1 and miR-361-3p were significantly negatively correlated (**B**), and the dual-luciferase assay verified their binding relationship (**C**).

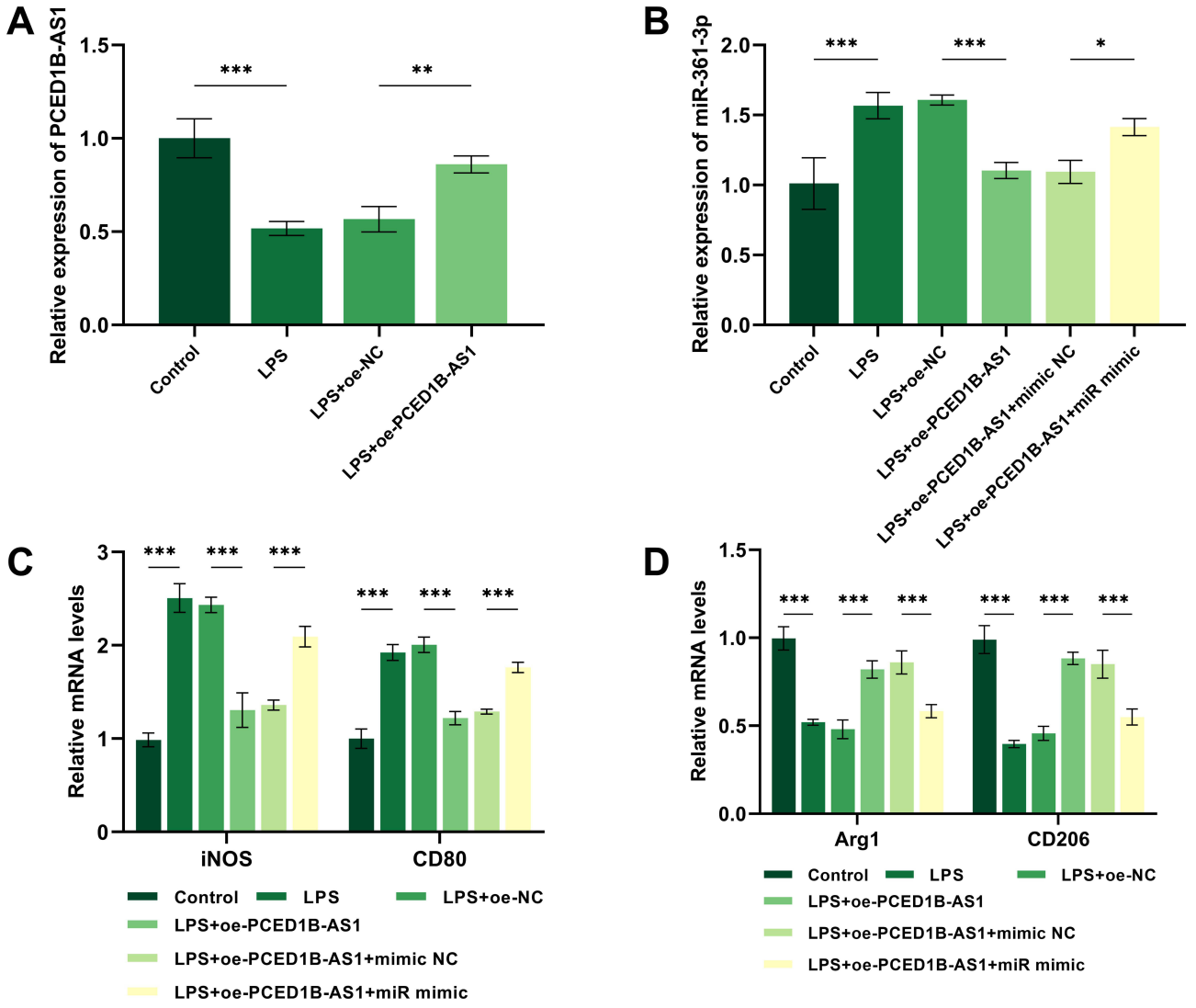

Figure 4 Overexpression of PCED1B-AS1 promoted M2 polarization of LPS-treated macrophages. ***P<0.001, **P<0.01, *P<0.05. In LPS-induced macrophages, the expression of PCED1B-AS1 decreased while miR-361-3p increased. Moreover, miR-361-3p mimic counteracted the inhibitory effect of PCED1B-AS1 overexpression on miR-361-3p (**A** and **B**). miR-361-3p mimic counteracted the effect of PCED1B-AS1 overexpression on M1 (**C**) and M2 (**D**) polarization markers.

transfection with miR-361-3p mimic reversed the expression level of miR-361-3p to a higher level (95% CI=−0.589 to −0.051, P<0.05, Figure 4B). To further explore the roles of PCED1B-AS1 and miR-361-3p in macrophage polarization, we examined the expression levels of M1 and M2 phenotypic markers. LPS treatment significantly upregulated the mRNA levels of M1 polarization markers (iNOS and CD80) (iNOS: 95% CI=−1.772 to −1.268, CD80: 95% CI= −1.175 to −0.6714, P<0.001, Figure 4C), while significantly downregulating the mRNA expression of M2 polarization markers (Arg1: 95% CI=0.343 to 0.611, CD206: 95% CI=0.459 to 0.727, P<0.001, Figure 4D). This indicates that LPS treatment induced macrophages towards the M1 type. However, in the case of overexpression of PCED1B-AS1, the expression of M1 markers iNOS and CD80 significantly decreased (iNOS: 95% CI=0.948 to 1.45, CD80: 95% CI=0.451 to 0.955, P<0.001), while the expression of M2 markers Arg1 and CD206 significantly increased (Arg1: 95% CI=−0.434 to −0.166, CD206: 95% CI=−0.621 to −0.353, P<0.001), suggesting that PCED1B-AS1 may promote macrophage polarization towards the M2 type. The upregulation of miR-361-3p counteracted the effects of PCED1B-AS1 on the markers of M1 and M2 polarization.

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Overexpression of PCED1B-AS1 Reduced Apoptosis and Inflammatory Responses in HK-2 Cells by Regulating miR-361-3p

The expression of PCED1B-AS1 in CM-incubated HK-2 cells was significantly downregulated (95% CI=0.183 to 0.657, $P<0.01$), but its expression level was significantly restored after transfection with oe-PCED1B-AS1 (95% CI=−0.621 to −0.146, $P<0.01$, Figure 5A). In contrast, the expression of miR-361-3p was significantly upregulated in HK-2 cells cultured with CM (95% CI=−1.052 to −0.588, $P<0.001$), but the overexpression of PCED1B-AS1 inhibited the levels of miR-361-3p (95% CI=0.368 to 0.832, $P<0.001$), while the transfection of miR-361-3p mimic reversed this trend (95% CI=−0.586 to −0.121, $P<0.01$, Figure 5B). Additionally, CM treatment significantly reduced the proliferation ability of HK-2 cells (95% CI=0.517 to 0.822, $P<0.001$), but the overexpression of PCED1B-AS1 enhanced the cell proliferation ability (95% CI=−0.566 to −0.261, $P<0.001$), and the upregulation of miR-361-3p weakened this effect (95% CI=0.247 to 0.552, $P<0.001$, Figure 5C). Meanwhile, CM treatment significantly increased the apoptosis rate of HK-2 cells (95% CI=−15.070 to −8.242, $P<0.001$) and enhanced the inflammatory response, which manifested as increased concentrations of TNF-α (95% CI=−208.7 to −137.5, $P<0.001$), IL-1β (95% CI=−121.0 to −49.75, $P<0.001$) and IL-6 (95% CI=−184.8 to −113.6, $P<0.001$), and decreased concentrations of IL-10 (95% CI=64.69 to 110.2, $P<0.001$) and TGF-β (95% CI=116.9 to 162.4, $P<0.001$). However, after transfection with oe-PCED1B-AS1, the apoptosis (95% CI=5.582 to 12.41, $P<0.001$) rate and inflammatory levels of cells significantly decreased, the concentrations of TNF-α (95% CI=119.8 to 191.0, $P<0.001$), IL-1β (95% CI=27.88 to 99.12, $P<0.001$) and IL-6 (95% CI=81.70 to 152.9, $P<0.001$) decreased, and concentrations of IL-10 (95% CI=−86.21 to −40.67, $P<0.001$) and TGF-β (95% CI=−110.6 to −65.01, $P<0.001$) increased, while the transfection of miR-361-3p mimic partially counteracted the inhibitory effect of PCED1B-AS1 on the apoptosis (95% CI=−10.10 to −3.269, $P<0.001$) and inflammatory response (TNF-α (95% CI=−145.0 to

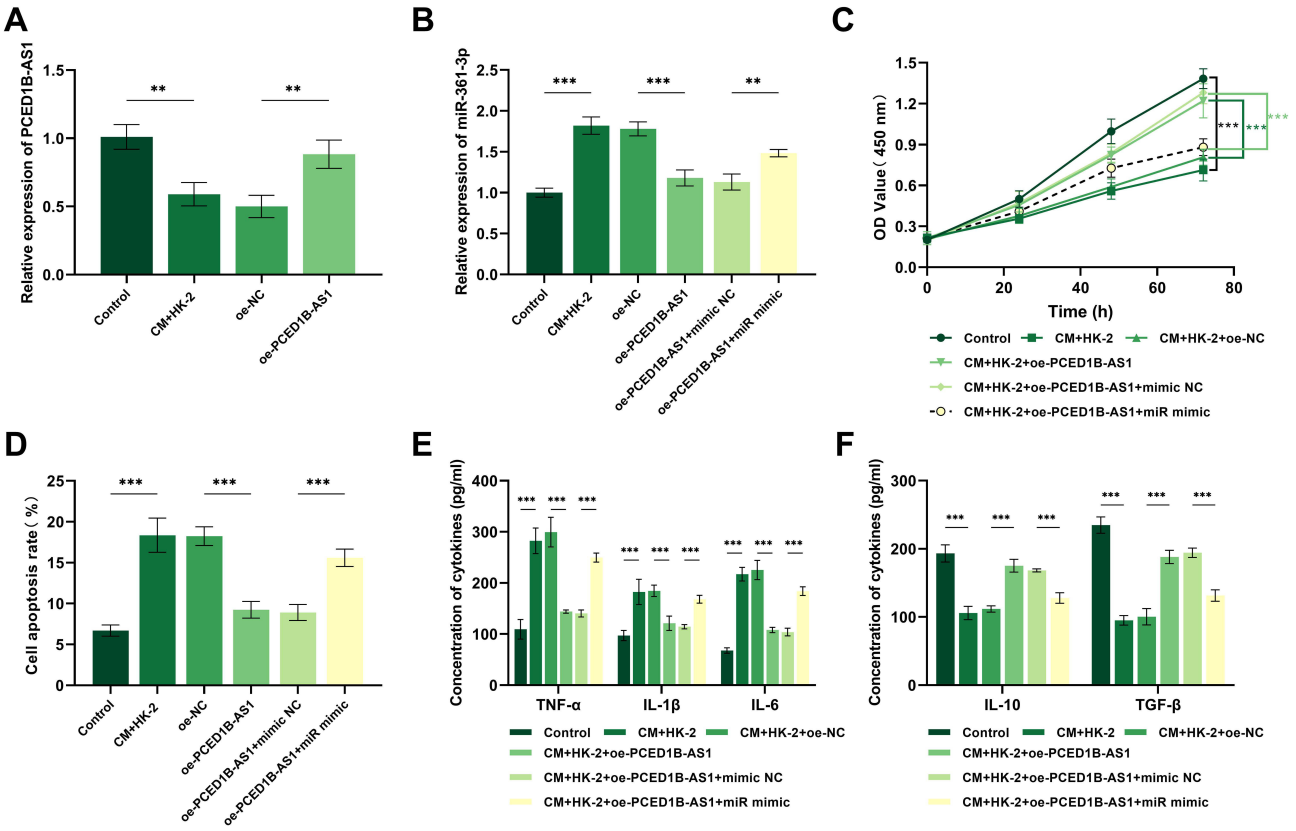

Figure 5 Overexpression of PCED1B-AS1 alleviated apoptosis and inflammatory responses in CM-treated HK-2 cells. ***$P<0.001$, **$P<0.01$. CM refers to conditioned media from macrophages incubated with LPS. In CM-treated HK-2 cells, the expression of PCED1B-AS1 decreased while miR-361-3p increased. Moreover, miR-361-3p mimic counteracted the inhibitory effect of PCED1B-AS1 overexpression on miR-361-3p (**A** and **B**). miR-361-3p mimic counteracted the effect of PCED1B-AS1 overexpression on proliferation (**C**), apoptosis (**D**), and inflammatory factors (**E** and **F**) in CM-treated HK-2 cells.

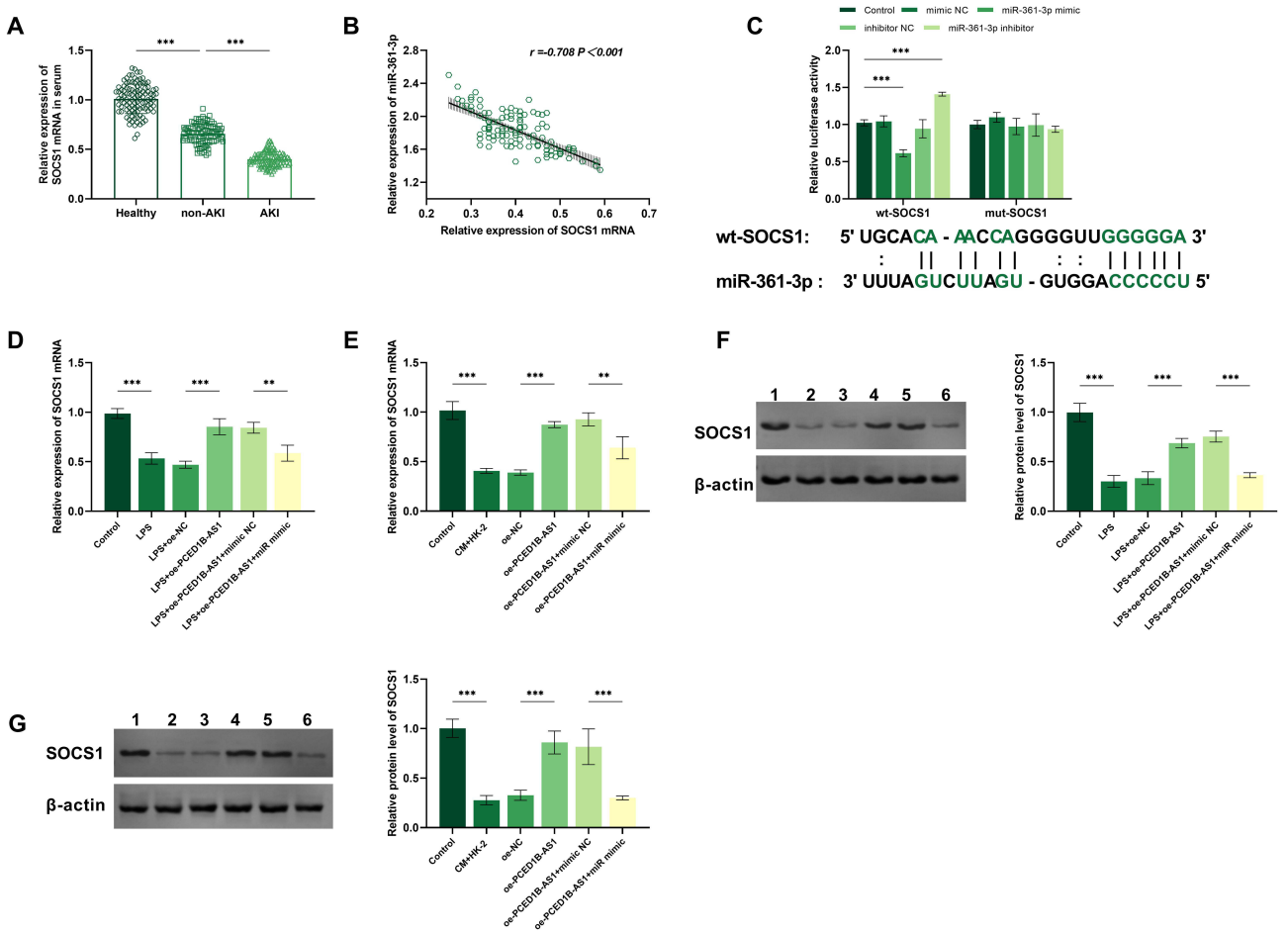

Figure 6 SOCS1 was one of the target genes of miR-361-3p. ***P*<0.001, **P*<0.01. CM refers to conditioned media from macrophages incubated with LPS. The expression level of SOCS1 in the serum of healthy individuals and sepsis patients with non-AKI and AKI (**A**). The expression levels of SOCS1 and miR-361-3p were significantly negatively correlated (**B**), and the dual-luciferase assay verified their binding relationship (**C**). In LPS-induced macrophages and CM-treated HK-2 cells, the mRNA and protein expression of SOCS1 decreased; overexpression of PCED1B-AS1 promoted the mRNA and protein expression of SOCS1, while miR-361-3p mimic inhibited the mRNA and protein expression of SOCS1 (**D**–**G**).

−73.75, *P*<0.001), IL-1β (95% CI=−89.55 to −18.32, *P*<0.001), IL-6 (95% CI= −115.6 to −44.38, *P*<0.001), IL-10 (95% CI= 17.84 to 63.38, *P*<0.001) and TGF-β (95% CI=40.05 to 85.60, *P*<0.001)) of HK-2 cells (Figure 5D–F).

SOCS1 Was One of the Target Genes of miR-361-3p

The expression level of SOCS1 was significantly decreased in non-AKI sepsis patients (95% CI=0.318 to 0.389, *P*<0.001) and further decreased in AKI patients (95% CI=0.221 to 0.291, *P*<0.001, Figure 6A). The expression of SOCS1 in AKI patients was significantly negatively correlated with miR-361-3p (r=−0.708, *P*<0.001,95% CI=−0.790 to −0.600, Figure 6B). miR-361-3p mimic significantly suppressed the luciferase activity of wt-SOCS1 (95% CI=0.207 to 0.613, *P*<0.001), and the miR-361-3p inhibitor markedly enhanced the luciferase activity of wt-SOCS1 (95% CI=−0.589 to −0.184, *P*<0.001). Notably, miR-361-3p mimic and miR-361-3p inhibitor exerted no significant effect on the luciferase activity of mut-SOCS1 (Figure 6C). Both LPS-stimulated macrophages (95% CI=0.282 to 0.624, *P*<0.001) and CM-exposed HK-2 cells (95% CI=0.425 to 0.795, *P*<0.001) exhibited significantly decreased levels of SOCS1. Overexpression of PCED1B-AS1 increased SOCS1 mRNA expression (LPS-stimulated macrophages: 95% CI=−0.554 to −0.212, CM-exposed HK-2 cells: 95% CI=−0.668 to −0.298, *P*<0.001), whereas miR-361-3p mimic had the opposite effect, leading to decreased SOCS1 mRNA levels (95% CI=−15.07 to −8.242, *P*<0.01, Figure 6D and E). SOCS1 protein expression was significantly suppressed in both LPS-stimulated macrophages (95% CI=0.530 to 0.864, *P*<0.001) and CM-exposed HK-2 cells (95% CI=0.453 to 1.00, *P*<0.001). Overexpression of PCED1B-AS1 counteracted this effect,

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upregulating SOCS1 protein (LPS-stimulated macrophages: 95% CI=−0.520 to −0.186, CM-exposed HK-2 cells: 95% CI=−0.807 to −0.260, $P<0.001$). By contrast, the introduction of miR-361-3p mimic downregulated SOCS1 expression (LPS-stimulated macrophages: 95% CI=0.223 to 0.557, CM-exposed HK-2 cells: 95% CI=0.243 to 0.790, $P<0.001$, Figure 6F and G). These findings not only documented the altered expression patterns of SOCS1 under these specific conditions but also highlighted the critical regulatory functions of PCED1B-AS1 and miR-361-3p in modulating SOCS1 levels.

Knockdown of SOCS1 Counteracted the Effects of PCED1B-AS1 Overexpression on Cells

After overexpression of PCED1B-AS1 in LPS-treated RAW264.7 cells, the mRNA (95% CI=−0.920 to −0.306, $P<0.001$) and protein expression of SOCS1 (95% CI=−1.472 to −0.867, $P<0.001$) were upregulated. Transfection with si-SOCS1 led to a decrease in the mRNA (95% CI=0.186 to 0.800, $P<0.01$) and protein expression (95% CI=0.877 to 1.509, $P<0.001$) of SOCS1 (Figure 7A and B). Additionally, SOCS1 knockdown reversed the inhibitory effect of PCED1B-AS1 overexpression on M1 polarization markers (iNOS: 95% CI=−0.492 to −0.088, CD80: 95% CI=−0.495 to −0.091, $P<0.001$, Figure 7C), and simultaneously, it reversed the promoting effect of PCED1B-AS1 overexpression on M2 polarization markers (Arg1: 95% CI=−0.874 to −0.486, CD206: 95% CI=0.399 to 0.787, $P<0.001$, Figure 7D). In addition, in CM-incubated HK-2 cells, overexpression of PCED1B-AS1 promoted the levels of SOCS1 mRNA (95% CI= −0.939 to −0.374, $P<0.001$) and protein expression (95% CI=−1.919 to −1.287, $P<0.001$), and si-SOCS1 transfection reversed the mRNA (95% CI=0.278 to 0.842, $P<0.001$) and protein levels (95% CI=0.877 to 1.509, $P<0.001$) of SOCS1 (Figure 7E and 7F). Moreover, SOCS1 knockdown reversed the promoting effect of PCED1B-AS1 overexpression on

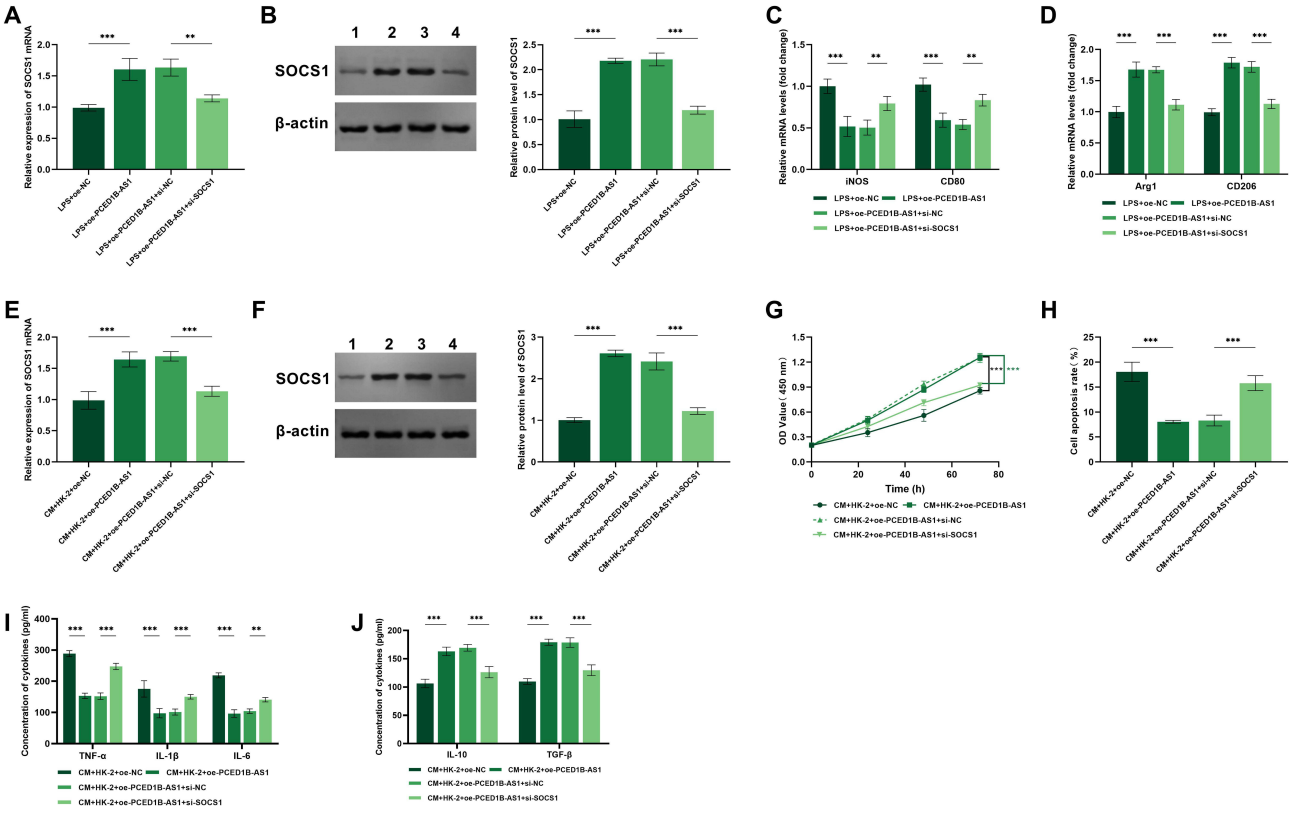

Figure 7 Knockdown of SOCS1 counteracted the effects of PCED1B-AS1 overexpression on cells. ***$P<0.001$, **$P<0.01$. CM refers to conditioned media from macrophages incubated with LPS. In LPS-induced macrophages, si-SOCS1 counteracted the promoting effect of PCED1B-AS1 overexpression on SOCS1 levels (**A** and **B**). si-SOCS1 counteracted the effect of PCED1B-AS1 overexpression on M1 (**C**) and M2 (**D**) polarization markers. In CM-treated HK-2 cells, si-SOCS1 counteracted the promoting effect of PCED1B-AS1 overexpression on SOCS1 levels (**E** and **F**). si-SOCS1 counteracted the effect of PCED1B-AS1 overexpression on proliferation (**G**), apoptosis (**H**), and inflammatory factors (**I** and **J**) in CM-treated HK-2 cells.

HK-2 cell proliferation (95% CI=0.240 to 0.413, $P<0.001$, Figure 7G) and the inhibitory effect on apoptosis (95% CI=−11.01 to −3.966, $P<0.001$, Figure 7H). Additionally, SOCS1 knockdown also reversed the inhibitory effect of PCED1B-AS1 overexpression on inflammation in HK-2 cells, resulting in increased concentrations of TNF-α (95% CI=−122.5 to −68.25, $P<0.001$), IL-1β (95% CI=−76.22 to −21.98, $P<0.001$), and IL-6 (95% CI=−63.86 to −9.624, $P<0.001$), and decreased concentrations of IL-10 (95% CI=25.27 to 61.01, $P<0.001$) and TGF-β (95% CI=31.01 to 66.75, $P<0.001$) (Figure 7I and J).

The Changes of PCED1B-AS1/miR 361-3p/SOCS1 in Renal Tissues of Septic Rats

To verify the expression changes of PCED1B-AS1, miR-361-3p, and SOCS1 in renal tissues related to sepsis-induced acute kidney injury, we established a sepsis animal model using the CLP method and detected the expression levels of these molecules in renal tissues by qRT-PCR. The results showed that PCED1B-AS1 was down-regulated in the renal tissues of septic rats (95% CI=−0.602 to −0.278, $P<0.001$, Supplementary Figure 1A), miR-361-3p was up-regulated (95% CI=0.430 to 0.806, $P<0.001$, Supplementary Figure 1B), and SOCS1 also showed a downward trend in mRNA expression (95% CI=−0.627 to −0.309, $P<0.001$, Supplementary Figure 1C). This change trend was consistent with the expression pattern we observed in patient serum.

Discussion

As a prototypical critical illness, AKI often exerts effects across numerous organ systems. In sepsis, AKI is characterized by an acute onset and strong inflammation, resulting in poor clinical outcomes for patients.[29] In this study, PCED1B-AS1 was downregulated in sepsis-induced AKI, and it may serve as a diagnostic and prognostic marker for sepsis-related AKI. Additionally, through in vitro experiments, this study initially revealed that PCED1B-AS1 might inhibit the development of sepsis AKI by suppressing M1 polarization and promoting M2 macrophage polarization. This study provides an important theoretical basis for the application of PCED1B-AS1 in sepsis AKI.

Previous studies have shown that multiple lncRNAs exhibit abnormal expression in sepsis-induced AKI. For instance, knockdown of NEAT1 might be a potential approach to alleviate sepsis-induced AKI.[30] Additionally, PMS2L2 shows a down-regulated trend in sepsis-induced AKI and inhibits LPS-induced podocyte apoptosis.[31] Research has demonstrated the diagnostic value of lncRNA NEAT1 in peripheral blood mononuclear cells from sepsis patients, with an AUC of 0.851.[32] NEAT1 is also linked to higher risk, disease severity, and poor prognosis, showing an AUC of 0.730 for sepsis diagnosis.[33] This study discovered that downregulated PCED1B-AS1 may serve as a potential diagnostic marker to distinguish healthy individuals from sepsis patients with a higher AUC of 0.886. This finding was consistent with previous studies that identified PCED1B-AS1 as a down-regulated diagnostic marker in sepsis patients.[15] More importantly, our study also revealed a new discovery: PCED1B-AS1 also effectively differentiated sepsis patients with AKI from those without AKI. Moreover, we conducted an in-depth analysis of its prognostic value. The levels of PCED1B-AS1 were significantly correlated with various AKI-related assessment indicators (such as Scr, eGFR, NGAL, etc). Additionally, the low expression of PCED1B-AS1 was often accompanied by a higher risk of death. These results suggest that PCED1B-AS1 may play an important role in sepsis-induced AKI and may serve as a potential diagnostic and prognostic marker.

In addition, this study analyzed the risk factors influencing the prognosis of patients with AKI induced by sepsis using a multivariate Cox model. However, since eGFR is dynamically changing in AKI patients, it may not be an ideal variable. Nevertheless, eGFR is a standardized and widely recognized surrogate for baseline renal function in multivariate regression models. This approach is widely adopted in clinical research to correct for the confounding effect of renal function impairment on outcomes, even in the population with acute kidney injury.[34,35] In the multivariate Cox model, both eGFR and PCED1B-AS1 were independently significant and could serve as prognostic factors for sepsis-induced AKI. PCED1B-AS1 may be used as an auxiliary prognostic indicator in clinical practice, but the clinical value of its combination with other indicators in predicting AKI remains a focus of our future research.

Septic AKI exhibits a significant correlation with the immune system, with particular emphasis on M2 macrophages. M2 macrophages possess the capacity not only to foster the regeneration of renal tubular cells and inhibit their apoptosis, but also to indirectly ameliorate renal damage by reducing inflammatory cell infiltration within the kidney

interstitium.[36,37] Significantly, M2 macrophages serve to antagonize the pro-inflammatory effects characteristic of M1 macrophages, thereby lessening the detrimental impact on the kidney that results from M1-mediated inflammation.[38] To further explore the role of PCED1B-AS1 in sepsis-induced AKI, we induced macrophage polarization in vitro and found that overexpression of PCED1B-AS1 might induce M1-type macrophages to polarize into M2-type, thereby reducing apoptosis and inflammation in HK-2 cells. Similarly, previous research has demonstrated that NEAT1 exerts an anti-inflammatory effect under LPS treatment, a mechanism potentially involving the promotion of M2 macrophage polarization.[39] Moreover, this study also found that overexpression of PCED1B-AS1 promoted the proliferation of HK-2 cells and inhibited apoptosis and inflammation. This is similar to the role of other lncRNAs in regulating sepsis-induced AKI, such as GAS6-AS2, which regulates apoptosis and inflammation in HK-2 cells and contributes to sepsis AKI progression.[40] These results not only verified the protective role of PCED1B-AS1 in sepsis-induced AKI but also initially clarified the specific mechanism by which it achieves this effect through regulating macrophage polarization and HK-2 cell function.

Previous studies have reported that PCED1B-AS1 acts as a sponge for miR-10a to regulate cell proliferation in hepatocellular carcinoma,[41] and PCED1B-AS1 promotes the progression of pancreatic ductal adenocarcinoma by regulating miR-411-3p.[42] This study demonstrated that PCED1B-AS1 functions as a sponge for miR-361-3p, and the overexpression of miR-361-3p counteracts the effects of PCED1B-AS1 overexpression on macrophage polarization and the protection of HK-2 cells. Furthermore, this study further revealed that miR-361-3p regulates the expression of SOCS-1. Previous studies showed that SOCS-1 plays a key role in metabolic reprogramming, prevents excessive inflammation, and protects against organ damage during sepsis.[26] Additionally, SOCS-1 has been proven to alleviate inflammatory responses in sepsis-related acute lung injury by inhibiting the polarization of M1-type macrophages.[43] We speculate that the overexpression of PCED1B-AS1 may promote the polarization of M1-type macrophages to anti-inflammatory M2-type through regulating the miR-361-3p/SOCS-1 axis. This polarization transformation helps to inhibit the apoptosis of HK-2 cells and the release of inflammatory factors and ultimately alleviates the occurrence and development of sepsis-induced AKI.

There are still some limitations that need further exploration and improvement. This study did not compare the diagnostic performance of PCED1B-AS1 with other lncRNAs (such as NEAT1 and GAS6-AS2) that are known to be associated with sepsis and its complications within the same cohort. Such comparisons would help comprehensively evaluate the position of PCED1B-AS1 among candidate molecules and provide stronger support for its potential as a biomarker. Future research will systematically detect and compare the expression levels of PCED1B-AS1 and other related lncRNAs in the same cohort and further analyze their predictive value and biological functions in sepsis and its complications. In addition, the current study has only verified the expression changes of PCED1B-AS1, miR-361-3p, and SOCS1 in the renal tissues of septic rats in animal models and has not yet explored the regulatory mechanism in depth through in vivo experiments. Therefore, the conclusions drawn so far still need to be verified through further animal experiments. For instance, constructing animal models with specific overexpression of PCED1B-AS1 and combining them with functional recovery experiments may clarify the biological significance of this regulatory axis at the animal level. Moreover, due to the limitations of conditions, this study only detected the mRNA expression of M1/M2-related markers. The focus of future research will be to conduct more precise phenotypic analysis using flow cytometry. Due to the challenges in clinical practice (difficulty in conducting predictive and frequent sampling before AKI occurs in patients), this study failed to obtain complete time-course data, especially before the decline of GFR, which is crucial for evaluating the potential of PCED1B-AS1 as an early diagnostic marker. Therefore, future research plans to establish a mouse sepsis model, collect serum at multiple key early time points after modeling, and collect kidney tissues to provide more solid evidence. At the same time, we failed to precisely trace the primary cell source of PCED1B-AS1 and miR-361-3p by isolating various white blood cell subpopulations (such as neutrophils, monocytes, lymphocytes) from patients. The future experimental plan will adopt techniques such as magnetic bead sorting to separate different types of cell populations from the peripheral blood of patients, and then quantitatively detect the expression levels of these molecules in various cells through the qPCR method, thereby more accurately identifying their source cells. Additionally, other potential molecular pathways regulated by PCED1B-AS1/miR-361-3p/SOCS-1 axis have not been deeply explored.

Future studies could further expand to these potential molecular pathways to more comprehensively understand the regulatory network of PCED1B-AS1 in diseases and its clinical significance.

Conclusion

PCED1B-AS1 was downregulated in sepsis and sepsis-induced AKI patients and may serve as a potential diagnostic and prognostic marker. Overexpression of PCED1B-AS1 promoted the polarization of M1 macrophages to M2 by regulating the miR-361-3p/SOCS1 axis, thereby inhibiting apoptosis and inflammatory responses in HK-2 cells.

Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Disclosure

The authors report no conflicts of interest in this work.

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