

## Original Article

# Long noncoding RNA MALAT1 promotes high glucose-induced inflammation and apoptosis of vascular endothelial cells by regulating miR-361-3p/SOCS3 axis

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**Abstract:** Vascular complications are the important pathophysiologic manifestations of patients with diabetes mellitus (DM) and many long non-coding RNAs (LncRNAs) are involved in this process. In this study, we aimed to investigate the relationships among LncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), microRNA-361-3p (miR-361-3p), and suppressor of cytokine signaling 3 (SOCS3) in high glucose (HG)-induced human umbilical vein endothelial cell (HUVEC) injury and its underlying mechanism. We found that HG treatment significantly promotes MALAT1 and SOCS3 expressions, but inhibits miR-361-3p expression in HUVECs. Furthermore, through bioinformatics analysis and dual luciferase assay, we found that MALAT1 directly sponges miR-361-3p to counteract its suppression on SOCS3 expression. Moreover, knockdown of MALAT1 evidently inhibits HG-induced inflammatory factors, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ) and IL-6 expressions in HUVECs (and HUVEC apoptosis) by regulating the miR-361-3p/SOCS3 axis. In conclusion, our results indicate that knockdown of MALAT1 inhibits HG-induced vascular endothelial injury through regulating miR-361-3p/SOCS3 axis, suggesting that inhibition of MALAT1 as a potential target for endothelial injury therapy for DM.

**Keywords:** Diabetes mellitus, metastasis-associated lung adenocarcinoma transcript 1, microRNA-361-3p, suppressor of cytokine signaling 3, high glucose

## Introduction

Diabetes mellitus (DM) is a commonly chronic metabolic disease and seriously harms human health [1]. Microvascular and macrovascular complications are considered as important pathophysiologic manifestations in patients with DM [2]. Hyperglycemia is viewed as the initial pathogenic factor of pathologic changes of DM, and vascular endothelial injury resulted from hyperglycemia is viewed as one of the early incidents of cardiovascular complications in DM [3]. Thus, ameliorating the endothelial injury may provide an efficacious therapeutic approach for vascular diseases and DM.

Long non-coding RNAs (LncRNAs), a class of non-coding RNA (over 200 nts) with no or weak protein-coding capacity, are involved in various biologic processes and pathologic mechanisms through functioning as competing endogenous RNAs [4]. LncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1),

one of the first discovered lncRNAs, is widely expressed in mammalian tissues and has been identified as an oncogene [5]. Recently, downregulation of MALAT1 has been found to inhibit high glucose (HG)-induced cardiomyocyte apoptosis by regulation of miR-181a-5p [6]. MALAT1 promotes HG-induced human endothelial cell pyroptosis through regulating miR-22/NLRP3 axis [7]. Given that each lncRNA could sponge many targeted miRNAs, the underlying mechanism of MALAT1 regulating HG-induced cell injury is still not fully known.

MicroRNAs (miRNAs), a class of small noncoding RNAs (20-25 nts), play important roles in regulating the development of diverse diseases, including DM, through binding to the 3'-UTR of target genes to mediate translational repression to affect disease states [8]. For example, miR-320/VEGFA axis affects high glucose (HG)-induced metabolic memory during human umbilical vein endothelial cell (HUVEC)

dysfunction in diabetes [9]. miRNA-181c-3p and -5p promotes HG-induced dysfunction in HUVECs by regulating leukemia inhibitory factor [10]. A recent study reports decreased levels of miR-361-3p and increased levels of insulin-like growth factor 1 mRNA in mononuclear cells from patients with hereditary hemorrhagic telangiectasia [11], suggesting that miR-361-3p may be involved in vascular dysplasias. However, whether miR-361-3p is related to vascular endothelial injury in DM is completely unknown.

Janus kinase (JAK)/signal transducers and activators of transcription (STAT) intracellular signaling has essential roles in mediating cell proliferation, inflammation, and apoptosis [12]. During the process of vascular endothelial injury, JAK2/STAT3 signaling is activated to trigger an inflammatory response and apoptosis [13-15]. Suppressor of cytokine signaling 3 (SOCS3) protein, which negatively regulates JAK2/STAT3 signaling, has been reported to be involved in the development of diabetes and disease-associated complications [16, 17]. Also, pharmacological agents targeting SOCS3 have already been used for the treatment of diabetes [18, 19]. Through bioinformatic analysis, MALAT1 might sponge miR-361-3p as a competing endogenous RNA, and SOCS3 mRNA is a potential target of miR-361-3p. In the present study, we aimed to investigate the relationships among MALAT1, miR-361-3p, and SOCS3 in HG-induced endothelial injury and its underlying mechanism.

## Materials and methods

### Cell culture

Primary human umbilical vein endothelial cells (HUVECs) were obtained from American Type Culture Collection (Manassas, VA, USA) and cultured in low glucose Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum and antibiotics including 80 U/ml penicillin and 80 µg/mL streptomycin (GIBCO, Invitrogen Co., Grand Island, NY, USA) at 37°C in a 5% CO<sub>2</sub>/95% air environment. Cells were incubated with normal glucose (5 mM) or high-glucose (HG) (25 mM) for the indicated hours and then continued for the following experiments.

### Cell transfection

Small interfering RNA against MALAT1 (si-MALAT1), si-SOCS3, miR-361-3p mimics, nega-

tive control mimics (NC mimics), and miR-361-3p inhibitor and its negative control (NC inhibitor) were synthesized by Genepharma Co., Ltd. (Shanghai, China). Lipofectamine 2000 transfection reagent, purchased from Invitrogen (Carlsbad, CA, USA), was then used to transfect all oligonucleotides and vectors into HUVECs.

### CCK8 assay

HUVECs were plated in a 96-well plate for a whole night and incubated with HG (25 mM) for the indicated hours. Then, cell viability was tested using the CCK-8 method (CCK8, Dojindo, Japan), according to the manufacturer's instruction.

### Assessment of lactate dehydrogenase (LDH) release

HUVECs were plated in a 96-well plate for a whole night and incubated with HG (25 mM) for the indicated hours. Released LDH in the culture supernatant was measured using the LDH kit (Thermo Fisher Scientific, USA), according to the manufacturer's instruction. Briefly, 50 µl culture medium was mixed with equal volume substrate in a 96-well plate to incubate for 30 min. Signals were recorded at 490 nm using a scanning multi-well spectrophotometer.

### Proinflammatory cytokine ELISA

5 × 10<sup>4</sup> HUVECs were seeded in a 6-well plate and stimulated with HG for 24 hours. Following treatment, concentrations of secreted TNF-α, IL-1β, and IL-6 in the culture supernatants were measured and quantified by commercial ELISA Kits from Abcam: human TNF-α SimpleStep ELISA Kit (ab181421, Abcam, USA); human IL-1β SimpleStep ELISA Kit (ab18142, Abcam, USA); human IL-6 SimpleStep ELISA Kit (ab178013, Abcam, USA), according to the manufacturer's instructions.

### Flow cytometry assay

5 × 10<sup>4</sup> HUVECs were seeded in a 6-well plate and stimulated with HG for the indicated hours. Following treatment, the cell apoptosis of HUVECs was determined using an FITC Annexin V/PI Apoptosis Detection Kit (BD Biosciences Pharmingen, San Jose, CA, USA) according to the manufacturer's instructions. Apoptotic cells were analyzed using flow

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cytometry (BD FACSVerse, BD Biosciences Pharmingen).

## *Reverse transcription-quantitative polymerase chain reaction (RT-qPCR)*

5 × 10<sup>4</sup> HUVECs were seeded in a 6-well plate and stimulated with HG for the indicated hours. Total RNA of HUVECs was extracted using TRIzol reagent following the manufacturer's instructions (Invitrogen, Carlsbad, CA, United States). Isolated total RNA (1 µg) was converted to complementary DNA (cDNA) using a First-Strand cDNA Synthesis Kit (Toyobo, Osaka, Japan). Power SYBR green master mix (Applied Biosystems, Foster City, CA, United States) was added to the cDNA samples, which were then subjected to qRT-PCR using a StepOne Real Time PCR system. GAPDH and U6 were used as endogenous controls for mRNAs and for miRNAs, respectively. The amplification results were calculated using the 2<sup>-ΔΔCt</sup> method. The PCR primers used were: MALAT1, forward 5-AGGTAAAGCTTGAGAAGAT-3, reverse 5-GGAAGTAATCAAGATCAA-3; SOCS3, forward 5'-CCTGCGCCTCAAGACCTTC-3', reverse 5'-GTCAGTGCCTCCAGTAGAA-3'; GAPDH, forward 5'-GGTGGTCTCCTCTGACTTCAA-3', and reverse 5'-GTTGCTGTAGCCAAATTCGTTGT-3'; miR-361-3p, forward 5'-ACACTCCAGCTGGGTCCCCCAGGTGTGATTC-3', reverse 5'-CTCAACTGGTGTGTCGGAGTCCGCAATTCAGTTGAGAAATCAGA-3'; U6, forward 5'-CTCGCTTCGGCAGCACA-3', reverse 5'-AACGCTTCACGAATTGCGT-3' (Reverse).

## *Bioinformatics*

Bioinformatics prediction is a powerful tool for the study of the functions of MALAT1 and miR-361-3p. To understand whether MALAT1 or SOCS3 is the potential target gene of miR-361-3p, we used Starbase (<http://starbase.sysu.edu.cn/>) for analysis.

## *Dual luciferase assay*

The binding sites between MALAT1/SOCS3 mRNA and miR-361-3p were predicted by Starbase (<http://starbase.sysu.edu.cn/>). The targeted sites of miRNA-361-3p in the MALAT1/SOCS3 mRNA 3'-untranslated region was amplified from cDNA of HUVECs and inserted into pMIR-luciferase reporter plasmid (Promega Corporation, Madison, WI, USA). pMIR-MALAT1 (wild type, WT)/pMIR-MALAT1

mutant, pMIR-SOCS3 WT/pMIR-SOCS3 mutant, miR-361-3p mimics, control mimics, miR-361-3p inhibitor and pRL-TK Renilla were co-transfected into HEK-293T cells using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). After 24 hours, the activity of luciferase and Renilla activity were detected using a Dual Luciferase Reporter Assay Kit (Promega, Madison, WI, USA).

## *Western blotting*

Cells were then harvested and lysed with 1 × sodium dodecyl sulfate (SDS) lysis buffer containing 50 mM Tris-HCl (pH 6.8), 10% glycerol, and 2% SDS. Cell lysates were boiled for 10 min then centrifuged at 12,000 g for 15 min at room temperature. Samples were separated by 12% SDS-PAGE and transferred to a polyvinylidene difluoride membrane (GE Healthcare, Piscataway, NJ, United States). The membranes were blocked in 5% bovine serum albumen for 2 h, followed by a 4°C overnight incubation with primary antibodies [Anti-SOCS3 antibody (ab14939) and Anti-GAPDH antibody (ab181602)]. Primary antibodies were detected with corresponding horseradish peroxidase-conjugated secondary antibodies (Zhongshan Jinqiao, Beijing, China) coupled with enhanced chemiluminescence reagents (Egreen, Beijing, China).

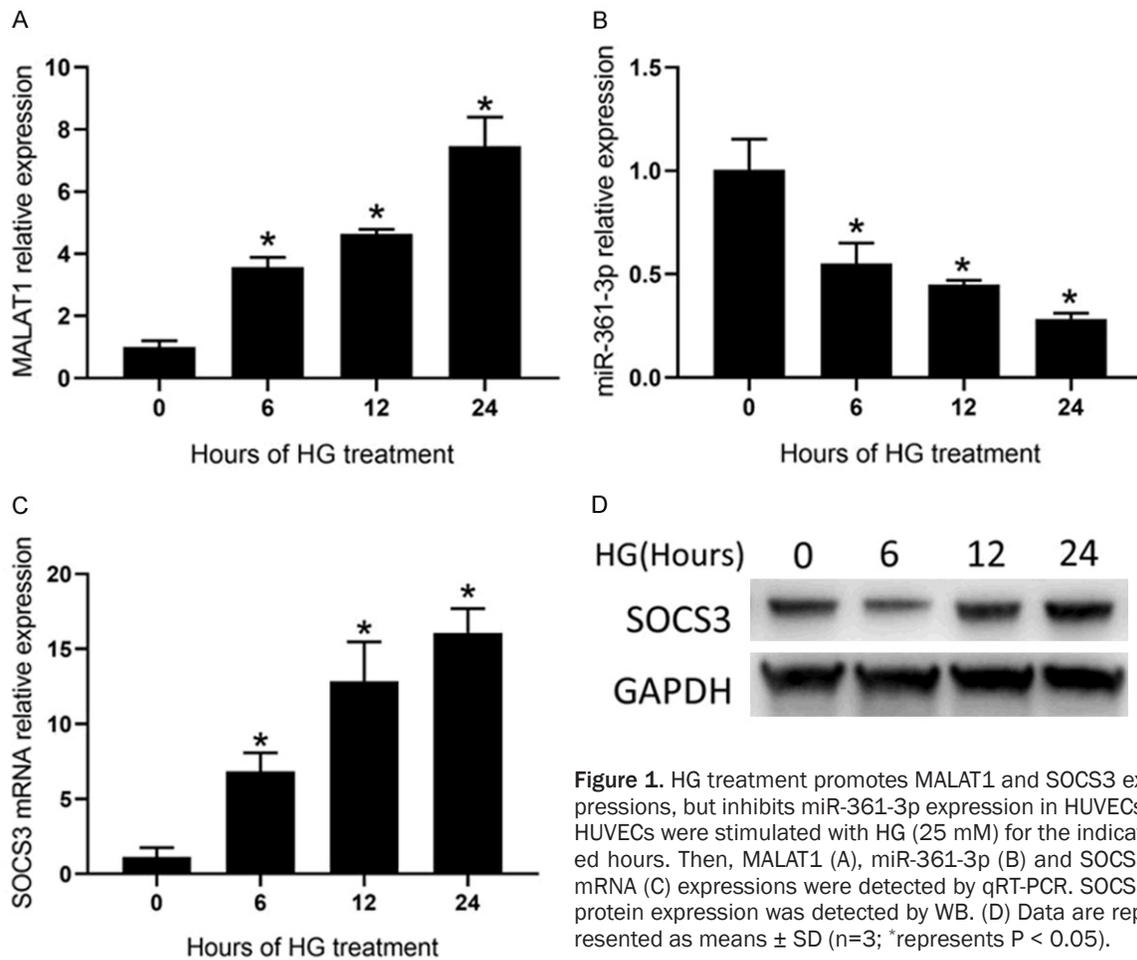
## *Statistical analysis*

Data are presented as the mean ± standard error of the mean. Statistical analysis was performed using GraphPad Prism software version 5.0 (GraphPad Software, Inc., La Jolla, CA, USA). The statistical significance of the differences between groups was evaluated using an unpaired Student's t-test for pairwise comparisons, or a one-way analysis of variance followed by the Tukey post hoc test for multiple comparisons. P < 0.05 was considered a significant difference.

## **Results**

### *HG treatment promotes MALAT1 and SOCS3 expressions, but inhibits miR-361-3p expression in HUVECs*

First, to investigate whether the effects of HG on MALAT1, miR-361-3p and SOCS3 mRNA expressions, HUVECs were stimulated with HG and then detected by qRT-PCR. As shown in



**Figure 1.** HG treatment promotes MALAT1 and SOCS3 expressions, but inhibits miR-361-3p expression in HUVECs. HUVECs were stimulated with HG (25 mM) for the indicated hours. Then, MALAT1 (A), miR-361-3p (B) and SOCS3 mRNA (C) expressions were detected by qRT-PCR. SOCS3 protein expression was detected by WB. (D) Data are represented as means  $\pm$  SD (n=3; \*represents P < 0.05).

**Figure 1A-C**, during the process of HG stimulation, MALAT1 and SOCS3 mRNA expression levels were progressively increased, but significantly decreased miR-361-3p expression. Moreover, western blotting analysis also confirmed HG stimulation promoted SOCS3 protein expression (**Figure 1D**). Overall, these results indicated that HG stimulation could promote MALAT1 and SOCS3 expression, and simultaneously decrease miR-361-3p expression in HUVECs.

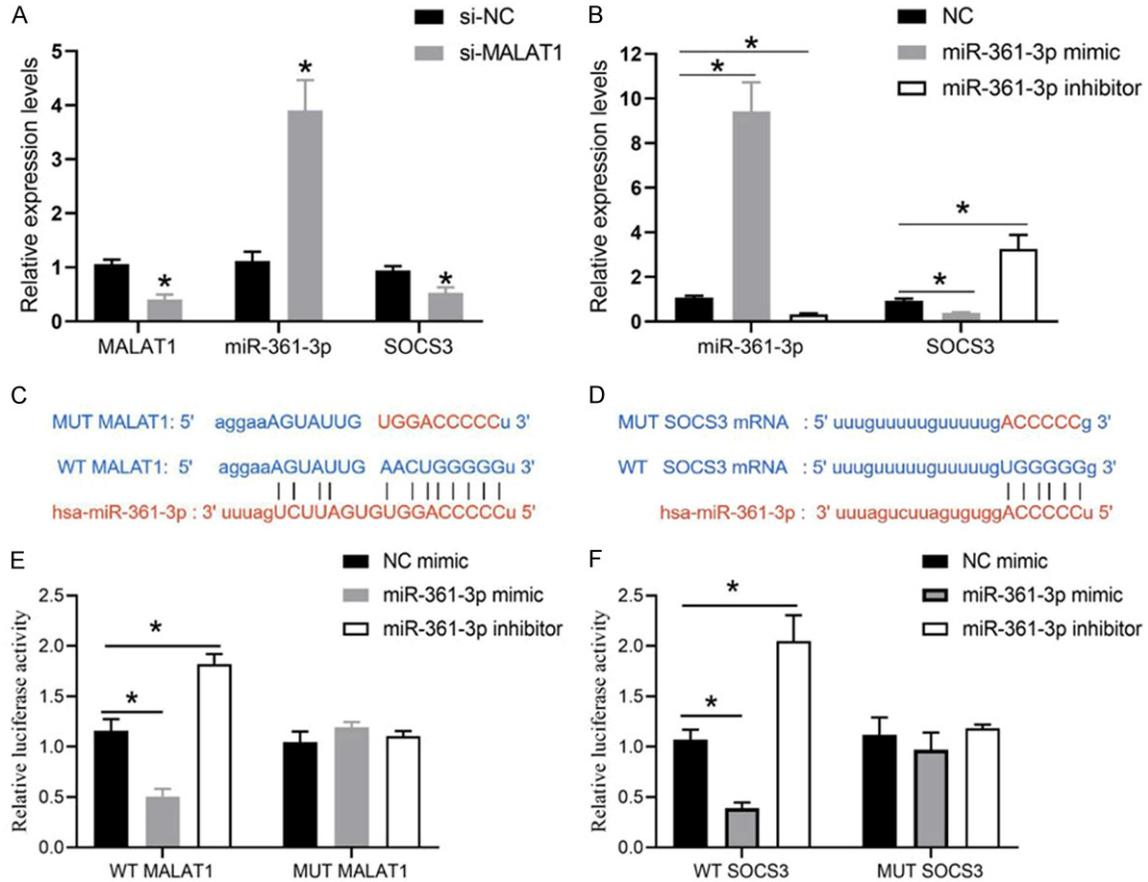
*MALAT1 directly sponges miR-361-3p to counteract its suppression on SOCS3*

Then, to explore the regulatory mechanism of MALAT1, miR-361-3p, and SOCS3, HUVECs were transfected with si-MALAT1 to knockdown MALAT1 expression. As shown in **Figure 2A**, knockdown of MALAT1 significantly increased miR-361-3p expression, and evidently decreased SOCS3 mRNA expression. Further-

more, we found that overexpression of miR-361-3p by transfection with miR-361-3p mimic significantly downregulated SOCS3 mRNA expression, while knockdown of miR-361-3p by transfection with miR-361-3p inhibitor evidently upregulated SOCS3 mRNA expression (**Figure 2B**), suggesting that MALAT1 might positively regulate SOCS3 mRNA expression, whereas miR-361-3p negatively regulates SOCS3 mRNA expression.

Subsequently, through bioinformatics analysis, we found that MALAT1 and SOCS3 mRNA are potential targets of miR-361-3p (**Figure 2C** and **2D**). To confirm the predictions, luciferase reporter assays were performed to examine the interaction between miR-361-3p and the predicted MALAT1 and SOCS3 3'-UTR targeting sequences. As shown in **Figure 2E** and **2F**, overexpression of miR-361-3p evidently inhibited the luciferase activity of WT MALAT1 or WT SOCS3 3'-UTR,

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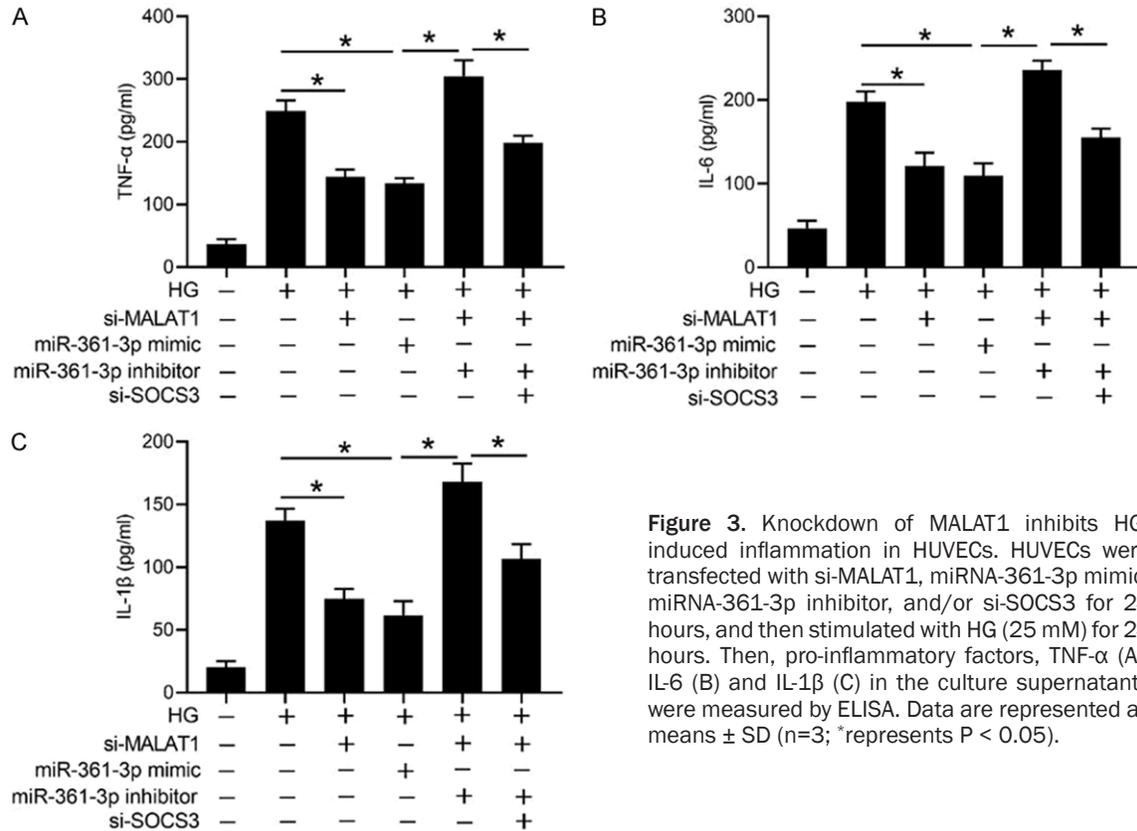
**Figure 2.** MALAT1 directly sponges miR-361-3p to counteract its suppression on SOCS3. **A.** HUVECs were transfected with si-NC or si-MALAT1 for 24 hours, then MALAT1, miR-361-3p, and SOCS3 mRNA expressions were detected by qRT-PCR. **B.** HUVECs were transfected with miRNA NC, miRNA-361-3p mimic, or miRNA-361-3p inhibitor for 24 hours, then miR-361-3p and SOCS3 mRNA expressions were detected by qRT-PCR. **C.** Predicted binding sites of miRNA-361-3p within MALAT1 and its mutated version are shown. **D.** Predicted binding sites of miRNA-361-3p within SOCS3 3'UTR and its mutated version are shown. **E** and **F.** HEK-293T cells were co-transfected with the indicated vectors and miRNA-361-3p mimic or miRNA-361-3p inhibitor and examined for luciferase activity. Data are represented as means  $\pm$  SD (n=3; \*represents P < 0.05).

and knockdown of miR-361-3p significantly increased. Whereas, overexpression or knockdown of miR-361-3p did not affect the luciferase activity of MUT MALAT1 and MUT SOCS3 3'UTR (**Figure 2E** and **2F**). Taken together, these results indicate that MALAT1 can directly sponge miR-361-3p to counteract its suppression on SOCS3.

### Knockdown of MALAT1 inhibits HG-induced inflammation in HUVECs by regulating miR-361-3p/SOCS3 axis

Since MALAT1 has reported to be a regulator of inflammatory cytokines in diabetic complications [20] and SOCS3 promotes inflammatory responses in diabetes [21], we further investi-

gated the effects of MALAT1/miR-361-3p/SOCS3 on HG-induced inflammation in HUVECs. As shown in **Figure 3A-C**, knockdown of MALAT1, or overexpression of miR-361-3p significantly inhibited HG-induced inflammatory factor, tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin 6 (IL-6), and interleukin 1 $\beta$  (IL-1 $\beta$ ) expressions. However, knockdown of miR-361-3p evidently reversed the inhibitory effects of knockdown of MALAT1 on HG-induced inflammatory factor expressions (**Figure 3A-C**). Moreover, knockdown of SOCS3 reversed the effects of co-transfection of si-MALAT1 and miR-361-3p inhibitor on HG-induced inflammatory factor expressions (**Figure 3A-C**). Taken together, these results indicate that knockdown of MALAT1 inhibits HG-induced inflam-



**Figure 3.** Knockdown of MALAT1 inhibits HG-induced inflammation in HUVECs. HUVECs were transfected with si-MALAT1, miRNA-361-3p mimic, miRNA-361-3p inhibitor, and/or si-SOCS3 for 24 hours, and then stimulated with HG (25 mM) for 24 hours. Then, pro-inflammatory factors, TNF-α (A), IL-6 (B) and IL-1β (C) in the culture supernatants were measured by ELISA. Data are represented as means ± SD (n=3; \*represents P < 0.05).

mation in HUVECs by regulating miR-361-3p/SOCS3 axis.

*Knockdown of MALAT1 inhibits HG-induced apoptosis in HUVECs by regulating miR-361-3p/SOCS3 axis*

We further investigated the effects of MALAT1/miR-361-3p/SOCS3 on HG-induced apoptosis in HUVECs. As shown in **Figure 4A** and **4B**, knockdown of MALAT1, or overexpression of miR-361-3p significantly relieved HG-induced decline of cell viability, and inhibited HG-induced LDH release. Knockdown of miR-361-3p reversed the protective effects of knockdown of MALAT1 on HG-induced cell injury (**Figure 4A** and **4B**). Whereas, knockdown of miR-361-3p reversed the effects of co-transfection of si-MALAT1 and miR-361-3p inhibitor on HG-induced cell injury (**Figure 4A** and **4B**). Consistently, flow cytometry analysis showed knockdown of miR-361-3p reversed the effects of co-transfection of si-MALAT1 and miR-361-3p inhibitor on HG-induced apoptosis (**Figure 4C** and **4D**). Taken together, these results indicate that knockdown of MALAT1 inhibits HG-induced apop-

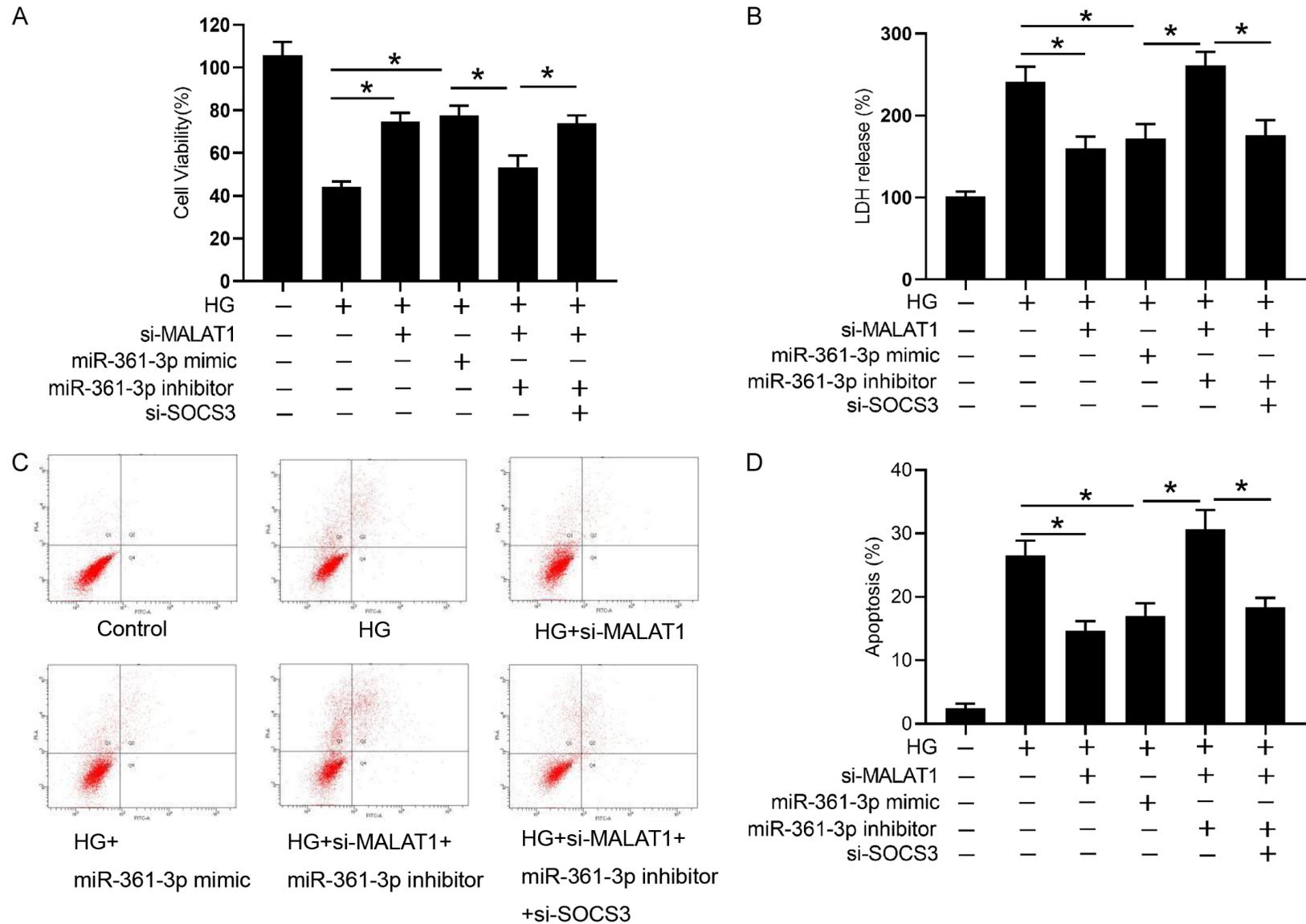
toxis in HUVECs by regulating the miR-361-3p/SOCS3 axis.

**Discussion**

Diabetes complications, including neuropathy, nephropathy, retinopathy, cardiovascular disease, and stroke, worsen patients' living quality [22]. Among these complications, high-glucose induced endothelial dysfunction is the major basic event involved in vascular injury [23]. Understanding the underlying mechanism of high-glucose induced endothelial dysfunction will provide essential reference for clinical therapy for DM. Recently, a number of lncRNAs were demonstrated to be centrally involved in development and progression of DM [24]. In this study, our group first identified that knockdown of MALAT1 inhibited HG-induced inflammation and apoptosis of HUVECs through regulating miR-361-3p/SOCS3 axis, suggesting that inhibition of MALAT1 may serve as a target for endothelial injury therapy for DM.

MALAT1 is an essential regulator of inflammatory cytokines in diabetic complications [20].

MALAT1 promotes glucose-induced endothelial injury through miR-361-3p/SOCS3 axis



**Figure 4.** Knockdown of MALAT1 inhibits HG-induced apoptosis in HUVECs by regulating miR-361-3p/SOCS3 axis. HUVECs were transfected with si-MALAT1, miRNA-361-3p mimic, miRNA-361-3p inhibitor and/or si-SOCS3 for 24 hours, and then stimulated with HG (25 mM) for 24 hours. Then cell viability (A), and LDH release (B), were detected. (C and D) Apoptosis was detected by flow cytometry. Data are represented as means  $\pm$  SD (n=3; \*represents P < 0.05).

MALAT1 promotes HG-induced inflammatory response of microglial cells through activating MyD88/IRAK1/TRAF6 signaling [25]. MALAT1 promotes HG-induced human endothelial cells pyroptosis through regulating miR-22/NLRP3 expression [7]. Consistently, we found that HG stimulation significantly increased MALAT1 expression in HUVECs. MALAT1 promotes HG-induced HUVECs inflammation and apoptosis by affecting SOCS3 expression through competitively binding miR-361-3p. However, MALAT1 has many potential targeted miRNAs predicted by Starbase. Whether other miRNAs are also involved in MALAT1 regulating endothelial injury in DM still needs further investigation.

Numerous studies indicate that miR-361-3p acts essential roles in the development of many human diseases, including cutaneous squamous cell carcinoma, non-small cell lung cancer, Alzheimer's disease, and parasitic diseases [26-29]. For example, miR-361-3p functions as a tumor suppressor in the carcinogenesis and progression of retinoblastoma by targeting sonic hedgehog signaling [30]. miR-361-3p inhibits  $\beta$ -amyloid accumulation and attenuates cognitive deficits through targeting BACE1 in Alzheimer's disease [28]. Our study for the first time reports that high-glucose stimulation decreased miR-361-3p expression in HUVECs, and miR-361-3p partly inhibits high-glucose induced-apoptosis and inflammatory factors secretion through targeting SOCS3 mRNA. Whether other target genes of miR-361-3p are also involved in the protective effects of miR-361-3p on HG-induced vascular endothelial injury still needs to be investigated in the following studies.

A previous study reports that SOCS3 aggravates HG-induced apoptosis, oxidative stress and inflammation in retinal pigment epithelial cells through negatively regulating JAK2/STAT3 signaling [15, 21]. Besides, several miRNAs have been identified to target SOCS3 mRNA to regulate inflammation and apoptosis [14, 31]. For example, miR-155 regulates lymphoma cell proliferation and apoptosis through targeting SOCS3/JAK-STAT3 signaling pathway [14]. miR-340 affects gastric cancer cell proliferation, cycle, and apoptosis through regulating SOCS3/JAK-STAT signaling pathway [31]. miR-221 affects proliferation and apopto-

sis of gastric cancer cells through targeting SOCS3 [32]. In this study, through luciferase reporter assays, we found that miR-361-3p specifically binds to 3'UTR of SOCS3 mRNA, and negatively regulates SOCS3 mRNA and protein expressions. Since many miRNAs participate in high-glucose-induced apoptosis and inflammatory factor secretion, whether other miRNAs targeting SOCS3/JAK-STAT3 signaling, cooperating with miR-361-3p, regulate HG-induced HUVEC injury will be explored in our following studies.

In conclusion, our study explored the relationships of MALAT1, miR-361-3p, and SOCS3 in HG-stimulated HUVECs and found MALAT1 promoted HG-induced inflammation and apoptosis of HUVECs through regulating miR-361-3p/SOCS3 axis, suggesting that inhibition of MALAT1 may serve as a target for endothelial injury therapy for DM.

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### Disclosure of conflict of interest

None.

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