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Original Article

MicroRNA-142-5p facilitates the pathogenesis of ulcerative colitis by regulating SOCS1

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Abstract: Background: Increasing evidence suggests that abnormal levels of microRNAs (miRNAs) are associated with ulcerative colitis (UC). It has been demonstrated that microRNA (miR)-142-5p was upregulated in UC patients. However, it remains unclear what the role of miR-142-5p is in UC. Methods: Samples from patients with active UC and healthy controls were performed with miRNA microarray to identify miRNAs involved in the pathogenesis of UC. The results of quantitative RT-PCR verified that miR-142-5p was upregulated in UC patients. Meanwhile, the decreased expression of suppressor of cytokine signaling 1 (SOCS1) was also detected at mRNA and protein levels. The regulatory effect of miR-142-5p on SOCS1 was evaluated by luciferase reporter assay. Levels of IL-6 or IL-8 were detected by quantitative RT-PCR or enzyme-linked immunosorbent assay in HT-29 cells to evaluate the roles of SOCS1 or miR-142-5p in the progression of UC. Results: The expression level of miR-142-5p was significantly upregulated and inversely correlated with SOCS1. Luciferase experiments showed that miR-142-5p interfered with the expression of SOCS1 by directly targeting its 3'-UTR. Furthermore, the level of miR-142-5p plays an important role in the secretion of IL-6 and IL-8. Moreover, lost function of SOCS1 reversed the miR-142-5p inhibitory effect. Conclusions: These results indicate that miR-142-5p improved the intestinal inflammation of active-UC patients by downregulating SOCS1 expression and increasing the cytokines IL-6 and IL-8 secretion.

Keywords: microRNAs, ulcerative colitis, miR-142-5p, SOCS1

Introduction

Ulcerative colitis (UC), which features lesions mostly located in the colon and rectum, is a chronic, non-specific and recurrent inflammatory disease. Over the last 20 years in China, the diet and lifestyle have been dramatically changed and the incidence of UC has increased year by year [1]. The pathogenesis of UC, which is still not very clear and is generally considered to be related to heredity and the environment, is characterized by mucosal ulceration and accompanied with abdominal pain and bloody diarrhea [2-4]. Previous research had reported that the NF-κB signaling pathway, which regulates the expression of diverse array of proinflammatory cytokines, plays a vital function in the development of UC [5]. It has been shown that NF-κB is upregulated in the mucosal macrophages of active-UC patients, and the high level of NF-κB increased the production and secretion of tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-8 [6]. During the recent years, accumulating evidences revealed the dysregulation of intestinal epithelial cells in UC patients; however, the molecular mechanism of UC is still limited.

MicroRNAs (miRNAs) are a class of short, non-coding RNA with 20-24 nucleotides in length that regulate gene expression by primarily binding to the complementary sequences in 3'-untranslated region (UTR) and cause either translational inhibition or degradation of the mRNA complex [7]. By downregulation of the expression level of target genes, miRNAs were involved in several biological processes, including cell proliferation, differentiation, motility, apoptosis, angiogenesis and metastasis, inflammation and autoimmunity [8, 9]. An increasing

Table 1. Gene-specific primers used for qRT-PCR

Gene	Forward sequence (5'-3')	Reverse sequence (5'-3')
SOCS1	CACGCACTTCCGCACATTC	TAAGGGCGAAAAAGCAGTTCC
IL-6	ACTCACCTCTTCAGAACGAATTG	CCATCTTTGGAAGGTTCAGGTTG
IL-8	GCAGAGGGTTGTGGAGAAGT	AACCCTACAACAGACCCACA
GAPDH	AGAAGGCTGGGGCTCATTTG	AGGGGCCATCCACAGTCTTC

number of miRNAs were shown to be involved in the pathogenesis, diagnosis, and therapy of UC [10]. In 2008, Wu et al. [11] first reported 11 miRNAs which were dysregulated in active-UC patients, and made a tight link between UC and miRNAs. Subsequently, recent reports have figured out that miRNAs might play important roles in UC by downregulating their targets. miR-19a could directly downregulated TNF-α expression in UC patients [12], while miR-155 is also reported to affect intestinal inflammation in UC patients by targeting FOXO3a [13].

Suppressor of cytokine signaling 1 (SOCS1) is a subtype of suppressors of cytokine signaling (SOCS) family, which are well-known negative regulators of cytokine receptor signaling consisting of eight structurally similar proteins [14]. SOCS1 was initially identified in a yeast two-hybrid assay and acts as a JAK-binding protein [15]. SOCS1 has been reported to be important for preventing chronic inflammation-mediated carcinogenesis. Knockout of SOCS1 in mice can activate STAT1 and then result in tumorigenesis in the colon [16]. Recent research shows that miR-155 directly targets at SOCS1 and regulates the inflammatory response of intestinal myofibroblasts [17]. These suggests that SOCS1 may involve in the progression of UC.

In the present study, we performed miRNA microarrays in UC and identified that miR-142-5p is extremely upregulated in UC tissues. We uncovered a role of miR-142-5p in stimulating inflammation of the colon. Furthermore, we found a novel mechanism that SOCS1 is a directly target of miR-142-5p and described proinflammatory function of miR-142-5p in intestinal inflammation.

Materials and methods

Patient tissue samples

Colonic mucosa tissue samples were collected from the sigmoid colon of 24 patients with active UC and 15 healthy people who underwent screening colonoscopies during June 2015 and July 2016 at the East Branch of the Second Hospital of Hebei Medical University. Each patient signed a written informed consent before collection. The biopsies were immediately snap-frozen and stored at -80°C after pinching. The use and conduct of all the human materials were approved by the Institutional Review Board.

miRNA microarray experiments

Total RNA was extracted from three UC patient samples and equal normal controls using TRIzol (Invitrogen) reagent. Small RNA (< 200 nt), which was used for miRCURYTM array microarray (Exiqon), was separated from the total RNA using mirVana miRNA isolation kit ((Ambion). miRNA microarray analysis was carried out according to the standard procedures of Illumina.

Quantitative real-time PCR (qRT-PCR)

Total RNA was isolated from frozen tissues or cells by TRIzol (Invitrogen) following the instructions of manufacturer. Isolated total RNA was using a reverse transcription kit (Takara, Tokyo, Japan) to obtain the miRNAs or mRNAs and SYBR® Premix Ex Taq™ (Takara) were employed for quantitative RT-PCR of miRNA and mRNA on an ABI 7500 Fast PCR system (Applied Biosystems). The primers used in this study are listed in **Table 1**. Primers for U6 and miR-142-5p were purchased from GeneCopoeia (RiboBio). U6 RNA and GAPDH were used as miRNA and mRNA internal control respectively. Each sample was run in triplicate. The relative expression was calculated using the relative quantification equation (RQ) = 2-ΔΔCt.

Cell culture and transfection

The human intestinal epithelial HT-29 cells were purchased from American Type Culture Collection (ATCC) and cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (Gibco) and 1% antibiotics (Invitrogen). Cells were seeded into 6-well plates and transfected with 100 nM mimics, inhibitors, or negative controls of miR-142-5p (GenePharma), respectively. Cells were

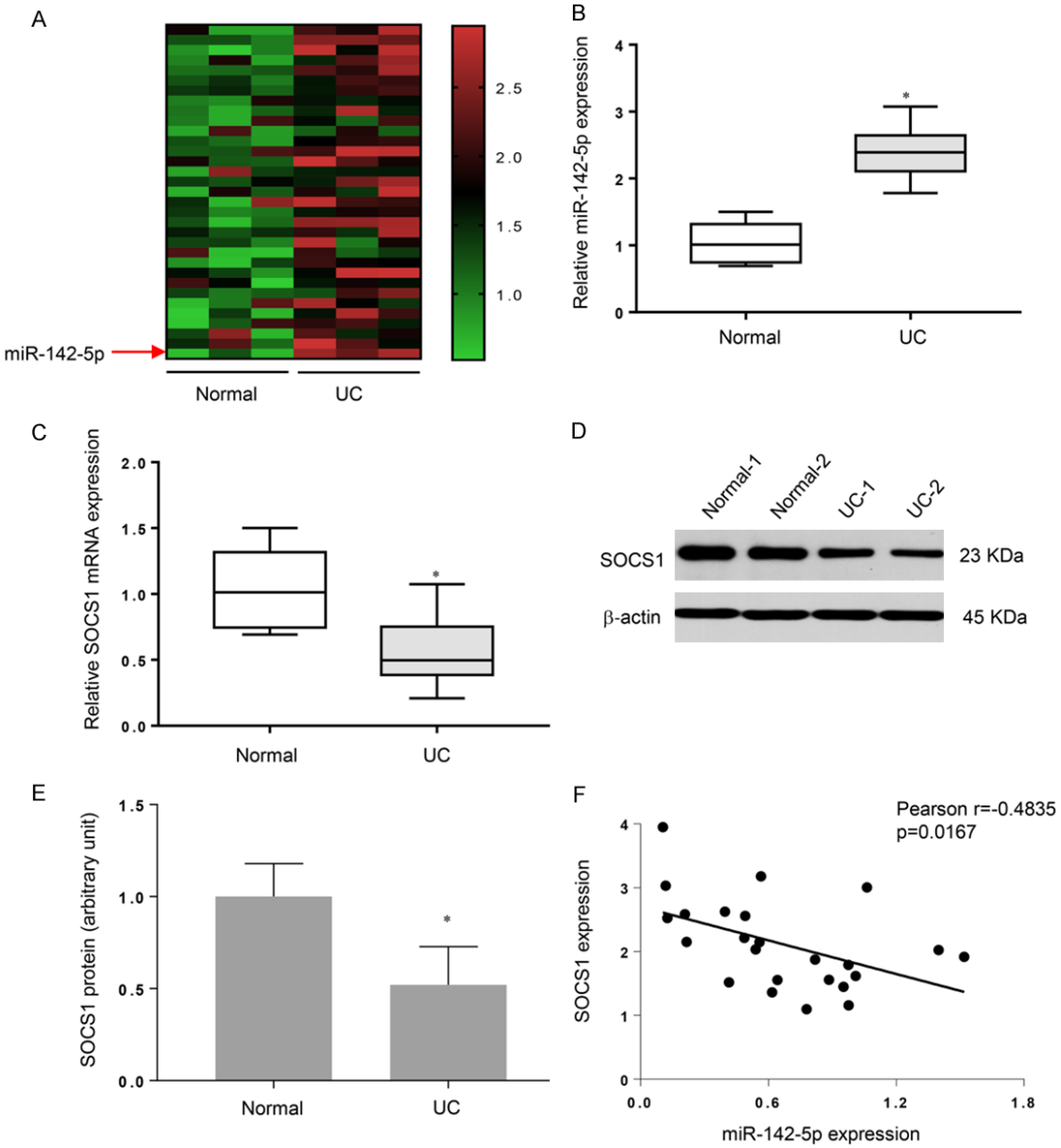

Figure 1. Expression and inverse correlation of miR-142-5p and SOCS1 in UC tissues. (A) miRNA microarray shows miR-142-5p is upregulated in UC tissues. Expression in UC and normal tissues of (B) miR-142-5p, (C) SOCS1 mRNA, and (D, E) SOCS1 protein. Data are presented as mean ± SD of three independent experiments. *$P < 0.05$; **$P < 0.01$. (F) Correlation of miR-142-5p and SOCS1 expression (Pearson correlation r =-0.4835, $P < 0.05$).

incubated in the medium containing the transfection mixture for 48 hours until protein extraction and media collection. HT-29 cells, which were transfected with mimics or inhibitors of miR-142-5p, were treated with TNF-α (10 ng/mL) for 1 or 24 hours and measured for IL-6 and IL-8 levels. The siRNA of SOCS1 and siRNA-NC were synthesized by GenePharma. All transfections of siRNAs or miRNAs were performed using Lipofectamine 2000 transfection regent (Invitrogen) according to instructions of the manufacturer.

Western blotting assay

Western blot of cell lysates was performed following standard procedures. Frozen tissue biopsies and cells were homogenized using RIPA buffer (Cell Signaling Technology, Inc.) within protease inhibitors (Roche), followed by

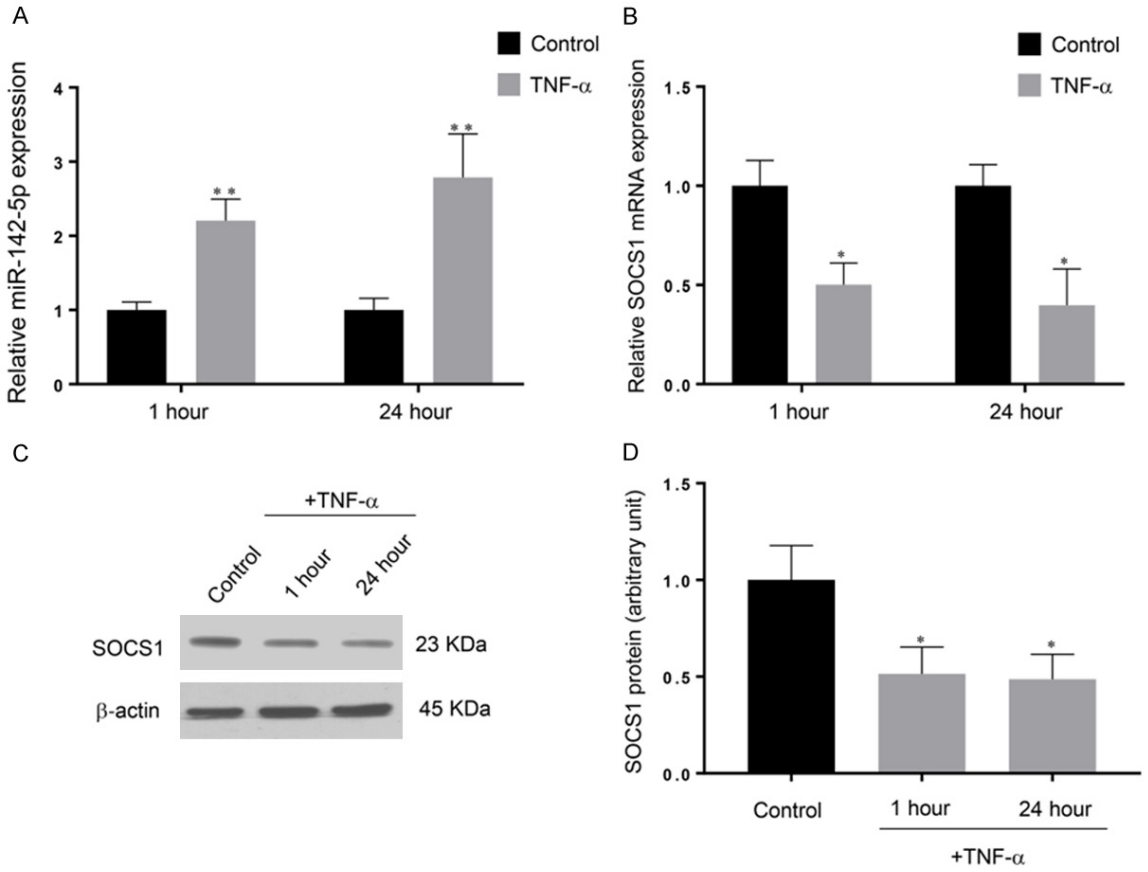

Figure 2. TNF-α regulates miR-142-5p and SOCS1 in HT-29 cells. (A) miR-142-5p expression, (B) SOCS1 mRNA expression and (C, D) SOCS1 protein expression were assessed at 1 and 24 hours after TNF-α treatment by using qRT-PCR and western blots, respectively. Data are presented as means ± SD of three independent experiments. **P* < 0.05; ***P* < 0.01.

sonication. Antibodies against SOCS1 (1:1000) was purchased from Cell Signaling Technology and antibodies against β-actin (1:10000) from Sigma-Aldrich. Protein bands were visualized with enhancer chemiluminescence (ECL) and quantified by using ImageJ software.

Enzyme-linked immunosorbent assay (ELISA)

In order to measure the secretion level of IL-6 and IL-8 in HT-29 cells, the culture medium after various treatments were collected 24 h later and quantified by commercially available ELISA kit (R&D Systems) according to the manufacturer's instructions.

Luciferase reporter assay

The 3'UTR fragments of the SOCS1 mRNA, which contained the wild -type or mutant putative miR-142-5p-binding sites, were inserted into the firefly luciferase reporter vector pMIR-Report (Applied Biosystems). Then the HT-29 cells were plated in 24-well plates, and co-transfected with 10 ng renilla luciferase vector pRL-SV40, 500 ng of wild-type (pMIR-SOCS1-wt) or mutant (pMIR-SOCS1-mut), and miR-142-5p mimics/inhibitors or their negative controls using Lipofectamine 2000 (Invitrogen). Luciferase activity was assessed using the Dual-Luciferase Reporter Assay System (Promega) via GloMax Luminometer 48 hours after transfection.

Statistical analysis

Statistical analyses were performed utilizing two-tailed Student *t*-test and the means ± standard deviation (SD) with SPSS statistics software. The relationship between the mRNA expression level ofmiR-142-5p and SOCS1 mRNA was analyzed by Pearson's correlation. All results are presented as mean ± SD and *p*-value < 0.05 was conidered significant.

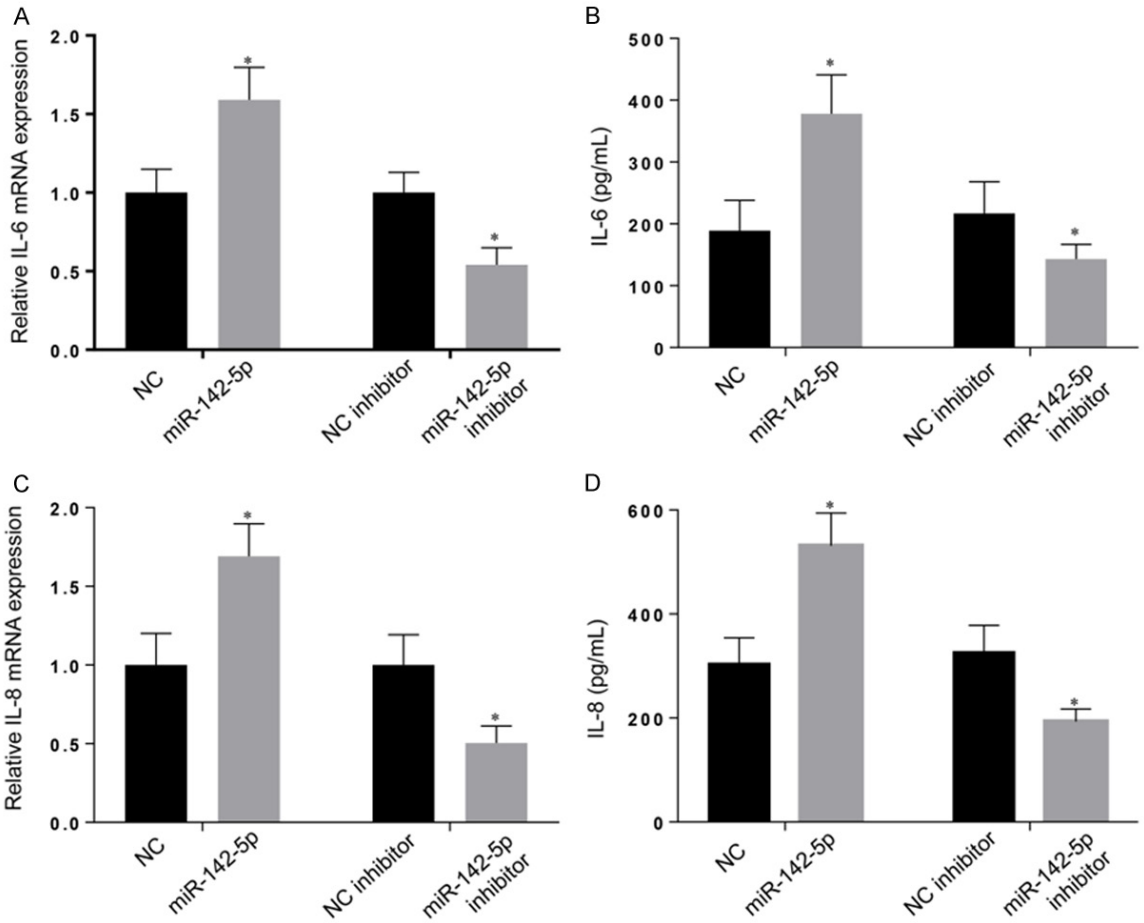

Figure 3. miR-142-5p increases IL-6/IL-8 expression in TNF-α-treated cells. Transfection with miR-142-5p mimic and inhibitor resulted, respectively, in an increase and decrease in IL-6 and IL-8 mRNA expression and protein release in TNF-α-treated cells. Results are expressed as fold-change relative to NC and presented as means ± SD of three independent experiments. *$P < 0.05$, compared with the corresponding NCs.

Results

Expression levels of miR-142-5p and SOCS1 in active ulcerative colitis patients

To investigate the biological function of miRNAs in UC, miRNA expression profiles were examined in colon tissues between patients with active UC (n = 3) and healthy controls (n = 3) by miRNA Microarray System and this identified that miR-142-5p was highly expressed in UC tissues when compared with normal tissues (**Figure 1A**). We used publicly available algorithm TargetScan to predict the targets of miR-142-5p and found that SOCS1 was a putative target of miR-142-5p. Next, we verified the results of microarrays using RT- PCR in more samples obtained from UC patients and normal controls. The results showed that miR-142-5p was highly expressed in UC patients (**Figure 1B**). Contrary to miR-142-5p expression levels, SOCS1 was downregulated in the patients with active UC at the mRNA and protein levels (**Figure 1C-E**). In addition, analysis of the mRNA expression levels of miRNA-142-5p and SOCS1 revealed an inverse relationship between them (Pearson's r = -0.4835, $P < 0.05$; **Figure 1F**).

TNF-α regulates miR-142-5p and SOCS1 expression in HT-29 Cells

Mostly, extracellular environment has a significantly influence on the inflammatory process of UC. Thus, to further examine the role of TNF-α in the progression, exacerbation and recurrence of UC, both the expression levels of miR-142-5p and SOCS1 in the context of inflammation induced by TNF-α. Interestingly, the levels of miR-142-5p were increased about 2-fold and

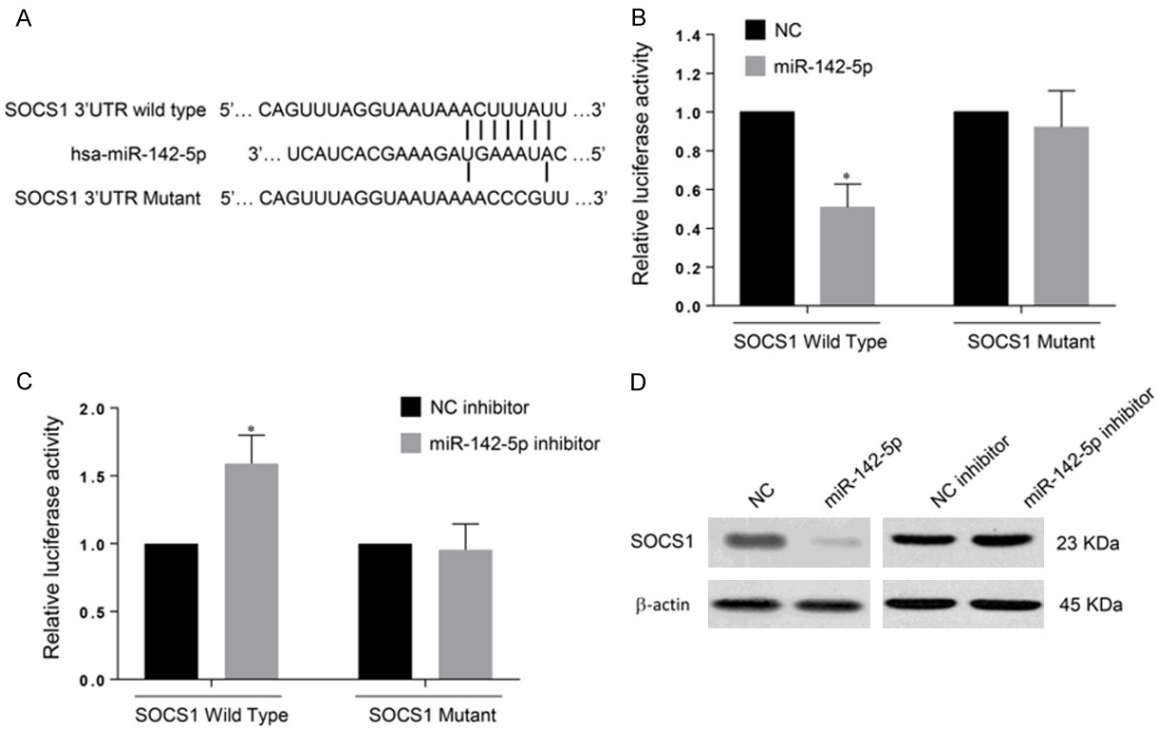

Figure 4. SOCS1 is a direct target of miR-142-5p. A. Bioinformatic analysis suggested that the 3'UTR of SOCS1 contained putative miR-142-5p binding sites. B, C. Luciferase activity assays of luciferase vectors containing wild-type or mutant SOCS1-3'-UTR were performed after transfection with miR-142-5p (or miR-142-5p inhibitor) in HT-29 cells. D. Western blotting shows the expression of SOCS1 protein in HT-29 cells after transfection with miR-142-5p (or miR-142-5p inhibitor), compared with corresponding NC groups. Results are expressed as fold-change relative to NC and presented as means ± SD of three independent experiments. **P* < 0.05, compared with NC group.

3-fold in HT-29 cells treated with TNF-α for 1 and 24 hours, respectively (**Figure 2A**). In contrast, the levels of SOCS1 mRNA and protein were obviously decreased in HT-29 cells after treated with TNF-α for 1 hour or 24 hours (**Figure 2B-D**). These results showed that miR-142-5p was upregulated in HT-29 cells after treating with TNF-α and accompanied by the degradation of SOCS1.

miR-142-5p promotes a pro-inflammatory phenotype by increasing the levels of IL-6/IL-8 in TNF-α-treated HT-29 cells

To further explore the function of miR-142-5p in the context of inflammation of HT-29 cells, both the mRNA expression and release levels of pro-inflammatory cytokines IL-6 and IL-8 were detected by RT-PCR and ELISA. Twenty-four hours after transfection with mimics or inhibitors of miR-142-5p, HT-29 cells were also treated with TNF-α (10 ng/mL) for 24 hours. Then both the cells and culture medium were harvested, and the expression level and concentration of IL-6/IL-8 mRNA were detected by qRT-PCR or ELISA. Indeed, overexpression of miR-142-5p significantly promoted mRNA expression and secretion levels of IL-6 and IL-8 in HT-29 cells, compared to the NC-transfected cells (**Figure 3A-D**). In contrast, inhibition of miR-142-5p by inhibitors dramatically decreased the level of IL-6 and IL-8 expressed and secreted (**Figure 3A-D**). Totally, these results showed that miR-142-5p acts as an activator in colonic inflammation and promotes the expression and secretion of IL-6 and IL-8 in TNF-α-stimulated HT-29 cells.

M iR-142-5p regulates SOCS1 expression through direct binding in SOCS1-3' UTR in HT-29 cells

Based on the computational searching above, SOCS1 was regarded as one of the potential target gene of miR-142-5p. Bioinformatic analysis identified sequence complementarity of miR-142-5p with the 3'UTR of SOCS1 (**Figure 4A**). To further confirm that SOCS1 is the direct

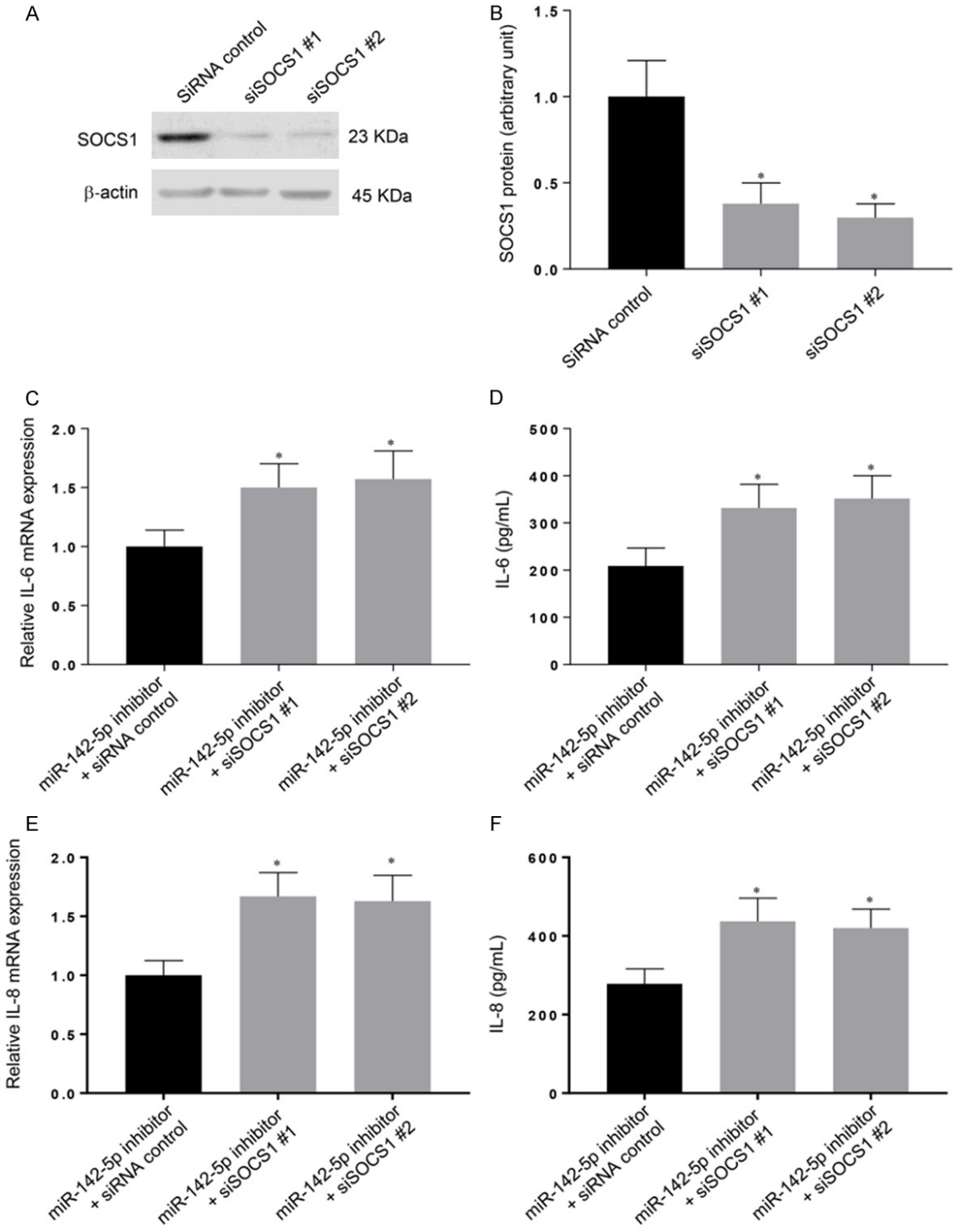

Figure 5. SOCS1 influences TNF-α-induced inflammatory response. A. Validation of SOCS1 silencing effective by western blotting after transfection with SOCS1 siRNA #1 and siRNA #2 or siRNA control in HT-29 cells. B. Densitometric quantification performed using β-actin as internal control. *$P < 0.05$ vs negative control. C-F. Compared with siRNA control transfection, SOCS1 siRNAs transfection reversed the miR-142-5p inhibitor effect on IL-6/IL-8 mRNA expression and secretion in TNF-α-treated HT-29 cells. Results are expressed as fold-change relative to the corresponding NC and are presented as means ± SD of three independent experiments. *$P < 0.05$.

target of miR-142-5p and SOCS1, the dual-luciferase assay was examined in HT-29 cells. The pMIR-Report constructs containing the segment of SOCS1 3′-UTR with either the wild type or mutant recognition sites of miR-142-5p were co-transfected with miR-142-5p mimics or negative control (NC). As compared with co-transfection with NC mimics, delivery of miR-142-5p suppresses SOCS1-3'UTR (wild type) luciferase activity without effects on SOCS1-3'UTR (mutant) (**Figure 4B**). Co-transfection of SOCS1-3'UTR with miR-142-5p inhibitor led to increased luciferase activity (**Figure 4C**). Furthermore, to further validate the correlation between SOCS1 expression and miR-142-5p level, western blot analysis was performed for total SOCS1 in HT-29 cells after transfection of mimics or inhibitors of miR-142-5p. As shown in **Figure 4D**, ectopic expression of miR-142-5p suppressed the basal SOCS1 protein level and miR-142-5p inhibitor exhibited the opposite function. In general, these results suggested that SOCS1 is a direct target of miR-142-5p.

SOCS1 has influences in TNF-α-induced inflammatory response

As previous reports that SOCS1 exerted a negative-feedback on inflammation [18], we suspected whether SOCS1 could affect IL-6 and IL-8 expression during inflammation. We initially transfected specific SOCS1 siRNAs to determine their ability to knockdown SOCS1 in HT-29 cells. As shown in **Figure 5A**, **5B**, these two specific siRNAs against SOCS1 dramatically interfered with the expression of SOCS1 after transfection for 48 h. For the next step, we co-transfected miR-142-5p inhibitors and two of the SOCS1 siRNAs into TNF-α treated HT-29 cells. Compared to co-transfection with control siRNA, co-transfection of miR-142-5p inhibitors with SOCS1 siRNAs led to increased expression and secretion of IL-6/IL-8 in TNF-α-treated cells (**Figure 5C-F**). These results indicated that SOCS1 knockdown in TNF-α-treated cells could abolish the anti-inflammatory effects of miR-142-5p inhibitor, suggesting that miR-142-5p regulated inflammation in patients with UC by inhibiting the SOCS1 expression.

Discussion

The abnormal expression of miRNA has been extensively described in many immune-mediated diseases, such as UC, and might facilitate diagnose and understand the pathogenesis of UC. In this present study, we compared miRNA microarray results of patients with active UC to normal controls and found that an epigenetic microRNA, miR-142-5p, was markedly upregulated in the active-UC patients as well as HT-29 cells after treatment with TNF-α. In addition, our results also showed out that miR-142-5p directly bound to the 3'-UTR of SOCS1 and that knockdown of SOCS1 could overturn the inhibitory effect of miR-142-5p inhibitors in the inflammatory process and TNF-α-treated HT-29 cells.

Much miRNA research investigates the role of miRNAs in cancer; with a small portionillustrating the function of miRNAs in inflammatory disease. Recently, revealing the role of miRNAs in inflammatory bowel disease (IBD) has provided novel ways for understanding mechanisms of this disease and developing new diagnostic and therapeutic approaches [19]. Meanwhile, miRNA profiling studies have provided an effective method for measuring the dysregulated miRNAs in tissue or blood of IBD patients [11, 20-23]. Totally, identifying aberrant miRNAs in active-UC patients is a key to understanding the inflammatory process and developing novel treatments.

Initially, we were interested in investigating the role of SOCS1 in UC, since in SOCS1 knockout mice can result in tumorigenesis in the colon. We then focused on miRNAs that can regulate the expression of SOCS1 and are upregulated in active-UC patients. We determined that miR-142-5p may involve the inflammation process of UC through miRNA microarray. It has been reported that miR-142-5p plays an important role in multiple pathological processes. For example, miR-142-5p participated in the progression of Hashimoto's thyroiditis by targeting CLDN1 [24]. miR-142-5p also acts as an oncomiR and promotes development of colorectal cancer [25] and renal cell carcinoma [26]. However, although it was reported that miR-142-5p was elevated in expression in UC patients, it was still necessary to clarify the role of miR-142-5p in colonic inflammation.

To further show the function of miR-142-5p in UC, we used an online bioinformatics tool to identify potential targets of miR-142-5p. The

dual-luciferase assays in HT-29 cells validated that miR-142-5p could directly interact with the SOSC1 3'UTR. SOCS1 is associated with multiple RTKs including stem cell factor (SCF) receptor (KIT), FMS-like tyrosine kinase 3 (FLT3), platelet-derived growth factor (PDGF) receptor (PDGFR), and colony-stimulating factor 1 (CSF1) receptor (CSF1R), and suppresses steel factor-dependent proliferation [27]. The most well-known function of SOCS1 is limiting the availability of downstream signaling proteins either through ubiquitin-mediated degradation or by competing for the same binding site in the receptor [14].

In our current study, both the expression levels of miR-142-5p and SOCS1 were evaluated in UC and normal controls. The results showed an inverse expression level between SOCS1 and miR-142-5p in UC patients and TNF-α-treated HT-29 cells. Furthermore, luciferase activity assays indicated that miR-142-5p directly targets SOCS1. In addition, qRT-PCT and western blotting assay verified that miR-142-5p could dramatically decrease SOCS1 expression in HT-29 cells. Our findings implied that miR-142-5p may inhibit the expression and release of inflammatory molecules by abolishing the function of SOCS1.

The results of miRNA microarray revealed that miR-142-5p was dysregulated in the active-UC patients. Our research also showed that miR-142-5p was a key regulator in colonic inflammation and functioned as a proinflammatory factor. However, we also need to clarify the role of miR-142-5p in the pathogenesis of UC.

Disclosure of conflict of interest

None.

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