

Decreased SOCS1 mRNA expression levels in peripheral blood mononuclear cells from patients with systemic lupus erythematosus in a Chinese population

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Abstract The aim of this study was to investigate the mRNA expression levels of suppressor of cytokine signaling 1 (SOCS1) in patients with systemic lupus erythematosus (SLE) compared with healthy controls. The associations of systemic lupus erythematosus disease activity index scores and clinical features of SLE with the expression levels of SOCS1 mRNA were also evaluated. Real-time quantitative reverse transcription-polymerase chain reaction was applied to detect the mRNA expression levels of SOCS1 in peripheral blood mononuclear cells from 34 patients with SLE and 34 healthy controls. The mRNA expression level of SOCS1 was significantly decreased in SLE patients in comparison with healthy controls ($Z = -4.207$, $P < 0.001$). Lower SOCS1 mRNA expression was detected in active SLE patients when compared with inactive ones ($Z = -2.428$, $P = 0.015$).

There was no significant difference found for the SOCS1 mRNA levels between SLE patients with nephritis and those without ($Z = -0.642$, $P = 0.521$). The presence of photosensitivity, proteinuria, positive antinuclear antibody, and C4 decline were associated with SOCS1 mRNA levels in SLE patients (all $P < 0.05$). Furthermore, the SOCS1 mRNA expression was negatively correlated with disease activity ($r_s = -0.372$, $P = 0.030$). Our results suggest that the dysregulation of SOCS1 might be associated with the pathogenesis of SLE.

Keywords Systemic lupus erythematosus · SOCS1 · SLEDAI · Lupus nephritis · Clinical feature

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease, which is characterized by overproduction of auto-antibodies, complement activation, and immune complex deposition, causing tissue and organ damage [1]. SLE predominantly affects women of childbearing age, with a female-to-male ratio of approximately 9:1 [2]. The pathogenesis of SLE still remains unclear, but available evidence indicated that dysregulation of cytokine signaling could cause disease initiation of SLE as well as its evolution.

Most cytokines utilize the so-called Janus kinase/signal transducer and activator of transcription (JAK–STAT) signaling pathway, and this signaling pathway is negatively regulated by suppressors of cytokine signaling (SOCS) proteins [3]. The SOCS proteins and cytokine-inducible Src homology 2 (CIS) protein make up a family of intracellular proteins [4–6]. There are 8 CIS/SOCS family proteins: CIS, SOCS1, SOCS2, SOCS3, SOCS4, SOCS5,

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SOCS6, and SOCS7. One of them, SOCS1, has a central SH2 domain containing kinase inhibitory region (KIR) domain, an N-terminal domain of variable length and sequence, and a conserved C-terminal SOCS box. The SOCS1 box plays a key role in the recruitment of the ubiquitin-transferase system and the mediation of the degradation of protein [7]. The SH2 domain of SOCS1 can bind to the activation loop of JAKs, and thereby inhibit the JAK-mediated signaling. The KIR domain, which is identified as a 12-residue motif downstream of the SH2 region, can target the JAK kinase domain, which leads to conformational changes of the catalytic site and induces ATP hydrolysis without transfer of the phosphate group to the tyrosine residues of substrates [8–11]. In immune responses, the binding of STAT with DNA induces the expression of SOCS1 mRNA and production of SOCS1 protein, which negatively feedback to regulate the cytokine-JAK-STAT pathway [6, 12]. Besides STAT, SOCS1 may be induced by NF- κ B and also negatively feedback to suppress NF- κ B [13, 14]. Furthermore, SOCS1 regulates the interferon- γ signaling, T cell development and activation, CD4 + T cell differentiation, lipopolysaccharide (LPS)-induced macrophage activation, and dendritic cell activation [15–20]. Collectively, SOCS1 plays a pivotal role in regulating immune responses and inflammation. In addition, Fujimoto et al. [21] found that mice with inadequate expression of SOCS1 spontaneously exhibited hyperactivation of lymphocytes, an increase in the levels of serum immunoglobulins and anti-DNA autoantibodies, and glomerulonephritis with glomerular IgG deposition, which are similar to those in human lupus. Therefore, dysfunction of SOCS1 may be a pathogenic factor in systemic autoimmune diseases such as SLE.

To further explore the association between SOCS1 and SLE, in the present study, we investigated the mRNA expression level of SOCS1 in peripheral blood mononuclear cells (PBMCs) from SLE patients and healthy controls. The associations of SLE disease activity index (SLEDAI) scores and clinical features of SLE with the expression levels of SOCS1 mRNA were also evaluated.

Patients and methods

Human subjects

Thirty-four patients with SLE (33 females and 1 male; mean age \pm SD = 32.82 ± 9.89 ; range 19–50) and 34 healthy controls (32 females and 2 males; mean age \pm SD = 31.74 ± 11.23 , range 17–58) were enrolled in this study. The patients were recruited from Anhui Provincial Hospital and the First Affiliated Hospital of Anhui Medical University, and the healthy control subjects

were selected from healthy blood donors without any rheumatologic conditions or any allergic status. The demographic and clinical data were collected via reviewing hospital records or by questionnaire and reviewed by experienced physicians. All the SLE patients fulfilled the American College of Rheumatology classification criteria [22]. The patients with renal involvement were defined by persistent proteinuria (> 0.5 g/24 h), hematuria or the presence of cellular casts by microscopic examination of urinary sediment, or renal biopsy demonstrating mesangial, focal proliferative, diffuse proliferative, or membranous glomerulonephritis. SLE disease activity was evaluated by systemic lupus erythematosus disease activity index (SLEDAI) 2,000 score [23]. The SLEDAI was divided into scores for active lupus (score ≥ 10) and inactive lupus (< 10). The protocol for this research was consistent with the provisions of the World Medical Association Declaration of Helsinki. Peripheral bloods were sampled from all the patients before they took any immunosuppressive drug, glucocorticoid or cytotoxic drugs to exclude the influence of drugs.

Collection of clinical and laboratory data

Clinical features of SLE patients such as butterfly erythema, photosensitivity, oral ulcer, arthritis, alopecia, and fever were recorded. Laboratory abnormalities were also recorded, including leukopenia ($< 3.0 \times 10^9/L$), thrombocytopenia ($< 100 \times 10^9/L$), the occurrence of blood urine ($> 5RBC/HP$) or proteinuria (> 0.5 g/24 h), elevated erythrocyte sedimentation rate (ERS) (> 20 mm/h), elevated C-reactive protein (CRP), the presence of anti-dsDNA, anti nuclear antibody (ANA), and anti-SSA; serum levels of C3/C4 (by immunoturbidimetry) were also reviewed.

Preparation of PBMC and extraction of RNA

Five milliliter peripheral blood was collected in evacuated tubes containing EDTA as the anticoagulant. PBMCs were purified from peripheral blood by centrifugation, using a Ficoll-Hypaque gradient (Tian Jin Hao Yang Biological Manufacture CO, Tianjin, China). Total RNA was extracted immediately from freshly isolated PBMCs in Biosafety Cabinet, using a TRIzol reagent from Invitrogen (Invitrogen California, USA).

Real-time quantitative reverse transcription-polymerase chain reaction (qRT-PCR) of SOCS1 mRNA.

Total RNA was reverse transcribed using RevertAidTM First Stand cDNA Synthesis Kit (Fermentas). Real-time quantitative polymerase chain reaction (RT-qPCR) was performed using ABI PRISM 7300 system (Applied Biosystems) to determine the expression of SOCS1 mRNA in PBMC from 34 patients with SLE and 34 healthy controls,

Assay-on-Demand TaqMan probe and primers (GAPDH Hs02758991_g1 and SOCS1 Hs00705164_S1). PCR was performed under the following conditions: initial incubation at 50 °C for 2 min, an enzyme activation step at 95 °C for 10 min, and 40 cycles of denaturation at 95 °C for 15 s and annealing extension at 60 °C for 1 min. The PCR for SOCS1 and GAPDH was duplicated twice in each sample. Results were corrected for GAPDH expression as an internal control. $2^{-\Delta\Delta CT}$ was used to compute the expression value of SOCS1.

Statistical analysis

The statistical analysis was performed by the SPSS 17.0 software (SPSS, Inc., Chicago, IL). Quantitative variables were described using mean ± SD. Nonparametric distribution data were expressed as median value and interquartile range (IQR), and the data of unpaired samples were tested by Mann–Whitney *U*-test. For the correlation analysis between the SOCS1 mRNA expression levels and SLEDAI, Spearman’s rank correlation coefficient was used. All tests were two-tailed, and a *P* value less than 0.05 was considered statistically significant.

Results

The expression levels of SOCS1 mRNA in PBMCs from patients with SLE and controls.

Table 1 Comparison of SOCS1 mRNA levels between different subgroups

Group	Number	SOCS1 mRNA levels <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)	<i>Z</i>	<i>P</i> Value
SLE patients	34	0.0399(0.0129, 0.2340)	-4.207	<0.001 ^a
Normal controls	34	1.0751(0.5832, 3.8389)		
SLE with nephritis	15	0.0721(0.0131, 0.7479)	-0.642	0.521 ^b
SLE without nephritis	19	0.0378(0.0121, 0.1264)		
Active SLE	17	0.0153(0.0085, 0.1153)	-2.428	0.015 ^c
Inactive SLE	17	0.0721(0.0260, 2.8169)		
Inactive SLE	17	0.0721(0.0260, 2.8169)	-1.658	0.097 ^a
Normal controls	34	1.0751(0.5832, 3.8389)		

^a versus normal controls

^b versus SLE without nephritis

^c versus inactive SLE

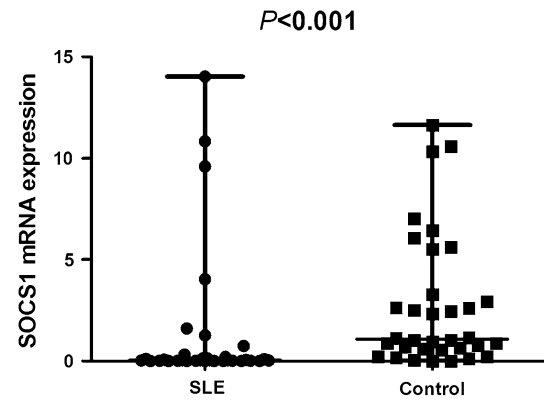


Fig. 1 SOCS1 mRNA expression levels in PBMC from patients with SLE and healthy controls. Real-time RT-PCR was performed to quantify the expression of SOCS1 mRNA in SLE patients (*n* = 34) and healthy controls (*n* = 34). Horizontal lines indicate medians (0.0399 in the patient group, 1.075 in the control group). There was a significant decrease in SOCS1 mRNA expression in SLE patients compared with healthy controls (*P* < 0.001)

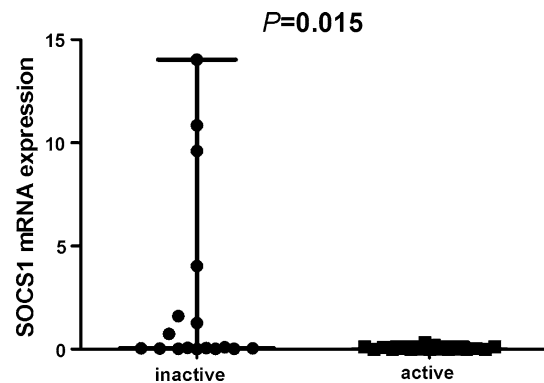


Fig. 2 SOCS1 mRNA expression levels in active and inactive SLE patients. The expression of SOCS1 mRNA in active SLE patients (*n* = 17) and inactive SLE patients (*n* = 17) were quantified, respectively. Horizontal lines indicate medians (0.015 in the active group, 0.072 in the inactive group). There was a significant decrease in SOCS1 mRNA expression in active SLE patients than in those inactive ones (*P* = 0.015)

As shown in Table 1, the SOCS1 mRNA expression levels were significantly decreased in patients with SLE when compared with those of the healthy controls (Fig. 1, *Z* = -4.207, *P* < 0.001). Nonetheless, no significant difference was found between patients with lupus nephritis (LN) and those without (*Z* = -0.642, *P* = 0.521). In addition, the SOCS1 mRNA levels in active SLE patients were significantly lower than in inactive SLE groups (*Z* = -2.428, *P* = 0.015) (Fig. 2).

Relationships between SOCS1 mRNA expression and SLEDAI or characteristics parameters in the patients with SLE.

The SOCS1 transcript levels were negatively correlated with SLEDAI scores in SLE patients (*r*_s = -0.372,

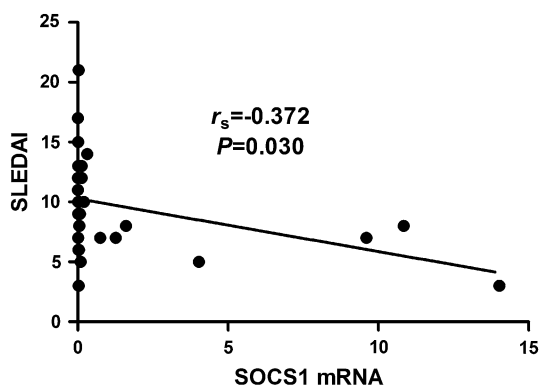


Fig. 3 Negative correlation between SOCS1 mRNA expression levels and SLEDAI in all the SLE patients ($n = 34$)

$P = 0.030$) (Fig. 3). The SOCS1 mRNA expression in SLE patients with photosensitivity was increased compared with those without photosensitivity ($Z = -2.891$, $P = 0.004$). However, no significant difference of other clinical features, such as butterfly erythema, oral ulcer, arthritis, alopecia and fever, were detected (Table 2). We also analyzed the associations of SOCS1 mRNA levels with major laboratory parameters of SLE, and the results indicated that the lower SOCS1 mRNA level was associated with the presence of proteinuria, positive antinuclear antibody, and C4 decline (all $P < 0.05$) (Table 3).

Discussion

SLE is a chronic inflammatory disease associated with dysfunction of multiple immunoregulatory genes. SOCS1 proteins are induced by various cytokines and in turn act as classical negative feedback regulator to cytokine signaling pathways. It has been reported that SOCS1 has a central SH2 domain, an amino-terminal domain of different length

and sequence, and a carboxy-terminal 40-amino-acid module known as the SOCS box [24]. More importantly, SOCS1 possess an additional domain in their amino-terminal region, named kinase inhibitory region (KIR), which enable them directly inhibit JAK activity by binding to the receptor or to the JAK activation loop [25]. Available data suggest that SOCS proteins are key regulators of immune homeostasis. Under the conditions of strong pro-inflammatory environments, SOCS1, through modulation of the cytokine peripheral environment, can contribute to the stability of the Foxp3⁺ peripheral Treg-cell population [26, 27]. In addition, SOCS1 can contribute to the development of T helper 17 (Th17) cells through the inhibition of the antagonistic effect of IFN- γ on Th17-cell differentiation [28].

In the present study, we examined the expression levels of SOCS1 mRNA in PBMCs of SLE patients and health controls. Relative quantification mRNA analysis of SOCS1 mRNA demonstrated that the SOCS1 mRNA expression in SLE patients was decreased when compared with healthy controls. It was also the case in the active SLE patients in comparison with inactive counterparties, and this study demonstrated that SLE patients with photosensitivity had a significantly higher expression of SOCS1 mRNA in PBMCs than the SLE patients without photosensitivity. Additionally, the lower SOCS1 mRNA level was associated with the presence of proteinuria, positive antinuclear antibody, and C4 decline. These defects may be attributed to the interaction of self-reactive CD4⁺T cells with B cells. The resulting hyper-activation of B cells, which produce an array of autoantibodies including ANA, promotes the formation of immune complexes, and might have a broad role in the pathogenesis of SLE, as evidenced by the increased incidence of glomerulonephritis with glomerular IgG deposition [8, 21]. Furthermore, we also found that the SOCS1 mRNA level was negatively correlated with

Table 2 Associations of SOCS1 mRNA level with clinical parameters of SLE patients

Group	±	Number	SOCS1 mRNA levels <i>M</i> (P_{25} , P_{75})	<i>Z</i>	<i>P</i> Value
Butterfly erythema	+	10	0.0747(0.0195, 0.9614)	-0.907	0.364
	-	24	0.0386(0.0124, 0.1307)		
Photosensitivity ^a	+	6	1.0067(0.1813, 3.9134)	-2.891	0.004 ^b
	-	28	0.0303(0.0117, 0.0899)		
Oral ulcer	+	8	0.0598(0.0091, 1.3883)	-0.162	0.871
	-	26	0.0399(0.0129, 0.1508)		
Arthritis	+	16	0.0271(0.0124, 0.0962)	-1.173	0.241
	-	18	0.0682(0.0127, 1.3495)		
Alopecia	+	10	0.0303(0.0090, 0.4716)	-0.454	0.650
	-	24	0.0415(0.0131, 0.2694)		
Fever (≥ 38 °C)	+	10	0.0136(0.0089, 0.0475)	-1.890	0.059
	-	24	0.0747(0.0172, 0.6379)		

^{+/-} with/without, ^athe average SLE disease activity index (SLEDAI) of 6 SLE patients with photosensitivity was 8.8333 ± 2.31661 , ^b $P \leq 0.05$

Table 3 Associations of SOCS1 mRNA level with Laboratory Parameters of SLE Patients

Group	±	Number	SOCS1 mRNA level <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)	Z	<i>P</i> Value
Anti-dsDNA	+	13	0.0313(0.0108, 0.0839)	−1.557	0.115
	−	21	0.0535(0.0143, 1.4336)		
Thrombocytopenia	+	8	0.0180(0.0080, 0.0403)	−1.949	0.051
	−	26	0.0628(0.0138, 0.8773)		
Leukopenia	+	12	0.0346(0.0129, 0.1209)	−0.216	0.829
	−	12	0.0480(0.0127, 0.4233)		
Blood urine	+	13	0.0378(0.0105, 0.0573)	−1.896	0.058
	−	21	0.0958(0.0147, 1.4336)		
Proteinuria	+	19	0.0313(0.0096, 0.1042)	−2.064	0.039 ^a
	−	15	0.0720(0.0228, 1.6017)		
ESR↑	+	11	0.0406(0.0140, 4.0320)	−0.755	0.450
	−	23	0.0393(0.0116, 0.1321)		
ANA	+	28	0.0303(0.0117, 0.0899)	−3.614	<0.001 ^a
	−	6	2.8169(1.1360, 11.6427)		
CRP	+	6	0.0430(0.0065, 6.5304)	−0.045	0.964
	−	28	0.0399(0.0131, 0.1883)		
Anti-SSA	+	8	0.0415(0.0172, 0.0962)	−0.203	0.839
	−	26	0.0385(0.0120, 0.8773)		
C3↓	+	19	0.0293(0.0096, 0.1042)	−1.648	0.099
	−	15	0.0720(0.0153, 1.2654)		
C4↓	+	12	0.0128(0.0047, 0.1021)	−2.306	0.021 ^a
	−	22	0.0480(0.0209, 1.3495)		

^{+/-} with/without, ^a*P* ≤ 0.05, *anti-dsDNA* Anti-double-stranded DNA, *ESR* Erythrocyte sedimentation rate, *ANA* Anti nuclear antibody, *CRP* C-reactive protein

SLEDAI scores in SLE patients. Thus, these data suggest the possibility that SOCS1 is involved in the pathogenesis of SLE, and this is supported by the fact that inadequate induction of SOCS1 causes systemic autoimmune diseases, and the insufficient SOCS1 expression mice results in lupus-like autoimmune disease [21].

Our study revealed that patients with SLE had lower expression of SOCS1 mRNA, which was different from the results of other groups [29–31]. Tsao et al. [29] showed that SOCS1 mRNA expression level was not significantly different between patients with SLE and controls of Taiwanese. However, Chan et al. [30] and Komatsuda et al. [29] showed that patients with SLE had significantly higher expression of SOCS1 mRNA in PBMCs than the controls of Taiwanese. This discrepancy may be explained by different methods for measurement of SOCS1 levels, clinical heterogeneity of patients and the condition of drug use. In Chan's study, all of those SLE patients received treatment with prednisolone and hydroxychloroquine [30]. However, our SLE patients were new incident patients who did not take any immunosuppressive agents. Maybe immunosuppressive agents had advanced the expression of SOCS1 mRNA which resulted in the discrepancy between Chan's and our study. There is a primary explanation for the results.

Indeed, in SLE model, SOCS1 deficiency impaired adaptive immune response through hyper-responsiveness of certain cytokine signaling, such as IL-2. This mechanism led to aberrant activation of antigen-presenting DCs and B cells, followed by perpetuating and aggravating the inflammatory process, in which engagement of over-activated signaling pathways, such as JAK1-STAT2, leads to up-regulated SOCS1 production, in turn results in negative feedback regulation of cytokine signaling transduction and inhibition of progression of autoimmune disease [19, 21]. Thus, although over-expressed SOCS was able to suppress the signaling transduction of various pathogenic cytokines, among the new cases, an insufficient or delayed expression of endogenous SOCS failed to protect from lupus. Therefore, the net effect of SOCS in SLE is in a dose-dependent manner, which explains why our SLE patients and the active SLE patients had lower expression of SOCS1 mRNA than the controls and inactive patients.

Given that the expression of SOCS1 is impaired in our patients with lupus, it is likely that exogenous SOCS1 may represent a novel therapeutic approach to this disease. The simplest paradigm involves therapeutic strategies that result in an up-regulation of SOCS protein expression, which would suppress the detrimental prolonged cytokine signaling. Treatment of wild-type mice with recombinant

SOCS or SOCS-expressing adenovirus significantly impaired the development of collagen-induced arthritis (CIA) [32] and attenuated the severity of cytokine-mediated β -cell toxicity [33]. Future investigations are still required to comprehensively uncover the therapeutic potential of recombinant SOCS or SOCS-expressing adenovirus in autoimmune lupus. Additionally, tyrosine kinase-inhibitor peptide (Tkip) has been reported to effectively inhibit pro-inflammatory cytokine signaling in experimental autoimmune encephalomyelitis (EAE) by suppressing JAK2-STAT1 signaling [34]. Furthermore, the SOCS1 kinase inhibitory region (KIR) mimetic PS-5 ameliorated IFN- γ -induced skin diseases, such as psoriasis, by blunting JAK2 kinase activity [35]. It will be very exciting to assess the above-mentioned (Tkip or PS-5) efficacies and to ascertain whether they are effective in autoimmune lupus.

In summary, this study demonstrated that the expression of SOCS1 mRNA was significantly decreased in patients with SLE compared with that of the controls. The SLE patients with active disease had lower expression of SOCS1 mRNA than the inactive patients. The SOCS1 mRNA level in SLE patients with photosensitivity was higher than that in SLE patients without photosensitivity. The SOCS1 mRNA level was negatively correlated with SLEDAI scores in SLE patients in this study. We must admit that our sample size was limited. Therefore, in order to determine the exact mechanisms of SOCS1 and to clarify the clinical relevance of SOCS1 in SLE, further studies with a larger sample size are required.

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Conflict of interest None.

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