Suppressor of cytokine signaling-1 ameliorates dextran sulfate sodium-induced colitis in mice

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Abstract

Inflammatory bowel disease (IBD) is a chronic disorder of the gastrointestinal tract. Although the etiology and pathogenesis of IBD remain unknown, pro-inflammatory cytokines including IFN-γ play an important role in the development of IBD. Suppressor of cytokine signaling-1 (SOCS-1) is a crucial inhibitor of cytokine signaling, particularly of IFN-γ. In this study, we investigated the role of SOCS-1 in the development of murine dextran sulfate sodium (DSS)-induced colitis, a model of colitis resembling human IBD. SOCS-1 heterozygous (SOCS-1+/−) and wild-type (WT) mice were given 3% DSS dissolved in drinking water for 5 days. Activation and expression of signal transducers and activators of transcription (STAT) in colon tissues were assessed by western blot analysis. The expression of CD4, IFN-γ, IL-4, IL-17 and Forkhead box P3 (Foxp3) in colonic lamina propria lymphocytes was analyzed by flow cytometry and cytokine concentrations in serum were measured. DSS-treated SOCS-1+/− mice developed more severe colitis than DSS-treated WT mice. Enhanced activation of STAT1, a higher ratio of CD4+IFN-γ+ T cells and a lower frequency of Foxp3+ regulatory T (Treg) cells, were observed in the colon of DSS-treated SOCS-1+/− mice compared with DSS-treated WT mice. DSS-treated SOCS-1+/− mice showed higher levels of IFN-γ in sera than did DSS-treated WT mice. Furthermore, T cell-specific SOCS-1-conditional knockout mice developed more severe colitis than control mice after DSS administration. Our findings suggest that SOCS-1, particularly in T cells, prevents the development of DSS-induced colitis in mice by inhibiting IFN-γ/STAT1 signaling and by subsequently regulating Treg cell development.

Introduction

Inflammatory bowel disease (IBD), consisting of ulcerative colitis (UC) and Crohn’s disease (CD), is characterized by chronic inflammation of the gastrointestinal tract. Although the etiology and pathogenesis of IBD have not yet been identified, an inappropriate and ongoing activation of the mucosal immune system has been found to play an important role in the pathogenesis of chronic mucosal inflammation (1, 2). The levels of pro-inflammatory cytokines such as IFN-γ, tumor necrosis factor-α (TNF-α), IL-1 and IL-6 are elevated in the inflamed mucosa of patients with IBD, thus disturbing the balance between pro-inflammatory and anti-inflammatory cytokines (2–4). Cytokines play an important role in the progression of IBD, and mAbs against pro-inflammatory cytokines or their receptors such as TNF-α, IL-6, IL-12 and IFN-γ have recently been shown to be effective in the treatment of IBD (5–10).

Suppressor of cytokine signaling-1 (SOCS-1) is a negative feedback molecule for cytokine signaling (11–13). SOCS-1
SOCS-1 ameliorates DSS-induced colitis in mice

DSS-induced colitis, 7- to 8-week old sex-matched SOCS-1-littermates for the experiments. In the experiments involving conditional knockout (24) and SOCS-1flox/flox (littermate control) mice (sex matched) were used when they were 21 weeks old. SOCS-1 mice and WT control mice received only ordinary water ad libitum (SOCS-1flox/flox) dissolved in drinking water provided ad libitum. This was also scored as to the percent involvement. Each subscore (inflammation severity score, inflammation extent score and crypt damage score) was the product of the grade multiplied by the percent involvement. Total colitis score was calculated as the sum of three subscores. Minimum total colitis score was 0 and maximum total colitis score was 40.

Western blot analysis
After DSS-treated SOCS-1flox/flox and WT mice were sacrificed on day 14, the colon was removed from each mouse. The distal third of the colon was used for western blot analysis because this segment is most severely affected in DSS-induced colitis (19). Colonic tissues were homogenized in ice-cold lysis buffer as described previously (26), and the supernatants were used as colonic lysates, which were separated on SDS-PAGE and transferred to polyvinylidene difluoride membranes. The membranes were then probed with the following antibodies: anti-phospho-STAT1, anti-phospho-STAT3, anti-phospho-STAT6 (Cell Signaling, Beverly, MA, USA) and glyceraldehyde-3-phosphate dehydrogenase (Santa Cruz Biotechnology, Santa Cruz, CA, USA), and then reprobed with the following antibodies: anti-STAT1, anti-STAT3, and anti-STAT6 (Santa Cruz Biotechnology).

Isolation of lamina propria lymphocytes from the colon
Lamina propria lymphocytes (LPLs) were isolated from the entire colon of SOCS-1flox/flox and WT mice as described previously (27). In brief, the entire colon, cut into 1-cm segments, was treated with PBS containing 10% FCS, 20 mM HEPES, 100 U ml\(^{-1}\) penicillin, 100 µg ml\(^{-1}\) streptomycin, 1 mM sodium pyruvate, 10 mM EDTA and 10 µg ml\(^{-1}\) polymyxin B for 20 min at 37°C to remove epithelial cells, and then washed extensively with PBS. The colon segments were digested with 400 Manidl U ml\(^{-1}\) Collagenase D (Roche, Mannheim, Germany) and 10 µg ml\(^{-1}\) DNase I (Roche) in RPMI 1640 containing 10% FCS while being stirred for 30 min at 37°C. EDTA was added (10 mM final concentration) and the digested tissues were incubated for 5 min at 37°C. The tissues were then passed through a nylon mesh (100 µm) and isolated cells were re-suspended in 75% Percoll (GE Healthcare Bio-Sciences, Uppsala, Sweden). This was
followed by layering of 40% Percoll onto the cell suspension in 75% Percoll and centrifugation at 2000 r.p.m. for 20 min and the lymphocyte-enriched population was recovered from the interface. The isolated LPLs were used for flow cytometry analysis.

**Flow cytometry analysis**

The isolated colonic LPLs from SOCS-1+/− and WT mice were stained with PerCP-Cy5.5-conjugated anti-CD4 (BD PharMingen), APC-conjugated anti-anti-IL-17 (BD PharMingen, San Jose, CA, USA), FITC-conjugated anti-anti-IL-4 (eBioscience, San Diego, CA, USA), PE-conjugated IFN-γ (BD Biosciences). Staining for Foxp3 was performed by using the Foxp3 staining kit from eBioscience. After stimulation of the cell suspension with 50 ng ml−1 phorbol myristate acetate (Sigma, St Louis, MO, USA) and 750 ng ml−1 ionomycin (Calbiochem, San Diego, CA, USA) for 3 h in the presence of 3 μM monensin (Sigma), intracellular cytokine staining was performed according to the manufacturer’s instructions (BD PharMingen). Staining for Foxp3 was performed by using the Foxp3 staining kit from eBioscience. Finally, the stained LPLs were analyzed on a FACSCanto (BD Biosciences, Franklin Lakes, NJ, USA) using FlowJo software (Tree Star, Ashland, OR, USA).

**Measurement of cytokine concentration in serum**

Blood was collected from SOCS-1+/− and WT mice by cardiac puncture under anesthesia and the serum was separated by centrifugation and stored at −30°C until used for analysis. IFN-γ, TNF-α, IL-4, IL-6 and IL-17 concentrations in serum were measured with the Bio-Plex system (Bio-Rad, Hercules, CA, USA) according to the manufacturer’s instructions.

IFN-γ concentrations in sera of Lck-cre SOCS-1+/− and SOCS-1+/− mice were measured by ELISA (eBioscience) according to the manufacturer’s instructions on day 7 after DSS administration.

**Statistical analysis**

Data are expressed as mean ± SD. For comparison of survival rates in DSS-treated groups, the Kaplan–Meier analysis and the log-rank test were used. Other data were analyzed with Student’s t-test. A P value <0.05 was considered statistically significant.

**Results**

**SOCS-1+/− mice developed more severe colitis than WT mice after DSS administration**

In initial studies that we performed using 10- to 12-week-old and sex-matched SOCS-1+/− mice and WT littermates under conventional conditions, the survival rate of SOCS-1+/− mice was significantly lower than that of WT mice after administration with 4% DSS for 7 days, and all SOCS-1+/− mice died during recovery phase (day 14; P < 0.05; Fig. 1A).

Thus, 3% DSS for 5 days was determined as the optimal dose in the present study. All SOCS-1+/− and WT mice survived during 5 days of treatment with 3% DSS, but the survival rate of SOCS-1+/− mice was lower, but not significantly, than that of WT mice even with this treatment (day 14; P = 0.58; Fig. 1B). Body weight loss was significantly greater in DSS-treated SOCS-1+/− mice than in DSS-treated WT mice (day 13; P < 0.05; Fig. 1C). On the other hand, body weight loss was observed in neither untreated WT nor SOCS-1+/− mice (data not shown). The colon length of DSS-treated SOCS-1+/− mice was significantly shorter than that of DSS-treated WT mice on day 14 (P < 0.001; Fig. 2), while there was no significant difference in colon length between untreated WT and SOCS-1+/− mice.
DSS-induced colitis in mice is characterized by infiltration of inflammatory cells such as neutrophils and lymphocytes, as well as by erosions, ulcers and crypt destruction in the colon (19, 20). Figure 3(A) shows representative histological appearances of the colons in WT and SOCS-1^{+/−} mice with DSS-induced colitis on day 14. More extensive inflammation and more severe destruction of the mucosal glandular architecture were observed in colonic tissues of DSS-treated SOCS-1^{+/−} mice than in DSS-treated WT mice. Whereas both untreated WT and SOCS-1^{+/−} mice showed little histological evidence of colonic inflammation (data not shown) and low histological scores (Fig. 3B), the mean histological score for total colitis was significantly higher for DSS-treated SOCS-1^{+/−} mice than for DSS-treated WT mice (P < 0.005; Fig. 3C).

Enhanced activation of STAT1 in SOCS-1^{+/−} mice with DSS-induced colitis

In previously reported studies, STAT1 and STAT3 were activated in the colon of human IBD and murine colitis models (28–31). We assessed the activation and expression of STAT1, STAT3 and STAT6 in the colon of DSS-treated mice by using western blot analysis (Fig. 4). It is well known that SOCS-1 is a crucial inhibitor of IFN-γ/STAT1 signaling (14). Expectedly, strong activation and enhanced expression of STAT1 were observed in DSS-treated SOCS-1^{+/−} mice compared with DSS-treated WT mice. Though STAT3 was strongly activated in DSS-treated SOCS-1^{+/−} mice, DSS-treated WT mice which developed severe colitis also exhibited strong activation of STAT3. On the other hand, activation of STAT6 was very weak in both DSS-treated WT and SOCS-1^{+/−} mice without any significant difference between the two groups. These results suggest that the enhanced STAT1 signaling in the colon is mainly responsible for the exacerbation of colitis in DSS-treated SOCS-1^{+/−} mice.

LPLs isolated from DSS-treated SOCS-1^{+/−} mice expressed higher level of CD4^{+}IFN-γ^{+} and lower level of CD4^{+}Foxp3^{+} than did DSS-treated WT mice

To investigate cytokine production and subsets of CD4^{+} T cells in the colon, we used flow cytometry analysis to
CD4+ cells (

Fig. 5A and C) and a significantly lower percentage of Total colitis scores of WT and SOCS-1−/− mice is caused mainly by enhanced IFN-γ production during the recovery period and that the low frequency contrast, a significantly higher ratio of CD4+ cells in colon of DSS-treated SOCS-1−/− mice compared with untreated WT mice. In addition, we detected not only enhanced IFN-γ signaling but also accumulation of CD4+ T cells which produce IFN-γ in the colon of DSS-treated SOCS-1−/− mice. These findings suggest that the exacerbation of colitis in DSS-treated SOCS-1−/− mice is caused mainly by enhanced IFN-γ/STAT1 signaling in the colon during the recovery period and that the low frequency of Foxp3+ regulatory T (Treg) cells in the colonic LP is also responsible for aggravation of colitis in DSS-treated SOCS-1−/− mice. On days 3 and 7, there was no significant difference between WT and SOCS-1−/− mice in the proportion of either CD4+IFN-γ+ or CD4+Foxp3+ cells (data not shown). The significant difference between WT and SOCS-1−/− mice in the ratio of neither CD4+IL-4+ nor CD4+IL-17+ cells was observed on days 0, 3, 7 and 14 (Fig. 5C and data not shown). These data indicate that SOCS-1 negatively regulates IFN-γ but not IL-4 or IL-17 signaling in the development of DSS-induced colitis.

Elevated levels of serum IFN-γ and IL-6 in SOCS-1−/− mice with DSS-induced colitis

Serum concentrations of cytokines in WT and SOCS-1−/− mice were measured on days 0 and 14. The sera of DSS-treated SOCS-1−/− mice showed increased levels of IFN-γ compared with DSS-treated WT or untreated SOCS-1−/− mice, although there was no statistically significant difference between the serum IFN-γ levels of DSS-treated WT and SOCS-1−/− mice (P = 0.16; Fig. 6A). Serum IL-6 levels were also significantly higher in DSS-treated SOCS-1−/− than in DSS-treated WT or untreated SOCS-1−/− mice (P < 0.05, respectively; Fig. 6B). On day 14, no significant difference was observed between the serum level of IFN-γ or IL-6 of untreated and DSS-treated WT mice (Fig. 6A and B) nor were there any significant differences in IL-4, IL-17 or TNF-α serum levels among the four groups (data not shown).

T cell-specific SOCS-1 deletion resulted in development of more severe DSS-induced colitis

To investigate in which cell types the protective role of SOCS-1 is important, we compared DSS-induced colitis in
T cell-specific SOCS-1-conditional knockout (Lck-cre SOCS-1<sup>fl/fl</sup>) mice with that in WT (SOCS-1<sup>fl/fl</sup>) mice. Following treatment with 3% DSS administration for 3 days, the survival rate of Lck-cre SOCS-1<sup>fl/fl</sup> mice was lower, but not significantly, than that of SOCS-1<sup>fl/fl</sup> mice (day 7; \( P = 0.059 \); Fig. 7A) and body weight loss was significantly greater in Lck-cre SOCS-1<sup>fl/fl</sup> mice than in SOCS-1<sup>fl/fl</sup> mice (days 2, 3, 5 and 6; \( P < 0.05 \), respectively; Fig. 7B). Serum IFN-\( \gamma \) levels were significantly higher in Lck-cre SOCS-1<sup>fl/fl</sup> mice than in SOCS-1<sup>fl/fl</sup> mice (day 7; \( P < 0.05 \); Fig. 7C). These results indicate that SOCS-1, particularly in T cells, plays an important role in preventing the development of DSS-induced colitis in mice by inhibiting IFN-\( \gamma \) production and/or IFN-\( \gamma \) signaling.

**Fig. 5.** Flow cytometry analysis of expression of CD4, IFN-\( \gamma \), IL-4, IL-17 and Foxp3 in colonic LPLs of WT and SOCS-1<sup>1<sup>−</sup></sup> mice before (day 0) and after DSS administration (day 14). (A) Representative results of flow cytometry analysis of CD4<sup>+</sup>IFN-\( \gamma \)^+ expression in colonic LPLs in each group. (B) Representative results of flow cytometry analysis of CD4<sup>+</sup>Foxp3<sup>+</sup> expression in colonic LPLs in each group. (C) The ratios of CD4<sup>+</sup>IFN-\( \gamma \)^+<sup>+</sup>, CD4<sup>+</sup>IL-4<sup>+</sup>, CD4<sup>+</sup>IL-17<sup>+</sup> and CD4<sup>+</sup>Foxp3<sup>+</sup> cells among total LP CD4<sup>+</sup> cells in each group. Data are expressed as mean \( \pm \) SD (n = 3, untreated WT and SOCS-1<sup>1<sup>−</sup></sup> groups and n = 5, DSS-treated WT and SOCS-1<sup>1<sup>−</sup></sup> groups); *\( P < 0.05 \), **\( P < 0.01 \) and ***\( P < 0.005 \).

The differentiation of Foxp3<sup>+</sup> Treg cells was markedly inhibited by IFN-\( \gamma \) signaling in SOCS-1<sup>−<sup>−</sup></sup>/IFN-\( \gamma \)-/ mice compared with IFN-\( \gamma \)-/ mice

We next used SOCS-1<sup>−<sup>−</sup></sup>/IFN-\( \gamma \)-/ and IFN-\( \gamma \)-/ mice to investigate whether SOCS-1 participates in Treg cell differentiation. It was recently reported that stimulation of naive CD4<sup>+</sup> T cells in vitro with TGF-\( \beta \) in combination with anti-CD3 and anti-CD28 induces the generation of Foxp3<sup>+</sup> Treg cells (32). We obtained naive CD4<sup>+</sup> T cells from SOCS-1<sup>−<sup>−</sup></sup>/IFN-\( \gamma \)-/ and IFN-\( \gamma \)-/ mice and cultured them in the presence of these factors. As reported previously, Foxp3<sup>+</sup> Treg cells are induced by this culture system and this induction was potently inhibited by IL-6 in both cell types (Fig. 8). In contrast, IFN-\( \gamma \) potently inhibited Treg cell generation from naive CD4<sup>+</sup>
T cells of the SOCS-1-/-IFN-γ-/- mice, while IFN-γ had a slightly suppressive effect on Treg cell generation from IFN-γ-/- mice (Fig. 8). In general, SOCS-1 is considered as a crucial inhibitor of IFN-γ/STAT1, but not IL-6/STAT3 signaling, because IL-6/STAT3 signaling is specifically inhibited by SOCS-3 in SOCS-1-/- mice (14). Therefore, these results suggest that SOCS-1 regulates Treg cell differentiation by inhibiting IFN-γ, but not IL-6 signaling, though both IFN-γ and IL-6 prevent the differentiation of Foxp3+ Treg cells. In addition, this supports the notion that DSS-treated SOCS-1+/- mice show the low frequency of Treg cells in the colonic LP due to dysregulation of IFN-γ, but not IL-6 signaling, compared with DSS-treated WT mice.

Discussion
According to recent reports, SOCS-1 regulates both IFN-γ and IL-4 in TCRα knockout (TCRα-/-) mice which spontaneously develop colitis (31, 33). In the study presented here, we investigated the role of SOCS-1 in murine DSS-induced colitis, a distinct model of colitis resembling human UC (19).

Although the etiology and pathogenesis of IBD remain unknown, it is known that cytokines play an important role in

Fig. 6. Serum cytokine concentrations in WT and SOCS-1+/+ mice before (day 0) and after DSS administration (day 14). Data are expressed as mean ± SD (n = 6, untreated WT and SOCS-1+/+ groups; n = 13, DSS-treated WT group and n = 14, DSS-treated SOCS-1+/+ group); *P < 0.05. (A) Serum levels of IFN-γ in each group. (B) Serum levels of IL-6 in each group.

Fig. 7. DSS-induced colitis in SOCS-1+/+ and Lck-cre SOCS-1+/+ mice. (A) Cumulative survival curves of SOCS-1+/+ and Lck-cre SOCS-1+/+ mice (21 weeks old and sex matched) after 3% DSS administration for 3 days under conventional conditions (n = 7, DSS-treated SOCS-1+/+ group and n = 6, DSS-treated Lck-cre SOCS-1+/+ group). (B) Body weight changes of SOCS-1+/+ and Lck-cre SOCS-1+/+ mice with DSS-induced colitis in the current study. Data are expressed as mean ± SD (n = 7, DSS-treated SOCS-1+/+ group and n = 6, DSS-treated Lck-cre SOCS-1+/+ group). *P < 0.05 versus DSS-treated SOCS-1+/+ group. (C) Serum levels of IFN-γ in SOCS-1+/+ and Lck-cre SOCS-1+/+ mice on day 7 after DSS administration. Data are expressed as mean ± SD (n = 3, each group); ++P < 0.05.
disease progression (1, 2). Increased levels of pro-inflammatory cytokines such as IFN-γ, TNF-α and IL-6 have been detected in the colon of patients with IBD and mice with DSS-induced colitis (2–4, 21, 22), while several recent studies have shown that STAT1 and STAT3 are activated in the colon of human IBD and murine colitis models (28–31). It has also been demonstrated that the activation of STAT1 and STAT3 is enhanced in inflamed tissues of both UC and CD patients and that the activation of STAT3 strongly correlates with the degree of inflammation (29, 30). Activation of STAT3 has been identified in various models of colitis such as DSS-induced colitis, TCRα−/− mice and IL-10−/− mice, and good correlation has been established between the levels of STAT3 phosphorylation and the severity of colitis (28). However, a relationship between levels of STAT1 in the colon and severity of DSS-induced colitis has not yet been clarified. In our study, STAT3 was strongly activated not only in DSS-treated SOCS-1−/− mice but also in DSS-treated WT mice which developed severe colitis, and the levels of STAT3 phosphorylation increased in parallel with the severity of colitis. We further think that the elevated levels of serum IL-6 in DSS-treated SOCS-1−/− mice during the recovery period may be also due to the development of severe colitis. In contrast, strong activation of STAT1 was shown only in DSS-treated SOCS-1−/− mice whereas STAT1 phosphorylation was very low level in DSS-treated WT mice. This result suggests that enhanced IFN-γ/STAT1 signaling in the colon exacerbates DSS-induced colitis and that SOCS-1−/− mice develop more severe colitis due to dysregulation of IFN-γ/STAT1 signaling, compared with WT mice. We also detected accumulation of CD4+ T cells, which produce IFN-γ in the colon, as well as elevation of IFN-γ concentrations in sera of DSS-treated SOCS-1−/− mice during the recovery period. On the other hand, there was no significant difference in IL-4 or IL-17 signaling between WT and SOCS-1−/− mice either before or after DSS administration. Furthermore, Lck-cre SOCS-1floxFlox mice devoid of SOCS-1 in T cells developed more severe colitis than SOCS-1floxFlox control mice after DSS administration. Our results indicate that SOCS-1, particularly in T cells, inhibits mainly IFN-γ, but not IL-4 or IL-17 signaling in mice with DSS-induced colitis and plays an important role in preventing the development of colitis. Recent studies have reported that fontolizumab, a humanized anti-IFN-γ antibody, was effective in the treatment of patients with active CD (9, 10). This suggests that SOCS-1, the main inhibitor of the IFN-γ signaling, may be useful in the treatment of IBD.

In addition, we investigated the frequency of Treg cell occurrence in the colonic LP of WT and SOCS-1−/− mice before and after DSS administration by using Foxp3, which is a specific marker of these cells (34–36). CD4+ Treg cells are traditionally thought to differentiate into Th1 cells, which produce predominantly IFN-γ and IL-2 or Th2, which secrete IL-4, IL-5, IL-10 and IL-13. It was recently reported that Treg cells differentiate into Th17, which produce IL-17, or CD4+CD25+ Treg cells. The transcription factor Foxp3 is specifically expressed by naturally occurring CD4+CD25+ Treg cells and plays a key role in their development and function (34–36). Recent studies have shown that Foxp3+ Treg cells accumulate in the inflamed LP of patients with IBD and that Treg cells isolated from the colonic LP of IBD patients have a suppressive effect in vitro (37, 38). In a T cell transfer model of IBD, Treg cells were found to accumulate in the colonic LP of mice and to be able to reverse established inflammation, which resulted in curing colitis (39). In our study, the proportion of Foxp3+ Treg cells among total LP CD4+ cells was significantly lower in DSS-treated SOCS-1−/− mice than in DSS-treated WT mice during the recovery period, and the lower ratio of Treg cells in the colonic LP of DSS-treated SOCS-1−/− mice was also responsible for the aggravation of colitis. We reported previously that SOCS-1 negatively regulates both Th1 and Th2 immune responses (40), and we were able to show in the current study that SOCS-1 also regulates Treg cell differentiation by inhibiting IFN-γ, but not IL-6 signaling in the experiments for comparing SOCS-1−/−IFN-γ−/− mice with IFN-γ−/− mice. Our results suggest that SOCS-1, subsequent to the regulation of Treg cell differentiation, also participates in Treg cell development by regulating IFN-γ, but not IL-6 signaling in murine DSS-induced colitis.

In conclusion, our study indicates that enhanced IFN-γ/STAT1 signaling in the colon exacerbates DSS-induced colitis and that SOCS-1, particularly in T cells, prevents the development of DSS-induced colitis by largely inhibiting IFN-γ, but not IL-4 or IL-17 signaling and by subsequently regulating Treg cell development.

Fig. 8. Representative results of flow cytometry analysis of Foxp3+ Treg cell generation from naive CD4+ T cells of SOCS-1−/−IFN-γ−/− and IFN-γ−/− mice after stimulation with anti-CD3, anti-CD28 and TGF-β in the absence or presence of IL-6 or IFN-γ. Percentages provided indicate Foxp3+ Treg cell percentage of total cell count.
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Abbreviations
CD  Crohn’s disease
DSS  dextran sulfate sodium
Foxp3  Forkhead box P3
IBD  inflammatory bowel disease
JAK  Janus kinase
LP  lamina propria
LPL  lamina propria lymphocyte
SOCS-1  suppressor of cytokine signaling-1
SOCS-1−/−  SOCS-1 heterozygous
SOCS-1−/−  SOCS-1 knockout
SOCS-1−/−  SOCS-1 double knockout
STAT  signal transducers and activators of transcription
TCRα−/−  TCRα knockout
TGF-β  transforming growth factor-β
TNF-α  tumor necrosis factor-α
Treg  regulatory T
UC  ulcerative colitis
WT  wild type

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