**Eur. Cytokine Netw.** Vol. 34, n° 4 , *December 2023* 46-53

RESEARCH ARTICLE

# Antibody targeting TSLP suppresses DSS-induced colitis and activation of the JAK2/STAT5 pathway in mice

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Article accepted on 11 October 2023

To cite this article: Zhuang W, Li Z. Antibody targeting TSLP suppresses DSS-induced colitis and activation of the JAK2/STAT5 pathway in mice. Eur. Cytokine Netw. 2023; 34(4): 46-53. doi: 10.1684/ecn.2023.0489

**ABSTRACT.** *Background:* There is currently no safe or effective treatment for inflammatory bowel disease (IBD), which is defined as recurrent and persistent intestinal inflammation. Thymic stromal lymphopoietin (TSLP) has been shown to be associated with the pathogenesis of IBD, and the JAK2/STAT5 signalling pathway has demonstrated much promise as a novel therapeutic target for IBD. *Materials and Methods:* In this study, we first evaluated levels of TSLP in dextran sodium sulphate (DSS)-induced IBD mice. Second, we applied tezepelumab, an anti-TSLP monoclonal antibody (20 μg per mouse, intraperitoneally), to DSS-induced IBD mice and quantified the signs of histopathological change, intestinal inflammation, whereas integrity of the mucosal barrier. In addition, the effect of DSS and/or tezepelumab on the phosphorylation of the JAK/STAT pathway was investigated. *Results:* TSLP expression levels were elevated in DSS-induced IBD mice, whereas TSLP antibody treatment suppressed the pathological features associated with IBD and alleviated intestinal inflammation and mucosal barrier disruption. Moreover, level of phosphorylated JAK2/STAT5 were increased in DSS-induced IBD mice, but were strongly decreased in the presence of tezepelumab. *Conclusions*: Our findings suggest that targeting TSLP via the JAK2/STAT5 signalling pathway may be an effective approach for the treatment of IBD.

**Key words:** inflammatory bowel disease, thymic stromal lymphopoietin, inflammation, mucosal barrier, JAK2/STAT5 pathway

Ulcerative colitis (UC) is a prevalent form of inflammatory bowel disease (IBD), characterized by recurrent inflammation and constitutive dysregulation of cytokine production, which is limited to mucosal tissues [1, 2]. The aetiology of UC may be related to a combination of environmental factors, genetic specificity, inflammation, oxidative stress, and intestinal immune dysfunction [2]. IBD is currently treated mostly with anti-inflammatory medications and biologics, such as corticosteroids, 5-aminosalicylic acid (5-ASA)-based medicines, azathioprine, and TNF-α inhibitors [3]. However, the majority of patients fail to achieve long-lasting, steroid-free remission and are particularly at risk of requiring surgery. Therefore, it is imperative to develop novel therapeutic strategies for the management of IBD.

Evidence suggests that abnormalities in intestinal epithelial cells (IECs) underlie the pathogenesis of IBD disease [4]. IECs play a crucial role in immune homeostasis by forming a physical and biochemical barrier to commensal and pathogenic microorganisms, as well as innate immune defence and the ability to modulate intestinal immune responses by sensing and responding to microbial stimuli [5]. As a result, IECs maintain a fundamental immunoregulatory role that affects the development and homeostasis of mucosal immune cells, and anomalies in these processes may play a role in the dysregulation of epithelial barrier function or aetiology of IBD.

Thymic stromal lymphopoietin (TSLP) is a cytokine that is mainly produced by epithelial cells in the skin, lungs, thymus, and other tissues. Moreover, TSLP is also clearly produced by IECs [6]. Studies have addressed the two distinct isoforms of TSLP: the short form (sf TSLP), which has a homeostatic function and is the primary isoform expressed in a steady state; and the long form (lf TSLP), which is elevated under inflammatory situations [7]. The aberrant expression of TSLP has been implicated in the pathogenesis of IBD. Patients with Crohn disease have demonstrated a reduction in intestinal TSLP expression [8]. However, intestinal TSLP expression reported in patients with UC remains controversial. Ordonez *et al*. found that TSLP levels were markedly enhanced in UC patients, while in another study, the expression level of TSLP was significantly lower in UC patients compared with the control group [9, 10]. Nevertheless, targeting TSLP may provide a new avenue for treating IBD.

In this study, we aimed to define the change in intestinal TSLP level in a DSS-induced colitis mouse model and further investigate whether treatment with an anti-TSLP mAb would suppress the signs of UC in this model, focussing on pathological change, intestinal inflammation, and mucosal barrier integrity. In addition, we investigated the possible involvement of the JAK/STAT pathway, in order to elucidate the underlying mechanism of TSLP on IBD.

doi: 10.1684/ecn.2023.0489

## MATERIALS AND METHODS

### *Animals*

Six-to-eight-week-old male C57BL/6 mice, weighing 20-24 g, were used for all studies. Animals were kept in individually ventilated cages with a 12-hour light/dark cycle at a temperature of 21 ± 2 °C and given access to food and water ad libitum. All procedures were approved by the Institutional Animal Care and Use Committee at Tongji Medical College, Huazhong University of Science and Technology (IACUC Number: 2419). All experiments were performed according to the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

### *Experimental design*

The mice were randomly divided into three groups: (1) a control group; (2) a DSS group which was given 3% DSS (W/V) (36,000-50,000 kDa; MP Biomedicals, Solon, OH, USA) in drinking water for seven days; and (3) an anti-TSLP group, which was given anti-TSLP mAb (MAB555; R&D Systems, USA), 20 μg per mouse intraperitoneally, during the period of acute colitis induced by 3% DSS in drinking water.

### *Histological studies*

The distal colon segments from each mouse were fixed in 4% paraformaldehyde (PFA), embedded in paraffin, and cut into 4-μm-thick sections. The sections were then stained with haematoxylin and eosin (H&E) for assessment of inflammation.

### *Assessment of colitis*

During drug treatment, daily records of changes in weight loss, stool consistency, and occult blood were taken, and the disease activity index (DAI) score was determined and expressed as the average of three scores [11].

### *Quantification of cytokines from intestinal homogenates*

For the analysis of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) and oxidative stress levels (MPO, SOD, and MDA), intestinal homogenates were prepared as described previously [12]. Samples were thawed and filtered for analysis using mouse-specific ELISAs (Bioswamp, China) following the manufacturer's instructions. The absorption was measured at 450 nm using a multi-well plate reader (AMR-100, Aosheng, China).

### *Western blot analysis*

We obtained colon samples of mice and homogenized them in lysis buffer (Beyotime, Wuhan, China). The mixture was centrifuged at 8,000 g for 10 minutes. The supernatant from each sample was then isolated and stored at -80 °C until analysis. We performed western blot analysis, as previously described [12].

### *Real-time quantitative reverse transcription polymerase chain reaction (RT-PCR)*

RNA extracted from the colon was reverse transcribed into complementary cDNA and PCR was performed, as previously described [12].

### *Statistical analysis*

Data are presented as mean ± SEM. GraphPad Prism software (version 8.0) was used for statistical analyses. The difference between the two groups was statistically examined through an unpaired student *t*-test, and the one-way ANOVA with Holm–Sidak correction was used for comparison among the three groups. *P* values below 0.05 were considered significant, and those above 0.01 and below 0.001 were considered highly significant.

## RESULTS

### *Effect of DSS on the expression of TSLP in the mouse intestine*

We performed RT-PCR and western blot analysis to measure gene and protein expression levels, respectively, of TSLP in DSS-treated mice after seven days of induction of colitis. We found that both gene and protein expression of intestinal TSLP were up-regulated in the DSS group when compared to the control group (*figure 1A-C*).

### *Effect of anti-TSLP mAb on acute colitis in DSS-induced mice*

To determine the impact of anti-TSLP mAb on DSS-induced colitis, changes in body weight, disease activity index (DAI), and colon histopathology of mice were investigated. Data showed that DSS-treated mice exhibited a noticeable reduction in body weight from day 2, whereas this decrease was significantly suppressed by anti-TSLP mAb (*figure 2*). Additionally, from day 5, mice treated with DSS showed obvious diarrhoea and rectal bleeding, and their DAI increased in a time-dependent manner. Again, anti-TSLP mAb treatment was shown to suppress these features in response to DSS (*figure 2B*).

Following the collection of colonic tissue samples, the severity of colitis was characterized by histological analysis of H&E-stained colonic sections. According to the H&E staining study, administration of DSS markedly increased the severity of colitis compared with normal mice; multifocal regions, mucosal erosion, loss of epithelial and goblet cells, branching of crypts, and submucosal oedema were all common features of colon inflammation in the DSS-treated group. Treatment with anti-TSLP mAb was shown to inhibit DSS-induced damage and reduce lesions of the colon in DSS-induced mice (*figure 2C*); the inhibitory effect of anti-TSLP mAb was particularly pronounced regarding injury to the colon. According to these findings, anti-TSLP mAb may therefore suppress acute colitis in mice induced by DSS.

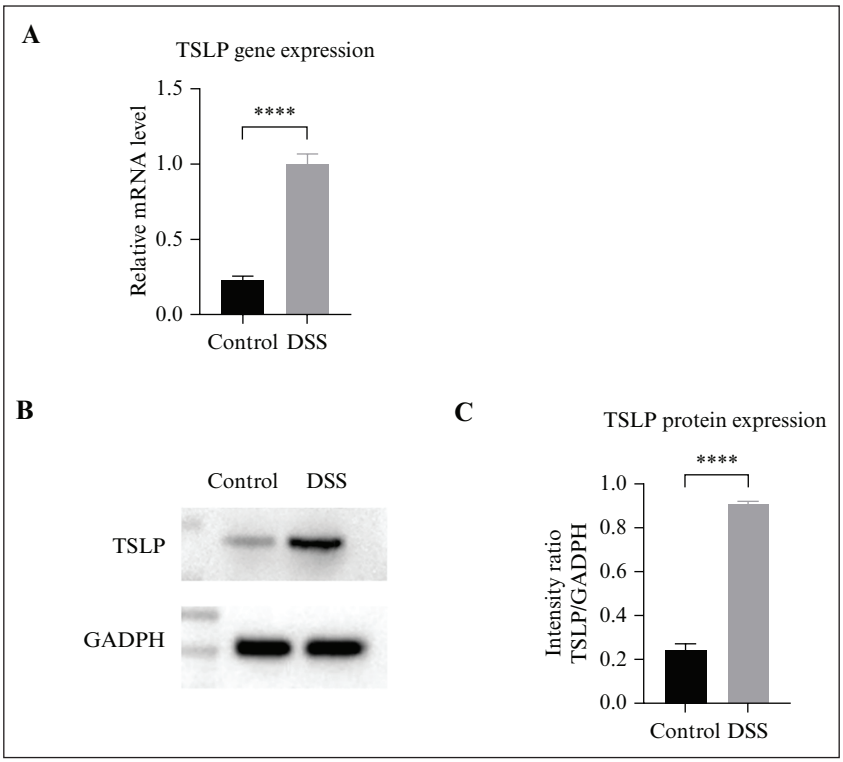


**Figure 1.**
DSS-induced expression of intestinal TSLP. **A**) RT-PCR analysis of TSLP gene expression in the control and DSS group. **B**) Western blot analysis of TSLP in the control and DSS group; bands are quantified in (**C**) (TSLP/GADPH). Data are shown as mean ± SD ($n$=3 per group). Statistics were calculated using the unpaired two-tailed Student's $t$-test; ****$p$<0.0001 *vs* control.

### *Effect of anti-TSLP mAb on intestinal inflammation and oxidative stress in DSS-induced mice*

To evaluate the anti-inflammatory effect of anti-TSLP mAb on colitis, the levels of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) were examined in colon tissues. The levels of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, were all much higher in DSS-treated mice than control mice, and this difference was most significant for TNF-α and IL-1β (*figure 3A-C*). However, treatment with anti-TSLP mAb significantly decreased the concentrations of inflammatory cytokines (*figure 3A-C*). TNF-α levels decreased from 2.55 ± 0.12 pg/mg to 2.38 ± 0.026 pg/mg, IL-1β levels from 0.454 ± 0.003 pg/mg to 0.447 ± 0.001 pg/mg, and IL-6 levels significantly dropped from 1.96 ± 0.047 pg/mg to 1.55 ± 0.067 pg/mg ($p$<0.01) in the DSS group and anti-TSLP mAb+DSS group, respectively (*figure 3C*).

To assess the impact of anti-TSLP mAb on oxidative stress in animals with colitis, we investigated the antioxidant factors, MDA, SOD, and MPO, in colon tissue. The concentration of MDA was 0.94 ± 0.03 nmol/mg, 3.72 ± 0.14 nmol/mg, and 2.12 ± 0.09 nmol/mg in the control group, DSS group, and anti-TSLP mAb+DSS group, respectively (*figure 3D*). The MPO level in the three groups was 0.25 ± 0.012 U/mg, 0.53 ± 0.01 U/mg, and 0.43 ± 0.014 U/mg, respectively (*figure 3E*). Both the amount of MDA and MPO were drastically elevated in the DSS-induced colitis group, but these levels were sharply reduced in the anti-TSLP mAb group (*figure 3D,E*). As displayed in *figure 3F*, the SOD levels in the three groups were 67.9 ± 3.35 U/mg, 52.9 ± 1.74 U/mg, and 64.8 ± 2.46 U/mg, respectively. Relative to the DSS group, a higher level of SOD was observed the control group as well as the DSS+anti-TSLP mAb group (*figure 3F*).

### *Effect of anti-TSLP mAb on the intestinal mucosa barrier in DSS-induced mice*

The intestinal epithelial barrier is made up of a single layer of enterocytes and tight junctions (TJs), which regulates the movement of molecules along transcellular and paracellular channels. The TJs are mainly composed of proteins including zonula occludens 1 (ZO-1), E-cadherin, and occludin [13]. ZO-1 constitutes the major rate-limiting barrier for the penetration of ions and larger solutes for paracellular transport. E-cadherin, an adhesion molecule involved in the polarity of epithelial cells, is necessary for maintaining paracellular permeability in mucosal tissue, together with claudin proteins [14]. Occludin is a transmembrane phosphoprotein that is expressed in the TJs of both epithelial and endothelial cells, and a decrease in occludin in TJs increases permeability. The expression levels of these three TJ proteins were measured in order to analyse the effect of anti-TSLP mAb on the intestinal mucosal barrier. The results showed that the expression levels of ZO-1, E-cadherin, and occludin were all dramatically decreased in the DSS-induced colitis mice, whereas anti-TSLP mAb treatment conversely increased the expression of the three TJ proteins (*figure 4*).

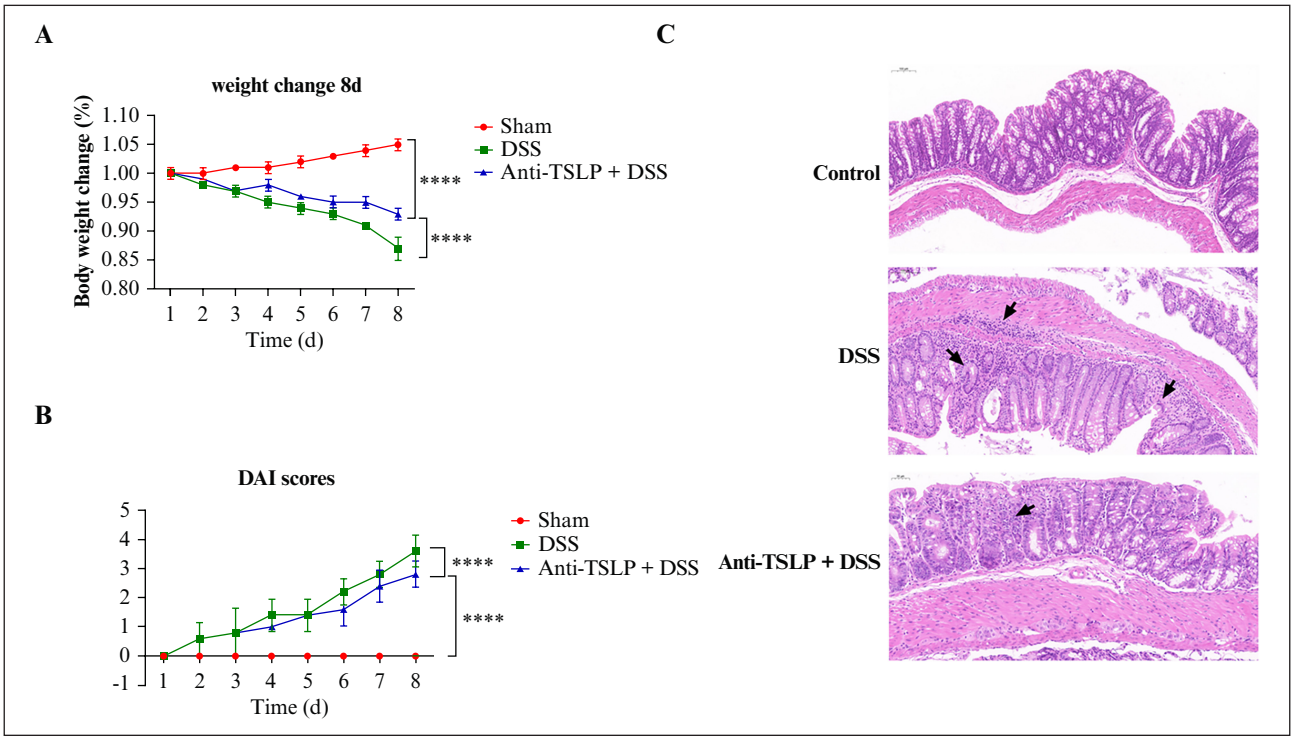


**Figure 2.**
Effect of anti-TSLP mAb on the control, DSS, and anti-TSLP mAb+DSS group, showing: daily mean weight change (**A**); changes in DAI score based on diarrhoea, bleeding, and body weight loss (**B**); and histological analysis of colon tissue (**C**). Scale bars=100 μm. One-way ANOVA tests were used for statistical analyses. Bars represent mean ± SD ($n$=5 per group); ****$p$<0.0001.

### *Effect of anti-TSLP mAb on the JAK2/STAT5 signalling pathway in DSS-induced mice*

JAK/STAT signalling is a well-recognized pathway that is required in innate and adaptive immune responses [15], and TSLP is documented to mediate signalling through this pathway [16]. Hence, we investigated the effect of anti-TSLP mAb in DSS-induced mice on the JAK2/STAT5 pathway. Our results showed that the level of JAK2 and STAT5 gene expression was elevated in the DSS group, but this increase was suppressed upon anti-TSLP mAb treatment (*figure 5A,B*). Western blot analysis showed that the levels of the phosphorylated forms, p-JAK2 and p-STAT5, were significantly higher in the DSS group compared with the control group, however, the addition of anti-TSLP mAb suppressed this increased phosphorylation in the presence of DSS; the levels of total JAK2 and STAT5 did not differ among the three groups (*figure 5C-E*). The data on gene expression and phosphorylation of JAK2 and STAT5 are therefore concordant, and indicate that anti-TSLP mAb inhibits the JAK2/STAT5 signalling pathway in DSS-induced mice.

## DISCUSSION

TSLP, a novel cytokine, plays significant roles in a wide range of disorders and diseases such as asthma, infectious diseases, inflammatory diseases, and cancer [17], and is currently being studied as a therapeutic target for a variety of illnesses. The disrupted expression of TSLP in the intestine has been implicated in the pathogenesis of IBD, and decreased TSLP levels have been associated with Crohn disease, however, the pattern of expression of TSLP in patients with UC patients is unclear. As a result, the current study aimed to investigate the expression level of TSLP in mice with DSS-induced colitis, as well as the effect of anti-TSLP mAb on these mice and the possible pathway mediating these effects.

Our results show that mice with colitis induced by DSS displayed a higher expression level of intestine TSLP compared to control mice. The expression of sfTSLP, which is constitutively expressed in a steady state in healthy mice, is widely known to be reduced in Crohn disease, whereas lfTSLP is only expressed in inflammatory conditions. Studies clearly show that the expression of sfTSLP is significantly decreased in the colonic mucosa of UC patients compared to controls [18], however, there is conflicting data on the expression of TSLP in UC patients. Hence, we reasoned that the contradictory evidence regarding differences in TSLP expression in UC patients may be due to the detection of different TSLP isoforms.

DSS-induced UC mice are the most common experimental model employed to investigate the aetiology and molecular mechanism of IBD. There are, however, few studies that define change in TSLP expression in DSS-induced UC mice. In a previous study, Keiichi *et al.* reported that DSS-induced mice had higher plasma TSLP levels than control mice, but TSLP levels in the colon were not examined [19]. Our results reveal that TSLP levels in DSS-induced UC mice were increased, which is inconsistent with the notion that the pattern of TSLP expression and regulation in mice closely resembles that of human lfTSLP [20].

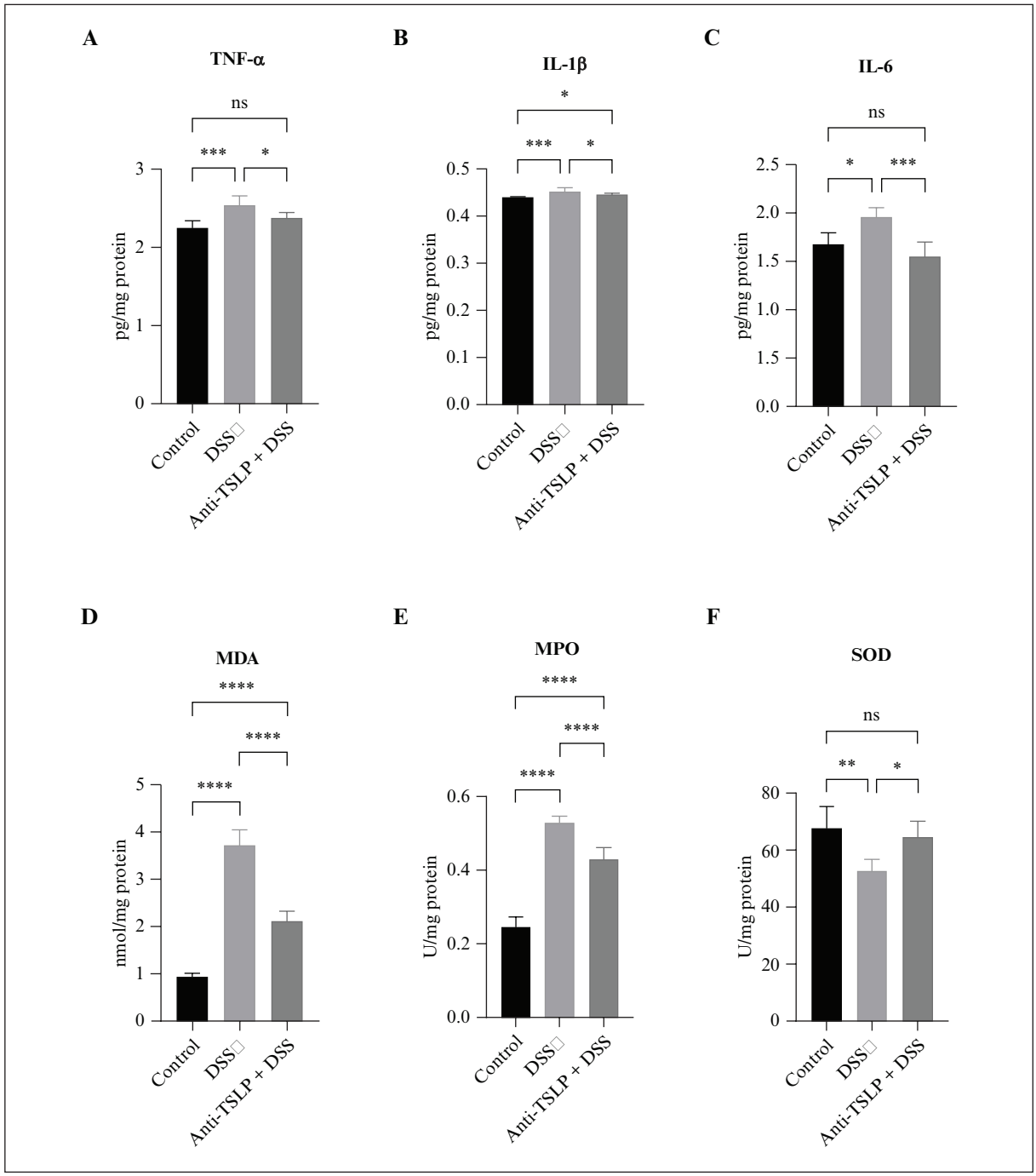


**Figure 3.**
Effect of anti-TSLP mAb on intestinal inflammation and oxidative stress factors in the control, DSS, and anti-TSLP MAb+ DSS group based on plasma concentrations of TNF-α (**A**), IL-1β (**B**), IL-6 (**C**), MDA (**D**), MPO (**E**), and SOD (**F**). One-way ANOVA tests were used for statistical analyses. Bars represent mean ± SD ($n$=5 per group); *$p$<0.05, **$p$<0.01, ***$p$<0.001, ****$p$<0.0001.

Since the level of TSLP expression was elevated in DSS-induced UC mice, we next focused on targeting TSLP in these mice. When anti-TSLP mAb was added to DSS-treated mice, the signs of colitis in mice were reduced, including weight loss, bloody stools, and loose stools. Additionally, goblet cells, crypts, and epithelial cell loss were also reduced in the colon.

The potential of anti-TSLP mAb as treatment for UC and the underlying mechanism, however, have not been fully investigated. Although the pathogenesis of UC is still poorly understood, there is evidence that these intestinal disorders cause immune-mediated inflammation, pathogen invasion, and inflammatory cell infiltration [21]. The condition of inflammation thus causes superficial mucosal inflammation that may harm the inner intestinal wall, causing ulcerations, bleeding, and painful and uncomfortable stomach cramps [21]. Hence, we examined the production of pro-inflammatory cytokines in the colon. As expected, treatment with anti-TSLP mAb also led to an improvement in inflammatory responses, as seen by the decline in the production of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β. Diffusive inflammatory cell infiltration and small intestinal mucosal crypt abscesses in colitis

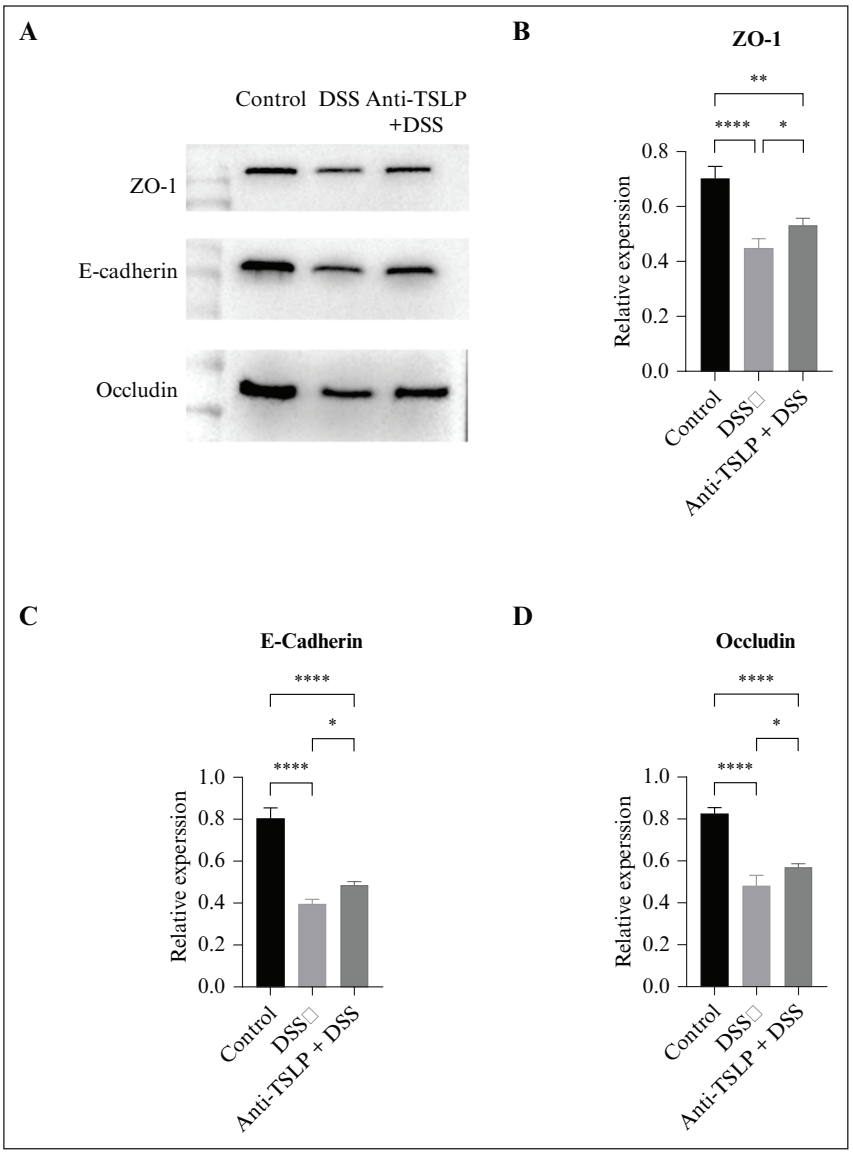


**Figure 4.**
**A**) Effect of anti-TSLP mAb treatment on intestinal mucosa barrier damage in the control, DSS, and anti-TSLP MAb+ DSS group, based on ZO-1, E-cadherin, and occludin protein expression. **B-D**) Relative expression levels based on (**A**). Data are presented as mean±SEM ($n$=3 per group). Statistical significance was determined using one-way ANOVA; *$p$<0.05, ***, $p$<0.001, and ****, $p$<0.0001.

trigger the overproduction of reactive oxygen species (ROS), which leads to oxidative stress damage to colon cells and increased permeability of the epithelial barrier, thus promoting pathogen invasion and amplifying inflammatory damage [22]. We therefore investigated ROS in the colon by measuring the levels of MDA, SOD, and MPO. The results show that anti-TSLP mAb administration suppressed the levels of MDA, SOD, and MPO in DSS-treated mice.

Upon inflammation and oxidative stress, the colon develops a damaged intestinal barrier, which is one of the key pathological features of UC. Disruption of the epithelial barrier has been reported to be caused by DSS in the mouse colon which shares pathological similarities with the colon of patients with UC [23]. Our results indicate that anti-TSLP mAb treatment improves mucosal intensity, possibly by enhancing the expression of TJ proteins, including ZO-1, E-cadherin, and occludin.

Lastly, we explored the inhibitory mechanism of anti-TSLP mAb on the inflammatory response. The signalling and subsequent biological consequences in response to inflammatory cytokine receptor binding, including various actions related to IBD pathogenesis, are mediated by the JAK tyrosine kinases and STAT proteins [24]. Small-molecule JAK inhibitors, which have the potential to influence numerous cytokine-dependent pathways, have been shown to be effective as treatment for IBD [25]. JAK is a member of the 130-kDa family of non-receptor protein tyrosine kinases, which includes JAK1, JAK2, JAK3, and TYK2. STATs are attracted to a complex of activated receptors which then become active. Seven STAT proteins have been identified. Cytokines and their receptors are the main activators of the JAK/STAT pathway [26]. Different JAKs and STATs are activated by different ligands. Multiple lines of evidence have shown that the JAK2/STAT5 pathway is the mechanism by which TSLP exerts its action

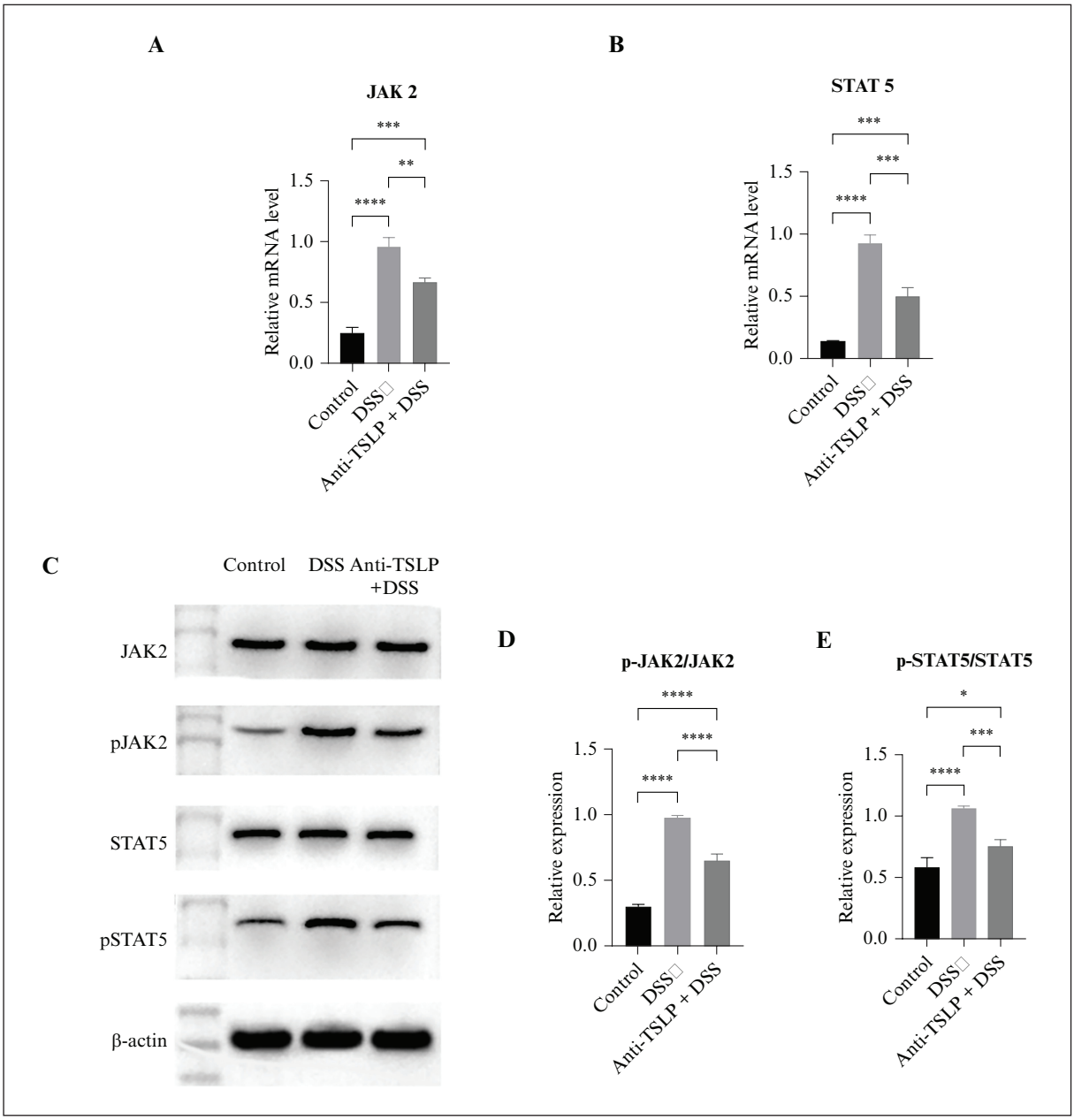


**Figure 5.**
Effect of anti-TSLP mAb on the JAK2/STAT5 signalling pathway in the control, DSS, and anti-TSLP MAb+ DSS group. **A, B**). JAK2 and STAT5 mRNA expression =($n$=3). **C**). Western blot of phosphorylated and unphosphorylated JAK2 and STAT5 ($n$=3). **D, E**) Relative quantification of protein levels in (**C**). *$p$<0.05, **$p$<0.01, ***$p$<0.001, and ****$p$<0.0001 when compared with the control group.

[27-29]. In this study, we examined the level of phosphorylation of JAK2 and STAT5 in the gut of DSS-treated mice and found that phosphorylation increased, while total protein levels of JAK2 and STAT5 remained unaltered. Treating the UC mice with anti-TSLP mAb further decreased the phosphorylation level of JAK2 and STAT5, indicating that TSLP may exert its inflammatory effects in DSS-treated mice through the JAK2/STAT5 pathway, and anti-TSLP mAb treatment may provide its protective effects by blocking the JAK2/STAT5 pathway.

In conclusion, our findings confirm the protective role of anti-TSLP mAb in mice with DSS-induced colitis based on investigation of pro-inflammatory cytokines, oxidative stress indicators, and the mucosal barrier. Additionally, we demonstrate that the protective effect of anti-TSLP mAb may potentially be mediated by the JAK2/STAT5 pathway.

## DISCLOSURE

**Financial support:** none. **Conflicts of interest:** none.

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