Basic Study

Sodium selenite ameliorates dextran sulfate sodium-induced chronic colitis in mice by decreasing Th1, Th17, and γδT and increasing CD4(+)CD25(+) regulatory T-cell responses

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Abstract

AIM
To assess the effect of sodium selenite on the severity of dextran sulfate sodium (DSS)-induced colitis in C57BL/6 mice.

METHODS
Mice were randomly divided into four groups (n = 10/group): normal group, selenium (Se) group, chronic colitis group, and Se + chronic colitis group. The
mice were sacrificed on day 26. Survival rates, clinical symptoms, colon length, and histological changes were determined. The percentages and absolute numbers of immune system cells in the lamina propria lymphocytes (LPL) of the colon, the expression of mRNA in colon tissue, and the concentrations of Th1, Th17, and Treg cytokines in LPL from the large intestine, were measured.

**RESULTS**

Se significantly ameliorated the symptoms of colitis and histological injury \((P < 0.05\) each), increasing the proportions of neutrophils and CD4\(^+\)CD25\(^+\) T cells \((P < 0.05\) each) and decreasing the proportions of γδT cells, CD4\(^+\), CD4\(^+\)CD44\(^+\), and CD4\(^+\)CD69\(^+\) T cells in LPL \((P < 0.05\) each). Moreover, Se reduced the expression of IL-6, IFN-γ, IL-17A, IL-21, T-bet, and RORγt \((P < 0.05\) each), but enhanced the expression of IL-10 and Foxp3 \((P < 0.05\) each).

**CONCLUSION**

These results suggest that Se protects against DSS-induced chronic colitis perhaps by increasing the number of CD4\(^+\)CD25\(^+\) Tregs that suppress the secretion of proinflammatory cytokines and populations of Th1, Th17, and γδT cells.

**Key words:** Sodium selenite; Dextran sulfate sodium; Chronic colitis

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Core tip: Se significantly ameliorated the symptoms of colitis and histological injury, increasing the proportions of neutrophils and CD4\(^+\)CD25\(^+\) T cells and decreasing the proportions of γδT cells, CD4\(^+\), CD4\(^+\)CD44\(^+\), and CD4\(^+\)CD69\(^+\) T cells in LPL. Moreover, Se reduced the expression of IL-6, IFN-γ, IL-17A, IL-21, T-bet, and RORγt, but enhanced the expression of IL-10 and Foxp3. The study suggests that Se protects against DSS-induced chronic colitis perhaps by increasing the number of CD4\(^+\)CD25\(^+\) Tregs that suppress the secretion of proinflammatory cytokines and populations of Th1, Th17, and γδT cells.

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**INTRODUCTION**

Inflammatory bowel disease (IBD) is a chronic, remittent-relapsing intestinal inflammatory condition. It consists of two major forms, ulcerative colitis and Crohn’s disease, which are more common in developed countries than in developing countries. The major symptoms of IBD include abdominal pain, diarrhea, weight loss, and intestinal bleeding. Although the pathogenesis of IBD has not been definitively elucidated, factors including genetic mutations, immunological disorders, environmental exposure, oxidative stress, and intestinal flora have been suggested to be involved in this process\(^{[1-5]}\). In addition, there is sufficient evidence linking IBD to the over-response of the mucosal immune system\(^{[6]}\). T cells are important components of the adaptive immune response. The activation and proliferation of colonic lamina propria (LP) T lymphocytes during immune responses are important in maintaining intestinal immune homeostasis. CD4\(^+\) T cells are especially important in regulating intestinal inflammation. CD4\(^+\) T cells have been divided into subsets, based on the cytokines they produce; these subsets include Th1, Th2, Th17, and Treg cells. Th1 and Th17 cells are involved in the pathogenesis of IBD\(^{[7,8]}\), whereas Treg cells ameliorate intestinal inflammation by suppressing Th17 cells\(^{[9]}\).

To date, treatment options for IBD have mainly focused on controlling symptoms by suppressing inflammatory responses. Infliximab, a monoclonal antibody against tumor necrosis factor (TNF)-α, has proven effective in IBD by inducing the apoptosis of mucosal T cells\(^{[10,11]}\), suggesting that strategies targeting lamina propria lymphocytes (LPL) in the intestinal mucosa may be effective in treating IBD. However, although immunomodulatory therapies are effective in many patients, many become refractory, suggesting the need to develop new agents to treat IBD.

Selenium (Se) is an important micronutrient for human health and has antioxidative properties. Se helps maintain the catalytic function of selenoproteins that indirectly alleviate oxygen-rich free radicals\(^{[16]}\). In addition, Se is necessary for the expression of glutathione peroxidase (GPX)\(^{[12]}\) that protects organisms from oxidative damage. Se levels are inversely correlated with cancer risk and IBD\(^{[12-14]}\). Clinical studies have shown that Se\(^{[15]}\) and Se protein P\(^{[16]}\) contents are significantly lower in patients with IBD than in healthy controls, and that Se supplementation can reduce intestinal symptoms in patients with IBD\(^{[17]}\). Se can also protect against experimental colitis and human ulcerative colitis (UC)\(^{[18,19]}\).

Little is known about the mechanism of action of Se in IBD. Activation of NF-κB and AP-1 is important in the pathogenesis of IBD\(^{[19,20]}\). Although Se has been shown to affect NF-κB and AP-1 activation\(^{[21-24]}\), the effect of Se on mucosal LPL in the colon remains unclear.

Experimental colitis can be induced in mice by oral administration of dextran sulfate sodium (DSS).
The pathogenesis and clinical features of this animal model of IBD resemble those of human UC. This study assessed the effect of sodium selenite on DSS-induced colitis in mice, revealing that sodium selenite pretreatment protected against chronic colitis by reducing the levels of Th1, Th17, and γδT type cytokines and increasing those of Treg cytokines.

**MATERIALS AND METHODS**

**Experimental animals**

Eight-week-old male C57BL/6 mice, weighing 20 ± 1 g, were purchased from the Animal Care Facility of China Medical University. The mice were maintained and bred under specific pathogen-free conditions (temperature 24-25 °C, humidity 70%-75%, and a 12-h light/12-h dark lighting regimen). Mice were fed chow, which had a basal selenium content of 0.1 μg/g diet. The study protocol was approved by the Animal Ethics Committee and Animal Care Committee of China Medical University.

**Induction of chronic DSS colitis**

Mice received oral 1.5% DSS (molecular mass 36-50 kDa; MP Biomedicals, Solon, OH, United States) on days 0-5, 10-15, and 20-25 and tap water on the other days.

**Experimental design**

The mice were randomly divided into four groups (n = 10/group): control group, Se group, chronic colitis group, and Se + chronic colitis group. The control group was fed a normal diet (0.1 μg Se/g diet) and tap water + once-daily gavage of 0.2 mL PBS for 25 d. The Se group was fed a normal diet (0.1 μg Se/g diet) and tap water + once-daily gavage of 2 μg Se/g body weight for 25 d. The chronic colitis group was subjected to chronic colitis induction and fed a normal diet (0.1 μg Se/g diet) + once-daily gavage of 0.2 mL PBS for 25 d. The Se + chronic colitis group was subjected to chronic colitis induction and fed a normal diet (0.1 μg Se/g diet) + once-daily gavage of 2 μg Se/g body weight for 25 d. Body weight and disease activity index were observed daily. Each mouse was weighed at the same time daily.

**Disease activity index and histopathology**

The severity of colitis was assessed using the disease activity index (DAI) based on weight loss, hemoccult or rectal bleeding, and stool consistency; the scores are described in Table 1. After sacrifice, colon tissue was fixed in 4% paraformaldehyde and embedded in paraffin, and sections 4 μm thick were stained with hematoxylin and eosin to evaluate colonic histology, with histological scores determined in a blinded fashion by two independent pathologists (Table 2).

**Cell preparation, culture, and stimulation**

The large intestine of each mouse was cut into 1-2 mm pieces. The pieces were stirred twice for 15 min each in PBS containing 3 mmol/L EDTA and twice for 20 min each in RPMI1640 (HyClone), containing 1 mmol/L EGTA, all at 37 °C, to eliminate epithelium. The remaining pieces were stirred for 90 min at 37 °C in RPMI 1640 (HyClone) containing 20% fetal bovine serum, 100 U/mL collagenase (C2139; Sigma-Aldrich Corp., St. Louis, MO, United States), and 5 U/mL DNase1 (Sigma-Aldrich Corp.). The suspensions were centrifuged, and the pellets were washed. LPL were isolated from the lamina propria (LP)-cell preparations by centrifugation through a 45%-66.6% discontinuous Percoll (Solarbio) gradient at 2500 rpm for 20 min.

LPL (1 × 10^7/well in 0.2 mL RPMI1640 containing 10% fetal bovine serum, 1% penicillin, and 1% streptomycin) were cultured for 48 h in 96-well plates coated with anti-CD3 (10 μg/mL e-Bioscience, San Diego, CA, United States) and soluble anti-CD28 (1 μg/mL, e-Bioscience) mAb at 37 °C in an atmosphere containing 5% CO2. After 48 h, the supernatants were collected and cytokine concentrations assayed by enzyme-linked immunosorbent assay.

**Enzyme-linked immunosorbent assay**

Supernatants of cell cultures were collected after centrifugation at 1000 rpm for 10 min, and cytokine concentrations were measured using mouse immunoassay kits (R&D Systems Inc., Minneapolis, MN, United States), according to the manufacturer’s protocol.

The levels of IL-6, IL-23, IL-1p, IL-12p70 and TNF-α were measured in supernatants without anti-CD3/anti-CD28 mAbs stimulations. The levels of IFN-γ, IL-17A, IL-21, IL-22 and IL-10 were measured in supernatants with or without anti-CD28/anti-CD3 mAbs stimulations.

**RNA extraction and real-time polymerase chain reaction**

Total RNA was extracted from colon tissue using Trizol reagent (Takara, Dalian, China), according to the manufacturer’s protocol. RNA was reverse transcribed to cDNA using reverse transcriptase (Takara), followed by PCR assays using primers for β-actin (forward, 5′-TTCAGCGTTCTCTTGGTAT-3′; reverse, 5′-GTTGGCATAAGGTTTTACGG-3′). IL-

| Table 1 Disease activity index score chart |
|------------------------------------------|
| Fecal property | Fecal occult blood | Body weight decrease (%) | Integral |
|---------------|--------------------|--------------------------|---------|
| Normal        | Normal             | 0                        | 0       |
| Relaxed       | Positive fecal occult blood | > 5-10 | 2       |
| Loose stools  | Naked eye fecal occult blood | > 10-15 | 3       |

Normal stool: shaped stool; Relaxed stool: pasty, unformed stools not attached to the anus; Loose stools: unshaped stools attached to the anus.
17F (forward, 5'-TCCCACGTGAATTTCCAGAC-3'; reverse, 5'-ATGGTGGCTTCTTCCCCAGC-3'), IL-21 (forward, 5'-TCAAGAGGCAAATCTCAAG-3'; reverse, 5'-TCACAGGAGGCGTATTACG-3'), IL-22 (forward, 5'-GAGGGCAGCCCATCCTGAC-3'); IL-6 (forward, 5'-GAGGAGCTTCCAGCTATCGG A-3'; reverse, 5'-ACCTGCTCCACTGCCTTGCT-3'), IL-17A (forward, 5'-GTCCTGAGAAGGCGTCAGA-3'; reverse, 5'-AGCTTTCCCTCCGCATTGA-3'), IFN-γ (forward, 5'-AAGAATCACTCGGCTCATGC-3'; reverse, 5'-TGGGGTGTGGACCTCAAAC-3'), T-bet (forward, 5'-CCAGGCAAGCCGTATATAG-3'; reverse, 5'-CTGGGTTGTTGACCTCAAACT-3'), Foxp3 (forward, 5'-GGGCCAAGCCTTATCGG-3'; reverse, 5'-AAGTGCATCATCGTTGTTCATATA-3'), IL-10, (forward, 5'-GGTTGCCAAGCCTTATCGG-3'; reverse, 5'-GACAGGTTCCAGCCCGATTGA-3'), IL-12p70 (forward, 5'-TCAGAAGGCCAAACTCAAGC-3'; reverse, 5'-ATGGTGCTGTCTTCCTGACC-3'), IL-21, IL-22, and IL-10 (Figure 2).

Cytokine production by LPL
Assessment of cytokine concentrations in the culture supernatants of unstimulated LPL showed that the levels of IL-6, IL-23, IL-1β, TNFα, IFN-γ and IL-17A were significantly lower in the Se + chronic colitis than in the chronic colitis group. There were no significant between-group differences in the levels of IL-12p70, IL-21, IL-22, and IL-10 (Figure 2).

When cytokine concentrations were assayed in culture supernatants of LPL stimulated with anti-CD3 and anti-CD28 mAbs for 48 h, the concentrations of IFN-γ, IL-17A and IL-21 were found to be significantly lower, while the concentration of IL-10 was significantly higher, in supernatants from the Se + chronic colitis than from the chronic colitis group. The level of IL-22, however, was similar in these two groups (Figure 2).

mRNA expression in colon tissue
RT-PCR assays of mRNA levels in cells showed that the expression levels of IL-6, IFN-γ, IL-17A, IL-21, IL-23, T-bet, and RORγt mRNAs were significantly lower, while the levels of IL-10 and Foxp3 mRNAs were significantly higher, in the Se + chronic colitis group than in the chronic colitis group. There was no significant between-group differences in the expression levels of IL-22 mRNA (Figure 3).
Figure 1 Sodium selenite ameliorates chronic dextran sulfate sodium-induced colitis in the C57BL/6 mice. A: Survival rate; B: Changes in body weight (%); C: Changes in the disease activity index (DAI); D and E: Colon length; F and G: Colon histopathological injury scores. The data are presented as the mean ± SD (Se + chronic DSS colitis vs chronic DSS colitis, *P < 0.05) (n = 10). DSS: Dextran sulfate sodium.
Flow cytometry analysis of LPL populations in mouse colon

There were no significant differences in the percentages and absolute numbers of neutrophils (CD11b+Gr1+F4/80), macrophages (CD11b+Gr1−F4/80), γδT cells, NK cells, NKT cells, CD4−, CD4+CD44−, CD4+CD25−, and CD4+CD69+ T cells in the colons of control and Se group mice. The percentages and absolute numbers of neutrophils and CD4+CD25+ T cells in LPL were significantly higher, while the percentages and absolute numbers of γδT and CD4+CD44− and CD4+CD69+ T cells in LPL were significantly lower, in the Se+ chronic colitis group than in the chronic colitis group. These two groups did not differ in the percentages and absolute numbers of macrophages (CD11b+Gr1F4/80), NK cells, and NKT cells (Figure 4).

Cytokine production by T-LPL cells in mice

There were no significant differences in the percentages and absolute numbers of CD4+IL-17A+, CD4+IFN-γ, and CD4+IL-10+ cells in LPL of the control and Se groups. The percentages and absolute numbers of CD4+IL-17A+ and CD4+IFN-γ+ cells in LPL were significantly lower, while the percentages and absolute numbers of CD4+IL-10+ cells in LPL were significantly higher, in the Se+ chronic colitis group than in the chronic colitis group (Figure 5).

**DISCUSSION**

Many diseases have been associated with lack of the essential trace element Se in the body, including asthma, rheumatoid arthritis, and cancer[26-28]. In these diseases, Se deficiency is abnormal, making
supplementation with exogenous Se a reasonable method of treatment. Se may be useful for the prevention and/or amelioration of several autoimmune diseases, including IBD\cite{29}. In support of this concept, our results demonstrate that Se sufficiency protects against DSS-induced chronic colitis by attenuating the symptoms of colitis, as shown by measurements of DAI, body weight, and colon length and by histological assessment of mucosal injury. Se may alleviate chronic colitis by enhancing the activity of Tregs, which suppress the secretion of proinflammatory cytokines and populations of Th1, Th17, and γδ T cells.

Although neutrophils have been reported to have a proinflammatory effect\cite{30}, these cells may play a protective role in intestinal colitis\cite{31,32}. Depletion of neutrophils has been shown to exacerbate colonic inflammation, suggesting that neutrophils be involved in mucosal repair processes\cite{33}. Neutrophils produce IL-22 in response to coordinated signaling by IL-23 and TNF-α\cite{34}. IL-22 is up-regulated in chronic colitis and considered beneficial for intestinal epithelial barrier function\cite{35-37}. Neutrophil recruitment was shown to ameliorate experimental colitis by genetic ablation of IL-21\cite{38}. Our results showed that Se reduced IL-21 and IL-23 expression, but had no effect on the IL-22 level, suggesting that Se may enhance neutrophil populations, leading to reductions in IL-21 and IL-23 expression.

LP macrophages are activated in many animal models of experimental colitis\cite{39}. These macrophages produced TNF-α in DSS-induced colitis. IL-10 suppresses macrophage-derived proinflamma-

Figure 3 mRNA expression changes in colonic tissue. Values represent mean ± SD (\( P < 0.05 \)) (\( n = 3 \)).
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A

Control                                      Se                                       Chronic DSS colitis                         Se + Chronic DSS colitis

Gated on CD11b+

F4/80

Gated on lymphocytes

γδ TCR

Gated on lymphocytes

NK1.1

Gated on αβ TCR

CD4

Control: 6.52 ± 1.26
Se: 7.13 ± 1.32
Chronic DSS colitis: 16.24 ± 1.87
Se + Chronic DSS colitis: 22.24 ± 2.97

A

6.52 ± 1.26                                       7.13 ± 1.32                                      16.24 ± 1.87                                    22.24 ± 2.97

3.95 ± 1.13                                         4.62 ± 1.07                                    11.32 ± 2.76                                   11.74 ± 1.02

1.18 ± 0.15                                        1.45 ± 0.28                                      3.60 ± 0.85                                     2.19 ± 0.09

3.45 ± 1.17                                       3.41 ± 0.86                                     8.69 ± 1.36                                       5.68 ± 1.95

5.17 ± 2.03                                         4.67 ± 1.57                                    10.37 ± 2.41                                     7.12 ± 2.11

49.20 ± 2.55                                   50.80 ± 4.31                                    68.80 ± 3.91                                   54.80 ± 2.62

50.80 ± 4.31                                     68.80 ± 3.91                                   54.80 ± 2.62

54.80 ± 2.62
tory cytokines and downregulates NO and ROS production\(^4\). Elimination of local macrophages in the intestine was shown to prevent chronic colitis in IL-10-deficient mice\(^4\). Macrophages may also ameliorate colitis by secreting immunosuppressive factors\(^4\), suggesting that macrophages may play a dual role in different stages of IBD. Our study found that Se did not alter the number of macrophages, but alterations...
Figure 5 Cytokine-producing T cells in the lamina propria lymphocytes of the colon in each group. A: The frequencies of CD4^+IL-17A^+ and CD4^+IFN-γ^+ T LPL. B: The frequency of CD4^+IL-10^+ T LPL. C: The absolute numbers of cytokine producing CD4^+IL-17A^+, CD4^+IFN-γ^+ T LPL and CD4^+IL-10^+ T LPL with and without stimulation. Data indicate mean ± SD of six mice of obtained from a representative of three independent experiments (*P < 0.05, **P < 0.01, ***P < 0.001).
in function were not determined. Selenoproteins in macrophages protect mice from DSS-colitis by enhancing 15-hydroxy-prostaglandin dehydrogenase (15-PGDH)-dependent oxidation of prostaglandin E2 (PGE2) to alleviate inflammation\textsuperscript{[43]}. The study showed that Se through its incorporation into selenoproteins suppressed inflammation and decreased the production of TNF-α and PGE2\textsuperscript{[46]}. We speculate that macrophages in selenoproteins may affect the differentiation of T cells. Therefore, further research is needed.

Mouse intestinal LP T lymphocytes include αβ and γδ T cells. γδ T cells are a minor T-cell subset present in the LP, but are active in inflammatory processes\textsuperscript{[45]}, for example, in patients with IBD\textsuperscript{[46,47]}. Changes in the repertoire and function of human mucosal γδ T cells have been associated with the disease process in IBD\textsuperscript{[46]}. γδ T cells play a protective role in acute DSS colitis\textsuperscript{[47]}, but are involved in the exacerbation of chronic colitis\textsuperscript{[48]}, suggesting that γδ T cells may represent a promising target in the treatment of human IBD. Our study showed that the absolute numbers and percentages of γδ T cells in T-LPL were significantly lower in the Se + chronic colitis group than in the chronic colitis group. Se has been found to upregulate CD4(+)CD25(+) Treg cells in iodine-induced autoimmune thyroiditis in NOD.H-2(h4) mice\textsuperscript{[49]}. γδ T cells positively regulate contact sensitivity reactions by modulating INF-γ, IL-12, and TNF-α production\textsuperscript{[50]}. Treg cells can inhibit the production of IFN-γ by antigen-specific memory γδ T cells\textsuperscript{[51]}. In addition, IL-10, TGF-β, and the transcription factor Foxp3 mediate immunoregulation\textsuperscript{[52]}. The Treg cells restrain immune responses that are dependent upon expression of the IL-10 and the transcription factor Foxp3. Treg cell-derived IL-10 limits inflammation at environmental interfaces\textsuperscript{[53]}. IL-10 may therefore play an important role in the suppressive function of Treg cells\textsuperscript{[54]}. Other mechanisms, however, cannot be excluded, including direct cell-surface contact. These findings indicate a potential new mechanism by which CD4(+)CD25(+) Tregs can specifically suppress γδ T cells and highlight the strategy of combining Treg inhibition with subsequent cytokine production to enhance γδ T-cell-mediated immunotherapy\textsuperscript{[55]}. Tregs can inhibit γδ T-cell proliferation \textit{in vitro} via a cell-cell contact-independent mechanism\textsuperscript{[55]}. Our data showed that IL-10 expression, as well as the absolute numbers and percentage of CD4(+)CD25(+) Treg cells in T-LPL, were significantly higher in the Se + chronic colitis group than in the chronic colitis group. Further understanding of the molecular mechanisms underlying γδ T-cell-mediated exacerbation of chronic colitis may suggest better therapeutic strategies for human IBD.

NK cells are a subset of innate lymphocytes that contribute to host resistance and provide immune surveillance. The roles of NK cells in DSS-induced colitis, however, are less clear. NK cells produce cytokines, including TNF-α and IFN-γ\textsuperscript{[56]}, as well as protective effects in colitis. The expression of transcription factor Foxp3 has been shown to direct Treg differentiation\textsuperscript{[57]}. However, Th1 and Th17 promote colitis whereas Tregs have protective effects\textsuperscript{[58,59]}. The numbers of Th1 and Th17 cells were increased by the high expression of cytokines supporting Th17 cell differentiation, thus exacerbating the immunopathogenesis of IBD. These cytokines include IL-1, TGFβ, IL-6, IL-21, and IL-23. Our results showed that the percentages and absolute numbers of Th1 and Th17 cells in T-LPL were significantly lower in the Se + chronic colitis than in the chronic colitis group. In addition, IL-6, IFN-γ, IL-17A, IL-21, T-bet, and RORγt expression levels were lower. IL-10 is a negative regulator of inflammation and counters the activity of many proinflammatory cytokines. IL-10 has been shown to suppress intestinal inflammation. Foxp3 functionally inhibits RORγt\textsuperscript{[58,59]}. Our data showed that IL-10 and Foxp3 expression levels were higher in the Se + chronic colitis group than in the chronic colitis group. Th17 cells are a subset of CD4(+) T cells that produce IL-17A. IL-21 induces and maintains T-cell-dependent inflammatory responses, including both Th1 and Th17 responses\textsuperscript{[60]}. IL-21 promotes Th17 cell differentiation by suppressing Foxp3 expression, with inhibition of IL-21 signaling reducing IL-17A and IFN-γ expression\textsuperscript{[61,62]}. Th17 cell subsets are regarded as unstable and may convert into other subsets of T cells under certain circumstances\textsuperscript{[75]}.

In summary, our results suggest that sodium selenite has a protective role in DSS-induced chronic
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colitis. Se may alleviate colitis by inducing Tregs to suppress the secretion of proinflammatory cytokines and populations of Th1, Th17, and γδT cells. As selenium selenite has been widely used to treat human autoimmune diseases, it may be useful in treating IBD.

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