

World Journal of *Gastroenterology*

World J Gastroenterol 2017 August 21; 23(31): 5645-5828



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2014-2017

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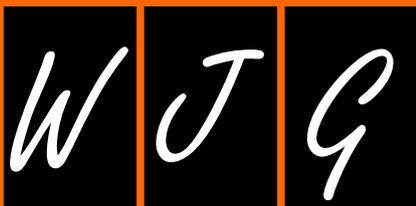
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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
 ISSN 1007-9327 (print)
 ISSN 2219-2840 (online)

LAUNCH DATE
 October 1, 1995

FREQUENCY
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PUBLICATION DATE
 August 21, 2017

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Basic Study

***Schistosoma japonicum* attenuates dextran sodium sulfate-induced colitis in mice *via* reduction of endoplasmic reticulum stress**

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Author contributions: Liu Y and Ye Q contributed equally to this work; Liu Y, Ye Q, Liu YL, Chen Y and Kang J performed the experiments and analysed the data; Liu Y wrote the manuscript; Ye Q revised the manuscript; all authors have read and approved this manuscript.

Institutional review board statement: This study was reviewed and approved by Wuhan University Institutional Review Board.

Institutional animal care and use committee statement: All procedures involving animals were reviewed and approved by the Institutional Animal Care and Use Committee of the Wuhan University.

Conflict-of-interest statement: To the best of our knowledge, no conflict of interest exists.

Data sharing statement: No additional data are available.

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Manuscript source: Unsolicited manuscript

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Received: February 16, 2017
Peer-review started: February 22, 2017
First decision: March 3, 2017
Revised: March 30, 2017
Accepted: April 21, 2017
Article in press: April 21, 2017
Published online: August 21, 2017

Abstract**AIM**

To elucidate the impact of *Schistosoma (S.) japonicum* infection on inflammatory bowel disease by studying the effects of exposure to *S. japonicum* cercariae on dextran sodium sulfate (DSS)-induced colitis.

METHODS

Infection was percutaneously established with 20 ± 2 cercariae of *S. japonicum*, and colitis was induced by administration of 3% DSS at 4 wk post infection. Weight change, colon length, histological score (HS) and disease activity index (DAI) were evaluated. Inflammatory cytokines, such as IL-2, IL-10 and IFN- γ , were tested by a cytometric bead array and real-time quantitative polymerase chain reaction (RT-PCR). Protein and mRNA levels of IRE1 α , IRE1 β , GRP78, CHOP, P65, P-P65, P-I κ B α and I κ B α in colon tissues were examined by Western blot and RT-PCR, respectively. Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling positive cells, cleaved-caspase 3 expression and

Bcl2/Bax were investigated to assess the apoptosis in colon tissues.

RESULTS

Mice infected with *S. japonicum* cercariae were less susceptible to DSS. Mice infected with *S. japonicum* cercariae and treated with DSS showed decreased weight loss, longer colon, and lower HS and DAI compared with mice treated with DSS alone. A substantial decrease in Th1/Th2/Th17 response was observed after infection with *S. japonicum*. Endoplasmic reticulum (ER) stress and the nuclear factor-kappa B (NF- κ B) pathway were reduced in mice infected with *S. japonicum* cercariae and treated with DSS, along with ameliorated cellular apoptosis, in contrast to mice treated with DSS alone.

CONCLUSION

Exposure to *S. japonicum* attenuated inflammatory response in a DSS-induced colitis model. In addition to the Th1/Th2/Th17 pathway and NF- κ B pathway, ER stress was shown to be involved in mitigating inflammation and decreasing apoptosis. Thus, ER stress is a new aspect in elucidating the relationship between helminth infection and inflammatory bowel disease (IBD), which may offer new therapeutic methods for IBD.

Key words: Endoplasmic reticulum stress; *Schistosoma japonicum*; Colitis

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Core tip: *Schistosoma (S.) japonicum* has been demonstrated to participate in the development of colitis in animal experiments as well as clinical trials. However, the effects of *Schistosoma* infection on colitis and the underlying mechanism are still elusive. Here, we studied the effects of exposure to *S. japonicum* cercariae on dextran sodium sulfate (DSS)-induced colitis. We found that *S. japonicum* attenuated DSS-induced colitis in mice by reducing inflammatory response and apoptosis in colon tissues. Besides Th1/Th2/Th17 pathway and nuclear factor-kappa B pathway, endoplasmic reticulum stress played an important role in the preventive effects of parasite infection on DSS-induced colitis.

Liu Y, Ye Q, Liu YL, Kang J, Chen Y, Dong WG. *Schistosoma japonicum* attenuates dextran sodium sulfate-induced colitis in mice via reduction of endoplasmic reticulum stress. *World J Gastroenterol* 2017; 23(31): 5700-5712 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i31/5700.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i31.5700>

INTRODUCTION

Inflammatory bowel disease (IBD), which involves

chronic and complicated inflammatory lesions of the intestinal tract, includes ulcerative colitis (UC) and Crohn's disease (CD)^[1,2]. Epidemiological investigations have shown that the incidence and morbidity of IBD are increasing worldwide^[3,4]. However, the mechanism of IBD is still unclear, and the environment, individual genetics, infection and host immunity are involved^[1,5]. Elucidating the exact mechanism of IBD and developing effective treatments will be valuable for ameliorating patients' quality of life.

Exposures to infectious agents (such as parasites) are suggested to have fundamental effects on the development and behavior of the immune system, which may decrease the incidence of both allergic and autoimmune diseases^[6]. Thus, several studies were performed to investigate the effects of helminth infections on IBD. Patients with UC or CD showed significant disease remission after administration of viable and embryonated eggs of *T. suis* (the porcine whipworm), suggesting the therapeutic effects of parasites on IBD^[7,8]. Seven of nine Crohn's patients infected with larvae of *Necator*, the human hookworm, showed an improved disease score, and their inflammatory cytokine (IFN- γ and IL-17) responses in duodenal biopsies were reduced compared to those of placebo-treated patients^[9,10]. In addition, a mouse model of experimental colitis induced with trinitrobenzene sulfonic acid (TNBS) or dextran sodium sulfate (DSS) also showed decreased susceptibility to IBD or attenuated symptoms after treatment with eggs or larvae of *Schistosoma (S.)*^[11-13]. However, infection with *S. mansoni* soluble egg antigen had no effect on mice with DSS-induced colitis^[14]. Moreover, Smith *et al*^[15] demonstrated that mice with colitis induced with DSS displayed worsening results after injection of *S. mansoni* eggs. These dissimilar outcomes of the impact of *Schistosoma* on IBD have yet to be investigated since the underlying mechanism is still unclear.

Here, we infected mice with *S. japonicum* cercariae *via* contact with the abdomen skin, which is a classical and natural method to infect hosts, such as mice^[16]. Then, we investigated the effects of *S. japonicum* infection on the relatively simple and replicable DSS-induced colitis model due to the limitations of human clinical trials. DSS-induced colitis has been widely used as an animal model of experimental IBD, especially UC, due to its similarities to IBD characteristics, such as diarrhea, mucosal ulceration, rectal bleeding and body weight loss^[17-19]. In the present study, we aimed to explore the effects of exposure to *S. japonicum* cercariae on DSS-induced colitis and identify the underlying pathogenesis of IBD.

MATERIALS AND METHODS

Ethics statement

All animal experiments during this research were performed in accordance with the recommendations in

Table 1 Disease activity index score parameters

Score	Body weight loss	Stool consistency	Rectal bleeding
0	0%-1%	Normal	None
1	1%-5%	Soft and shaped	Between
2	5%-10%	Loose	Slight
3	10%-15%	Between	Between
4	> 15%	Diarrhea	Gross bleeding

the Guide for the Care and Use of Laboratory Animals of Wuhan University.

Materials and grouping

Oncomelania hupensis snails infected with *S. japonicum* were obtained from the Institute of Parasitic Disease Control and Prevention, Jiangsu Province, China. Male Kunming mice, weighing 14-16 g, were purchased from the Hubei Provincial Center for Disease Control.

DSS for inducing acute colitis was purchased from MP Biochemicals (Solon, OH, United States). Antibodies for immunofluorescence, Western blot and cytokine tests were purchased from Abcam (Cambridge, MA, United States), Bioworld Technology (Minneapolis, MN, United States), Millipore (Billerica, MA, United States), Santa Cruz Biotechnology (Santa Cruz, CA, United States) and Cell Signaling Technology (Danvers, MA, United States).

Forty mice were randomly divided into four groups with ten mice in each group. The mice only treated with DSS were termed the DSS group, and those only infected with cercariae were called the CER group. The mice in the CER + DSS group were infected with cercariae and subsequently treated with DSS. In the control group, the mice were treated with saline instead.

Infection with *S. japonicum*

The infected snails were illuminated to induce cercarial shedding. The mice from the CER group and CER + DSS group were percutaneously infected with 20 ± 2 cercariae of *S. japonicum*, while those in the control group and DSS group were treated with saline by dermal contact.

Induction and evaluation of colitis

After 4 wk of the infection, the mice in the CER + DSS group and DSS group were fed 3% (wt/vol) DSS freely to induce acute colitis. The status of each mouse, including weight, morbidity, stool properties, and bleeding, was recorded daily. Disease activity index (DAI) was assessed as described in Table 1^[20].

All mice were sacrificed on day 7 after DSS feeding. Blood samples were collected and centrifuged to isolate serum, which was subsequently stored at -80 °C. The entire colon was cut away and gently washed with saline precooled to 4 °C, most of which was dried and frozen in liquid nitrogen immediately for subsequent

Western blot or RT-PCR analysis. The distal segment of the colon (approximately 0.5 cm) was fixed in 10% buffered formalin for histological observation.

Histological observation

To assess colon inflammation, the formalin-treated colon was embedded into paraffin. Serial sections with 5 mm thickness were cut and stained with hematoxylin and eosin (H and E, Richard Allen Scientific, Kalamazoo, MI, United States). Histological score (HS) was calculated in a blinded manner three times as shown in Table 2^[21]. CD3 and Ly6G monoclonal antibodies were used to assess the infiltration of inflammatory cells. Cleaved caspase 3 (C-C3) was tested to identify the cellular apoptosis in colon tissues. All digital images were taken using a fluorescence microscope (Olympus DX51, Olympus, Tokyo, Japan) and processed with a digital image analysis system (Image-Pro Plus version 6.0, Media Cybernetics, Bethesda, MD, United States). Then the original pictures were merged and the positive cells were quantified. Data were obtained from 3 or more mice per group.

Detection of inflammatory cytokines

Cytometric bead array (CBA) was used to detect the expression of several inflammatory cytokines (IL-2, IL-4, IL-6, IL-10, IL-17A, TNF α and IFN- γ) in the serum of different groups. Serum samples were assayed with a mouse Th1/Th2/Th17 Cytokine Kit (560484, BD), which included seven specific capture beads. After reacting with the bead mixture for 3 h in a dark environment at room temperature, blood samples were analyzed by flow cytometry (Aira III, BD) to identify the numbers of different positive beads. FCAP Array v3 version 3.0.1 from BD Biosciences was employed to translate the images into data.

Western blot analysis

The proteins extracted from colon tissues of the mice in different groups were boiled with loading buffer and subjected to SDS-PAGE. Then, they were blotted onto polyvinylidene fluoride membranes (IPVH00010, Millipore), which were then washed and blocked with Tris-buffered saline containing 5% milk and 0.1% Tween-20 for 2 h. The treated membranes were incubated with particular antibodies overnight at 4 °C. An enhanced chemiluminescence reagent (LiDE110, Canon) was used to detect the expression of proteins according to the protocol. All images were analyzed with AlphaEaseFC software, and GAPDH was used as the reference.

Real-time PCR

Total RNA was obtained from 1 mg of colon tissue using TRIzol reagent (15596-026, Invitrogen) and converted into cDNA using a PrimeScriptTM RT reagent Kit with gDNA eraser (RR047A, TaKaRa). The parameters for RT-PCR amplification were as follows: 95 °C for 1 min,

Table 2 Histological scoring system used in this study

Score	Damaged area	Mucodepletion of glands	Tissue damage	Inflammatory cell infiltration
0	N/A	None	No mucosal damage	Occasional inflammatory cells in the lamina propria
1	≤ 25%	Mild	Discrete epithelial lesions	Increased numbers of inflammatory cells in the lamina propria
2	≤ 50%	Moderate	Surface mucosal erosion or focal ulceration	Confluence inflammatory cells, extending into the submucosa
3	≤ 75%	Moderate	Extensive mucosal damage and extension into deeper structures of the bowel wall	Transmural extension of the infiltrate
4	≤ 100%	Severe		

Table 3 Gene-specific primer pairs used in the study

Primer name		Primer sequence	Product length (bp)
M-GAPDH	Forward	5'-TGAAGGGTGGAGCCAAAAG-3'	227
	Reverse	5'-AGTCTTCTGGGTGGCAGTGAT-3'	
M-IL-6	Forward	5'-CTTCTTGGGACTGATGCTGGT-3'	171
	Reverse	5'-CACAACTCTTTTCTCATTCCACG-3'	
M-IL-10	Forward	5'-TACAGCCGGGAAGACAATAACT-3'	142
	Reverse	5'-AGGAGTCGGTTAGCAGTATGTTG-3'	
M-TNF- α	Forward	5'-TCCCAAAGGGATGAGAAGTT-3'	298
	Reverse	5'-GAGGAGGTGACTTTCTCCTGG-3'	
M-TGF- β	Forward	5'-AGAGCCTGGATACCAACTATIG-3'	286
	Reverse	5'-TGGCACCCACGTAGTAGACG-3'	
M-IFN- γ	Forward	5'-CTCAAGTGGCATAGATGGGAAG-3'	250
	Reverse	5'-GACCTCAAACITGGCAATACTCA-3'	
M-IL-1b	Forward	5'-GGCCTCAAAGGAAAGAATCT-3'	195
	Reverse	5'-GAGGTGCTGATGTACCAGTTGG-3'	
M-IL-17a	Forward	5'-GTCITTAACCTCCITGGCGC-3'	136
	Reverse	5'-GGCACTGAGCTTCCCAGATC-3'	
M-IRE1a	Forward	5'-ACACACCGACCACCGTATCTC-3'	157
	Reverse	5'-GGGTAAGTGTATGATGAACGCC-3'	
M-IRE1b	Forward	5'-TGGACGGTCCCACAACAGAT-3'	140
	Reverse	5'-GGGAGGTTCTGGTATCCAA-3'	
M-GRP78	Forward	5'-GATGAAATTGTCTGGTGGTGG-3'	203
	Reverse	5'-AGTGTAAGGGGACAAACATCAAG-3'	
M-CHOP	Forward	5'-GGAGCTGGAAGCCTGGTATG-3'	285
	Reverse	5'-GGCACTGACCACTCTGTTTC-3'	

followed by 40 cycles of 95 °C for 15 s, 58 °C for 20 s and 72 °C for 45 s. Primers for RT-PCR are listed in Table 3, and GAPDH was used as the housekeeping gene.

Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling assay

Transferase-mediated dUTP nick-end labeling (TUNEL) (ApopTag Plus In Situ Apoptosis Fluorescein Detection Kit, Millipore) assay was performed to assess cellular apoptosis. Paraffin-embedded tissue sections were treated with protease K solution for 15-30 min at 37 °C after dewaxing and rehydrating. Sections were washed and incubated with TUNEL reaction mixture for 60 min at 37 °C in a moist chamber. Addition of converter-POD for 30 min at 37 °C and substrate solution for 30 min at room temperature was performed sequentially. Fluorescence microscopy was used to analyze the sections, and Image-Pro Plus version 6.0 was adopted to process the digital images. Then the original pictures were merged and the positive cells were quantified. Data obtained from 3 or more mice per group were

calculated in a blinded manner.

Statistical analysis

One-way analysis of variance or Kruskal-Wallis *H* test was performed to analyze all the data (SPSS 20.0 software). *P* < 0.05 was considered statistically significant.

RESULTS

Effect of *S. japonicum* infection on the development of colitis

To evaluate the effect of exposure to *S. japonicum* cercariae on the development of colitis, a chemical model of mucosal inflammation induced by oral administration of 3% DSS was established in mice infected with cercariae for 4 wk. Various indexes, including body weight, DAI, colon length, histological observation and HS, were used to assess the severity of acute colitis in mice.

On the 7th day of DSS treatment, three mice from the DSS group had died due to substantial weight

loss (15.4%-19.3%). One of ten mice in the CER + DSS group died on the 5th day due to collision with the cage, and another died for unclear reasons before DSS treatment. From the 5th day, the body weights of mice in both the CER + DSS and DSS groups began to decline, while those in the control and CER groups remained stable. On the 7th day, the mice in the DSS group presented a more significant weight loss than those in the CER + DSS group (Figure 1A; $P < 0.0001$). In addition, the DAI scores of the mice in the CER + DSS group were lower than those in the DSS group (Figure 1B, $P = 0.005$). Among the mice in the four groups, the colon length was shortest in DSS mice and shorter in CER + DSS mice (Figure 1C and D; $P < 0.001$ DSS vs control, $P = 0.004$ DSS vs CER + DSS). There was no significant difference between control mice and CER mice with regard to colon length. Although evident colon hyperemia and edema were observed in both colon tissues of DSS mice and CER + DSS mice, reduced architecture loss, goblet damage and inflammatory cell infiltration were observed in colon tissues of CER + DSS mice compared to those of DSS mice under a microscope (Figure 1E). No pathological lesions were found in the control and CER groups. According to blind assessments from three independent experimenters, the HS of DSS mice was much larger than that of CER + DSS mice (Figure 1F; $P = 0.004$).

Detection of inflammatory cell infiltration by immunofluorescence

CD3 (indicates lymphocytes) and Ly6G (indicates neutrophils) were detected to assess the infiltration of inflammatory cells in colon tissues. CD3 and Ly6G were both labeled red, and nuclei were stained with 4', 6-diamidino-2-phenylindole (DAPI). CD3 positive cells were more abundant in DSS mice than those in control mice after merging CD3 with nuclei using Image-Pro Plus (Figure 2A and B; $P < 0.001$). Mice in the CER + DSS group presented fewer CD3 positive cells compared to those of mice in the DSS group (Figure 2A and B; $P < 0.05$). As for Ly6G, there were differences among the four groups (Figure 2C; $P = 0.019$). The number of Ly6G positive cells was larger in the DSS group than that in mice of the CER+DSS group (Figure 2C). Nevertheless, mice in the control group and CER group showed no difference in the abundance of CD3 positive cells and Ly6G positive cells.

Expression of inflammatory cytokines in serum samples and colon tissues of treated mice

The expression levels of IL-2, IFN- γ and TNF α were detected to assess the Th1 response in mice of each group, and IL-4, IL-6 and IL-10 were examined to evaluate the Th2 response. In addition, IL-17A was tested to assess the Th17 response. CBA tests indicated that the mice in the CER + DSS and DSS groups showed higher levels of inflammatory cytokines compared with control and CER mice (Figure 3). The

expression levels of IL-2, IFN- γ , TNF α , IL-6, IL-10 and IL-17a in CER + DSS mice were much lower than those in DSS mice, especially for IL-6, IL-10 and IFN- γ (Figure 3A, $P < 0.001$ for IL-6, IL-10 and IFN- γ). However, there were no significant differences between control and CER mice. IL-4 was hardly detected in any samples. Higher mRNA levels of IL-1 β , IL-6, IL-10, IL-17a, IFN- γ , TNF α and TGF β were observed in colon tissues of CER + DSS and DSS mice compared to control mice (Figure 3B). Among the four groups, mice in the DSS group displayed the highest expression of IL-6, while mice in the CER + DSS group presented much lower expression of IL-6 compared with that in mice of the DSS group (Figure 3B; $P < 0.001$). Additionally, IL-10 and IFN- γ were lower in the CER+DSS group than in the DSS group (Figure 3B; $P < 0.001$ for IL-10; $P < 0.05$ for IFN- γ). No significant difference was observed between mice of the control group and CER group.

Expression of proteins involved in the NF- κ B signaling pathway and endoplasmic reticulum stress pathway in inflamed colitis

The expression level of phosphorylated-p65 (P-p65) in colon tissues of DSS mice was the highest among the four groups (Figure 4A and B). Mice in the CER + DSS group presented lower P-p65 expression than mice in the DSS group (Figure 4A and B; $P < 0.05$). Consistent with the P-p65 results, mice in the DSS group showed much higher expression of phosphorylated-I κ B α (P-I κ B α) compared with the control group (Figure 4A and D; $P < 0.05$). The expression level of P-I κ B α in CER + DSS mice was lower than that in mice of the DSS group (Figure 4A and D). There were no differences in expression levels of P-p65, P65, P-I κ B α and I κ B α between mice of the control group and CER group.

For endoplasmic reticulum (ER) stress markers, the expression levels of IRE1 α , IRE1 β and CHOP were significantly higher in DSS mice than in control mice as revealed by both Western blot (Figure 5A-D, $P < 0.0001$ for IRE1 α and IRE1 β , $P < 0.01$ for CHOP) and RT-PCR (Supplementary Figure 1). Compared with mice in the DSS group, mice in the CER + DSS group presented much lower expression levels of IRE1 α and IRE1 β (Figure 5A and B; $P < 0.01$; Figure 5A and C; $P < 0.05$). Furthermore, there were clear differences in the expression levels of GRP78 among the four groups (Figure 5A and E; $P = 0.0006$ for 4 groups). The expression levels of GRP78 and CHOP in mice of the CER + DSS group were lower than those in mice of the DSS group (Figure 5A, D and E). Mice in the control group and CER group showed no difference in ER stress markers.

Observation of cellular apoptosis in colon tissues

To estimate cellular apoptosis in colon tissues, TUNEL and C-C3 positive cells were investigated. C-C3 and TUNEL positive cells were labeled red and green, respectively. Nuclei were stained with DAPI. There

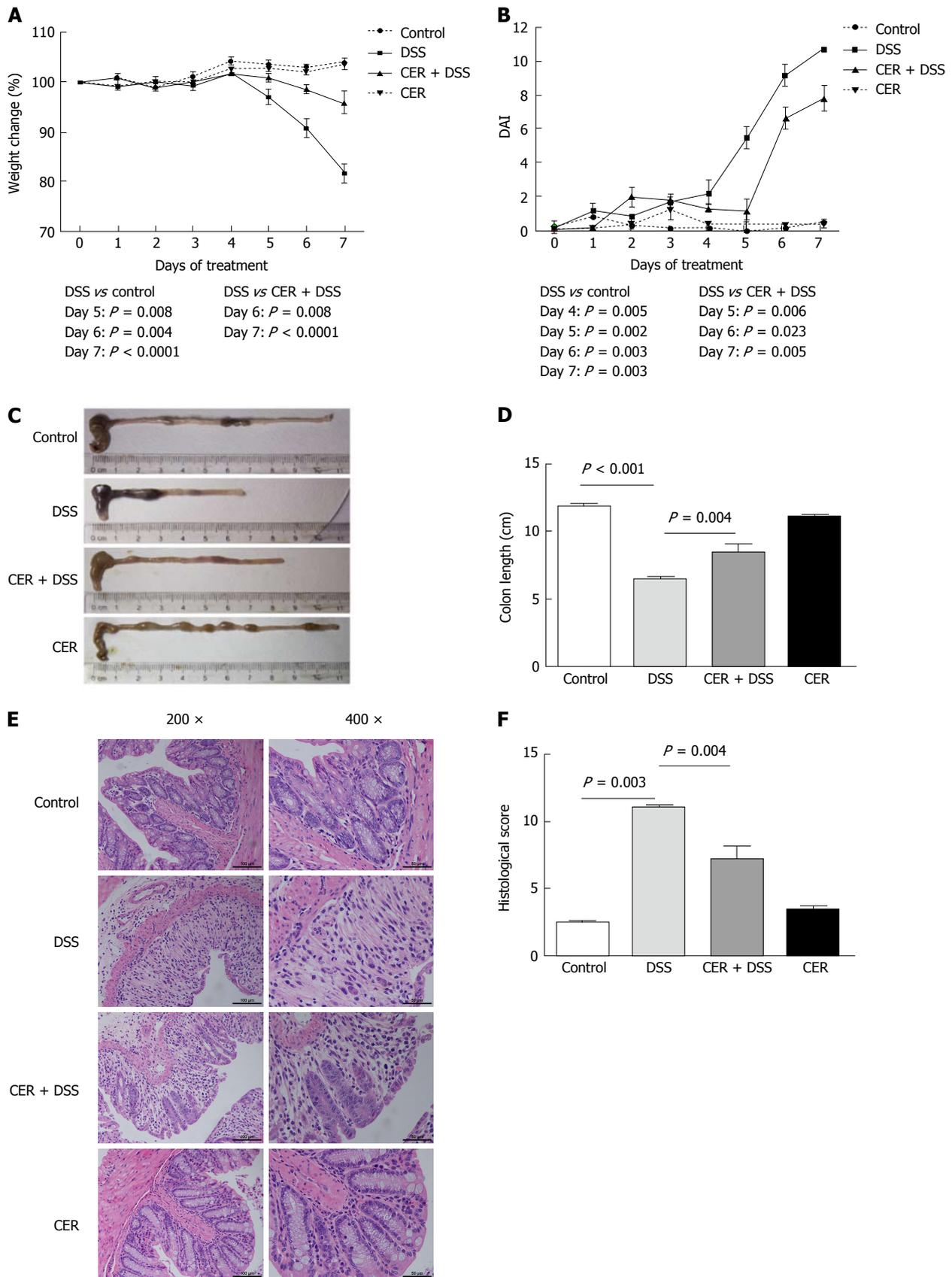


Figure 1 Treatment with *S. japonicum* cercariae results in reduced susceptibility to dextran sodium sulfate-induced colitis in mice. Mice were infected with 20 ± 2 *S. japonicum* cercariae percutaneously, and experimental colitis was induced by administration of 3% DSS at 4 wk post infection. A: Weight change in percent; B: DAI based on weight change, stool characteristics and bleeding; C and D: Colon length; E: H and E staining was performed in colonic sections (original magnification, $\times 200$ and $\times 400$); F: HS was scored as described in Materials and Methods. $n = 6$. The mice infected with *S. japonicum* cercariae presented longer colons, decreased weight loss and lower DAI and HS after being induced with DSS compared to those without parasite infection. DSS: Dextran sodium sulfate treatment alone; CER + DSS: Infection with *S. japonicum* before DSS treatment; CER: *S. japonicum* infection alone.

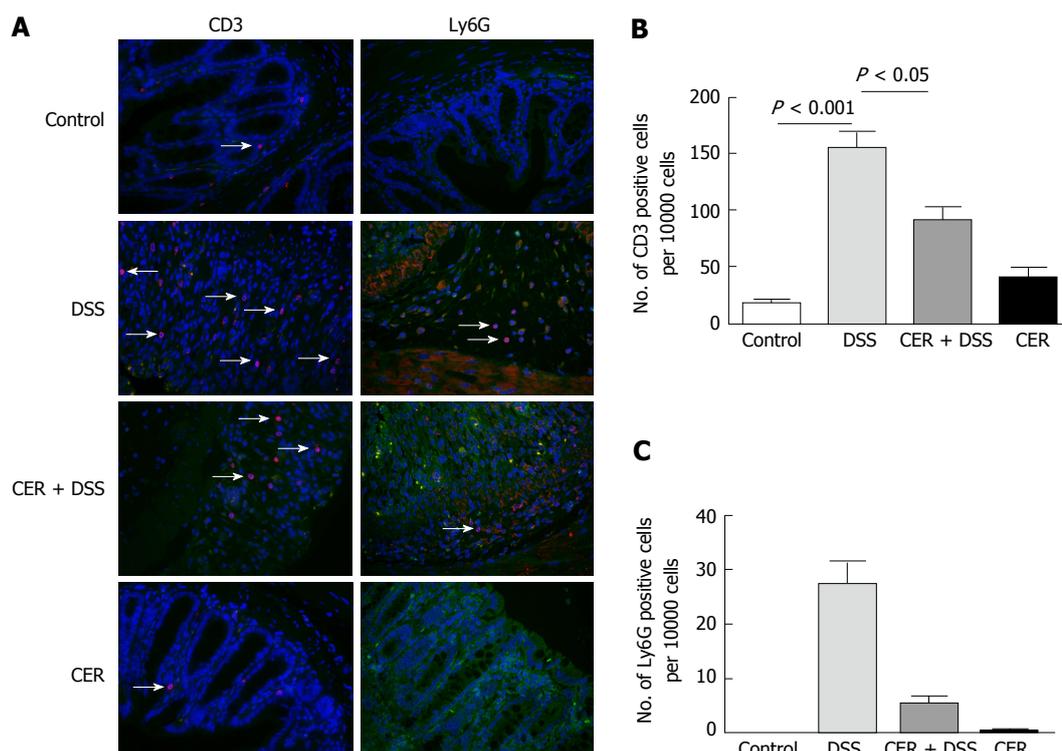


Figure 2 Infection with *S. japonicum* decreases infiltration of inflammatory cells in colon tissues. A: Immunofluorescence staining of CD3 and Ly6G in the colon sections; B and C: Respective quantification of CD3 and Ly6G positive cells. $n = 3$. DSS: Dextran sodium sulfate treatment alone; CER + DSS: Infection with *S. japonicum* before DSS treatment; CER: *S. japonicum* infection alone.

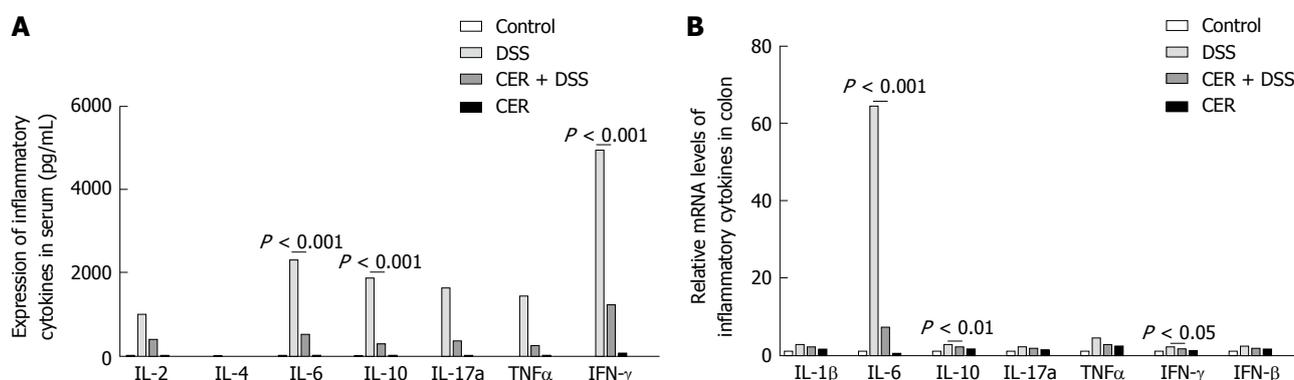


Figure 3 Administration of *S. japonicum* leads to lowered inflammatory cytokines in dextran sodium sulfate-induced colitis mice. A: The production of IL-2, IL-6, IL-10, IL-17A, TNFα and IFN-γ in blood samples was detected by CBA and flow cytometry; B: IL-1β, IL-6, IL-10, IL-17a, IFN-γ, TNFα and TGFβ levels in colon tissues were tested by RT-PCR. $n = 3$ or 4. Exposure to *S. japonicum* protected mice from DSS-induced colitis with down-regulation of the Th1/Th2/Th17 pathway. DSS: Dextran sodium sulfate treatment alone; CER + DSS: Infection with *S. japonicum* before DSS treatment; CER: *S. japonicum* infection alone.

were significant difference in the numbers of C-C3 positive cells and TUNEL positive cells among the mice of the four groups (Figure 6A-C, $P = 0.015$ for the four groups). Mice of the DSS group presented a dramatically larger number of C-C3 positive cells than mice of the control group as well as the CER group (Figure 6A and B). Large numbers of TUNEL positive cells were observed in colon tissues of DSS mice (Figure 6A and C). There were fewer C-C3 positive cells and TUNEL positive cells in CER+DSS mice compared with DSS mice (Figure 6A-C). Hardly any difference in the abundance of C-C3 positive cells and TUNEL positive

cells was observed between mice in the control group and CER group.

In addition, mice in the DSS group showed distinctly lower Bcl-2 expression than mice in the control group (Figure 6D and F; $P < 0.0001$). The expression level of Bcl-2 was much higher in mice of the CER + DSS group than in mice of the DSS group (Figure 6D and F; $P < 0.05$). Additionally, there was a difference in Bax levels among the four groups (Figure 6D and E; $P = 0.015$ for 4 groups). Mice of the CER + DSS group had much lower Bax expression than mice of the DSS group (Figure 6D and E). Mice in the control group and

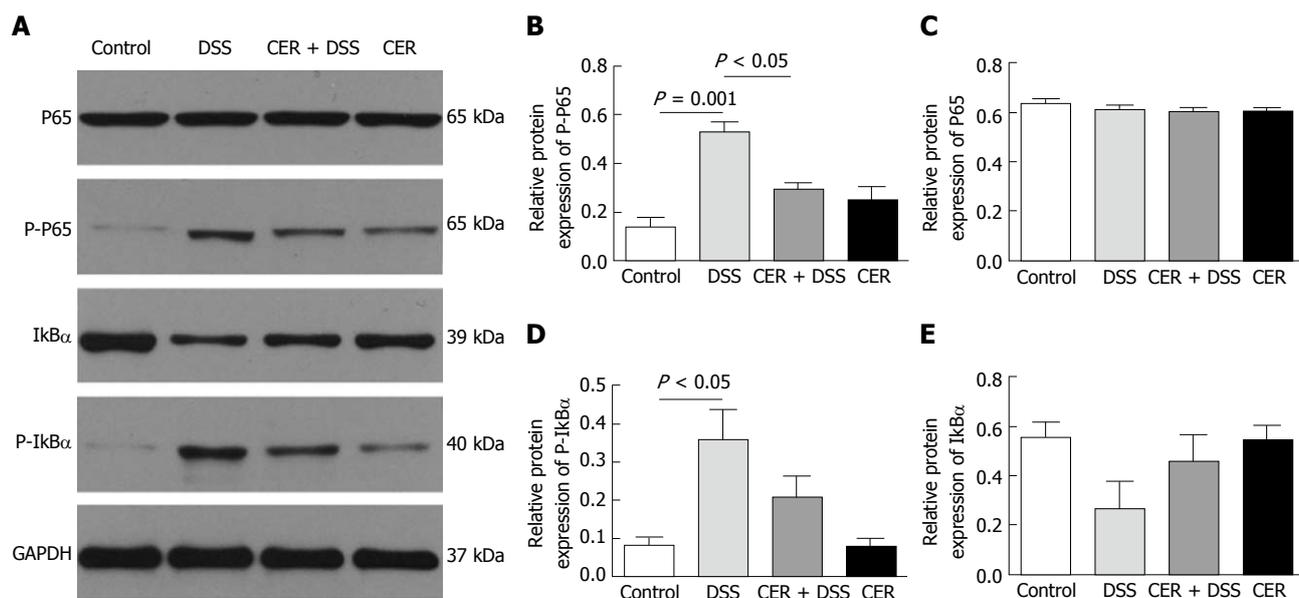


Figure 4 Infection with *S. japonicum* decreases the expression of phosphorylated-p65 in mice treated with dextran sodium sulfate. A: The expression of P-P65 and P65 in colon tissues was examined by Western blot; B and C: Respective quantification of P-P65 and P65; D and E: Respective quantification of P-IkB α and IkB α . $n = 3$. DSS: Dextran sodium sulfate treatment alone; CER + DSS: Infection with *S. japonicum* before DSS treatment; CER: *S. japonicum* infection alone.

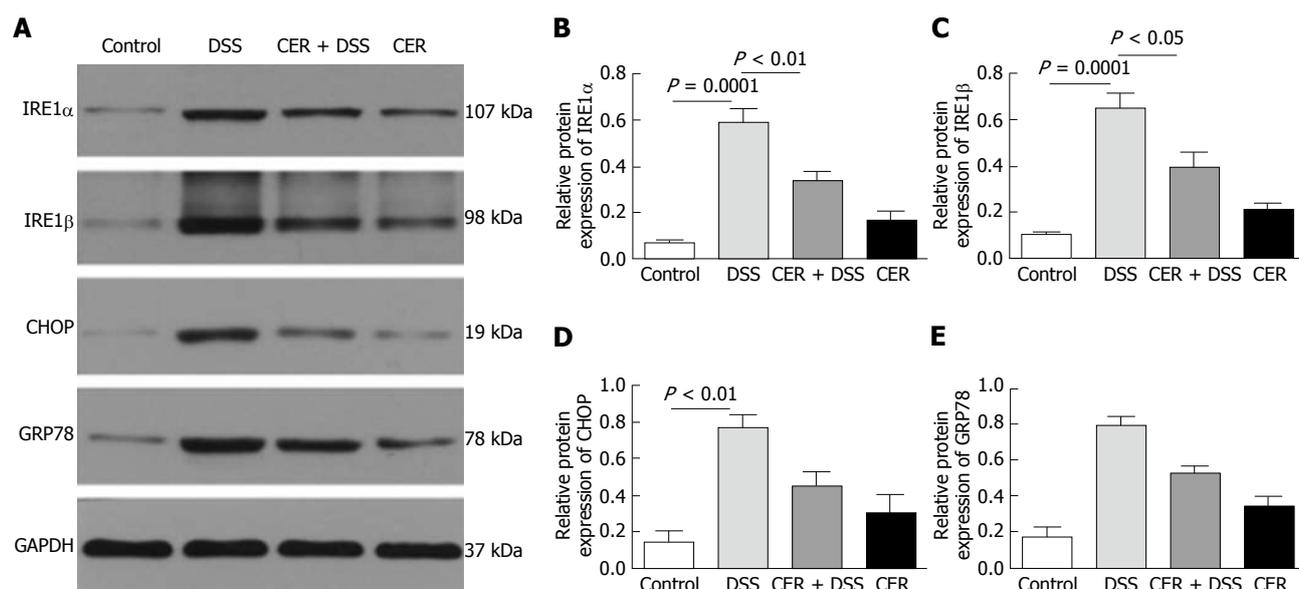


Figure 5 Endoplasmic reticulum stress markers are downregulated in mice induced with dextran sodium sulfate after infection. A: The expression of IRE1 α , IRE1 β , GRP78 and CHOP in colon tissues was examined by Western blot; B-E: Respective quantification of IRE1 α , IRE1 β , GRP78 and CHOP. $n = 4$. DSS: Dextran sodium sulfate treatment alone; CER + DSS: Infection with *S. japonicum* before DSS treatment; CER: *S. japonicum* infection alone.

CER group displayed no difference in the expression levels of Bcl-2 and Bax.

DISCUSSION

According to the “hygiene hypothesis”, which was first proposed by Strachan^[22] in 1958, early childhood infections were associated with decreased atopy in children. Although the concept began with allergic disorders, it has been extended and is currently related to autoimmunity, neuroinflammatory disorders,

atherosclerosis, and some cancers^[23]. In the 1990s, the “inflammatory bowel disease hygiene hypothesis” was first proposed, which stated that children in extremely hygienic environments that might impede the proper maturation of their immune system were predisposed to IBD later in life^[11]. According to epidemiological investigations, helminth infection was suggested to decrease the susceptibility to or prevent the development of IBD^[11]. Here, we investigated the effects of *S. japonicum* infection on a DSS-induced colitis model, and we found that *S. japonicum* infection reduced the

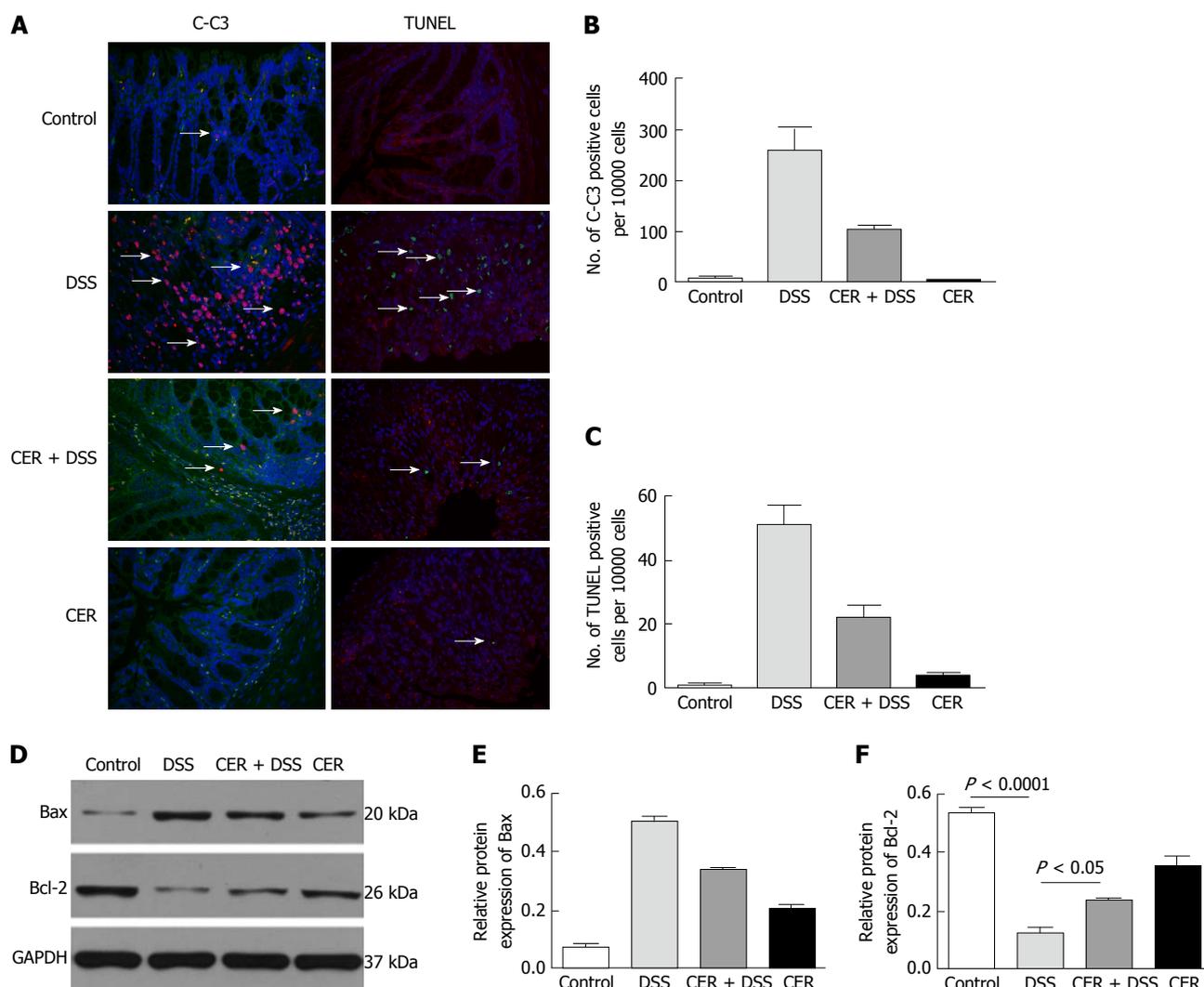


Figure 6 Apoptosis in colitic mice after infection with *S. japonicum*. A: Immunofluorescence staining of cleaved-caspase3 (C-C3) and TUNEL staining; B and C: Respective quantification of C-C3 and TUNEL positive cells; D: Bax and Bal-2 were tested by Western blot; E and F: Respective quantification of Bax and Bal-2. *n* = 3. DSS: Dextran sodium sulfate treatment alone; CER + DSS: Infection with *S. japonicum* before DSS treatment; CER: *S. japonicum* infection alone.

susceptibility to DSS and decreased the infiltration of inflammatory cells, ER stress and the NF- κ B pathway.

There were no significant differences in colon length, weight loss, DAI and HS between the mice in the control and CER groups. The colon length of mice in the DSS group was not only shorter than that of control mice but also shorter than that of mice in the CER + DSS group. The weights of the mice in the DSS group decreased significantly from the 5th day of DSS treatment, while the mice in the CER + DSS group showed a slower decrease from the 6th day of DSS treatment. Both DAI and HS were highest in the DSS group mice and were significantly higher than those of mice infected with *S. japonicum* cercariae prior to DSS treatment (CER + DSS mice). In addition, less lymphocyte and neutrophil infiltration was observed in colon tissues of CER + DSS mice compared with DSS mice. All results indicated that exposure to *S. japonicum* contributed to preventing the development of colitis induced with DSS.

Although the mechanism underlying IBD is complicated, the influence of *Schistosoma* or its molecules on animal colitis was predominantly suggested to be related to the balance between Th1 response and Th2 response^[12,14,24,25]. Research by Elliott *et al*^[12] illustrated that infection with eggs of *S. mansoni* attenuated TNBS-induced colitis by reducing Th1 response and increasing Th2 response. However, DSS-induced colitis mice presented diminished expression levels of TNF α , IL-2 and IL-4 mRNA after exposure to *S. mansoni* larvae^[14]. Recombinant cystatin from *S. japonicum* showed a therapeutic effect on mice with TNBS-induced colitis by suppressing IFN- γ and IL-17a and enhancing IL-4 and IL-13^[24]. In addition, Ruysers *et al*^[25] reported augmented IL-10 mRNA expression and diminished IFN- γ mRNA and IL-17 mRNA expression. In our study, compared with DSS mice, significant decreases in IL-6, IL-2, IL-10, IL-17, IFN- γ and TNF α were observed in CER + DSS mice as revealed by the CBA technique, which are consistent with the

diminished levels of inflammatory cytokines and transcription factors detected by RT-PCR, especially for IL-10, IL-6 and IFN- γ . In other words, we observed that *S. japonicum* infection ameliorated DSS-induced colitis with decreased Th1, Th2 and Th17 responses. Thus, we hypothesize that the Th1/Th2/Th17 pathway may not be the dominant mediator during colitis following exposure to *S. japonicum*. Additionally, these results might be caused by the different time points we chose to induce colitis, diverse infection methods, disparate animal models and other factors compared to those of other studies. For example, Elliott *et al.*^[12] and Xia *et al.*^[26] adopted TNBS-induced colitis and Bodammer *et al.*^[14] used *S. mansoni* larvae to infect mice.

Oh *et al.*^[27] identified an important effect of NF- κ B in regulating differentiation and maturation of Th cells. Furthermore, connections between the NF- κ B pathway and IBD have been reported in previous studies^[28,29]. In our previous study, CARD3 deficiency alleviated the infiltration of inflammatory cells and cellular apoptosis during DSS-induced colitis followed by decreased NF- κ B activation^[21]. Hence, we examined the protein levels of P65, P-P65, I κ B α and P-I κ B α in colon tissues of mice. The results showed high expression of P-P65 and P-I κ B α in DSS mice. Consistent with the cytokine results of serum samples and colon tissues, CER + DSS mice displayed lower P-P65 and P-I κ B α levels compared to DSS mice. It was reported that NF- κ B was essential for the production of IL-2^[27], and the absence of P65 could impair IFN- γ production in Th1 cells^[30]. Additionally, NF- κ B activation played an important role in regulating the expression of the GATA3 and ROR γ t genes, which are transcription factors of Th2 cells and Th17 cells, respectively^[31,32]. Thus, the attenuation of the DSS-induced colitis in mice *via* exposure to *S. japonicum* as well as the change in cytokines related to Th1, Th2 and Th17 responses was probably due NF- κ B activation.

ER stress participates in many inflammatory diseases, such as CD and T2DM, and has shown great potential in regulating inflammatory responses through the unfolded protein response (UPR) pathway^[33,34]. Increased expression of ER stress markers was observed in ileal and/or colonic epithelial tissues of active IBD patients^[34,35]. Adolph *et al.*^[36] also demonstrated spontaneous transmural ileitis similar to CD accompanied by activated IRE1 α in intestinal epithelial cells of mice with *Xbp1* and *Atg1611* deletions. However, addition of ER stress inhibitors, such as tauroursodeoxycholate and 4-phenylbutyrate, mitigated intestinal inflammation in *IL-10*^{-/-} and *Tnf*^{ARE} mice induced with DSS^[37]. In addition, taurine supplement attenuated hepatic granuloma and fibrosis in *S. japonicum*-infected mice, with a significant decrease in ER stress^[38]. In our study, the expression levels of IRE1 α , IRE1 β , GRP78 and CHOP and their coding genes were notably highest in DSS mice among the four groups. Although the expression levels of these molecules were still higher in CER + DSS mice compared with those in control

mice, they were much lower than those in DSS mice. Coupling of the UPR in cells triggered inflammation and played an important role in the pathogenesis of inflammatory diseases^[39]. Additionally, IRE1 α activation by binding with TNF α receptor-associated factor 2 (TRAF2) may affect TRAF2 and subsequently activate the NF- κ B pathway^[40,41]. Inflammation induced by *Brucella abortus* accompanied by high expression levels of IL-6 and ER stress in an NOD1/NOD2-dependent manner was suppressed by IRE1 α kinase inhibitor^[42]. Hence, we hypothesized that the decrease in NF- κ B activation detected in the CER + DSS group might be influenced by ER stress. Two hypotheses were proposed here: first, the damage in enterocytes caused by DSS treatment triggered inflammation and ER stress/UPR, and UPR probably aggravated inflammation *via* the NF- κ B pathway simultaneously; second, *S. japonicum* infection regulated the activation of ER stress or UPR directly.

Moreover, colon inflammation was reported to lead to dysfunction in epithelial barrier and apoptosis of intestinal epithelial cells^[43]. In this study, we tested the expression of C-C3, TUNEL, Bcl-2 and Bax to assess the apoptosis in colon tissues of the treated mice. DSS mice showed more C-C3 positive cells and TUNEL positive cells compared with control mice. However, fewer C-C3 positive cells and TUNEL positive cells were observed in CER + DSS mice than in DSS mice. DSS mice displayed the highest expression level of Bax and the lowest expression level of Bcl-2 among the mice in the four groups. CER + DSS mice exhibited significantly lower Bax levels and higher Bcl-2 levels than DSS mice. On one hand, this remissive apoptosis in colon tissues might be caused by the attenuation of colon inflammation in DSS-induced colitis mice infected with *S. japonicum*. On the other hand, Chen *et al.*^[44] showed that activation of the NF- κ B signaling pathway enhanced the apoptosis of dental epithelial cells *in vitro*; thus, the high apoptosis level in DSS-treated intestinal cells might be affected by the strong response of NF- κ B, which is consistent with our previous research showing that diminished NF- κ B activation accompanied by decreased apoptosis in colon tissues, especially enterocytes in *CARD3*^{-/-} mice induced with DSS.

Additionally, ER stress also exhibited a connection with apoptosis through multiple mechanisms. Wang *et al.*^[45] found that overexpression of IRE1 could promote apoptosis of HEK193 human embryonic kidney cells. Under ER stress, IRE1 α could not only prevent cell apoptosis caused by sustained ER stress *via* activation of *Xbp1*^[36] but also promote mitochondrion-dependent cell death by binding to Bax on the outer membrane of mitochondria^[46,47]. When IRE1 associates with TRAF2 and Ask1 to form the IRE1-TRAF2-ASK1 complex, it can play a pro-apoptotic role by enhancing the JNK pathway. Additionally, enhanced expression of CHOP might lead to apoptosis by reducing expression of Bcl-2, decreasing endocellular glutathione and increasing

generation of reactive oxygen intermediates^[48]. By forming a dimer with cAMP response element binding protein, CHOP could also promote apoptosis by inhibiting the expression of Bcl-2 and enhancing the mitochondria sensitivity to pro-apoptotic factors^[49]. Thus, we propose that the less severe apoptosis in CER + DSS mice was associated with a lower level of ER stress in contrast to DSS mice.

In conclusion, exposure to *S. japonicum* cercariae can prevent inflammation progression and apoptosis in colon tissues of DSS-induced experimental colitis. In addition to the Th1/Th2/Th17 pathway and NF- κ B pathway, ER stress was also shown to be involved in attenuating the inflammatory response by parasite infection in DSS-induced colitis. Further investigations are needed to determine the exact mechanism of its action for further development as a therapeutic strategy for IBD treatment.

ACKNOWLEDGMENTS

The authors thank Professor Hui-Fen Dong at Department of Medical Parasitology and Research Laboratory of Schistosomiasis, Wuhan University School of Medicine for experimental guidance.

COMMENTS

Background

Schistosoma (S.) and its protein extracts have shown therapeutic effects in ameliorating colitis. It was supposed that the Th1/Th2/Th17 pathway might be involved in the induction of remission while the outcomes were dissimilar and the underlying mechanism is still unclear. To further elucidate the role and mechanism of *S. japonicum* infection on inflammatory bowel disease (IBD), the authors studied the effects of exposure to *S. japonicum* cercariae on dextran sodium sulfate (DSS)-induced colitis.

Research frontiers

Nuclear factor-kappa B (NF- κ B) has been reported to play an important role in regulating differentiation and maturation of Th cells. In previous studies, NF- κ B also showed a pro-inflammation and pro-apoptosis effect on DSS-induced colitis. In addition, endoplasmic reticulum (ER) stress, which has a close relationship with inflammation and apoptosis, takes a significant part in the development of IBD.

Innovations and breakthroughs

This is the first time to elucidate the effect of *S. japonicum* infection on IBD from the aspect of considering NF- κ B pathway, ER stress pathway and apoptosis together.

Applications

S. japonicum attenuates DSS-induced colitis in mice and decreases the cellular apoptosis in colon tissues accompanied by reduced expression of NF- κ B and ER stress proteins, especially ER stress proteins. Therefore, ER stress-related proteins might be potential therapeutic targets for IBD.

Terminology

ER stress is a cellular stress response related to the endoplasmic reticulum, which has been found to be conserved between all mammalian species, as well as yeast and worm organisms. Unfolded protein response is activated by the accumulation of unfolded or misfolded proteins in the lumen of the ER.

Peer-review

Authors demonstrated down-regulated expression of cytokines and transcriptional factors such as IL-6, IL-10 and IFN- γ as well as phosphorylated-P65 and ER stress-related proteins after exposure to *S. japonicum* in DSS-induced colitis mice. Besides, ER stress probably contributed to the cellular apoptosis in colon tissues during *S. japonicum* infection in colitis mice.

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P- Reviewer: Hashimoto N, Tomizawa M **S- Editor:** Qi Y

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ISSN 1007-9327

