

Basic Study

Therapeutic effect of curcumin on experimental colitis mediated by inhibiting CD8⁺CD11c⁺ cells

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Abstract

AIM

To verify whether curcumin (Cur) can treat inflammatory bowel disease by regulating CD8⁺CD11c⁺ cells.

METHODS

We evaluated the suppressive effect of Cur on CD8⁺CD11c⁺ cells in spleen and Peyer's patches (PPs) in colitis induced by trinitrobenzene sulfonic acid. Mice with colitis were treated by 200 mg/kg Cur for 7 d. On day 8, the therapeutic effect of Cur was evaluated by visual assessment and histological examination, while co-stimulatory molecules of CD8⁺CD11c⁺ cells in the spleen and PPs were measured by flow cytometry. The levels of interleukin (IL)-10, interferon (IFN)- γ and transforming growth factor (TGF)- β 1 in spleen and colonic mucosa were determined by ELISA.

RESULTS

The disease activity index, colon weight, weight index of colon and histological score of experimental colitis were obviously decreased after Cur treatment, while the body weight and colon length recovered. After treatment with Cur, CD8⁺CD11c⁺ cells were decreased in the spleen and PPs, and the expression of major histocompatibility complex II, CD205, CD40, CD40L and intercellular adhesion molecule-1 was inhibited. IL-10, IFN- γ and TGF- β 1 levels were increased compared with those in mice with untreated colitis.

CONCLUSION

Cur can effectively treat experimental colitis, which is realized by inhibiting CD8⁺CD11c⁺ cells.

Key words: CD8; CD11c; Curcumin; Experimental colitis; Therapeutic effect

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Core tip: CD11c is highly expressed in CD8⁺ and CD8⁺ dendritic cells (DCs). Overaccumulation of CD8⁺ DCs is seen in colonic mucosa in experimental colitis and patients with inflammatory bowel disease (IBD). CD8⁺CD11c⁺ cells may be a potential strategy to explore the mechanism of action of drugs in IBD. The immunosuppressant curcumin (Cur) plays a therapeutic role in various immune diseases, including IBD and rheumatoid arthritis. However, it is unclear whether Cur regulates level of CD8⁺CD11c⁺ cells to treat IBD. We found that the therapeutic effect of Cur in experimental colitis was closely related to decreased levels of CD8⁺CD11c⁺ cells.

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INTRODUCTION

As one of integrin family, CD11c is a type I transmembrane protein that mediates adherence between leukocytes and endothelial cells, and participates in exudation and phagocytosis of leukocytes. It is suggested that CD11c induces tissue injury and the inflammatory response^[1]. Importantly, CD11c is a specific marker in dendritic cells (DCs) and is highly expressed in CD8⁺ and CD8⁺ DCs^[2].

As professional antigen-presenting cells, DC precursors capture antigens and promote T-cell migration to regions of the draining lymph nodes where they can mature into functional DCs and present antigens to initiate T-cell-mediated immune responses^[3]. Increasingly, it has been reported that DCs are critical to maintaining intestinal immunity and mucosal immune tolerance to resist the pathogenicity of commensal microorganisms, which is one of the pivotal inflammatory etiologies of induced inflammatory bowel diseases (IBD)^[4].

High expression of co-stimulatory molecules and major histocompatibility complex (MHC) II of DCs, which is a known marker of DC maturation, and a "danger signal" of induced inflammatory mucosal damage in the gut, occurs in the colonic mucosa of animal models of colitis^[5,6]. Moreover, DCs can develop from both myeloid and lymphoid progenitors. In mice, CD8⁺ DCs have been designated as lymphoid DCs, and CD8⁺ DCs as myeloid DCs^[7]. More importantly, CD8⁺ DCs predominantly stimulate T helper (Th)1-inducing cytokines such as interleukin (IL)-12p70 and IL-12p40, which can lead to Th1 differentiation^[8], and have been reported to play a key role in controlling viral infection^[3,9,10]. Overaccumulation of CD8⁺ DCs induces inflammatory injury in the colonic mucosa when they migrate into Peyer's patches (PPs) in experimental colitis and IBD patients^[11,12]. Thus, CD8⁺ DCs may be a potential therapeutic target to explore the mechanisms of clinical treatment of IBD.

Many studies have indicated that CD11c expressed in DCs can promote maturation and activation of DCs; present antigen for CD4⁺ or CD8⁺ T cells; accelerate T-cell activation and proliferation; and produce various cytokines^[13-15]. CD11c⁺ DCs are depleted by diphtheria toxin during treatment of experimental colitis, induced indirectly by CD4⁺ CD62L⁺ T cells, with oligodeoxynucleotides containing unmethylated cytosine-guanosine^[16]. These results suggest that CD11c⁺ DCs play an important role in the pathogenetic process of IBD.

Curcumin (Cur) is the major constituent of turmeric powder that is extracted from the rhizomes of *Curcuma longa* L. Cur has a long history of

Table 1 Scoring of disease activity index

Score	Decrease in growth or weight loss	Stool consistency	Occult/gross rectal bleeding
0	0%	Normal	Normal
1	1%-5%	Normal	Occult blood+
2	5%-10%	Loose stools	Occult blood++
3	10%-15%	Loose stools	Occult blood+++
4	> 15%	Diarrhea	Gross bleeding

effectively treating chronic colitis by blocking nuclear factor- κ B signaling in human IBD and experimental colitis, including trinitrobenzene sulfonic acid (TNBS)-induced and dextran sulfate sodium (DSS)-induced experimental colitis^[17-19]. Multifunctional Cur has exhibited antioxidant, anti-inflammatory, antimutagenic, and anticarcinogenic activities, as well as antiplatelet, hypoglycemic, cholesterol-lowering, antibacterial, wound-healing and antifungal effects^[17,20-22]. In addition, Shirley *et al.*^[23] have shown that Cur prevents DCs from responding to immunostimulants and DC-mediated induction of CD4⁺ T-cell proliferation by blocking maturation marker expression, cytokine and chemokine expression, and reducing migration and endocytosis. Shirley *et al.*^[23] also concluded that Cur might play a therapeutic role as an immunosuppressant in the treatment of various immune diseases including IBD and rheumatoid arthritis. In our previous study, we found that Cur repaired colonic structure, decreased colonic weight and histological injury score, and recovered colonic length, indicating that Cur restored damaged colonic mucosa in mice with TNBS-induced colitis^[24]. However, it is unclear whether Cur can regulate the expression levels of CD8⁺CD11c⁺ cells to treat IBD.

In the present study, we investigated the effects of Cur on CD8⁺CD11c⁺ cells in the spleen and PPs in a murine model of TNBS-induced colitis to explore the possible therapeutic mechanisms of Cur in experimentally induced IBD.

MATERIALS AND METHODS

Mice

Nine to twelve-week-old male C57BL/6 mice (20-24 g) were purchased from the Animal Center of Peking University Health Science Center (Animal Certificate No.: SCXK 2012-0001). Mice were housed in a special room with a humidity of 50% \pm 5% and an equal 12-h light/dark cycle at 20 \pm 2 $^{\circ}$ C throughout the experimental period. Animals were allowed free access to a commercial diet and clean water *ad libitum*. All animals were allowed to acclimatize for 4 d before the start of the experiment. The experimental protocols (JZ2015-016) were approved by the Biomedical Ethics Committee Experimental Animal Ethics Branch of Jiangxi University of Traditional Chinese Medicine.

Induction of experimental colitis

Colitis was induced according to the procedure described previously by Huang *et al.*^[25], Salaga *et al.*^[26], Fina *et al.*^[27] and Bai *et al.*^[28]. Mice were fasted for 12 h. Each mouse was anesthetized with pentobarbital sodium (40 mg/kg), following which, 100 mg/kg TNBS (Sigma-Aldrich, St. Louis, MO, United States; 100 g/L dissolved in 0.3 mL 50% ethanol) was instilled *via* a rubber catheter that was inserted approximately 4 cm into the colon *via* the anus. The rubber catheter was modified with numerous holes positioned over the final 4 cm of its length. The instillation procedure required only a few seconds, following which the mice were maintained in a head-down position for 5 min to prevent solution leakage. Mice in the Normal group received 50% ethanol of the same volume that was delivered using the same technique as described above.

Treatment protocols

To explore the effect of Cur (purity \geq 95% by HPLC; Gangrun Biotechnology, Nanjing, China) on CD8⁺CD11c⁺ cells in colitis mice, C57BL/6 mice (20-24 g) were randomized into four groups of eight with comparable average body weight: Normal group (receiving ethanol only, and not treated); TNBS group (received TNBS and were not treated); TNBS + Cur group [received TNBS and 100 mg/kg/d Cur intragastrically (i.g.)]; and TNBS + mesalazine (Mes) group (received TNBS and mesalazine at 300 mg/kg/d i.g.). Before administration, Cur was dissolved in 5% dimethylsulfoxide (DMSO) in physiological saline, which was used as a vehicle. Twenty-four hours after colitis was induced, mice in the TNBS + Cur group were administered Cur, and in the TNBS + Mes group, they were administered Mes for 7 d until the mice were killed. Mice in the Normal and TNBS groups received the same volume of 5% DMSO in physiological saline daily (which was the vehicle for Cur) until the end of the experiment.

Assessment of severity of colitis: disease activity index

Disease activity index (DAI) was analyzed according to the previous study^[29,30], which was the combined score of weight loss, stool consistency, and bleeding. The criteria for DAI scores are described in Table 1. The changes in growth rate, stool consistency, and gross bleeding or occult blood in the feces were scored daily from 0 to 4 for each animal after TNBS treatment.

Evaluation of colonic damage

On day 8, all mice were killed after being anesthetized with pentobarbital sodium (40 mg/kg) by intraperitoneal injection. The colon was removed rapidly and its length was measured, opened longitudinally, rinsed with phosphate-buffered saline (PBS), assessed immediately for weight, and the weight index of the colon was calculated (colonic

weight/body weight \times 100%). Segments of the colon were fixed in 4% paraformaldehyde for at least 7 d. Subsequently, colon tissues were dehydrated, embedded in paraffin, sectioned at 5 μ m and mounted onto slides. These sections were stained with hematoxylin and eosin.

A histological damage score was determined according to the criteria of Nicole and Schmidt *et al.*^[31]. The histological score included inflammatory cell infiltration and tissue damage. Scores for infiltration were as follows: 0: no infiltration; 1: increased number of inflammatory cells in the lamina propria; 2: inflammatory cells extending into the submucosa; and 3: transmural inflammatory cell infiltration. The scores of tissue damage were as follows: 0: no mucosal damage; 1: discrete epithelial lesions; 2: erosions or focal ulcerations; and 3: severe mucosal damage with extensive ulceration extending into the bowel wall.

Isolation of lymphocyte from spleen and PPs

PPs were separated and collected from the small intestine to the terminal rectum. To prepare single-cell suspensions, spleens or PPs were minced and digested in 2 mg/mL collagenase D (Roche Diagnostics, Basel Switzerland) in 1% fetal calf serum (FCS)/RPMI 1640 for 15 min at 37 °C. Next, 10 mM EDTA was added for the last 5 min, and the cell suspensions were then pipetted up and down several times and filtered through a fine-mesh sieve. The cell suspensions were centrifuged at 380 $\times g$ at 4 °C for 5 min and suspended at a density of 10⁶–10⁷/mL in 3% FCS/PBS. Remnant supernatants of spleen and PPs were used separately to analyze the levels of cytokines by ELISA.

Assay of CD8⁺CD11c⁺ cells by flow cytometry

After removal of RBC, splenic and PPs cells were labeled with V450-anti-mouse CD8a⁺ antibody (0.125 μ g/100 μ L; BD Biosciences, San Jose, CA, United States) and APC/Cy7 anti-mouse CD11c (eBioscience, San Diego, CA, United States), respectively, at 37 °C in the dark. Cells were centrifuged at 380 $\times g$ at 4 °C for 5 min, and fixed in 1% paraformaldehyde/PBS. In addition, fluorescence-activated cell sorting analysis was performed on a FACSCalibur flow cytometer (BD Biosciences).

Measurement of co-stimulatory molecules of CD8⁺CD11c⁺ cells by flow cytometry

Cell suspensions were stained according to the appropriate isotypic control antibody match of different fluorochromes and incubated for 30 min with V450-anti-mouse CD8a⁺ antibody (0.125 μ g/100 μ L; BD Biosciences), APC/Cy7 anti-mouse CD11c (eBioscience), PerCP/Cy5.5 anti-mouse I-A/I-E (MHC II), PE anti-mouse CD40, APC anti-mouse CD154 (*i.e.*, CD40 ligand), FITC anti-mouse CD54, and PerCP/Cy5.5 anti-mouse CD205. Limits for the quadrant markers were based on negative populations and

isotype controls.

ELISA

The levels of IL-10, IFN- γ and TGF- β 1 in spleen and colonic mucosa supernatants were measured using ELISA (eBioscience).

Statistical analysis

Data were expressed as mean \pm SEM. The statistical significance was evaluated by analysis of variance followed by Tukey's test for multiple comparisons using GraphPad Prism version 5.0 (La Jolla, CA, United States). Nonparametric data were analyzed with the Mann-Whitney *U* test. *P* < 0.05 was considered statistically significant.

RESULTS

Cur attenuated TNBS-induced colitis

The body weight of mice and the disease activity index of experimental colitis in the TNBS group were significantly decreased compared with the Normal, TNBS + Cur and TNBS + Mes groups (Figure 1B and C). Colonic weight and the weight index of the colon from the TNBS groups were higher than those in the Normal group, but lower than in the TNBS + Cur and TNBS + Mes groups (Figure 1D and E). However, the colonic length in the colitis mice was shorter in the TNBS group compared with the Normal, TNBS + Cur, and TNBS + Mes groups (Figure 1A and G). Histological evaluation of colonic sections from untreated mice with colitis showed that TNBS-induced colitis was characterized by a loss of mucosal architecture, thickening of the colon wall, cryptic abscesses, ulcer formation, and extensive inflammatory cell infiltration in the colonic mucosa (Figure 1F). Treatment with Cur and Mes inhibited these pathological symptoms and kept histo-progressive restoration, reduced inflammatory cell infiltration in the mucosa and submucosa, and maintained the integrity of colonic mucosa (Figure 1F). We observed visually ulceration, hyperemia and edema in the colonic mucosa in colitis mice without treatment, which were ameliorated in mice treated with Cur and Mes (Figure 1A). Moreover, the histological scores in the colon of mice from the Normal, TNBS + Cur, and TNBS + Mes groups were significantly lower than those in untreated mice with colitis (Figure 1F and H). All results demonstrated that Cur effectively treated experimental colitis.

Cur inhibited levels of CD8⁺CD11c⁺ cells in spleen and PPs in colitis mice

We analyzed the numbers of CD8⁺CD11c⁺ cells in the spleen and PPs of mice with colitis (Figure 2). Data clearly indicated a significantly increased tendency in this parameter in the spleen (Figure 2A and D) and PPs (Figure 2A and C) in the TNBS group as compared with the Normal group. Significantly, after 7 d treatment

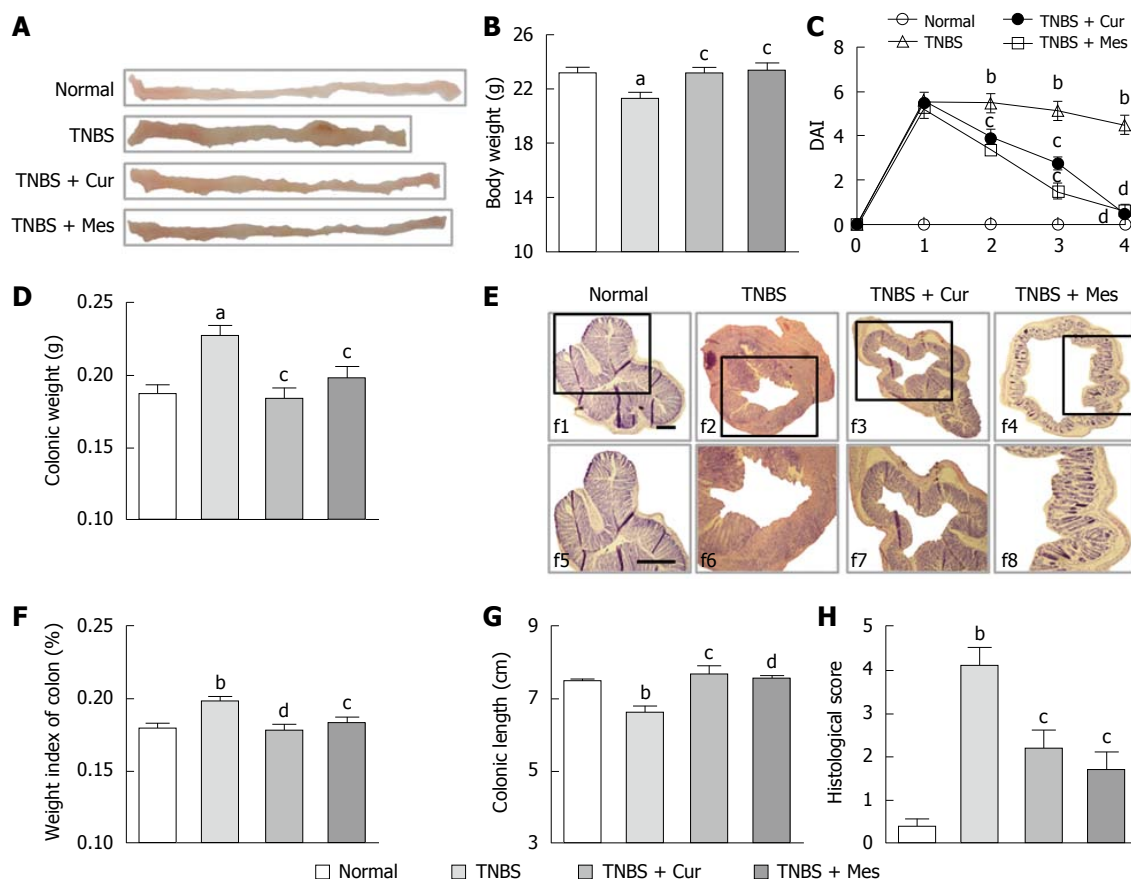


Figure 1 Macroscopic and microscopic observation. A: Macrography of the opened colon; B: Body weight; C: DAI score; D: Colonic weight; E: Weight index of the colon; F: Typical histological images stained by hematoxylin and eosin, f1-4: Bar = 40 μ m, f5-8: Bar = 100 μ m; G: Colonic length; H: Histological scores. Data are presented as mean \pm SEM ($n = 8$). ^a $P < 0.05$ and ^b $P < 0.01$ vs Normal group; ^c $P < 0.05$ and ^d $P < 0.01$ vs TNBS group.

with Cur, the numbers of CD8⁺CD11c⁺ cells in the spleen and PPs in the TNBS + Cur and TNBS + Mes groups were decreased dramatically as compared with the TNBS group.

Cur increased IL-10, IFN- γ and TGF- β 1 secretion in spleen and colonic mucosa in colitis mice

To understand the effects of activated CD8⁺CD11c⁺ cells in the development of murine colitis, the secretion of IL-10, IFN- γ and TGF- β 1 was determined (Figure 3). There was significantly increased expression of TGF- β 1 in the colonic mucosa of untreated colitis mice (Figure 3B). In addition, the secretion of TGF- β 1 in the colonic mucosa in the TNBS + Cur and TNBS + Mes groups was lower than that in the TNBS group. However, expression of TGF- β 1 in the spleen of mice treated with Cur and Mes was higher than that in the TNBS group compared with the Normal group, levels of IFN- γ (Figure 3B and E) and IL-10 (Figure 3C and F) in the spleen and colonic mucosa in untreated colitis mice were decreased 7 d after TNBS-induced colitis. In the colonic mucosa and spleen, the expression of both IL-10 and IFN- γ was increased in colitis mice treated with Cur and Mes as compared with untreated colitis mice.

Cur suppressed expression of co-stimulatory molecules of CD8⁺CD11c⁺ cells in colitis mice

Expression of co-stimulatory molecules of CD8⁺CD11c⁺ cells, including CD40 (Figure 4), CD40L (Figure 5), CD54 (Figure 6), CD205 (Figure 7) and MHC II (Figure 8), was detected in normal spleen and PPs. Expression increased after TNBS-induced colitis. Treatment with Cur decreased expression of CD40 (Figure 4), CD40L (Figure 5), CD54 (Figure 6), CD205 (Figure 7) and MHC II (Figure 8) in the spleen and PPs.

DISCUSSION

In the present study, the DAI, colonic weight, weight index of the colon, and histological score of colonic of experimental colitis were significantly decreased after Cur treatment, while the body weight and colonic length were recovered. The results indicate that Cur can effectively treat experimental colitis. The numbers of CD8⁺CD11c⁺ cells in the spleen and PPs were decreased, which showed that the therapeutic effect of Cur on colitis was related to the number of CD8⁺CD11c⁺ cells.

As a positive regulatory factor, CD11c, which is an adhesion molecule in the CD11/CD18 family,

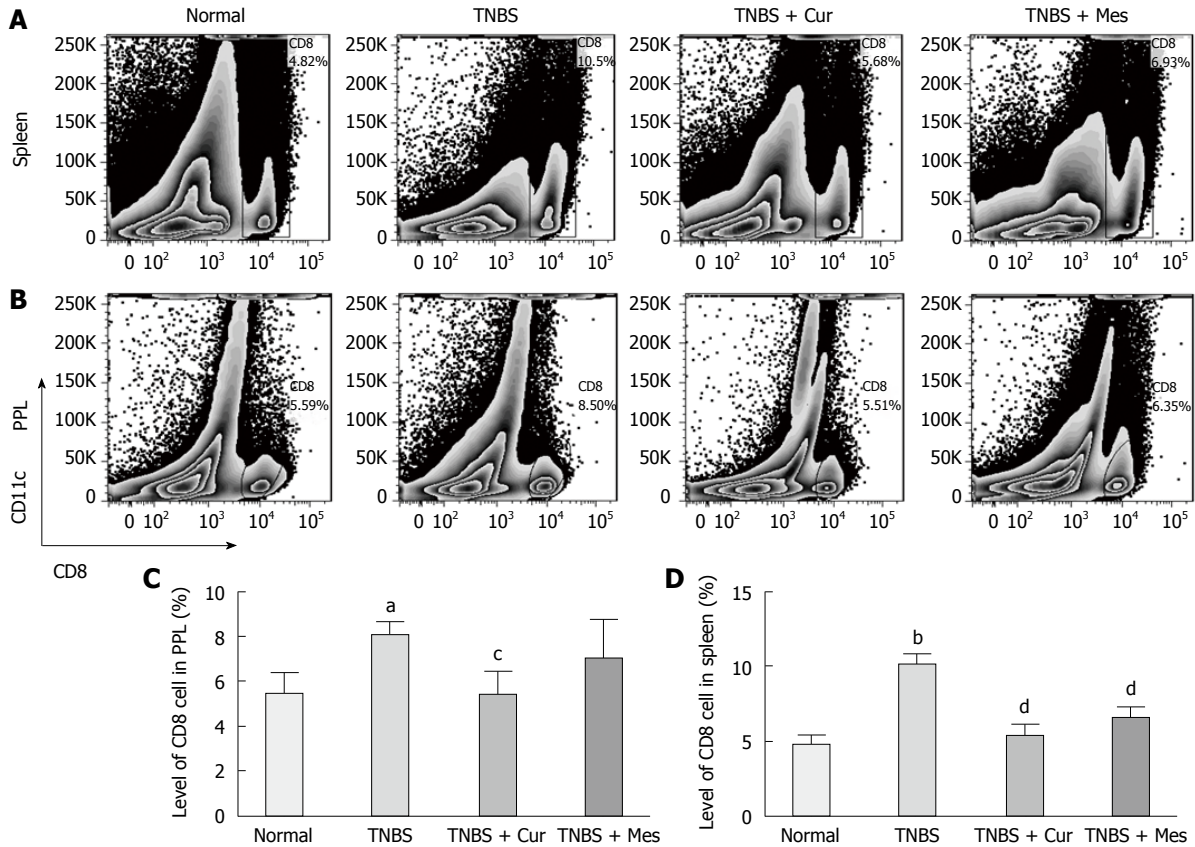


Figure 2 Typical histograms and levels of CD8⁺CD11c⁺ cells in the spleen and PPs. A: Typical graphs and mean fluorescence intensity (MFI) levels of CD8⁺CD11c⁺ cells in the spleen; B: Typical graphs and MFI levels of CD8⁺CD11c⁺ cells in PPs; C: MFI levels of CD8⁺CD11c⁺ cells in the spleen; D: MFI levels of CD8⁺CD11c⁺ cells in PPs. Data are shown as mean ± SEM (*n* = 8). ^a*P* < 0.05 and ^b*P* < 0.01 vs Normal group; ^c*P* < 0.05 and ^d*P* < 0.01 vs TNBS group.

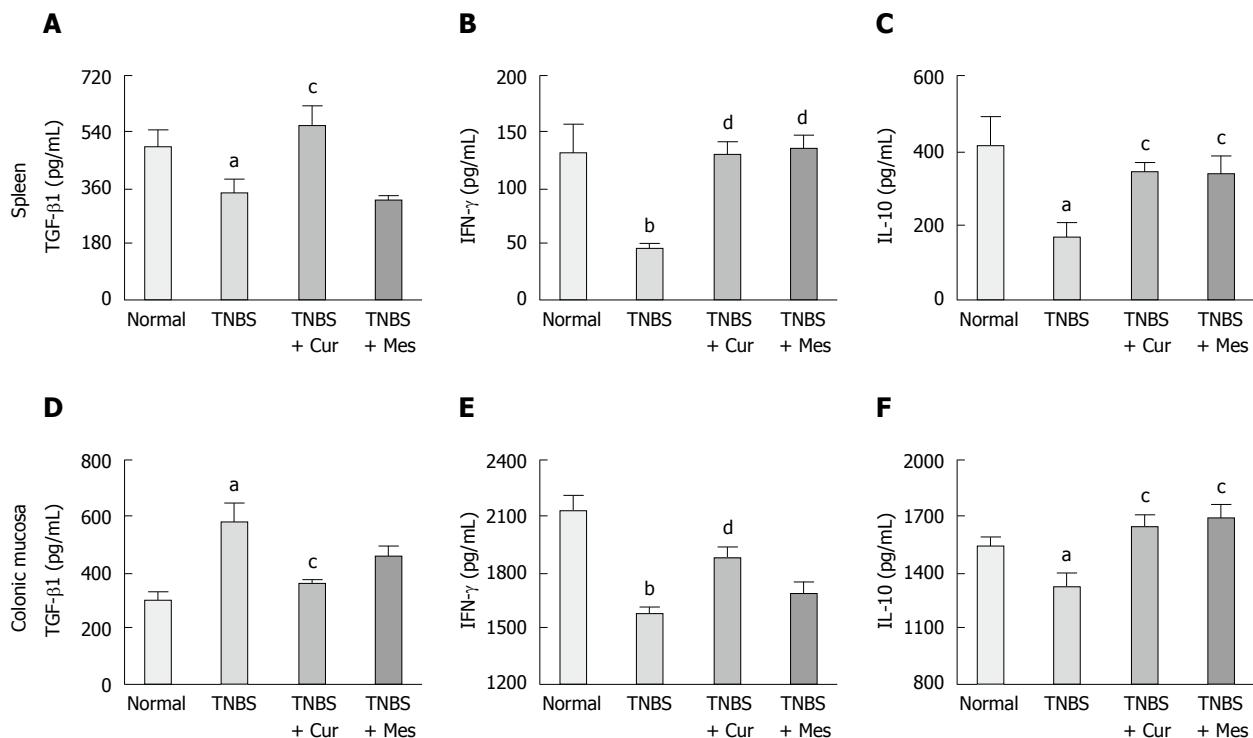


Figure 3 Levels of TGF-β1, IFN-γ and IL-10 in spleen and colonic mucosal supernatants. A-C: Concentration of TGF-β1, IFN-γ and IL-10 in the spleen from different groups; D-F: Concentration of TGF-β1, IFN-γ and IL-10 in the colonic mucosa from different groups. Data are shown as mean ± SEM (*n* = 8). ^a*P* < 0.05 and ^b*P* < 0.01 vs Normal group; ^c*P* < 0.05 and ^d*P* < 0.01 vs TNBS group.

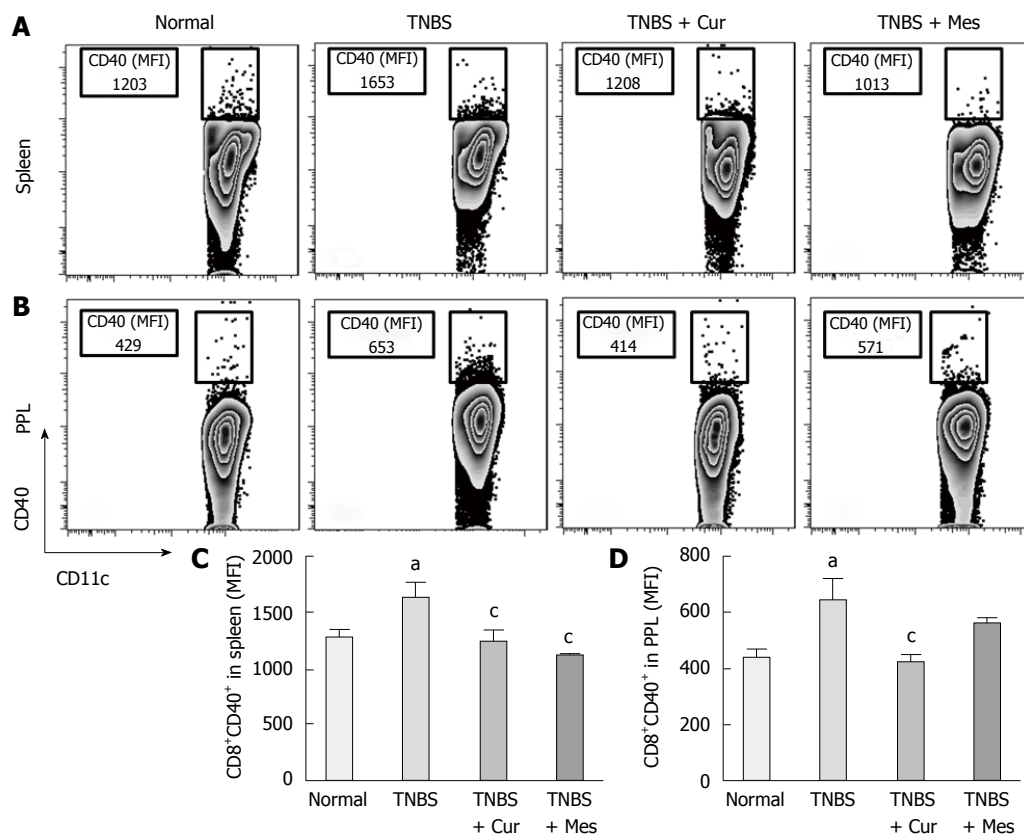


Figure 4 Typical histograms and levels of CD11c⁺CD40⁺ cells in spleen and PPs. A: Typical graphs of CD11c⁺CD40⁺ cells in the spleen; B: Typical graphs of CD11c⁺CD40⁺ cells in the PPs; C: MFI levels of CD11c⁺CD40⁺ cells in the spleen; D: MFI levels of CD11c⁺CD40⁺ cells in the PPs. Data are described as mean \pm SEM ($n = 8$). ^a $P < 0.05$ vs Normal control group; ^c $P < 0.05$ vs TNBS group.

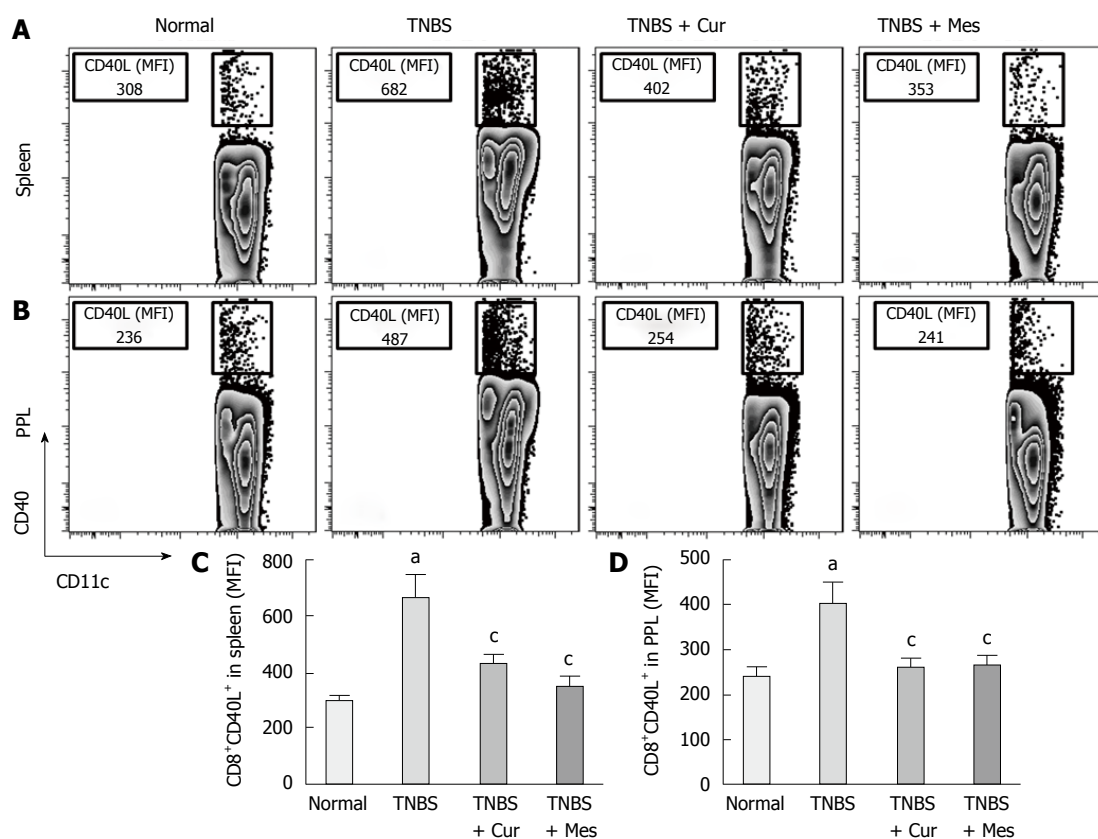


Figure 5 Typical histograms and levels of CD11c⁺CD40L⁺ cell in spleen and PPs. A: Typical graphs of CD11c⁺CD40L⁺ cells in the spleen; B: Typical graphs of CD11c⁺CD40L⁺ cells in PPs; C: Levels (MFI) of CD11c⁺CD40L⁺ cells in the spleen; D: Levels (MFI) of CD11c⁺CD40L⁺ cells in PPs. Data are described as mean \pm SEM ($n = 8$). ^a $P < 0.05$ vs Normal control group; ^c $P < 0.05$ vs TNBS group.

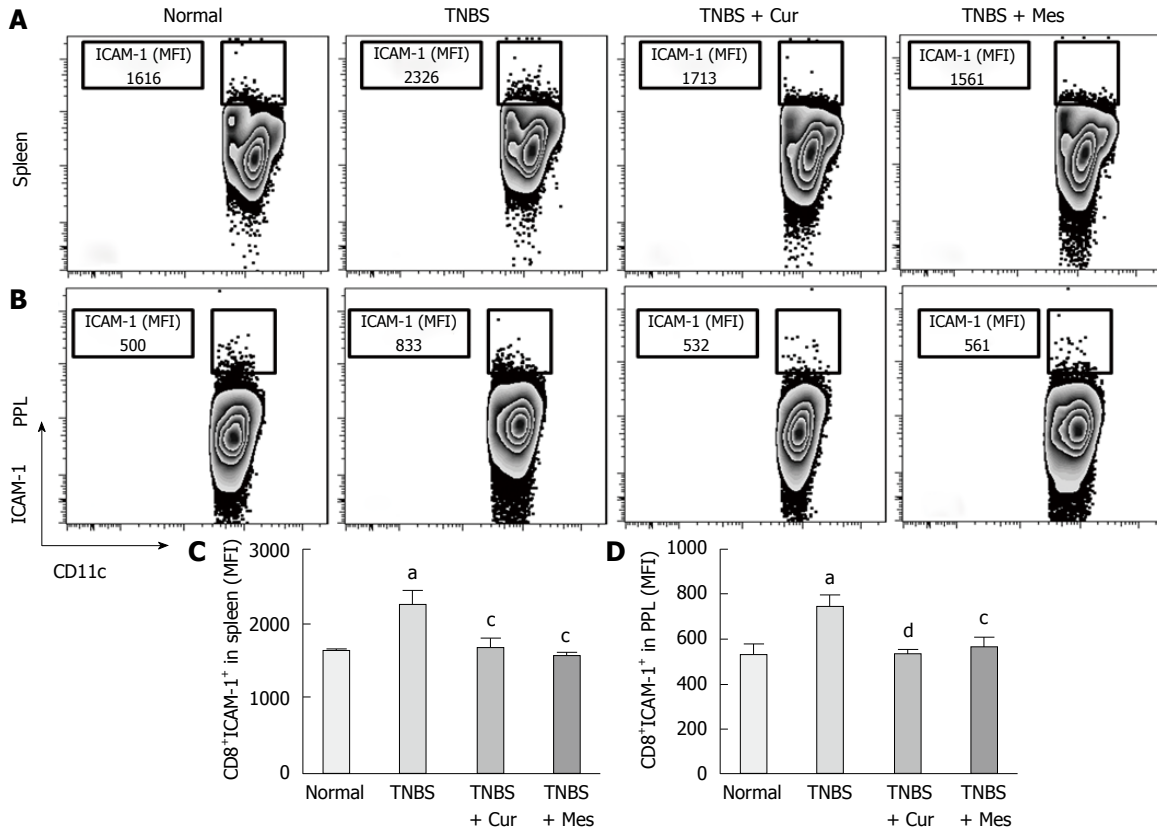


Figure 6 Typical histograms and levels of CD11c⁺ ICAM-1⁺ cells in spleen and PPs. A: Typical graphs of CD11c⁺ ICAM-1⁺ cells in the spleen; B: Typical graphs of CD11c⁺ ICAM-1⁺ cells in the PPs; C: Levels (MFI) of CD11c⁺ ICAM-1⁺ cells in the spleen; D: Levels (MFI) of CD11c⁺ ICAM-1⁺ cells in the PPs. Data are shown as mean \pm SEM ($n = 8$). ^a $P < 0.05$ vs Normal control group; ^c $P < 0.05$ and ^d $P < 0.01$ vs TNBS group.

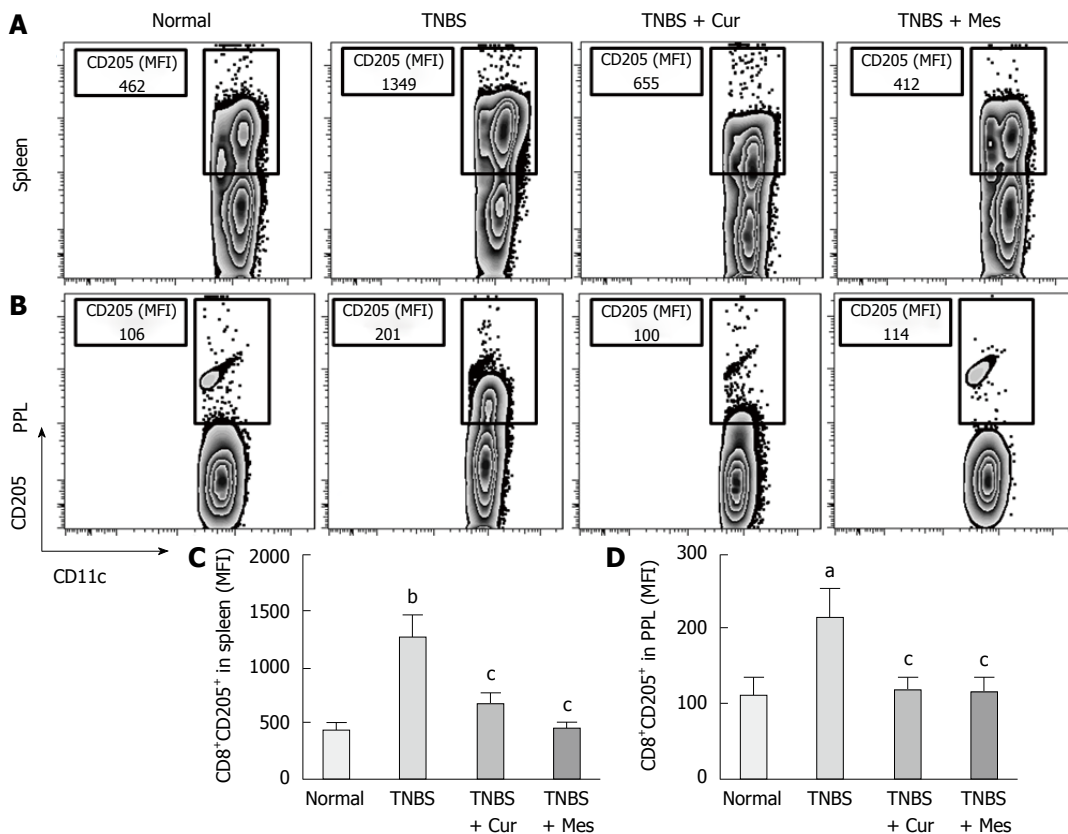


Figure 7 Typical histograms and levels of CD11c⁺ CD205⁺ cells in the spleen and PPs. A: Typical graphs of CD11c⁺ CD205⁺ cells in the spleen; B: Typical graphs of CD11c⁺ CD205⁺ cells in the PPs; C: Levels (MFI) of CD11c⁺ CD205⁺ cells in the spleen; D: Levels (MFI) of CD11c⁺ CD205⁺ cells in the PPs. Data are mean \pm SEM ($n = 8$). ^a $P < 0.05$ and ^b $P < 0.01$ vs Normal group; ^c $P < 0.05$ vs TNBS group.

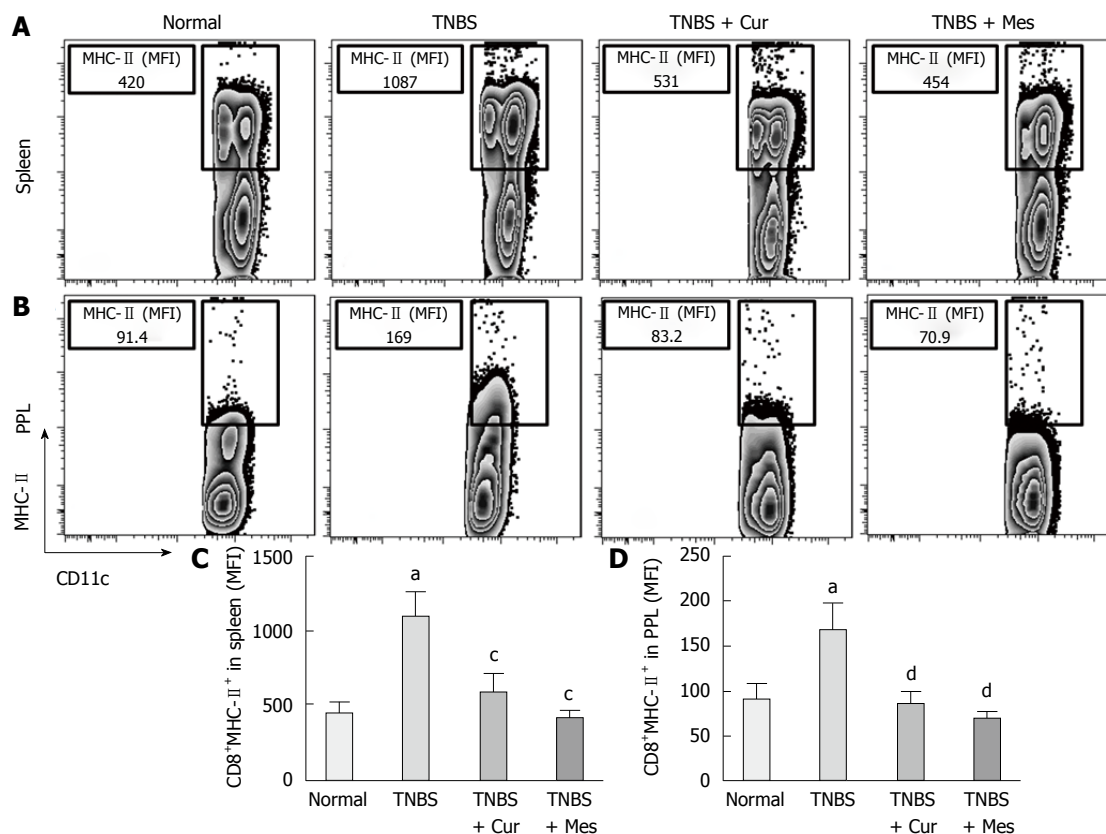


Figure 8 Typical histograms and levels of CD11c⁺MHC II⁺ cells in the spleen and PPs. A: Typical graphs of CD11c⁺MHC II⁺ cells in the spleen; B: Typical graphs of CD11c⁺MHC II⁺ cells in the PPs; C: Levels (MFI) of CD11c⁺MHC II⁺ cells in the spleen; D: Levels (MFI) of CD11c⁺MHC II⁺ cells in the PPs. Data are mean \pm SEM ($n = 8$). ^a $P < 0.05$ vs Normal control group; ^c $P < 0.05$ and ^d $P < 0.01$ vs TNBS group.

participates in conglutination, migration, antigenic recognition and presence of DCs, and activates CD4⁺, CD8⁺ T cells to regulate the immune response. CD11c can promote DC activation and maturity by elevating expression of co-stimulatory molecules^[32,33]. Activated CD11c⁺ DCs secrete a large number of inflammatory factors (including IL-1 β , IL-6, IL-12 and IL-20) and promote CD4⁺ T cells transformation into Th 1 cells, inducing inflammatory injury^[34]. In the present study, the total number of CD8⁺CD11c⁺ cells in the spleen and PPs increased in colitis mice, which decreased with Cur treatment. Our previous study indicated that Cur alleviated inflammatory injury in the colonic mucosa of colitis mice, using the same model as in the present study^[24]. These results show that Cur exerts its therapeutic effect on TNBS-induced colitis by decreasing the number of CD8⁺CD11c⁺ cells.

Previous research has shown that CD8⁺ DCs play an important role in the development of experimental colitis and human IBD^[11,12]. Our study showed that co-stimulatory molecules of DCs were increased in the spleen and PPs in untreated colitis mice, and Cur attenuated expression of MHC II, CD205, CD40, CD40L and CD54 (ICAM-1) in CD8⁺ DCs in the spleen and PPs. Our previous and present studies show that Cur can treat experimental colitis induced by TNBS or DSS^[35,36]. The present study proves that Cur regulates the levels of CD8⁺ DCs to treat TNBS-induced colitis.

DCs are essential in the activation of the adaptive immune system^[37], and can be distinguished into myeloid and lymphoid DCs based on the cell-surface expression of CD8^[8,9], which is one of the most important DC subset markers. Research has previously demonstrated that lymphoid DCs express CD8 in mice, whereas myeloid DCs do not^[38-40]. Thus, DCs in the spleen and PPs of mice are considered to be CD8⁺ DCs, which were identified in the present study^[39,41].

Overwhelming evidence suggests that activation of CD8⁺ DCs is a significant pathway to generate specific CD8⁺ T-cell immune responses^[42,43]. The complex pathway includes activation of Toll-like receptor 3^[44], MHC and co-stimulatory molecule expression. MHC can promote DCs to migrate into lymphoid tissues such as the spleen and PPs, and accelerate antigen presentation, activation and maturation of DCs.

Researchers have previously incorporated MHC II as a phenotypic segregation marker for *ex vivo* analysis of DCs under inflammatory settings such as influenza^[44]. Waithman *et al.*^[45] have shown that many of the CD8⁺ DC subpopulations undergo a phenotypic change from CD11c^{high} MHC II^{int} in naïve mice to CD11c^{int} MHC II^{high} mice infected with influenza A virus. According to MHC II and CD11c expression levels, CD8⁺ DCs, which are a classic migratory DC phenotype, could be segregated into both lymphoid-resident DC subsets and migratory subsets found at

inflammatory zones^[46-48]. Based on the high expression of MHC II, CD8⁺ DCs capture antigens and promote T-cell migration at regions of the draining lymph nodes where they mature into functional DCs and present antigens to initiate primary immune responses^[49,50]. In the process of maturation and activation of CD8⁺ DCs, co-stimulatory molecules are highly expressed and include expression of CD205, CD24, CD40 and CD40L^[2].

As a symbol of maturation and activation, DCs express co-stimulatory molecules including members of the tumor necrosis factor (TNF)/TNF receptor protein family, CD40/CD40L and OX40/OX40L, and members of the immunoglobulin superfamily including ICAM-1/lymphocyte function-associated antigen (LFA-)-1, and CD28/cytotoxic T lymphocyte associated antigen 4/B7. Collectively, these cell-surface expressed protein receptors and their cognate ligands regulate the balance between Th1 and Th2 responses, and were found to be highly expressed in human and animal colitis^[51]. For example, CD40/CD40L signaling can stimulate DCs to secrete IL-12, and direct the differentiation of CD4⁺ T cells into Th1 cells. Similar functions are present in the context of ICAM-1/LFA-1 signaling and the B7-1 molecular signaling pathway (*i.e.*, the B7/CD28 signal)^[52,53].

More importantly, CD8⁺ DCs predominantly produce Th1-promoting cytokines like IL-12 p70 and IL-12 p40, while CD8⁺ DCs lead to Th1 differentiation with reduced secretion of IFN- γ and IL-10^[8,54,55], and enhanced secretion of the proinflammatory cytokine IL-6, which is associated with autoimmunity and chronic inflammatory diseases^[56]. These cytokines were previously shown to be closely related to the pathogenesis of IBD^[57,58]. Therefore, we have experimental evidence to believe that CD8⁺ DCs played a critical role in the development of TNBS-induced colitis in our study. This was confirmed by the increased numbers of CD8⁺ DCs in the spleen and PPs in untreated colitis mice. The results showed high expression of MHC II, CD205, CD40, CD40L and ICAM-1. These co-stimulatory molecules and MHC II promoted CD8⁺ DCs to migrate into the colonic mucosa. Here, CD8⁺ DCs secreted proinflammatory cytokines and suppressed anti-inflammatory cytokine production, and ultimately induced inflammatory injury in the colonic mucosa.

Seven days after administration of Cur, the total number of CD8⁺CD11c⁺ cells was decreased, and the expression of these co-stimulatory molecules of DCs was inhibited. Although it is uncertain that Cur regulated the function of CD8⁺CD11c⁺ cells, Shirley *et al.*^[23] indicated that Cur prevented DCs from inducing CD4⁺ T-cell proliferation by blocking maturation marker expression, cytokine and chemokine secretion, and reducing migration and endocytosis of DCs.

The present study suggested that Cur restricted the quantity and activation of CD8⁺CD11c⁺ cells by

downregulating expression of the co-stimulatory molecules of DCs in an attempt to improve the level of anti-inflammatory cytokines (*i.e.*, IL-10, IFN- γ and TGF- β 1). These data suggest a therapeutic role for Cur as an immunosuppressant in the treatment of IBD. However, the level of TGF- β 1 in the colonic mucosa was decreased by Cur, which is contrary to that seen in the spleen. We speculated that overproduction of TGF- β 1 in the colonic mucosa was related to the chronicity and fibrosis of experimental colitis. Thus, Cur might inhibit fibroplasia at the base of the colonic ulcer. However, the signaling pathway remains unknown under conditions in which Cur controls maturation and migration of CD8⁺ DCs. Future work is important in this area in an attempt to explore the pathway that regulates the function of CD8⁺ DCs by TGF- β 1 signaling.

In conclusion, we demonstrated that Cur effectively treated experimental colitis, which was realized by inhibiting CD8⁺CD11c⁺ cells.

COMMENTS

Background

CD11c is a specific marker of dendritic cells (DCs) and is highly expressed in CD8⁺ and CD8⁻ DCs. Overaccumulation of CD8⁺ DCs is seen in colonic mucosa in experimental colitis and patients with inflammatory bowel disease (IBD).

Research frontiers

CD8⁺ DCs predominantly stimulate T helper (Th)1-inducing cytokines like interleukin (IL)-12p70 and IL-12p40, which can lead to Th1 differentiation, and have been reported to play a key role in controlling viral infection. Overaccumulation of CD8⁺ DCs induces inflammatory injury in the colonic mucosa when they migrate into Peyer's patches in experimental colitis and in patients with IBD. Thus, CD8⁺ DCs may be a potential therapeutic target to explore the mechanisms of clinical treatment of IBD.

Innovations and breakthroughs

The present study is believed to be the first to show that curcumin (Cur) can effectively treat experimental colitis, which was realized by inhibiting CD8⁺CD11c⁺ cells.

Applications

It is known that Cur has a long history of effectively treating human IBD and experimental colitis. Cur prevents DC-mediated induction of CD4⁺ T-cell proliferation by blocking expression of maturation markers, cytokines and chemokines. However, it is unclear whether Cur can regulate expression of CD8⁺CD11c⁺ cells to treat IBD. The present study suggests that Cur can treat experimental colitis, via inhibition of CD8⁺CD11c⁺ cells.

Terminology

CD11c is a type I transmembrane protein that mediates adherence between leukocytes and endothelial cells, and participates in exudation and phagocytosis of leukocytes.

Peer-review

The manuscript is presented in an easy understandable manner. The topic in the manuscript is very well explained. But it requires substantial corrections for the acceptance. According to detailed experimental data and reliable results, the present study had proved that Cur effectively treated experimental colitis, which was realized by inhibiting CD8⁺CD11c⁺ cells.

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