

Basic Study

Enterocyte dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin expression in inflammatory bowel disease

Jing-Qing Zeng, Chun-Di Xu, Tong Zhou, Jing Wu, Kai Lin, Wei Liu, Xin-Qiong Wang

Jing-Qing Zeng, Chun-Di Xu, Tong Zhou, Jing Wu, Kai Lin, Wei Liu, Xin-Qiong Wang, Department of Pediatrics, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

Jing-Qing Zeng, Department of Pediatrics, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200127, China

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Correspondence to: Chun-Di Xu, MD, Professor, Department of Pediatrics, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, 197 Ruijin Erlu, Shanghai 200025, China. chundixu55@163.com
Telephone: +86-21-64370045

Fax: +86-21-64333548

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SIGN) expression in intestinal epithelial cells (IECs) in inflammatory bowel disease (IBD).

METHODS: The expression of DC-SIGN in IECs was examined by immunohistochemistry of intestinal mucosal biopsies from 32 patients with IBD and 10 controls. Disease activity indices and histopathology scores were used to assess the tissue lesions and pathologic damage. Animal studies utilized BALB/c mice with dextran sodium sulfate (DSS)-induced colitis treated with anti-P-selectin lectin-EGF domain monoclonal antibody (PsL-EGFmAb). Controls, untreated and treated mice were sacrificed after 7 d, followed by isolation of colon tissue and IECs. Colonic expression of DC-SIGN, CD80, CD86 and MHC II was examined by immunohistochemistry or flow cytometry. The capacity of mouse enterocytes or dendritic cells to activate T cells was determined by co-culture with naïve CD4⁺ T cells. Culture supernatant and intracellular levels of interleukin (IL)-4 and interferon (IFN)- γ were measured by enzyme-linked immunosorbent assay and flow cytometry, respectively. The ability of IECs to promote T cell proliferation was detected by flow cytometry staining with carboxyfluorescein diacetate succinimidyl ester.

RESULTS: Compared with controls, DC-SIGN expression was significantly increased in IECs from patients with Crohn's disease ($P < 0.01$) or ulcerative colitis ($P < 0.05$). DC-SIGN expression was strongly correlated with disease severity in IBD ($r = 0.48$; $P < 0.05$). Similarly, in the DSS-induced colitis mouse model, IECs showed upregulated expression of DC-SIGN, CD80, CD86 and MHC, and DC-SIGN expression was positively correlated with disease activity ($r = 0.62$; $P < 0.01$). IECs from mouse colitis stimulated naïve T cells to generate IL-4 ($P < 0.05$). Otherwise, dendritic cells promoted a T-helper-1-skewing phenotype by stimulating IFN- γ secretion. However, DC-SIGN expression and T cell differentiation were suppressed following treatment of mice with DSS-

Abstract

AIM: To investigate dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-

induced colitis with PsL-EGFmAb. The proliferation cycles of CD4⁺ T cells from mice with DSS-induced colitis appeared as five cycles, which was more than in the control and treated groups. These results suggest that IECs can promote T cell proliferation.

CONCLUSION: IECs regulate tissue-associated immune compartments under the control of DC-SIGN in IBD.

Key words: Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; Dendritic cells; Immune compartmentalization; Inflammatory bowel disease; Intestinal epithelial cells

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Core tip: Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) functions as an adhesion and antigen-presenting molecule. We found that DC-SIGN was expressed by intestinal epithelial cells, which induced differentiation and proliferation of T cells under the control of DC-SIGN.

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INTRODUCTION

Inflammatory bowel disease (IBD), primarily comprised of Crohn's disease and ulcerative colitis, is an idiopathic disease characterized by chronic, relapsing, nonspecific inflammatory reactions of the bowel^[1,2]. The exact etiology of IBD is still unknown. Recent studies have provided substantial insight into how functional mucosal immunity is maintained and how the pathogenesis of IBD is initiated. IBD is generally attributed to inappropriate and continuing inflammatory stimulations^[3-6].

Dendritic cells (DCs) play a key role in the initiation of inflammation, which is associated with the migration of DCs mediated by the adhesion molecule P-selectin. Adhesion and migration of DCs is inhibited by anti-P-selectin lectin-EGF domain monoclonal antibodies (PsL-EGFmAb), which target the carbohydrate recognition domain of P-selectin^[7,8]. Our previous work demonstrated that PsL-EGFmAb had a blocking effect on DC-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) in a mouse model of nephritis and improved disease progression and outcome^[7]. DC-SIGN, also designated as CD209, is a member of the C-type lectin superfamily, and has a carbohydrate recognition domain similar to P-selectin^[9].

In this study, we investigated the expression of DC-

SIGN in the intestinal tissues of patients with IBD and its significance in the disease activity. To further study the mechanisms of how DC-SIGN functions in colitis, we examined expression with PsL-EGFmAb treatment in an experimental model of dextran sodium sulfate (DSS)-induced colitis.

MATERIALS AND METHODS

Patients

A total of 32 children with IBD were randomly recruited from the Department of Pediatrics, Ruijin Hospital between January 2006 and June 2010. All children were diagnosed with IBD by endoscopy and histopathologic examination according to the pediatric Crohn's disease activity index (PCDAI) and pediatric ulcerative colitis activity index (PUCAI). The patients included 20 boys and 12 girls, with a mean age of 8.68 ± 5.21 years. We recruited two major disease groups: Crohn's disease ($n = 18$) and ulcerative colitis ($n = 14$). Ten age- and sex-matched children with abdominal pain, diarrhea and no histologic enteritis were enrolled as controls. Human intestinal mucosal tissues from patients with Crohn's disease, ulcerative colitis and the control group were collected by endoscopic biopsy.

The study was approved by the Ethical Committee of Shanghai Jiao Tong University School of Medicine, China.

DSS-induced colitis mouse model

The DSS-induced colitis mouse model of IBD was described by Okayasu *et al*^[10]. Thirty female BALB/c mice (aged 6-8 wk, 16-20 g) were purchased from the Hayes Lake Experimental Animals Co. (Shanghai, China) and randomly assigned into three groups ($n = 10$ each): control, DSS-treated, and PsL-EGFmAb + DSS-treated. The DSS-treated group was orally administered a 5% DSS solution for 7 d. The PsL-EGFmAb + DSS-treated group were given daily injections with 2 mg/kg PsL-EGFmAb (ip) for 3 d during the 7 d of 5% DSS administration. Control animals were orally administered a sterile saline solution. Clinical Disease Activity Index for DSS-induced colitis was measured by weight loss, stool consistency, and bleeding^[11]. All the mice were sacrificed at day 7, and intestinal mucosa and spleens were quickly removed for histologic and cellular function analyses.

Immunohistochemical staining

Paraffin sections of human and mouse intestinal mucosal tissues were treated with endogenous peroxidase and nonspecific protein blocking, and incubated with 1:100 primary antibody at 4 °C overnight and 1:400 secondary antibody for 1 h at room temperature. Antibodies used were as follows: mouse anti-human DC-SIGN mAb (R and D Systems, Minneapolis, MN, United States) and biotinylated anti-mouse IgG (Invitrogen of Thermo Fisher Scientific Inc., Waltham, MA, United States) for human tissues, and rat anti-mouse DC-SIGN mAb (eBioscience Inc., San Diego, CA, United States) with biotinylated anti-

rat (Invitrogen) for mouse tissues. Finally, the sections were stained by diaminobenzidine for microscopic examination. The primary antibody was replaced with phosphate-buffered saline as a negative control and known positive sections were used as positive controls.

The positive cells showed distinct brown-orange coloration within the cell membrane or cytoplasm of epithelial cells. Immunohistochemistry scores were based on the percentage of positive cells ($< 10\% = 0$; $10\%-30\% = 1$; $31\%-50\% = 2$; $51\%-75\% = 3$; and $> 75\% = 4$) multiplied by stain intensity ($0 = \text{negative}$, $1 = \text{weak}$, $2 = \text{moderate}$, $3 = \text{strong}$) in five different high-power fields for each section. A score of 4+ was called “DC-SIGN positive”^[12].

Disease severity assessment of colitis

Paraffin-embedded sections ($5\ \mu\text{m}$) prepared from the distal colons of experimental mice were stained with hematoxylin/eosin and examined under a Zeiss Axioplan 2 imaging microscope equipped with an AxioCam MRc5 camera (Carl Zeiss AG, Oberkochen, Germany). Histologic scoring was ranked according to the amount and depth of inflammation, and the amount of crypt damage^[13]. Isolated mouse splenic cells (1×10^5 cells/mL) were incubated with fluorescein isothiocyanate-labeled CD4 mAb and stained with allophycocyanin-labeled interferon (IFN)- γ mAb and phycoerythrin-labeled interleukin (IL)-4 mAb to evaluate the systemic inflammatory response in mice^[14].

Flow cytometry

Mouse intestinal epithelial cells (IECs) were sorted by flow cytometry using anti-mouse phycoerythrin-conjugated CD326 (epithelial cell adhesion molecule) and incubated with fluorescein isothiocyanate-labeled DC-SIGN, CD80, CD86 or MHC mAb at a density of 5×10^5 cells/mL. Phenotypic analysis was performed by flow cytometry using a FACS Calibur and FACS Aria Cell Sorter (Becton, Dickinson and Co., Franklin Lakes, NJ, United States) and data were analyzed with FCS Express version 3.

T lymphocyte differentiation and proliferation

Mouse splenic CD4⁺ T cells were isolated using mouse naïve CD4⁺ T cell isolation Kit (R and D Systems), and CD11c⁺ DCs were purified using magnetic activated cell sorting beads (Miltenyi Biotec, Bergisch Gladbach, Germany). The IECs ($5 \times 10^5/\text{mL}$) or CD11c⁺ DCs ($2 \times 10^5/\text{mL}$) were co-cultured with CD4⁺ T cells ($1 \times 10^6/\text{mL}$) in 96-well plates in the presence of IL-2, anti-CD3 and anti-CD28 for 5 d. Cells were stimulated with phorbol 12-myristate 13-acetate ($50\ \text{ng}/\text{mL}$), ionomycin ($1\ \mu\text{g}/\text{mL}$) and brefeldin A ($10\ \mu\text{g}/\text{mL}$) for 6 h, and harvested for intracellular IFN- γ or IL-4 staining with allophycocyanin-conjugated IFN- γ mAb and phycoerythrin-labeled IL-4 mAb, followed by flow cytometry analysis. In addition, IFN- γ or IL-4 levels in the co-culture supernatants were measured by enzyme-linked immunosorbent assay^[15]. The ability of IECs to promote T cell proliferation was detected by flow cytometry after staining with carboxyfluorescein diacetate succinimidyl ester.

Statistical analysis

SPSS version 16.0 (SPSS Inc., Chicago, IL, United States) was used for the database analysis. Data are presented as mean \pm standard deviation and were measured by nonparametric rank sum test and one-way analysis of variance. Numerical data were measured using Fisher's exact test. The correlation between groups was analyzed using Spearman coefficients. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Expression of DC-SIGN in human IECs

Expression of DC-SIGN was rarely detected in the intestinal mucosa of healthy children, but was elevated in the intestinal mucosa of children with IBD, especially in the IECs and mesenchymal cells (Figure 1). DC-SIGN expression was significantly higher in children with Crohn's disease (61% ; $P = 0.002$) and ulcerative colitis (50% ; $P = 0.019$) compared with controls (10%). However, there was no significant difference between expression in Crohn's disease and ulcerative colitis.

Correlation of DC-SIGN expression with IBD disease activity

To determine if increased expression of DC-SIGN was correlated with IBD progression and severity, we used PDAI and PUCAI to evaluate disease activity in children with IBD. The scores were significantly higher in the DC-SIGN-positive group than in the DC-SIGN-negative group (PDAI: 25.91 ± 10.20 *vs* 13.93 ± 7.20 , PUCAI: 32.14 ± 13.50 *vs* 15.71 ± 8.86 ; $P_s < 0.01$), and DC-SIGN expression was strongly correlated with disease severity in IBD ($r = 0.48$; $P < 0.05$) (Figure 2).

Characterization of DSS-induced colitis model

Hematoxylin and eosin staining revealed greater neutrophil infiltration in the intestinal tissue from the DSS and DSS + PSL-EGFmAb groups compared with the control group (Figure 3A). The disease activity index score was significantly elevated in DSS-treated mice compared with the controls (11.4 ± 0.70 *vs* 0.5 ± 0.53 , $P < 0.01$), and was significantly decreased by PSL-EGFmAb treatment (8.6 ± 3.60 , $P < 0.05$) (Figure 3B). In addition, histologic examination of intestinal biopsies showed significantly higher scores in the DSS-treated group (6.6 ± 1.78 , $P < 0.01$) compared with the controls (0.7 ± 1.06) but suppressed disease following treatment with PSL-EGFmAb (4.7 ± 1.06 , $P < 0.05$) (Figure 3C). IL-4 and IFN- γ expression levels in mouse splenic CD4⁺ T cells were increased in the DSS-treated group compared with the control and DSS + PSL-EGFmAb groups (Figure 3D).

Expression of DC-SIGN, CD86, CD80 and MHC II in mouse IECs

DC-SIGN expression was rarely detected in normal intestinal tissues, but was clearly observed in the intestinal

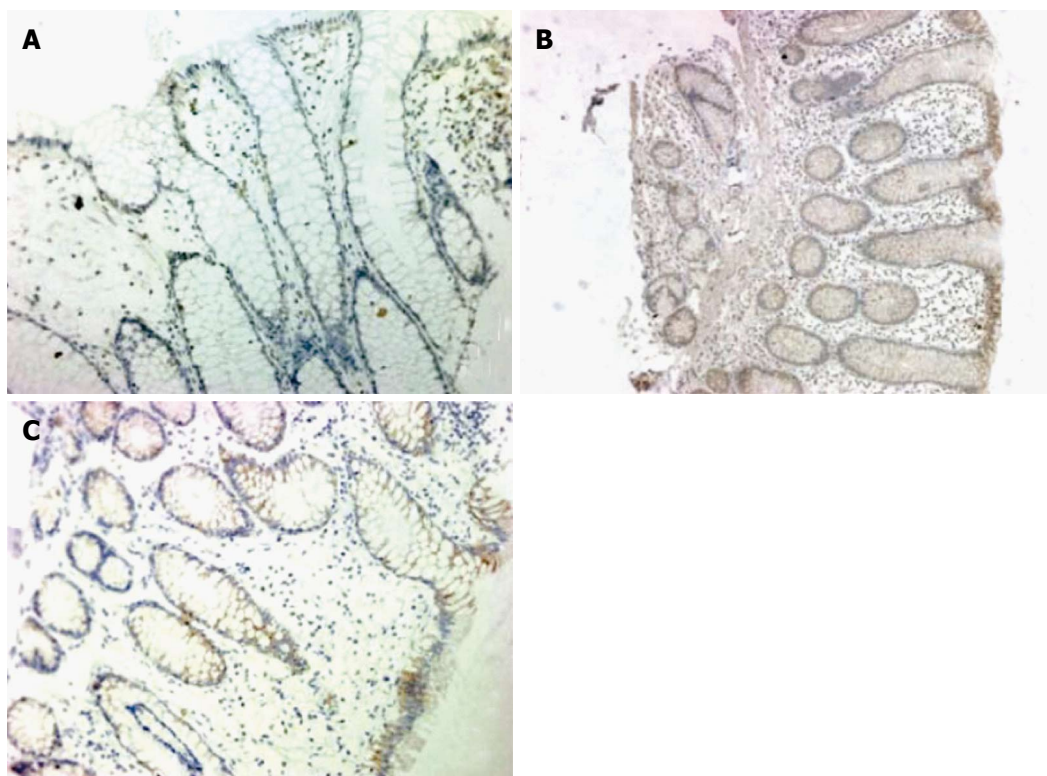


Figure 1 Immunohistochemistry of dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin expression in intestinal epithelial cells. Intestinal tissue samples from A: Control patient; B: Ulcerative colitis patient; C: Crohn's disease patient (magnification $\times 200$).

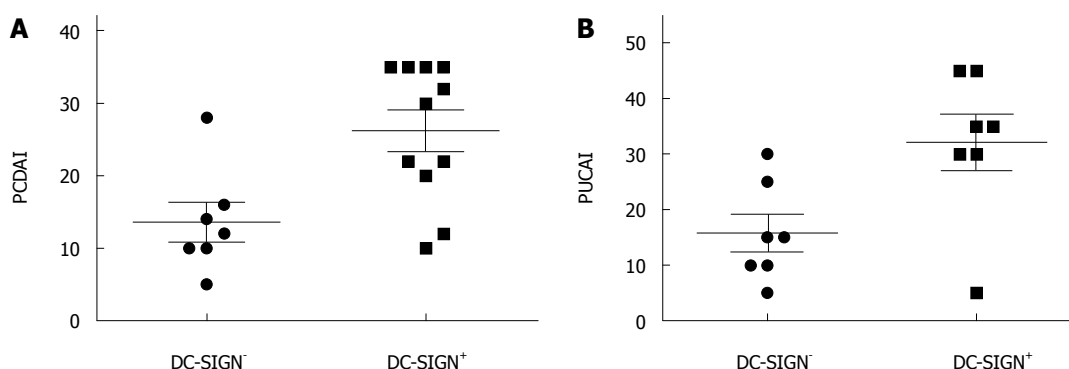


Figure 2 Inflammatory bowel disease activity in patients with and without dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin expression. Disease activity was assessed in dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) + and DC-SIGN⁻ patients using the A: Pediatric Crohn's disease activity index (PCDAI); and the B: Pediatric ulcerative colitis activity index (PUCAI).

tissues of the DSS-treated and DSS + PsL-EGFmAb groups (Figure 4A). Further analysis revealed that DC-SIGN expression was significantly correlated with disease activity scores ($r_s = 0.62$; $P < 0.01$). Flow cytometric analysis revealed that, as well as co-stimulatory molecules, CD80, CD86 and MHC II were markedly elevated in IECs of DSS-treated mice and downregulated with PsL-EGFmAb treatment (Figure 4B).

T cell differentiation and proliferation induced by mouse IECs

IECs are not traditional antigen-presenting cells. However, we report here that after co-culturing naïve CD4⁺ T

cells and IECs, T cells were activated and T helper (Th) cytokines (IFN- γ and IL-4) were detected by flow cytometry and enzyme-linked immunosorbent assay. The results show that compared with controls, IL-4 expression levels peaked in the DSS-treated group ($P < 0.05$), and increased in the PsL-EGFmAb + DSS-treated group (Figure 5A and B). No significant changes in IFN- γ were observed among the three groups. In addition, the IL-4/IFN- γ ratio of the co-culture supernatant was higher in the DSS-treated group, but downregulated with PsL-EGFmAb treatment ($P < 0.05$). The proliferation cycles of CD4⁺ T cells in the DSS-induced colitis group appeared as five cycles, which was more than in the other

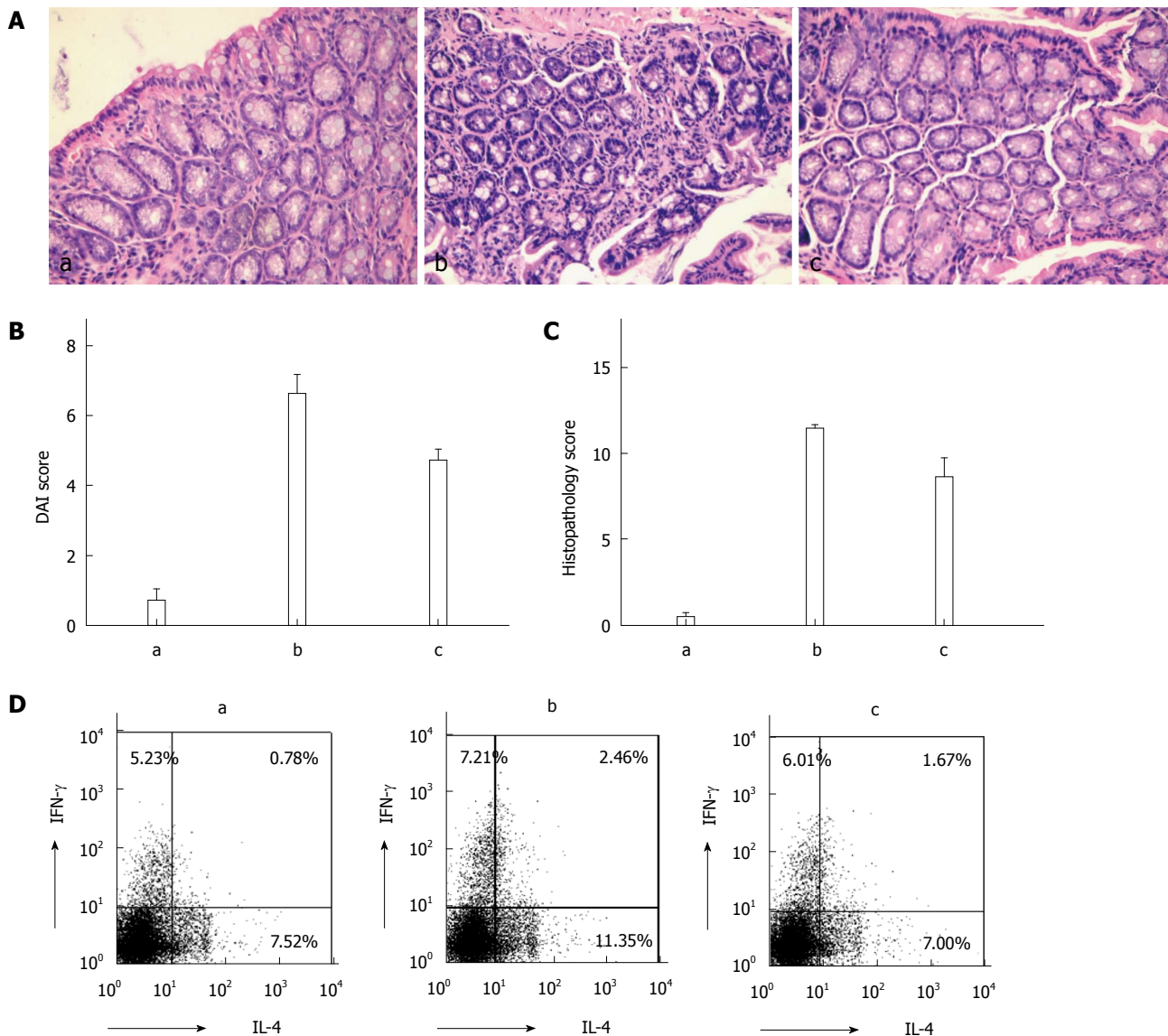


Figure 3 Histology, disease activity index, and cytokine expression profiles in mouse splenic CD4⁺ T cells. A: Hematoxylin and eosin staining in intestinal tissue (magnification $\times 200$); B: Disease activity index (DAI) scores; C: Histopathology scores from examination of intestinal biopsies; D: Interferon (IFN)- γ and interleukin (IL)-4 expression levels in mouse splenic CD4⁺ T cells. a: control group, b: dextran sodium sulfate-treated group, c: anti-P-selectin lectin-EGF domain monoclonal antibody-treated group; ^a $P < 0.05$, ^b $P < 0.01$ vs control.

groups (Figure 5C).

T cell differentiation induced by DCs

Co-culturing of naïve T cells from normal BALB/c mice and DCs from mouse spleens resulted in an increased proportion of IFN- γ in the DSS-treated group compared with the PsL-EGFmAb-treated and control groups (Figure 6).

DISCUSSION

IBD is a chronic intestinal disorder of unknown etiology and pathogenesis. However, it is generally believed that uncontrolled intestinal immune response facilitates onset and development of IBD^[6,16,17]. Murine models of IBD have demonstrated that the imbalance in Th1/Th2 cells plays a pivotal role in determining the type of immune

response generated in the gut and that distinct cytokine profiles characterize each CD4⁺ T cell subset^[18,19].

The formation of a physical barrier by IECs plays an important role in innate immune defense^[20-22]. Recently, it has been found that IECs are not only a passive barrier that limits the access of pathogens, but also participate in mucosal immune regulation through the pattern recognition receptors^[23-25].

DCs are dysregulated in IBD, which leads to overproduction of chemokines and proinflammatory cytokines that stimulate the activation and differentiation of pathogenic Th cells^[26-28]. DCs are antigen-presenting cells that are responsible for the regulation of abnormal T cell activation. Upon activation, a number of cell surface molecules and maturation markers are expressed, such as Toll-like receptors, Nod-like receptors, and C-type lectin receptors. Among them, DC-SIGN is a member of the

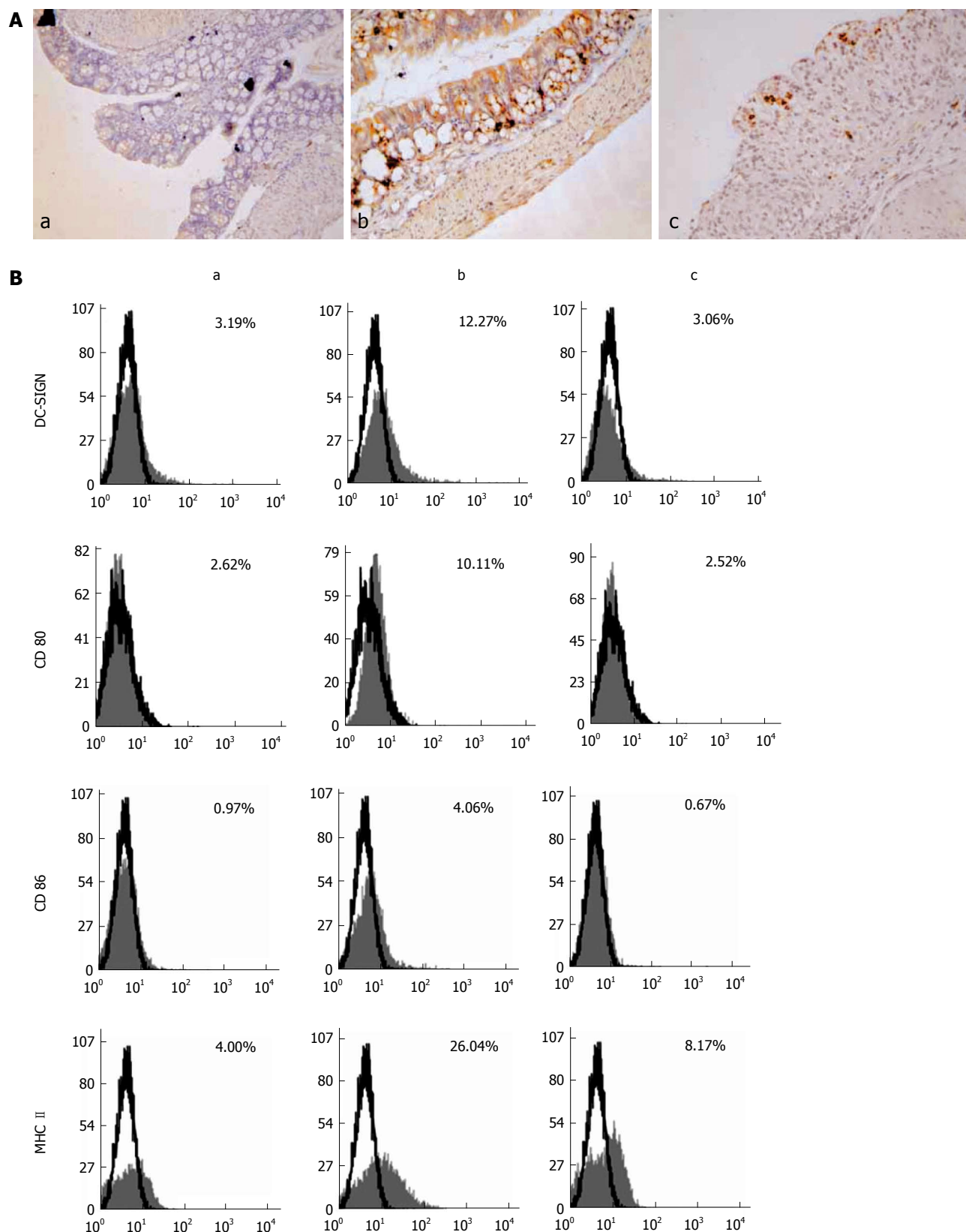


Figure 4 Expression of dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin, CD80, CD86 and major histocompatibility complex II. A: dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) immunostaining in intestinal samples from BALB/c mice (magnification $\times 200$); B: Flow cytometric analysis of DC-SIGN, CD80, CD86 and major histocompatibility complex (MHC) II in mouse intestinal epithelial cells. a: Control group, b: Dextran sodium sulfate-treated group, c: Anti-P-selectin lectin-EGF domain monoclonal antibody-treated group.

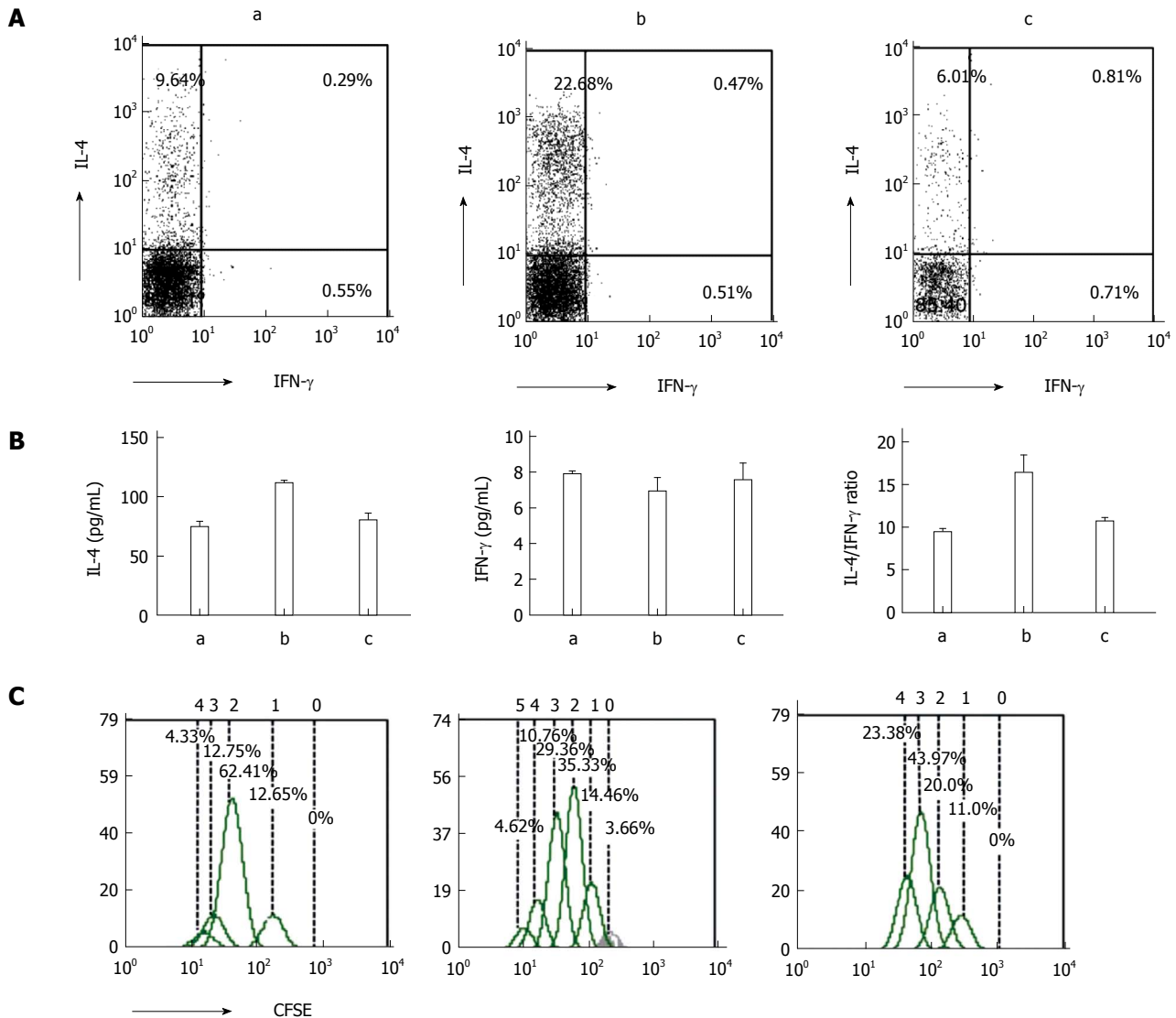


Figure 5 T lymphocyte differentiation and proliferation induced by mouse intestinal epithelial cells. A: Flow cytometric analysis of interferon (IFN)- γ and interleukin (IL)-4 levels in CD4⁺ T cells; B: Enzyme-linked immunosorbent assay of IFN- γ and IL-4 levels in co-culture supernatants; C: Flow cytometric analysis of T cell proliferation (0, undivided cells; 1, generation 1; 2, generation 2; 3, generation 3; 4, generation 4; 5, generation 5). a: Control group, b: Dextran sodium sulfate-treated group, c: Anti-P-selectin lectin-EGF domain monoclonal antibody-treated group; * $P < 0.05$ vs controls; ^a $P < 0.05$ vs dextran sodium sulfate-treated group. No significant changes in IFN- γ groups.

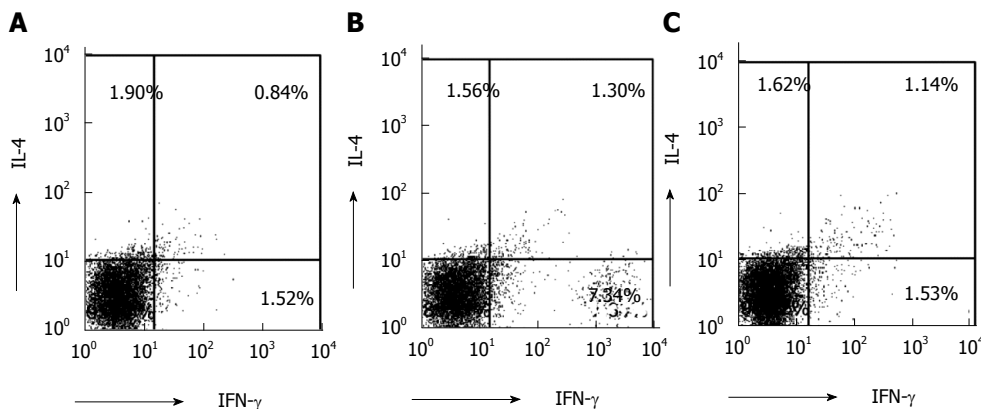


Figure 6 T lymphocyte differentiation induced by mouse dendritic cells. Flow cytometric analysis of interferon (IFN)- γ and interleukin (IL)-4 levels in mouse CD11c⁺ dendritic cells. A: Control group; B: Dextran sodium sulfate-treated group; C: Anti-P-selectin lectin-EGF domain monoclonal antibody-treated group.

C-type lectin superfamily, functioning as an adhesion receptor and a pattern recognition receptor^[29,31]. It plays a critical role in regulating the migration of DCs and subsequent activation of T lymphocytes involved in the immunoregulation of infectious and inflammatory diseases^[9,32].

Our study showed that IECs express DC-SIGN, which is significantly correlated with intestinal disease severity. *In vitro*, we further demonstrated that IECs stimulate CD4⁺ T cells to secrete IL-4, suggesting that they potently induce a Th2-predominant host immune response in experimental colitis. In contrast, DCs from animals with experimental colitis induced T cells towards a Th1-skewing phenotype by IFN- γ secretion. Based on the above results, we propose that the injured IECs might trans-differentiate, leading them to acquire immune properties. Trans-differentiation is a biologic process by which one differentiated cell type converts into another^[33,34]. In disease states, IECs exert antigen-presenting function by trans-differentiation and regulate mucosal immunity together with DCs in the local microenvironment, to determine the type of immune response. This phenomenon may be associated with the regulation of gut immune compartmentalization^[35,36].

In summary, DC-SIGN modulates the trans-differentiation of IECs, interacts with DCs as well as the local intestinal immune compartment, and might play a vital role in facilitating damage to the gut mucosa in IBD. Further study is needed to investigate the underlying mechanisms for the immunomodulatory effects of IECs.

COMMENTS

Background

Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) is a DC phenotypic molecule and plays an important role in mediating DC adhesion and migration, inflammation, and activation of primary T cells. This study aimed to confirm if intestinal epithelial cells (IECs) express DC-SIGN and explore if it plays a role in inflammatory bowel disease (IBD).

Research frontiers

The authors found that DC-SIGN was expressed by IECs. This may have implications for cellular immunology.

Innovations and breakthroughs

This study confirmed that DC-SIGN expression increased significantly in IECs from patients with IBD and in the dextran sodium sulfate-induced colitis mouse model. IECs can promote T cell proliferation and differentiation to regulate tissue-associated immune compartments under the control of DC-SIGN.

Applications

The findings highlight DC-SIGN expression in IECs, which modulates the interaction of IECs with the local intestinal immune compartment in IBD. This provides new ideas for the underlying mechanism of IBD.

Terminology

The carbohydrate recognition domain can selectively recognize sugar structures on the surface of pathogens. Anti-P-selectin lectin-EGF domain monoclonal antibody targets the targeting the carbohydrate recognition domain of P-selectin.

Peer review

In this study, the authors investigated the expression of DC-SIGN in IECs and its significance in IBD, based on a mouse colitis model and human (pediatric) IBD samples. The idea is novel and interesting.

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