Role of the CXC12-CXCR4 Axis and CXCL16 in Inflammatory Bowel Disease

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Numerous studies of colitis in IBD (inflammatory bowel diseases) patients and in animal models have demonstrated that both inflammatory cytokines and chemokines are up-regulated in settings of active inflammation. Blockade or absence of various cytokines and chemokines attenuates the disease in murine models of IBD. Therefore, identifying cytokines and chemokines involved in intestinal inflammation provide promising targets for the development of new drugs in the treatment of IBD. In general, chemokines have been implicated in many fundamental immune processes including lymphoid organogenesis, immune cell differentiation, development and positioning. Many chemokines are markedly increased in intestinal tissue from patients with IBD. In this study, we focused on the role of CXCL12-CXCR4 and CXCL16. CXCL12-CXCR4 axis plays a crucial role in the pathophysiology of IBD, especially UC, while SR-PSOX/CXCL16 plays a significant role in the pathophysiology of CD. Our present data suggest new insights into the etiology of IBD and we hope that the manipulation of these chemokines may have therapeutic value. (Intest Res 2012;10:125-133)

Key Words: Inflammatory Bowel Diseases; Chemokine; CXCL12-CXCR4 Axis; CXCL16

INTRODUCTION

UC and CD are chronic intestinal IBD. IBD is characterized by an increased influx of immune cells to the mucosa of genetically susceptible hosts. The characteristic increase of inflammatory infiltrate mainly comprises T cells recruited to the lamina propria (LP) by a multistep process that involves the integrated interactions and effects of adhesion molecules and chemokines.1 Numerous studies in IBD patients and in animal models of colitis have demonstrated that both inflammatory cytokines and chemokines are upregulated in settings of active inflammation.2 More importantly, the blockade or absence of various cytokines and chemokines attenuates disease in murine models of IBD. Thus, identifying the cytokines and chemokines that are involved in intestinal inflammation will provide promising targets for new drug development toward the treatment of IBD.

DEFINITION OF CHEMOKINES

Chemokines are implicated in many fundamental immune processes, including lymphoid organogenesis, immune cell differentiation, development and positioning.3 Chemokines are small 8 to 12-kDa cytokines that can direct the recruitment and migration of circulating leukocytes and play a critical role in the differentiation of secondary lymphoid organs. There are approximately 50 known chemokines and 20 known receptors. Chemokines are classified into four separate families based on the pattern of their cysteine residues (C, CC, CXC, and CX3C).4 The CC family of chemokines contains two adjacent cysteine residues. The CXC family has two cysteine residues separated by a non-cysteine amino acid,
whereas the CX3C family has two cysteine residues separated by three non-cysteine amino acids. The C family has only one cysteine residue. The dramatic increase in the secretion of chemokines during inflammation results in the selective recruitment of leukocytes into the inflamed tissue. The main stimuli for chemokine production are early proinflammatory cytokines, such as interleukin (IL)-1 and tumor necrosis factor (TNF)-α, interferon (IFN)-γ and IL-4 and bacterial products. 5 Chemokines often act in concert with other cytokines to cause tissue infiltration of leukocytes.

Chemokine secretion is detected in a wide variety of diseases. In several diseases, chemokines are likely to cause the accumulation and activation of leukocytes in tissues. The type of inflammation that characterizes a specific disease is controlled, in part, by the subgroup of chemokines expressed in the diseased tissue. In many acute disease processes, such as bacterial infection, there is a massive influx of neutrophils into the tissue. In contrast, in many chronic diseases, lymphocytes and macrophages are mainly infiltrated into tissues.

IBD is characterized by chronic inflammation with superimposed acute inflammatory exacerbations. In the chronic phase, macrophages and lymphocytes infiltrate the bowel, and in the acute phase, neutrophils and perhaps eosinophils leave the circulation and enter the intestinal mucosa. Many chemokines (monocyte chemoattractant protein-1, macrophage inflammatory protein-alpha, eotaxin, and inducible protein-10, etc.) are markedly increased in intestinal tissue from patients with IBD. 6,7 Here, we review the role of CXC chemokine ligand (CXCL)12-CXC chemokine receptor (CXCR)4 and CXCL16, which have been investigated in the context of IBD.

**CXCL12 (SDF-1) AND CXCR4**

Among chemokines, CXCL12 (stromal cell-derived factor [SDF]-1/pre-B-cell-growth-stimulating factor) is particularly intriguing because it is definitively involved in various developmental processes, including hematopoiesis. 8,9 CXCL12 was first characterized as a pre-B-cell growth-stimulating factor and the primary physiologic receptor for CXCL12 is CXCR4, which also functions as an entry receptor for strains of human immunodeficiency virus-1. 10 Studies using mutant mice with targeted gene disruption revealed that CXCL12 and CXCR4 are essential for B cell development and colonization of bone marrow by hematopoietic stem cells and myeloid lineage cells during ontogeny as well as blood vessel formation in the gastrointestinal tract, cardiac ventricular septum formation, and cerebellar development. 11-13 CXCL12-CXCR4 chemokine signaling is essential for the development of plasmacytoid dendritic cells, which could rapidly produce a huge amount of type 1 IFN (α, β) following microbial stimulation. 14 This axis also plays a crucial role in the development of natural killer cells, which are generated from hematopoietic stem cells and play vital roles in the innate immune response against viral infection. 15 Thus, CXCL12-CXCR4 axis is widely involved in the development of immune cell. The concept of CXCL12 as being solely a constitutive chemokine was recently challenged by data from other groups that investigated immune-mediated inflammatory disorders and demonstrated its role in joint, lung, and liver inflammation. 16,17 Nanki et al. 18 showed that CXCL12 is highly expressed in the synovium of patients with rheumatoid arthritis (RA) in contrast to patients with osteoarthritis, and that anti-CD40 stimulation enhances CXCL12 production by cultured synoviocytes from RA patients. These investigators hypothesized that the CD40 ligand (CD154) expressed on activated memory T cells may stimulates the production of CXCL12 by synoviocytes and increases the migration of T cells.

**INVOLVEMENT OF CXCL12-CXCR4 AXIS IN THE PATHOPHYSIOLOGY OF IBD**

Mikami et al. 19 investigated the role of the CXCL12-CXCR4 axis in patents with IBD by analyzing CXCR4 expression on peripheral T cells. They demonstrated that CXCR4 expression on peripheral T cells in patients with active UC was significantly higher than that in inactive UC and controls. Moreover, CXCR4 expression was significantly correlated with disease activity in patients with UC. Hosomi et al. 20 focused on the role of immature plasma cells in the pathophysiology of IBD. They demonstrated that the proportion of immature plasma cells was positively correlated with clinical activities of UC and CD and the expression of...
CXCR3 and CXCR4 on immature plasma cells in UC patients was significantly higher than that in controls. In addition, Dotan et al.\textsuperscript{21} reported that CXCR4 was expressed by intestinal epithelial cells and LP cells and CXCR4-positive cells are significantly increased in the LP of IBD. Moreover, a recent report indicated that evaluation of CXCR4 expression on CD4 T cells by FACS analysis could be a biomarker of leukocytapheresis with a leukocyte removal filter (Cellsoba; Asahi Medical, Tokyo, Japan) (Fig. 1).\textsuperscript{22} These data strongly suggested that CXCR4-positive cells could be involved in the pathophysiology of IBD, particularly in UC.

**CELL PRODUCING CXCL12**

Dotan et al.\textsuperscript{21} reported that CXCL12 expression in normal intestinal mucosa was more limited to the surface epithelium, whereas expression was enhanced and more diffused in intestinal mucosa of IBD patients. Interestingly, this upregulation was specific to mucosa of IBD patients, and did not occur in non-IBD inflammatory conditions. Moreover, in patients with IBD, CXCL12 was significantly upregulated in the inflamed epithelium compared to the non-inflamed epithelium and stronger expression of CXCL12 in intestinal tissues was observed in patients with UC than in those with CD. Thus, this expression is likely to be more specific in active UC patients than in CD patients. Using CXCL12/green fluorescent protein knock-in approach, however, Mikami et al.\textsuperscript{19} observed that CXCL12-expressing cells were mainly observed in the perivascular sites of the normal colonic mucosa, suggesting that the CXCL12-expressing cells were morphologically considered to be pericytes (adjacent to the endothelial cell) but not epithelial cells. CXCL12 gene expression was strongly induced in mice with dextran sulfate sodium (DSS) induced-colitis, which is consistent with human IBD data reported by Dotan et al.\textsuperscript{21} (Fig. 2). Thus, further investigation is required to identify CXCL12-expressing cells in the intestinal mucosa under normal and pathogenic conditions.

**CXCL12-CXCR4 AXIS MAINLY INVOLVED IN THE PATHOPHYSIOLOGY OF UC**

Jourdan et al.\textsuperscript{23} reported that IL-4 (product of Th2 lymphocytes) induces surface CXCR4 expression on human T cells. On the other hand, CXCL12-CXCR4 signaling is associated with RA, in which IL-6 and TNF-\(\alpha\) (products of Th1 lymphocytes) are mainly involved. Fuss et al.\textsuperscript{24} reported that LP CD4+ T lymphocytes from UC patients produce both Th1 and Th2 cytokines. Taken together, these findings could contribute to an acute flare of UC and lead to the higher CXCR4 expression on peripheral T cells in UC patients in comparison with CD patients.
Fig. 2. (A) CXC chemokine ligand (CXCL)12 expression was analyzed in CXCL12/GFP knock-in mice before (left) and 10 days after dextran sulfate sodium (DSS) administration (right). At 10 days after DSS administration, the number of CXCL12-expressing cells was increased in the inflamed colonic mucosa compared with normal colonic tissues. (B) CXCL12mRNA expression in colonic tissue of normal and mice with DSS-induced colitis. Expression of CXCL12mRNA was significantly higher in the colonic tissue of mice with DSS-induced colitis than that of normal mice. Modified from Mikami et al.19 (Adapted with permission from The American Society for Pharmacology and Experimental Therapeutics).

Fig. 3. CXC chemokine ligand (CXCL)12-CXC chemokine receptor (CXCR)4 axis in the pathophysiology of IBD. TNF, tumor necrosis factor; IL, interleukin.

BLOCKADE OF CXCL12-CXCR4 SIGNALING AS FUTURE THERAPY FOR IBD

As mentioned above, the CXCL12-CXCR4 signaling axis may be strongly involved in the pathophysiology of IBD, particularly UC (Fig. 3). An important question is whether blocking the CXCL12-CXCR4 axis could be a potential therapy for IBD. Mikami et al demonstrated that the effect of a CXCR4 antagonist (TF14016) on colitis in mice with DSS-induced colitis and in IL-10 knockout (KO) models.19

As expected, CXCR4 expression on CD4-positive cells was significantly increased after the start of DSS administration, compared with normal mice and gene expression of CXCL12 was also significantly higher in the colonic tissue of mice with DSS-induced colitis than in that of normal mice. The effect of a CXCR4 antagonist (TF 14016) on DSS-induced colitis was evaluated. Administration of TF 14016 clinically and histologically attenuated intestinal inflammation of DSS-induced colitis. Immunohistochemical analysis revealed not only the improvement of colonic inflammation but also a reduction of lymphoid aggregation. They also investigated the effect of TF 14016 on cytokine production from mesenteric lymph node cells. Surprisingly, TF 14016 treatment reduced the production of pro-inflammatory cytokine such as TNF-α and IFN-γ but did not alter IL-10 production.

Why was IL-10 production not affected by TF 14016 treatment? TF 14016 administration did not alter the percentage of FOXP3+CD25+ T cells. This finding suggests that the ameliorating action of TF 14016 on
DSS-induced colitis is mainly due to its inhibitory effect of CD4+CD25− T cells with increased CXCR4 expression. TF 14016 treatment also ameliorated colonic inflammation in IL-10 KO mice.

**DEFINITION OF SR-PSOX/CXCL16**

SR-PSOX/CXCL16, a scavenger receptor that binds phosphatidylserine and oxidized lipoprotein, is a chemokine of the CXC family and its ligand is a CXCR6. CXCL6 is a membrane-bound chemokine domain with a mucin-like domain, transmembrane domain and an cytoplasmic domain. This structure is similar to that of fractakine/CX3CL1, which is another membrane-bound chemokine. After cleavage, soluble CXCL16 acts as a chemoattractant for activated CD8 T cells, NK T cells and Th-1 polarized T cells that express CXCR6. Cleavage is considered to be mediated by a disintegrin and metalloproteinase family protease, A disintegrin and metalloproteinase domain-containing protein 10. In the static state, SR-PSOX/CXCL16 is expressed in various lymphoid tissues including the thymus, spleen, lymph nodes and Peyer's patches, and in non-lymphoid tissues including the lung, liver, kidney and small intestine, but not colonic tissue. In general, CXCL16 is expressed on the surface of antigen-presenting cells (APCs), including subsets of CD19-positive B cells and CD14-positive monocytes/macrophages. Additionally, CXCL16 is expressed in cholangiocytes, sinusoidal endothelial cells, hepatocytes and epidermal keratinocytes. Thus, CXCL16 seems to have a role in the innate immune response in several organs.

Membrane-bound CXCL16 mediates adhesion and phagocytosis of both Gram-negative and Gram-positive bacteria, whereas soluble CXCL16 is a strong chemoattractant for CXCR6-positive T cells. Importantly, anti-CXCL16 antibodies, which suppress the chemotactic activity of CXCL16, significantly inhibit bacterial phagocytosis by human antigen presenting cells. Therefore, CXCL16 is considered to play a critical role in facilitating the uptake of various pathogens and the initiation of host defenses (Fig. 4). Little is known, however, about the role of CXCL16 in the pathophysiology of IBD.

**SR-PSOX/CXCL16 INVOLVED IN THE PATHOPHYSIOLOGY OF IBD**

Next we measured the serum SR-PSOX/CXCL16 levels in patients with IBD. The serum levels were significantly higher in patients with active CD and UC than in control subjects. Also, serum SR-PSOX/CXCL16 levels were significantly higher in patients with active CD and UC than in those with inactive CD and UC, respectively. The correlation among SR-PSOX/CXCL16, CRP and clinical activities in CD and UC, demonstrated that SR-PSOX/CXCL16 might be a more suit-

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**Fig. 4.** Role of CXC chemokine ligand (CXCL)16 in innate and acquired immunity. CXCR, CXC chemokine receptor; APC, antigen-presenting cell; TNF, tumor necrosis factor.
able marker of the disease activity of CD than of UC.\textsuperscript{32}

To confirm whether the serum CXCL16 level is a useful therapeutic biomarker, we evaluated changes in serum CXCL16 levels in patients with CD during granulocytapheresis (GMA) using an Adacolumn (Japan Immunoresearch Laboratories, Takasaki, Japan), which modulates the function of monocyte-derived dendritic cells by depleting both peripheral CD14\textsuperscript{+}CD16\textsuperscript{+} monocytes and CD16\textsuperscript{+} myeloid dendritic cells producing large amounts of TNF-\textalpha.\textsuperscript{33} Mean serum CXCL16 levels decreased significantly from 2.73 to 1.88 in CD patients that responded to GMA. This finding suggests that CXCL16 is a possible marker of the efficacy of GMA in patients with CD.\textsuperscript{34}

**ROLE OF CXCL16 IN EXPERIMENTAL COLITIS**

*In vivo* expression of SR-PSOX/CXCL16 in the DSS-induced colitis model was investigated. To examine whether the expression of SR-PSOX/CXCL16 increases in inflamed tissues, we analyzed the colonic tissues of mice with or without DSS-induced colitis. The gene expression of SR-PSOX/CXCL16 was significantly higher in colonic tissues of mice with DSS-induced colitis than in normal colon. SR-PSOX/CXCL16-expressing cells were markedly increased in the colonic tissues of mice with DSS-induced colitis compared with normal colons, and these cells were observed from the mucosae to the submucosa. Immunofluorescent studies revealed that SR-PSOX/CXCL16-expressing cells were mainly CD11b-positive cells (Fig. 5).\textsuperscript{32}

Previous reports demonstrated that several inflammatory cytokines including IFN-\gamma, TNF-\textalpha and IL-18 induce the expression of SR-PSOX/CXCL16.\textsuperscript{35,36} Thus, increased concentration of various inflammatory cytokines in the inflamed colonic mucosa might contribute to the enhanced expression of SR-PSOX/CXCL16 on macrophages.

**ROLE OF SR-PSOX/CXCL16 IN BOTH MACROPHAGE PHAGOCYTIC ACTIVITY AND CYTOKINE PRODUCTION**

We next focused on macrophages that play a critical role in the uptake of luminal antigens and examined the phagocytic ability of macrophages from SR-PSOX/CXCL16 KO and wild (WT) mice. Therefore, we examined phagocytosis and bacteria-stimulated-cytokine production in peritoneal macrophages from SR-PSOX/CXCL16 KO mice *in vitro*. Fluorescence microscopy showed that the uptake of *Esherichia coli* by macrophages from both SR-PSOX/CXCL16 KO mice and WT mice increased in a time-dependent manner. Measure-
ment of fluorescence intensity revealed that the fluorescence value was significantly lower from 60 to 120 min in SR-PSOX/CXCL16 KO macrophages than in WT macrophages. Thus, these findings clearly suggest that the phagocytic ability of the SR-PSOX/CXCL16 KO mice macrophages was impaired.32

**SR-PSOX/CXCL16 IS RELATED TO THE TH1 BUT NOT TH17 IMMUNE RESPONSE IN DSS-INDUCED COLITIS**

An interesting finding is that SR-PSOX/CXCL16 KO macrophages have an impaired ability to produce IL-12 in response to bacterial antigens (lipopolysaccharides and commensal bacteria), whereas their production of IL-6 was unaffected. Moreover, we measured cytokine production by mesenteric lymph node cells from both SR-PSOX/CXCL16 KO and WT mice with DSS-induced colitis. The production of IFN-γ on day 5 after DSS administration was significantly lower in SR-PSOX/CXCL16 KO mice than in WT mice. In contrast, the production of IL-17 did not differ significantly between SR-PSOX/CXCL16 KO and WT mice with DSS-induced colitis throughout the experiment.32 IL-6 is essential for the induction of Th17 cells37 and the lack of difference in IL-6 production by macrophages or IL-17 production by mesenteric lymph node cells between SR-PSOX/CXCL16 KO and WT mice suggests that SR-PSOX/CXCL16 is not involved in the Th17-mediated immune response. Taken together, our data indicate that SR-PSOX/CXCL16 plays a colitogenic role by enhancing the Th1 immune response. Thus, targeting SR-PSOX/CXCL16 seems to be an ideal target for the prevention of Th1-mediated colitis, without affecting the IL-17-mediated immune response.

![Fig. 6. Effect of SR-PSOX/CXCL16 monoclonal antibody on dextran sulfate sodium (DSS)-induced colitis. Representative histological findings and the scores of colonic inflammation on day 8. Modified from Uza et al.32 (Adapted with permission from British Society of Gastroenterology, H&E stain, ×100). IgG, immunoglobulin G.](image-url)
SR-PSOX/CXCL16 ANTIBODY TREATMENT AS A FUTURE THERAPY OF IBD

To assess the neutralizing effect of a mAb to SR-PSOX/CXCL16 in mice with colonic inflammation, we analyzed two experimental murine colitis models: DSS-induced colitis as an epithelial injury model and 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis as a Th1-mediated colitis model. The body weight of mice treated with SR-PSOX/CXCL16 monoclonal (mAb) was significantly higher than that of IgG-treated control mice. Furthermore, administration of SR-PSOX/CXCL16 mAb significantly attenuated the shortening of colonic length, and significantly reduced colonic damage and the colitis score of mice with DSS-induced colitis (Fig. 6). In TNBS-induced colitis, administration of SR-PSOX/CXCL16 mAb significantly ameliorated the body weight change compared to IgG-treated control mice. Also, the colitis score was significantly lower in SR-PSOX/CXCL16 mAb-treated mice than in control IgG-treated mice.

CONCLUSION

Chemokines control the movement of leukocytes and play important roles in the pathophysiology of several diseases. CXCL12 and CXCR4 have a constitutive and inflammatory roles in the intestinal mucosa. Data from several human and mouse studies strongly suggest that CXCL12-CXCR4 axis plays a crucial role in the pathophysiology of IBD, especially UC. On the other hand, SR-PSOX/CXCL16 has a significant role in the pathophysiology of CD. The present data provide new insight into the etiology of IBD and suggest that manipulation of these chemokines has potential therapeutic value.

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