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Role of Interferon-γ-Inducible Protein (IP)-10/ (IP-10/CXCL10) in Ulcerative Colitis; A Review of the Present Status

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1. Introduction

Ulcerative colitis (UC) is a chronic, relapsing inflammatory bowel disease (IBD) affecting the colonic mucosa; it is of unknown etiology (Baumgart & Carding, 2007). UC clinically displays bloody diarrhea, abdominal pain and weight loss, and often leads to a severe outcome since the therapeutic approaches, including corticosteroid and 5-aminosalicylic acid, are not always successful in inducing long-term remission (Baumgart & Sandborn, 2007). Although the incidence of UC varies from 1 to 15 per 100,000 population in different locations, it increases year by year. Moreover, UC generally acts upon young people, and approximately 30% of patients with UC will undergo colectomy in the course of their life-times (Stewenius et al., 1996). Thus, UC is a serious disease affecting the quality of life for a long period.

It is now considered that IBD is not a simple inflammatory disease but a rather complicated disorder of intestinal components including epithelial cells, immune cells, neural cells, and extracellular matrix. Particular types of microbes, environmental factors including sanitary conditions and food, and genetic factors are also suggested to be involved (Xavier & Podolsky, 2007; Kaser et al., 2010;Asakura & Suzuki, 2010). Global approaches are therefore needed to reveal the pathogenesis of IBD, and to develop new therapeutic approaches for IBD as well.

Chemokines have taken great attention since their discovery, because this family of chemotactic cytokines is intimately involved in the pathogenesis of many important human diseases. Developing new therapeutic approaches targeting several chemokines have been tried (Viola & Luster, 2008).

In this chapter, we will review the role of interferon-γ-inducible protein (IP)-10 (IP-10/CXCL10) in the colon of normal condition and UC, introducing our recent findings about the effect of neutralization of IP-10 on animal models of UC. We also discuss about the possibility of clinical application of antagonist therapies targeting IP-10.

2. Chemokines and chemokine receptors

Chemokines are small 8-12 kDa proteins with 20 to 70 percent homology in amino acid sequence, are relatively resistant to inactivation, and have a long half-life in vivo (Rossi &

Zlotnik, 2000). They can direct the recruitment and migration of circulating leukocytes and play a critical role in the differentiation of secondary lymphoid organs. At present approximately 50 chemokines and 20 chemokine receptors are known. The chemokine system is characterized by redundancy (Mantovani,1999). A single chemokine can interact with several different chemokine receptors and a single chemokine receptor can respond to multiple chemokines. No chemokine is uniquely active on one leukocyte population, and usually a given leukocyte population has receptors for and responds to different molecules.

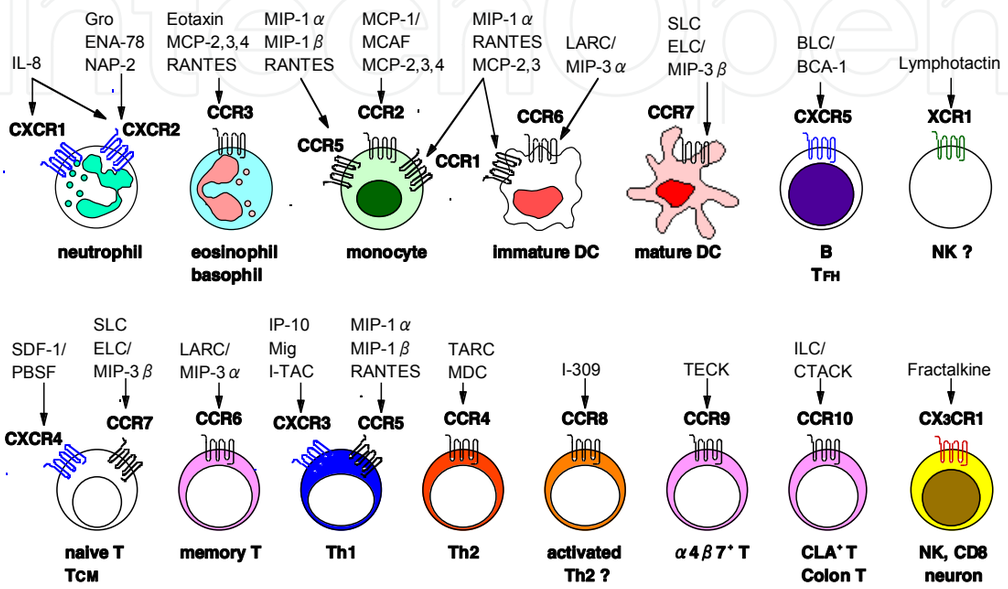


Fig. 1. Chemokines and chemokine receptors

Chemokines are classified into four families on the basis of the pattern of the first two of four cysteine residues of the ligands (Rossi & Zlotnik, 2000). The CXC family (α chemokine) has two cysteine residues separated by a non-cysteine amino acid. The CC family (β chemokine) contains two adjacent cysteine residues. The CX3C family (γ chemokine) has two cysteine residues separated by three non-cysteine amino acids, whereas the C family (δ chemokine) has only one cysteine residue.

Chemokine receptors are G-protein-coupled receptors possessing a seven transmembrane domain that upon binding to calcium influx and activation of several downstream targets including the PI3 kinase pathway (Rossi & Zlotnik, 2000). Based on the chemokine class they bind, the receptors have been named CXCR1, 2, 3, 4 and 5 (bind CXC chemokines); CCR1 through CCR10 (bind CC chemokines); XCR1 (binds the C chemokine, Lymphotactin); and CX3CR1 (binds the CX3C chemokine, fractalkine or neurotactin).

Schematically, CXC chemokines are active on polymorphonuclear neutrophis (PMNs) and T and B cells. IL-8 is a typical CXC chemokine that acts on PMNs. An essential structural element of CXC chemokine for neutrophil activation is a Glu-Leu-Arg (ELR) motif in the 5'-structure of the protein. Thus CXC chemokines are divided into two groups; ELR motif chemokine and non-ELR motif chemokine. In contrast, CC chemokines exert their action on multiple leukocyte subtypes, including monocytes, basophils, eosinophils, T cells, dendritic cells and natural killer (NK) cells, but they are generally inactive on PMNs. The representative CC chemokines, eotaxins, are active selectively on eosinophils and basophils.

Lymphotactin is a C chemokine, and fractalkine is a CX3C chemokine. They both act on T cells and NK cells, and fractalkine is also active on monocytes.
Thus chemokines facilitate leukocyte migration and positioning to sites of tissue damage as well as other process such as angiogenesis and leukocyte degradation (Mackay, 2001). Chemokines and their receptors also important in dendritic cell maturation, B and T cell development, Th1 and Th2 responses, infections, angiogenesis, wound healing and tumor growth as well as metastasis (Rossi & Zlotnik, 2000).
Chemokines can be divided into two categories: inducible inflammatory chemokines are produced by activated cells and recruit leukocytes in response to physiological stress, whereas homeostatic chemokines are constitutively produced and involved in maintaining basal leukocyte trafficking as well as the architecture of secondary lymphoid organs (Gerard & Rollins, 2001).
Recent advance of clinical and basic research have revealed that several diseases are associated with inappropriate activation of the chemokine-chemokine receptor network, and they include cardiovascular disease, allergic inflammatory disease, transplantation, neuroinflammation, cancer and HIV-associated disease (Gerard, & Rollins, 2001).
Unlike cytokines, which have pleiotropic effects, chemokines target specific leukocyte subsets and, in some settings, may only attract these cells without activating them. Antagonism of a single chemokine ligand or receptor would be expected to have a relatively circumscribed effect, thereby endowing the antagonism with a limited side effect profile (Gerard & Rollins, 2001; Viola & Luster, 2008; Nishimura et al., 2009).

Type of inflammation	Main target cells	Chemokine	Chemokine receptor
Acute inflammation	Neutrophil Monocyte	CXCL1 (GROα), CXCL2 (GROβ), CXCL8 (IL-8) CCL2 (MCP-1)	CXCR2, CXCR1 CCR2
Th1–type inflammation	Monocyte Th1 cell $CD8^+$ T cell B cell	CCL2 (MCP-1), CCL4 (MIP-1β),CCL5 (RANTES), CX3CL1(Fractalkine) CXCL9 (Mig), CXCL10 (IP-10), CXCL11 (I-TAC) CCL3 (MIP-1αS), CCL4 (MIP-1β), CXCL9 (Mig), CXCL10 (IP-10) CXCL13 (BCA-1)	CCR2, CCR5, CCR1, CCR3, CX3CR1 CXCR3 CCR5, CCR1, CXCR3 CXCR5
Th2-type inflammation	Th2 cell Eosinophil Mast cell B cell	CCL17 (TARC), CCL22 (MDC), CCL1 (I-309) CCL11 (Eotaxin), CCL26 (Eotaxin-3) CCL2 (MCP-1), CCL11 (Eotaxin), CXCL10 (IP-10) CXCL13 (BCA-1)	CCR4, CCR8 CCR3 CCR2, CCR3, CXCR3 CXCR5
Th17- type inflammation	Th17, DC	CCL20 (MIP-3α)	CCR6

* modified from Viola & Luster, 2008

Table 1. The type of inflammation and chemokine/chemokine receptor system

3. Interferon-γ-inducible protein (IP)-10 and its receptor CXCR3

Luster et al. initially identified human IFN-γ-inducible protein of 10 kDa (IP-10/CXCL10) as an early response gene induced by IFN-γ in U937 cells (a monocyte-like cell line) (Luster et al, 1985). IP-10 is secreted by a diverse range of tissue under proinflammatory conditions (Nevelle et al., 1997; Farber, 1997). It is a key mediator of the interferon response, preferentially attracts activated Th1 lymphocytes to sites of inflammation, and is an inhibitor of angiogenesis (Taub et al., 1993). IP-10 is constitutively expressed at low levels in thymic, splenic, and lymph node stroma. However, its expression can be highly induced in endothelial cells, keratinocytes, fibroblasts mesangial cells, astrocytes, monocytes, and neutrophils by stimulation with IFN-α, IFN-β, IFN-γ, or LPS and in T cells by antigen activation.

Dufour et al. have generated mice deficient in IP-10 by targeted gene deletion mutagenesis (Dufour et al., 2002). IP-10$^{-/-}$ mice showed no overt developmental or morphological abnormalities, and fertile. Immunophenotyping of leukocyte subsets were similar between wild-type and IP-10$^{-/-}$ mice. In contrast, immunological analysis revealed a role for IP-10 in both the generation of effector T cells and their delivery to sites of tissue inflammation.

Although described above chemokines and chemokine receptors are redundant in their action on target cells (Mantovani, 1999), IP-10 is somewhat atypical, in that it specifically activates a single receptor, CXCR3 (Loetscher et al., 1996). While CXCR3 binds two other interferon-γ-induced, angiostatic CXC chemokines: monokine induced by interferon-γ (Mig:CXCL9) and interferon-inducible T cell α chemoattractant (I-TAC; CXCL11) (Loetscher et al, 1996; Cole et al.,1998), it is becoming clear that they exhibit unique expression patterns in vivo, and several data support the concept that these three chemokines may have nonredundant function in vivo (Dufour et al., 2002; Khan et al, 2000). Crystal structures of IP-10 revealed that IP-10 's action may involve oligomerization of the protein, and that IP-10 shares the ability to bind to cell surface glycosaminoglycan (GAGs) with most, if not all, chemokines (Swaminathan et al.,2003; Luster et al., 1995). Chemokine-GAG interactions can promote chemokine oligomerization (Hoogewerf et al., 1997)), and the formation of immobilized chemokine gradients (Tanaka et al.,1993) , which are likely to be important for chemokine action.

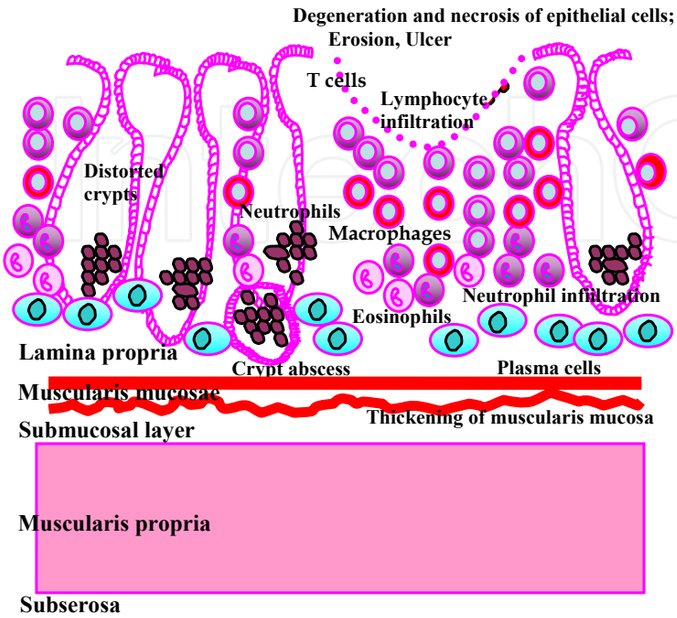
It has been reported that the expression of IP-10 was elevated in several diseases such as UC (Uguccioni et al., 1999), hepatitis (Narumi et al, 1998), multiple slcerosis (Sorensen et al., 2002), and Sjoegren's syndrome (Ogawa et al., 2002), suggesting the involvement of IP-10 in the development of these diseases.

4. IP-10 and other chemokines in ulcerative colitis

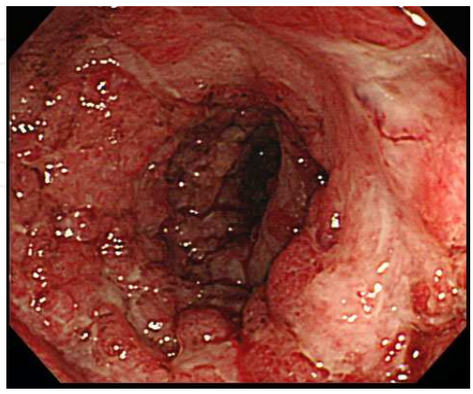
UC is a chronic relapsing disease of unknown etiology with a prominent leukocyte infiltrate, which is confined to the mucosa and submucosa of the colon and contributes largely to the tissue damage (Baumgart & Carding, 2007; Xavier & Podolsky, 2007). The disease usually involves the rectum and extends proximally to involve all or part of the colon (Baumgart & Sandborn, 2007). Proximal spread occurs in continuity without areas of uninvolved mucosa. The affected regions exhibit a mixture of acute and chronic inflammatory aspects accompanied by massive infiltration of macrophages, neutrophils, eosinophils, T cells, and plasma cells. The neutrophils invade the epithelium, usually in the crypts, giving rise to cryptitis and, ultimately, to crypt abscess. The following two major histological findings suggest chronicity of UC (Friedman & Blumberg, 2010). The first is basal plasma cytosis; multiple basal lymphoid aggregates are observed in some patients. The second is the distorted crypt architecture of the colon; crypts may be bifid and reduced in number, often with a gap between the crypt bases and the muscularis mucosae. The immune system seems to be shifted to atypical Th2 dominance, with coexistence of Th1 response.

The recruitment and activation of leukocytes in inflamed tissues is a complex process driven by chemokines and possibly other attractants that induces cell adhesion and locomotion (Luster, 1998). Chemokines may play a central role in UC because chemokines are relatively resitant to inactivation in vivo, compared with other chemoattractants such as leukotriene B4, *N*-formyl-methionyl-leucyl-phenylalanin, and peptide activating factor, which have shorter half-lives (MacDermott et al., 1998). Furthermore, chemokines are produced by a wide variety of different cell types after stimulation by proinflammatory cytokines. The

ability of chemokines to activate cells to produce destructive molecules also makes them excellent candidates to be involved in the perpetuation of UC (MacDermott et al., 1998).



(a) Histological hallmarks of ulcerative colitis. Massive cellular infiltraion is confined to mucosa and submucosa. Infiltrates are neutrophils, macrophages, eosinophils, T cells, and plasma cells. Distorted crypt architecture and basal plasma cytosis are the two pathognomonic findings of chronicity of UC.



(b) Endoscopic picture of ulcerative colitis. In severe ulcerative colitis, macroulceration, occasionally deep, with mucopurulent exudate, pseudopolyposis, and spontaneous hemorrhage are seen.

Fig. 2. Histological features and endoscopic findings of ulcerative colitis

Studies have demonstrated that IL-8, MCP-1, and ENA-78 are highly expressed in the intestinal mucosa in areas of UC as well as Crohn disease. Neutrophils and macrophages in the inflamed intestine synthesize and secrete large amounts of chemokines in patients with UC. Increased chemokine expression has also been observed in colonic epithelial cells, endothelial cells and smooth muscle cells (MacDermott, 1999).
Several studies have reported increased expression of IP-10 in the mucosa of patients with UC and pouchitis (Uguccioni, 1999; Helwig, 2004; Autschbach, 2002; Grimm & Doe, 1996). However, there is a controversy about the source of IP-10 in the colonic mucosa; whether epithelial cells or immune cells. Generally, IP-10 is secreted by neutrophils, monocytes, fibroblasts, keratinocytes, dendritic cells, and epithelial cells. Dwinell et al. and Shibahara et al. have reported that human intestinal epithelial cell lines produce chemoattractants including IP-10 for IEL, and such chemokine production is regulated by proinflammatory cytokines such as IFN-γ (Dwinell et al., 2001, Shibahara et al., 2001). Intestinal subepithelial myofibroblasts have been also reported to produce IP-10 (Inatomi et al., 2005).

5. IP-10 in animal models of IBD

Mechanistic studies of IBD are difficult to perform in humans, hence animal models have been developed to analyse and develop new therapeutic approaches.

IL-10$^{-/-}$ mice spontaneously develop colitis at ~ 3 months of age (Kuhn et al., 1993). This murine disease is similar to that seen in human Crohn disease with small intestine and colon disease localization, chronic mucosal inflammation, alterations in mucosal architecture, bowel-wall thickening, and a chronic progressive disease course. However, this murine model differs from human Crohn disease, because colitis in IL-10$^{-/-}$ mice does not yield focal granulomatous, or transmural inflammation.

Singh et al. administered rabbit anti-IP-10 polyclonal IgG antibody to IL-10$^{-/-}$ mice by i.p. injection every 3 days at the onset of asymptomatic colitis (Singh, U.P. et al., 2003). They monitored serum amyloid A protein and IL-6 levels every other week, and determined the onset. mRNA expression analysis shows upregulated IP-10 and CXCR3 in the inflamed colon of IL-10$^{-/-}$ mouse, while IP-10 is predominantly expressed in the mesenteric lymph nodes (MLNs). Neutralization of IP-10 ameliorated the severity of colitis along with decrease of SAA and several inflammatory cytokines. In their additional report, they showed that IP-10 is largely produced by CD4^{+} T cells in the mesenteric lymph nodes and lamina propria during colitis, and that IP-10 blockade decreased the number of CD4^{+} CXCL10^{+} cells in MLNs and lamina propria of IL10$^{-/-}$ mice (Singh et al., 2007). These results suggest intestinal inflammation is driven by the presence of CD4^{+} CXCR3^{+} T cells and cells that produce IP-10.

In confirmation, Hyun et al. have shown that anti-IP-10 antibody treatment can mitigate colitis in IL-10$^{-/-}$ mice through decreased trafficking of Th1 cells (Hyun et al, 2007) , with administration of hamster antimurine CXCL10 monoclonal antibody (1F11). They also revealed that CXCL10 blockade specifically decreased recruitment of transferred Th1 cells into MLNs and colon of IL-10$^{-/-}$ mice. These data suggest that IP-10/CXCL10 plays a dual role in colitis development by enhancing Th1 cell generation in inductive sites (MLNs) and promoting effector cell recruitment to inflamed tissue (effector sites; colon).

6. Our recent findings about IP-10

IBD consists of two major forms: UC and Crohn disease. Crohn disease is suggested to be mediated by Th1/Th17-associated cytokines such as IL-23, IL-12, IL-17, and IFN-γ that are overproduced by macrophages and Th1/Th17 cells of the intestine (Strober & Fuss, 2011). Th17 cells are important in host defense against bacterial and fungal infections, in particular at mucosal surfaces (Ouyang, W. et al., 2008). Among many IBD animal models, colitis observed in both IL-10$^{-/-}$ mice and Rag2$^{-/-}$ mice reconstituted with CD4^{+}CD45RB^{high}T cells has been characterized as a Th1/Th17-dependent disease, mimicking Crohn disease.

In contrast, Th2-cytokines have been linked to UC, and UC is regarded as an atypical Th2 disease with coexistence of Th1 type (Strober & Fuss, 2011). Okayasu et al. have reported a murine colitis model induced by administration of dextran sulphate sodium (DSS) as a model for UC (Okayasu et al., 1990). Additionally, we have esatablished a new chronic colitis using murine AIDS virus, which we termed MAIDS colitis, as a UC model (Suzuki et al.,1997).

Thus, to reveal the involvement of IP-10 in pathophysiology of UC, these two animal models; DSS colitis and MAIDS colitis, are ideal for mechanistic study using neutralizing anti-IP-10 antibody.

6.1 Blockade of IP-10 ameliorated acute colitis and enhances crypt cell survival

We have revealed that the endogenously produced chemokine IP-10 regulates crypt cell proliferation (Sasaki et al., 2002). IP-10 was constitutively expressed by basal crypts in

normal mouse colon, but the expression of IP-10 as well as CXCR3 was enhanced in the proliferative zone during acute phase of the colitis after oral administration of DSS. Neutralization of IP-10 with mouse monoclonal anti-IP-10 antibody protected mice from epithelial ulceration by promoting crypt cell survival without evidence of altered immune cell infiltration. Furthermore, recombinant IP-10 administration into normal mice inhibited intestinal epithelial cell proliferation. These findings suggest that IP-10 negatively regulates crypt cell growth to maintain intestinal homeostasis in an acute DSS colitis by enhancing crypt cell survival.

Besides colonic crypt epithelial cells, IP-10 is also active on non-leukocytes/T cells such as endothelial cells and fibroblasts. Campanella et al. have recently reported that IP-10 can inhibit endothelial proliferation through a CXCR3-independent mechanism (Campanella et al., 2010). They speculate that the ability of IP-10 to inhibit endothelial cell proliferation is more associated with its binding to glycosaminoglycans than its binding to CXCR3.

We should further reveal the exact molecular mechanism how IP-10 could down regulate crypt cell proliferation.

6.2 Blockade of IP-10 ameliorated pancreatitis-like injury of mice with MAIDS

The LP-BM5 murine leukemia virus (MuLV) is a retrovirus that is known to induce profound immunodeficiency with splenomegaly and generalized lymphadenopathy in susceptible strains of mice, and occasionally brings about lymphoid malignancy (Mosier et al., 1985). Resembling the severe immunodeficiency with human acquired immunodeficiency syndrome (AIDS), the virus-infected mice have been studied as a mouse model of AIDS, termed murine AIDS (MAIDS) (Jolicoeur 1991). Based on the findings that systemic exocrinopathy resembling Sjoegren's syndrome was induced in salivary glands and lacrimal glands as well as in the pancreas, we proposed that MAIDS mice could be an animal model for Sjoegren's syndrome as well as AIDS (Suzuki et al., 1993). The pancreas-infiltrating cells comprise both Th1 and Th2 type $CD4^+$ T cells, although with a predominance of Th2 over Th1. Thus, the pancreatic lesions of MAIDS mice have some similarities to autoimmune-related chronic pancreatitis, especially the lesions associated with Sjoegren's syndrome (Watanabe et al., 2003).

We administered anti-IP-10 monoclonal antibody to MAIDS mice, and showed that anti-IP-10 administration ameliorated the pancreatic lesions by blocking the cellular infiltration of $CD4^+$ T cells and IFN-γ^+ Mac-1^+ cells into the pancreas (Kawauchi et al., 2006).

6.3 Blockade of IP-10 ameliorated MAIDS colitis

Systemic exocrinopathy resembling Sjoegren's syndrome and autoimmune pancreatitis-like pancreatic lesions were induced in mice with MAIDS, but colitis was not observed in MAIDS mice (Suzuki et al., 1993). In contrast, nude mice inoculated with lymph node cells from mice with MAIDS developed chronic inflammatory bowel disease-like colitis, which we termed MAIDS colitis (Suzuki et al., 1997). The precise mechanism of pathogenesis of the colitis remains largely unknown, however, regulatory T cells (Treg) deficiency might play a role in its development because there are some reports of colitis modulated by Treg (Izcue et al., 2006). We demonstrated that the pathological lesions of MAIDS colitis resembled ulcerative colitis and that the major populations of colon-infiltrating cells in MAIDS colitis were $Mac1^+$ macrophages and $CD4^+$ T cells with polarized immune responses toward Th2 (Suriki et al., 2000). Thus, MAIDS colitis could serve as an animal model for UC.

Using our MAIDS colitis, we examined the effect of IP-10 blockade (Suzuki et al., 2007). Anti-IP-10 antibody treatment reduced the number of colon infiltrating cells when compared to those mice given a control antibody. The treatment made the length of the crypt of the colon greater than control antibody. The number of $Ki67^+$ proliferating epithelial cells was increased by the anti-IP-10 antibody treatment. Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labelling $(TUNEL)^+$ apoptotic cells were observed in the epithelial cells of the luminal tops of crypts in control MAIDS colitis, whereas $TUNEL^+$ apoptotic epithelial cells were rarely observed with anti-IP-10 antibody treatment. In summary, blockade of IP-10 attenuated MAIDS colitis through blocking cellular trafficking and protecting intestinal epithelial cells, suggesting that IP-10 plays a key role in the development of UC as well as in chronic MAIDS colitis.

6.4 Our hypothesis of the role of IP-10 in UC, and theoretical therapeutic approach

From our research findings about blockade of IP-10 for UC animal models, we propose the hypothesis of the role of IP-10 in UC as follows (Fig. 3.).

In normal condition, naive T cells are activated by dendritic cells through IP-10 in mesenteric lymph nodes (inductive site) where they immediately express CXCR3 and differentiate into Th1 effector cells. IP-10 is constitutively expressed in normal colon, and promotes colonic recruitment of Th1 cells from blood vessels (Fig. 3a). Colonic epithelial cell regeneration and proliferation are regulated by a net balance between positive regulating factors and negative regulating factors (Podolsky, 1999). Several growth factors such as epidermal growth factor (EGF), keratinocyte growth factor (KGF), and hepatocyte growth factor (HGF) are typical positive regulating factors for intestinal epithelial proliferation and regeneration. They are secreted from both the local epithelial cells and the mesenchymal cells. In contrast, TGF-β is a typical negative regulator which inhibit proliferation of intestinal epithelial cells. Additionally, as we described above, we found that IP-10 is another negative regulator of crypt epithelial proliferation (Sasaki et al., 2002). In normal intestine, the net balance between these two factors is well balanced, and normal intestinal epithelial renewing is maintained (Fig. 3a).

In UC, IP-10 production is increased in both the mesenteric lymph nodes and the diseased colon, and more Th1 cells are differentiated and recruited into the effector site of colon (Fig. 3b). In the colon of patients with UC, IP-10, a negative regulator for epithelial proliferation, is relatively over produced against positive regulators such as HGF (Fig. 3b). We have reported previously that intrinsic HGF is over produced in the colon of mice with DSS colitis (Hanawa, et al., 2006). In UC, net balance between positive and negative regulators are shifted toward negative ones, and colonic epithelial proliferation and regeneration are inhibited (Fig. 3b).

Thus IP-10 plays two roles in the pathophysiology of UC: First, IP-10 is a chemokine which differentiates naive T cells into Th1 cells, and recruits them into the inflamed colon. Second, it is a negative regulator for intestinal epithelial proliferation and regeneration (Fig. 3b).

Therefore, theoretically, blocking IP-10 is an ideal therapeutic approach for UC as we reported using two mouse models (Sasaki et al., 2002; Suzuki et al., 2007).

We think that blockade of IP-10 promotes crypt epithelial cell proliferation and regeneration as well as inhibiting differentiation of Th1 cells and their trafficking into the diseased colon (Fig. 3c).

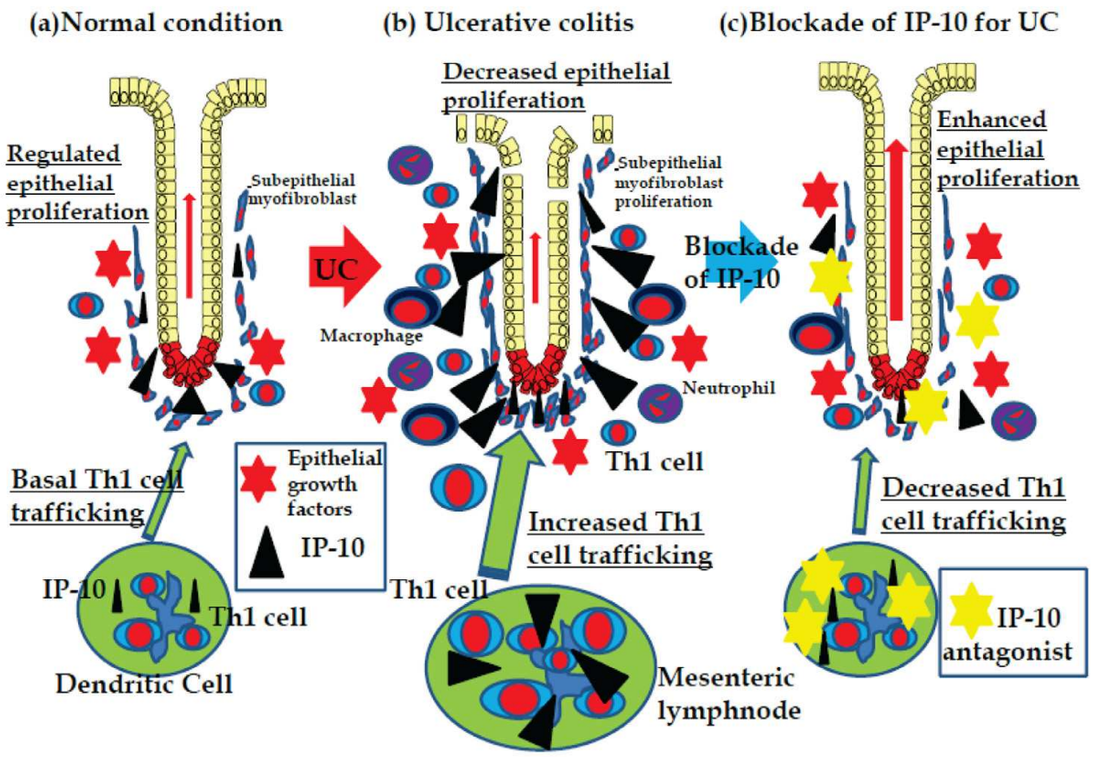


Fig. 3. Our hypothesis of the role of IP-10 in UC, and IP-10 blockade for UC therapy

CXCR3 is a receptor for IP-10, and IP-10/CXCR3 axis plays a critical role in pathophysiology in several diseases including IBD (Singh et al., 2007; Groom & Luster, 2011).
Several clinical trials using CXCR 3 antagonists are now under investigation for psoriasis, rheumatoid arthritis, and nephritis (Singh et al., 2007).
CXCR3 respond not only for IP-10, but also for Mig and I-TAC. In addition, IP-10 exerts its effects through at least two systems such as CXCR3 and CXCR3-independent mechanism (Campanella et al., 2010).
Therefore, we think that blockade of IP-10 using anti-human-IP-10 monoclonal antibody is a realistic strategy for the development of a new therapy targeting IP-10 for UC.

7. Application of antagonist therapies targeting IP-10 for UC

Chemokine and chemokine receptors are central to the inflammatory process and are attractive therapeutic targets. Several approaches are being pursued simultaneously, including antibodies to chemokines or their receptors, small molecule inhibitors of chemokine receptors modified chemokine antagonists, and inhibitors of chemokine presentation or higher-order structure (Viola & Luster, 2008). Schall and Proudfoot propose that inappropriate target selection and ineffective dosing, not the 'redundancy' of the chemokine system, are the main barriers to the use of chemokine receptor antagonists as anti-inflammatory therapies (Schall & Proudfoot, 2011).
Recently, Phase 2, multi-dose, double-blind, placebo-controlled, randomized, multicenter study of MDX-1100 (anti-CXCL10 human monoclonal antibody) has been completed for patients with moderately-to-severely active UC (ClinicalTrials.gov Web;

http://www.clinicaltrials.gov/ct2/show/NCT00656890?term=MDX-1100&rank=2).
We are looking forward to seeing all the data about this proof-of-concept study.

8. Conclusion

As shown in this review, several important clinical and experimental data suggest that IP-10 plays a critical role in the pathophysiology in UC, and it is an attractive therapeutic target. IP-10 is unique not only for its chemoattractant feature for activated Th1 cells, but also for its negative regulator activity for crypt epithelial cell cycle. Regulation of IP-10 could become a novel therapeutic approach for UC, which has both anti-inflammatory feature and facilitating ability of crypt epithelial cell regeneration.

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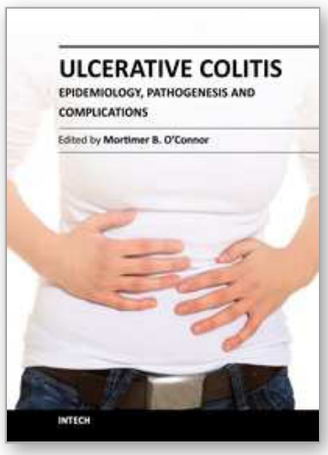

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This book is intended to act as an up-to-date reference point and knowledge developer for all readers interested in the area of gastroenterology and in particular, Ulcerative Colitis. All authors of the chapters are experts in their fields of publication, and deserve individual credit and praise for their contributions to the world of Ulcerative Colitis. We hope that you will find this publication informative, stimulating, and a reference point for the area of Ulcerative colitis as we move forward in our understanding of the field of medicine.

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