MIG in Crohn’s disease

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Abstract

High levels of chemokine (C-X-C motif) receptor (CXCR)3 and monokine induced by interferon (IFN)-γ (MIG) expression were revealed in the intestinal mucosa of mice with experimental colitis, and in lymphocytes, macrophages and epithelial cells of patients with Crohn’s disease (CD). CXCR3 and its chemokines expression were induced by IFN-γ in epithelial intestinal cells. These chemokines are involved in the recruitment of granulocytes and mononuclear cells, therefore in the maintenance of inflammation in CD. Serum MIG levels reflect CD disease activity, and it could be a marker for the responsiveness of patients to treatments. Efforts have been made to block MIG or CXCR3 in CD as a potential therapy of CD. Clin Ter 2019; 170(3):e206-210. doi: 10.7417/CT.2019.2134

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Introduction

MIG, and CXCR3

Chemokine (C-X-C motif) receptor (CXCR)3 is a receptor of the CXC chemokines family. It is a Gαi protein-coupled receptor that exists in two isoforms: CXCR3-A and CXCR3-B. These receptors bind CXC chemokines, monokine induced by interferon (IFN)-γ (MIG)/CXC chemokine ligand 9 (CXCL9), IFN-γ-inducible protein 10 (IP-10)/CXCL10 and IFN-inducible T-cell α chemoattractant (I-TAC)/CXCL11, instead CXCL4 is only binded by CXCR3-B (1).

Different cells, such as activated T lymphocytes and Natural Killer (NK) cells, some epithelial and endothelial cells express CXCR3, that is highly expressed on Type-1 helper (Th1) cells, as the chemokine (C-C motif) receptor (CCR)5.

Th1 cells are attracted by chemokines MIG, IP-10 and I-TAC which are released in the inflammatory lesions by local cells; this process sustained the central role played by CXCR3 and its ligands in the recruitment of inflammatory cells (2).

MIG, IP-10 and I-TAC are strongly correlated and their genes are all located on human chromosome 4. IFN-γ induces MIG that is a T-cell chemoattractant (3, 4).

High circulating levels of MIG could be considered as a marker of a host orientated Th1-immune response (5, 6).

IFN-γ, and tumor necrosis factor (TNF)-α, released by Th1 lymphocytes, stimulate several cells to produce MIG in the inflamed site that recruit other Th1 lymphocytes; this cause an amplification feedback loop (5, 6). An increased tissue expression, and high circulating levels, of MIG, and other Th1 chemokines, were observed in different organ specific autoimmune diseases [like autoimmune thyroiditis (7-13), Graves’ disease (14, 15) Graves’ ophthalmopathy (16-20), type 1 diabetes (21-25)], or systemic rheumatological disorders [like rheumatoid arthritis (26), systemic lupus erythematosus (27-29), systemic sclerosis (30-35), psoriasis or psoriatic arthritis (36-39), sarcoidosis (40-42), HCV-related cryoglobulinemia (43-46), other HCV immune mediated disorders (11, 47-54), other disorders, and also in cancers (55-72).

Crohn disease

Crohn’s disease (CD) is a type of inflammatory bowel disease (IBD). Any part of the gastrointestinal tract from mouth to anus can be affected by this regional enteritis (73). CD can occur at any age even if the usual onset is between 15 and 30 years. The initial symptom of CD is abdominal pain that can be accompanied by diarrhea. The diarrhea may or may not be bloody. Watery feces in large-volume are typically of the ileitis, while a smaller volume of feces are observed in colitis. In areas of the bowel with stenoses this pain is often most severe and stenosis from small bowel obstruction can cause persistent vomiting and nausea. Inflammation, fistulization or abscess around the anal area, anal fissure, or perianal skin tags can cause perianal discomfort (74, 75). Growth failure, frequent among children, fever and malabsorption of carbohydrates or lipids, which can induce weight loss, are various systemic symptoms of CD. Uveitis, episcleritis, gallstones, rheumatologic diseases, etc. are some
of the disorders associated with this disease which can also affect many other organ systems (74, 76). The diagnosis of CD is particularly difficult in the small bowel, while a colonoscopy can be effective in approximately 70% of the diagnoses. The capsule endoscopy is a support in endoscopic diagnosis. The lesions of CD are usually characterized from the presence of the multinucleated giant cells (74, 76).

Until now there is no cure for CD, remission may not be possible, or if it’s possible, it could be prolonged. Relapse can be prevented by medications, lifestyle and changes of dietary and eating habits (eating smaller amounts more often), reduction of stress, moderate activity and exercise can be used to control the symptoms (77, 78).

In the acute phase, treatment with antibiotics are used to control infections, moreover medications, as aminosalicylate, anti-inflammatory drugs and corticosteroids, are used to reduce inflammation (79, 80). CD is a primary T cell autoimmune disorder; though the exact cause is not known, probably an overactive Th1 cells and Th17 cytokine response are involved (81-84).

The objective of this narrative review is to study the role of MIG in CD. The presentation of data has been reported according to the International Narrative Systematic Assessment tool (85).

MIG in Crohn’s disease

Crohn’s disease is closely associated with Th1 cells that secrete IFN-γ. At sites of inflammation of CD, IP-10, MIG, and CXCR3 are expressed. The effects of IP-10, MIG, I-TAC, and CXCR3+ T cells on mucosal immune response were studied to understand the role of CXCR3 interactions during CD.

Antigen-specific serum and mucosal antibodies were significantly increased by IP-10, MIG, and I-TAC, through Th1-mediated events and CD28 modulation.

A study was conducted to investigate if MIG, IP-10, I-TAC are expressed by the eosinophils in CD. As shown by quantitative reverse transcriptase-polymerase chain reaction, a rapid and sustained gene expression of MIG, IP-10, and I-TAC were induced by IFN-γ in eosinophils. After incubation with IFN-γ MIG and IP-10 were released by eosinophils. The production of MIG and IP-10 induced by IFN-γ was increased by TNF-α, but not by interleukin (IL)-1β. On the contrary, the synthesis of MIG and IP-10 induced by IFN-γ was down-regulated after the addition of the Th2 cytokine IL-4. Immunohistochemistry detected the presence of MIG in eosinophils obtained from the lesions of this disease. These results demonstrated that eosinophils have an immunoregulatory role during the course of CD in association with a Th1-polarized inflammation (87).

The role of these chemokines and their receptor, in patients with ulcerative colitis (UC), CD, and normal controls, was investigated from another study. Flow cytometry showed a full size CXCR3 mRNA (FS) expression, in CD+ peripheral blood lymphocytes (PBL) from controls and UC; while high mRNA expression of the spliced variant CXCR3 (TV) was detected in CD+ PBL from CD patients. Moreover, an increased chemokine expression and production was observed in colonic biopsies and serum from CD, compared to UC patients. Proinflammatory cytokines stimulated the epithelial cells to produce chemokines. These results demonstrated that a spliced variant of the CXCR3 receptor is expressed by PBL of CD patients and suggested that the colonic epithelial cells have a role in T-lymphocyte migration in intestinal inflammation (88).

The gene expression in colonic biopsies of active and inactive IBD was evaluated in patients with UC, and CD, from another study (89). Among the upregulated genes there were the chemokine IP-10 and its receptor CXCR3. On colonic biopsies (n = 133), obtained from patients with IBD, was made a microarray gene expression analysis. In biopsies from active UC and CD were found higher levels of IP-10 and CXCR3 mRNA, than in inactive disease and controls. It was observed an increased immunostaining of IP-10 in active IBD, mainly localized to mucosal epithelial cells, CXCR3+ cells were scattered in the lamina propria. The Toll-like receptor 3 (TLR3) ligand polyinosinic: polycytidylic acid (poly(I:C)) induced the IP-10 secretion from the colonic epithelial cell lines in IBD patients, and also in peripheral blood mononuclear cell from IBD patients and controls. These results suggested that in active IBD, IP-10 and CXCR3 are upregulated genes in colonic mucosa. It can be assumed that in IBD patients, IP-10 release from mucosal epithelial cells is TLR3-mediated; in fact, TLR3-ligand poly(I:C) markedly increased the release of IP-10 in colonic epithelial cell lines (89). CXCR3 and its chemokines were reviewed in CD in a recent paper (90).

Conclusion

Many studies have demonstrated that in the intestinal mucosa of mice with experimental colitis and in lymphocytes, macrophages and epithelial cells of patients with CD there is a strong overexpression of CXCR3 and its ligand chemokines (MIG, IP-10 and I-TAC). In fact, CXCR3 and its chemokines have an important role both in the recruitment of granulocytes and mononuclear cells, and in the maintenance of inflammation in CD. Furthermore, IFN-γ induces Th1 chemokines expression and secretion by epithelial intestinal cells, that participate in the induction and maintenance of inflammation. CD inflammatory activity is reflected by high serum MIG levels, which has been suggested to be a marker for the responsiveness of patients to treatments. A potential therapy of CD can be the inhibition of CXCR3 or its chemokine MIG.

References

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