CXCL9 chemokine in ulcerative colitis

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Review


Abstract

The aim of this narrative review is to highlight the role of CXCL9 in Ulcerative Colitis (UC), in order to understand the mechanism underlying the inflammation in UC and to investigate also if Th1 chemokines could be useful as a marker of disease. It was shown that chemokine (C-X-C motif) receptor (CXCR)3 and its ligand chemokine, monokine induced by interferon (IFN)-γ (MIG)/chemokine (C-X-C motif) ligand 9 (CXCL9), are highly overexpressed both in the intestinal mucosa of mice with experimental colitis and in patients with UC (specifically, in lymphocytes, macrophages and epithelial cells). In epithelial colonic cells CXCL9 expression is increased by IFN-γ. MIG has an important role in the recruitment of mononuclear cells and granulocytes, so in maintaining the inflammation in UC. Since serum CXCL9 levels are related with UC disease activity, it could be a marker for the responsiveness of patients to treatments. It has been recently suggested that blocking CXCL9 may be a potentially effective therapy for moderately-to-severely active UC. Clin Ter 2018; 169(5):e235-241. doi: 10.7417/CT.2018.2085

Key words: CXCR3, CXCL9, ulcerative colitis

Introduction

CXCL9, and CXCR3

Chemokine (C-X-C motif) receptor (CXCR)3 is a G protein-coupled receptor belonging to CXC chemokine receptor family, with two isoforms: CXCR3-A and CXCR3-B; both binding CXC chemokines, monokine induced by interferon (IFN)-γ (MIG)/chemokine (C-X-C motif) ligand 9 (CXCL9), (IFN)-γ-inducible protein 10 (IP-10)/CXCL10 and IFN-inducible T-cell α chemoattractant (I-TAC)/CXCL11. CXCR3-B binds also chemokine CXCL4 (1).

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

Chemokines CXCL9, CXCL10 and CXCL11 are commonly produced by local cells in inflammatory lesions and are able to attract Th1 cells; then both CXCR3 and its ligands have a central role in the recruitment of inflammatory cells (2).

CXCL9 is a small cytokine known as MIG. CXCL9 is a T-cell chemoattractant, which is induced by IFN-γ. It is closely related to two other CXC chemokines called CXCL10 and CXCL11, whose genes are located near the gene for CXCL9 on human chromosome 4 (3, 4).

Therefore high level of CXCL9 revealed in peripheral liquids, can be considered as a marker of host immune response, especially of that involving Th1 cells (5, 6).

Indeed recruited Th1 lymphocytes increase IFN-γ and tumor necrosis factor (TNF)-α production that stimulates CXCL9 secretion from several cells of the inflamed site, leading to an amplification feedback loop (5, 6).

An increase of serum CXCL9 (as well as that of other Th1 chemokines) and/or of the tissue expressions in different organ specific of autoimmune diseases has been reported by various studies.

Acturally this has been found in several specific autoimmune diseases such as: autoimmune thyroiditis (7-12), Graves’ disease (13, 14) Graves’ ophthalmopathy (15-18), type 1 diabetes (19-23), or systemic rheumatological disorders, like rheumatoid arthritis (24), systemic lupus erythematosus (25, 26), systemic sclerosis (27-30), psoriasis or psoriatic arthritis (31-33), sarcoidosis (34, 35), HCV-related cryoglobulinemia (36-41), other HCV immune mediated disorders (11, 42-47), other disorders, and also in cancers (48-69).

Ulcerative colitis

Ulcerative colitis (UC) belongs to the inflammatory bowel diseases (IBD) and it is characterized by a chronic inflammatory condition normally involving colon and rectum (70, 71).
Typical symptomatology includes diarrhea mixed with blood and mucus (that lasts for weeks), and it could be followed by abdominal pain, that ranges from a mild discomfort to painful abdominal cramping (72).

The diagnosis of UC is mainly based on endoscopy, which usually reveals signs of inflammation of the colon (73). Ulcerative colitis pathology usually involves distortion of crypt architecture, crypt inflammation, crypt abscess, and haemorrhages and inflammatory cells in the lamina propria (LP) (74).

It is an autoimmune disease characterized by T cells infiltrating the colon (75-78). Patients may have comorbidities that lead to symptoms and complications outside the colon. The incidence of these extraintestinal manifestations was between 6 and 47 % (79); among them: osteoporosis, aphthous ulcer, iritis or uveitis, seronegative arthritis, ankylosing spondylitis, erythema nodosum, autoimmune hemolytic anemia, etc. Moreover a possible link between IBD or its therapy with glucocorticoids and osteonecrosis has been reported by a clinical study (80).

Therapy’s goals are to induce and maintain remission, reducing the risk of complications. The treatment depends on the severity of the symptoms. Mesalazine is the mainstay of treatment in mild to moderate disease (81).

Therapy with corticosteroids followed by transition to a steroid-sparing agent with a thiopurine, anti-TNF agent, or adhesion molecule inhibitor usually is administered in patients with failed 5-Aminosalicylate therapy or with severe disease (82, 83).

Monoclonal antibodies are the last pharmacotherapeutic option before surgery and, despite all the above mentioned therapies, 10-15% of patients required proctocolectomy (84).

UC is characterized by a clinical course of relapse and remission. A crucial step in the development and progression of the disease is the infiltration of leukocytes in the colon, where chemokines and their receptors orchestrate the tissue-specific and cell type-selective trafficking of leukocytes (85, 86).

The objective of this narrative review is to evaluate the role of CXCL9 in UC. The presentation of data has been reported according to the International Narrative Systematic Assessment (INSA) tool (87).

CXCR3 and CXCL9 in ulcerative colitis

In a first study, human epithelial, and intraepithelial lymphocytes (IEL) lineages were used to study epithelial chemotactic agents for IEL (88). Pre-stimulation of the epithelium with IFN-γ significantly improved the induced IEL chemotaxis by the epithelial-conditioned medium. Chemotaxis was significantly inhibited by using antibodies against CXCL10, or CXCL9. Chemokine CXCL10 and CXCL9 were detected in high amounts in epithelial-conditioned media stimulated with IFN-γ. These results showed that epithelial cells, under IFN-γ stimulation, produce chemoattractants (CXCL10 and CXCL9) for IEL (88).

In a second study, it has been shown that CXCR3-mediated chemotaxis of human T cells (in UC, and other autoimmune diseases) is regulated by a Gi- and phospholipase C-dependent pathway and not via activation of MEK/p44/p42 MAPK nor Akt/PI-3 kinase (89).

The crucial role of CD4 T-cells in the pathogenesis of human IBD has been shown by another study that suggests a higher percentage of CXCR3 expression on mesenteric lymph node (MLN) CD4 T-cells isolated from inflamed intestinal tissue in IBD (90).

A further study has been conducted on 8 controls and on 11 patients affected by UC in the distal part of the colon, before and during topical treatment with corticosteroids, in order to investigate the expression of CXC-chemokines (91). Perifusates (before as well after 7 and 28 days of treatment), and pinch biopsies (before and after 28 days of treatment) were collected by colonoscopy. High levels of growth related oncogene (GRO)-α, interleukin (IL)-8, and CXCL9 were detected in perfusates with respect to controls. GRO-α and MIG decreased in responders during treatment with corticosteroids. Epithelial cells and granulocytes too, expressed GRO-α and CXCL9 (91).

The mRNA expression of eighty-eight genes from various biological contexts on colon biopsies of patients affected by Crohn’s disease (CD), and UC, were evaluated in order to determine new susceptibility genes involved on UC disease. A CXCL9 overexpression was observed in the colon tissue of 3/5 CD and 3/3 UC patients compared to healthy controls. SNP genotyping for the 77147452G→A polymorphism of the CXCL9 gene on 114 pediatric patients affected by IBD and 120 ethnically matched unaffected adults detected a minor allele frequency of 20.3% in CD patients compared to 31.3% in controls (p=0.016). Remarkably, children with homozygosity for the wild-type allele had a significant earlier onset of CD than heterozygous individuals (11.1 versus 13.8 years) (92).

Development of dextran sulfate sodium (DSS)-induced colitis was investigated in CXCR3 (-/-) mice in order to evaluate wether CXCR3 knock-out mice would have impaired cellular transport thereby attenuating the course of colitis (93). Their results demonstrated an attenuated DSS-induced colitis in CXCR3 (-/-) mice (at macroscopic and microscopic level), with a lower neutrophils recruitment, as well as a decreased IFN-γ production (93); therefore suggesting the important role played by CXCR3 in recruiting pro-inflammatory cells to the colon during colitis. These findings suggested that CXCR3 could be a therapeutic target to reduce pro-inflammatory cells recruitment in the inflamed colon.

A further study examined peripheral blood immature plasma cells and their mechanisms of migration into inflamed sites in UC, reporting a significative higher number of these cells in patients with active UC and active CD, than in healthy controls. The proportion of immature plasma cells correlates in a positive manner with clinical activities of UC and CD. Many peripheral blood immature plasma cells were positive for CXCR3, CXCR4, CCR9; and CCR10 and mRNA levels of Th1 chemokines were higher in colonic mucosa of inflamed IBD respect to controls. CXCR3-positive immature plasma cells in the inflamed colonic mucosa of UC has been evidenced by Immunofluorescence too. Therefore this study suggested that increased numbers of immature plasma cells could migrate across the CXCR3 axis to inflammatory UC sites and then may be involved in the pathogenesis of UC (94).
The role of CXCR3 chemokines has been also studied in the pathogenesis of pediatric IBD by comparing inflammatory molecules expression in colon samples obtained from active UC and CD patients, in comparison with those of controls. In this study three children were involved, each with UC and CD (both in the active and remission phase), and their controls, and through microarray was investigated the inflammatory gene expression in the mucosa. They also carried out a real-time reverse transcription polymerase chain reaction and an immunohistochemical study involving six children from each group, in order to examine the expression of CXCL9, 10, 11, CXCR3, matrix metalloproteinase (MMP)-1, -3, -7, and -10. Microarray analysis revealed a higher expression of Th1 chemokines genes in the active phase of CD that has been confirmed by real-time reverse transcription polymerase chain reaction too. An enhanced expression of Th1 chemokines in the LP and in epithelial cells too has been showed by immunohistochemical analysis; CXCR3-positive cells were shown in the LP too. These results suggested the crucial role played by CXCR3 axis components and MMP in the mucosal damage in pediatric IBD (95).

Experimental models of colitis in mice were used to analyze the molecular events implicated in the development of IBD.

One study used global models of gene expression from two sets of pediatric IBD and two models of colitis in mice to compare directly the genomic signatures of murine and human IBDs. Comparing the two pediatric data sets of IBD microarrays, it has been found that 83 genes were expressed in a similar manner between pediatric CD and UC. Microarray data showed common signatures among pediatric IBD and experimental colitis, that include an up-regulation of CXCL9 and CXCL10, and inflammatory cytokines (IL-4, IL-13, IL-1, IL-6, IL-17) in vivo. The effect of exacerbation of recombinant IL-33 treatment in DSS-induced acute colitis was abolished in IL-4(-/-) BALB/c mice (99).

For the treatment of UC it has been also successfully used VSL#3, that is a mixture of 8 different probiotic bacteria. A study investigated about the stimulation of human dendritic cells with LPS, VSL#3, or a combination of both, showing that this leads to their maturation and to the induction of different CXCR3 chemokines. It is interesting that a set of LPS-induced chemokines, among which CXCL9 and CXCL10, were suppressed by VSL#3 (100).

Conclusion

The importance of cytokines and chemokines in the pathogenesis of different and/or associated autoimmune diseases has been shown by many studies (20, 39, 46, 101-118).

In this review we focused on CXCR3 and its ligand chemokine CXCL9. It was shown that CXCR3 and its ligand chemokine MIG, are highly overexpressed both in the intestinal mucosa of mice with experimental colitis and in patients with UC (specifically, in lymphocytes, macrophages and epithelial cells). In epithelial colonic cells CXCL9 expression is increased by IFN-γ. CXCL9 has an important role in the recruitment of mononuclear cells and granulocytes, so in maintaining the inflammation in UC.

Since serum CXCL9 levels are related with UC disease activity, it could be a marker for the responsiveness of patients to treatments. It has been recently suggested that blocking CXCL9 may be a potentially effective therapy for moderately-to-severely active UC.

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