

Role of cytokines in inflammatory bowel disease

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Author contributions: Sanchez-Muñoz F wrote most of the paper; Dominguez-Lopez A contributed in compilation of scientific papers and review; Yamamoto-Furusho JK participated in the designing, writing, editing and reviewing the whole paper.

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Received: April 1, 2008 Revised: May 30, 2008

Accepted: June 6, 2008

Published online: July 21, 2008

Abstract

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), represents a group of chronic disorders characterized by inflammation of the gastrointestinal tract, typically with a relapsing and remitting clinical course. Mucosal macrophages play an important role in the mucosal immune system, and an increase in the number of newly recruited monocytes and activated macrophages has been noted in the inflamed gut of patients with IBD. Activated macrophages are thought to be major contributors to the production of inflammatory cytokines in the gut, and imbalance of cytokines is contributing to the pathogenesis of IBD. The intestinal inflammation in IBD is controlled by a complex interplay of innate and adaptive immune mechanisms. Cytokines play a key role in IBD that determine T cell differentiation of Th1, Th2, T regulatory and newly described Th17 cells. Cytokines levels in time and space orchestrate the development, recurrence and exacerbation of the inflammatory process in IBD. Therefore, several cytokine therapies have been developed and tested for the treatment of IBD patients.

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Key words: Cytokines; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Inflammation

Peer reviewers: Atsushi Mizoguchi, Assistant Professor,

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Sanchez-Muñoz F, Dominguez-Lopez A, Yamamoto-Furusho JK. Role of cytokines in inflammatory bowel disease. *World J Gastroenterol* 2008; 14(27): 4280-4288 Available from: URL: <http://www.wjgnet.com/1007-9327/14/4280.asp> DOI: <http://dx.doi.org/10.3748/wjg.14.4280>

INTRODUCTION

Inflammatory bowel disease (IBD) comprises two forms, Ulcerative Colitis (UC) and Crohn's disease (CD). Currently, the pathogenesis of UC and CD is not completely understood, although the chronic relapsing inflammation is thought to be result from a dysregulated, aberrant immune response to intestinal flora in a context of genetic predisposition. In IBD, this loss of immune tolerance toward the enteric flora it is mediated by different molecules.

Cytokines are key signals in the intestinal immune system, and are known to participate in the disruption of the so-called normal state of controlled inflammation (physiological inflammation of the gut)^[1]. Cytokines are small peptide proteins produced mainly by immune cells that facilitate communication between cells, stimulate the proliferation of antigen specific effector cells, and mediate the local and systemic inflammation in an autocrine, paracrine, and endocrine pathways^[2]. In IBD, the innate immune response plays a critical role. Activated dendritic cells (DC) and macrophages secrete several cytokines that actively regulate the inflammatory response in UC and CD. Once secreted by these antigen presenting cells (APC), these cytokines trigger and differentiate many T cells activating the adaptive immune response. IBD has also a T cell dysregulation where clearance of overreactive and autoreactive cells is disturbed, in addition to an imbalance of Treg/Th1, Th2 and newly described Th17 cells populations in the activated state. The lack of appropriate regulation from T cells, or an over-production of effector T cells, participates in the development and exacerbation of IBD^[3].

Altogether, APCs, Th1, Th2, T regulatory cells and

Table 1 Role of cytokines and cell lines involved in their production in patients with IBD

Cytokine	UC	CD	Cells involved in the production
TNF- α	Up-regulated	Up-regulated	Macrophages
TL1 α	Unknown	Up-regulated	Th1
IL-1 β	IL-1ra/IL-1 ratio	IL-1ra/IL-1 ratio	Macrophages
IL-6	Up-regulated	Up-regulated	Macrophages, DC, Th17 and others
IL-18	Not	Yes, not in all patients	Macrophages
TGF- β	Not clear, maybe defective signalling	Not clear, maybe defective signalling	Th0, Th3, Treg
IL-10	Not clear	Yes, up-regulated	Tr1 and Breg
IL-4	Not clear	Not clear	Th2, NK
IL-12	Up-regulated	Up-regulated	Macrophages, DC
IL-23	Yes	Yes	Macrophages, DC
IL-27	Not clear	Up-regulated	APCs
IL-17	Up-regulated	Up-regulated	Th17
IL-13	Up-regulated	Not	Th1, NK
IL-5	Up-regulated	Not	Th2, NK

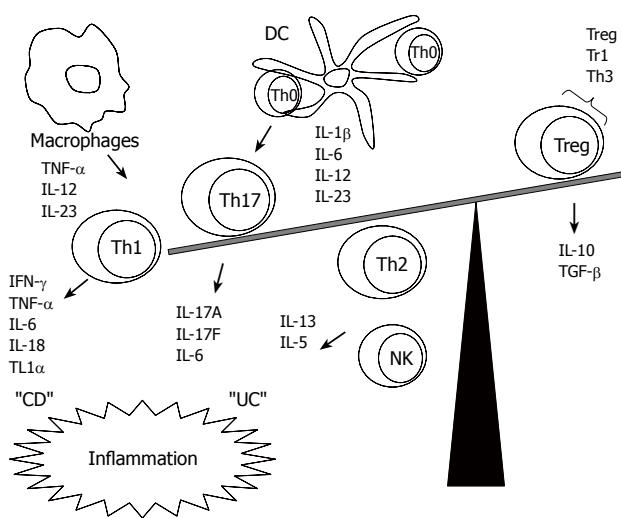


Figure 1 Cytokines imbalance between effector and T regulatory cells in IBD.

most recently characterized Th17 and their cytokine products play a complex role in IBD^[4]. These cellular interactions are modulated by both traditionally studied cytokines (such as TNF- α , INF- γ , IL-1, IL-6, IL-4, IL-5, IL10, TGF- β) and others recently characterized (like IL-13, IL-12, IL-18, IL-23), considered to be either pro or anti-inflammatory, as shown in Table 1^[5]. Although many common responses in IBD are mediated by cytokines, such as the regulation of the production of inflammatory mediators, reactive oxygen metabolites, nitric oxide, leukotriens, platelet-activating factor, and prostaglandins, activation of the nuclear factor κ B (NF- κ B) and inhibition of apoptosis, how cytokines determine the nature of the immune response in IBD may be quite different among IBD forms^[6]. CD is associated with a Th1 T cell mediated response, characterized by enhanced production of IFN- γ and TNF- α . IL-12 and IL-23 govern the Th1 differentiation which in combination with IL-15, IL-18 and IL-21 will induce the stabilization of polarized Th1. On the other hand, in UC, the local immune response is less polarized, but it is characterized by CD1 reactive natural killer T cell production of IL-13 and Th2 cytokine production, as shown in Figure 1^[7].

CLASSICAL PRO-INFLAMMATORY CYTOKINES

Lymphocytes and APCs orchestrate a lot of the inflammation in IBD, mainly the production of TNF- α , a 17-kD pleiotropic cytokine produced by innate immune cells as macrophages, monocytes, and also by differentiated T cells. TNF- α exerts its pro-inflammatory effects through increased production of IL-1 β and IL-6, expression of adhesion molecules, proliferation of fibroblasts and procoagulant factors, as well as initiation of cytotoxic, apoptotic, acute-phase responses, and inhibition of apoptosis^[8,9]. TNF- α expression in human macrophages was discovered in the colonic tissue and macrophages in both patients with CD and UC^[10] and serum levels of TNF- α correlate with clinical and laboratory indices of intestinal disease activity^[11]. Clinical studies have reported a dramatic improvement in CD patients treated with anti-TNF- α therapy such as infliximab, adalimumab and certolizumab pegol^[12]. Reductions in the number of IFN- γ producing, lamina propria mononuclear cells (LPMC) in colonic biopsies results from anti-TNF- α treated patients^[13].

The signalling of TNF- α starts with serum soluble TNF receptor I and II (sTNF-R I, II) levels correlate with disease activity in IBD patients. More specifically, sTNF-R I is up-regulated in the serum of IBD patients compared to healthy controls and could be used as a marker for disease activity^[14]. sTNF-R II levels are significantly more elevated in serum from active CD patients as compared to UC and could be used as an additional parameter to discriminate both diseases^[12]. Recently TNF receptor type 1-dependent activation of innate responses was shown to reduce intestinal damage-associated mortality^[15].

Related to the TNF- α , the TNF-like factor (TL1A) seems to stimulate IFN- γ secretion by binding to the death receptor 3 (DR3). A higher percentage of cells express the TL1A receptor DR3 in mucosal biopsies taken in CD and UC, and increased synthesis of IFN- γ has been observed to correlate with severity of disease in IBD patients^[16]. This molecule links TNF related apoptosis in inflammatory intestinal epithelial lesions,

tumour-necrosis-factor related apoptosis inducing ligand (TRAIL) messenger RNA and protein were markedly up-regulated in IEC and lamina propria lymphocytes in animal model. Interferon-gamma and TNF-alpha potently induced TRAIL in IEC and TRAIL is highly up-regulated in IEC in inflammatory ileum and colon^[9].

In addition to TNF- α , IL-1 seems to be important in the pathogenesis of IBD because of its immunological up-regulatory and pro-inflammatory activities. The IL-1 system consists of IL-1 α and IL-1 β , both of which are produced by various cell types through the initiation of cyclooxygenase type 2, phospholipase A, and inducible nitric oxide synthase (iNOS)^[17]. The IL-1 system can be also highly regulated by IL-1 receptor antagonist (IL-1Ra), as supported by the findings of high plasma and tissue levels of IL-1Ra in patients with IBD, indicating that IL-1Ra may be part of the host mechanism for downregulation of inflammation^[18]. The IL-1Ra/IL-1 ratio decreases with increasing IBD activity, while remaining constant in uninvolved CD and inflammatory control specimens: this may contribute to the pathogenesis of chronic gut inflammation^[19]. Increased levels of IL-1 in IBD may be result of stimulation of colonic macrophages that can activate interleukin (IL)-1 converting enzyme (ICE) and hence release mature IL-1 β into the colonic mucosa^[20].

In contrast to other cytokines, IL-6 is a pleiotropic cytokine that exerts its proinflammatory effects largely by means of its soluble IL-6 receptor (sIL-6R). The combination of soluble IL-6 receptor (sIL-6R) and IL-6 stimulates cells that only express gp130 and not IL-6R, a process known as trans-signalling. IL-6 signalling through signal transducer and activator of transcription-3 (STAT3) has been extensively studied^[21]. This system plays a central role in several immunologic reactions during the development of IBD, and circulating levels of IL-6 and sIL-6R correlate with many clinical features of CD and UC^[22-24]. Blockade of IL-6 trans-signalling causes T-cell apoptosis, indicating that the IL-6-sIL-6R system mediates the resistance of T cells to apoptosis in CD^[24]. Yamamoto *et al* (Kallen K)^[25] introduced the anti-IL-6 receptor monoclonal antibody to a murine colitis model and found that the treatment with this antibody reduced IFN- γ , TNF- α , and IL-1 β mRNA, and suppressed expression of several intracellular adhesion molecules in the colonic vascular endothelium. The anti-IL-6 receptor monoclonal antibody also abrogates murine colitis by effectively blocking the recruitment of leukocytes and increasing T-cell apoptosis^[26]. Peripheral immune cells as well as colon epithelial and lamina propria cells with an active form of IL-6/STAT3 system may be responsible of the high correlation with the degree of mucosal inflammation^[27]. The signaling of IL-6/STAT3 in the activation of mucosal T cells has been suggested as a major therapeutic target for the future^[28]. STAT-3 itself induces the anti-apoptotic factors Bcl-2 and Bcl-xL, thus resulting in T-cell resistance against apoptosis. This circle of T-cell accumulation, mediated by apoptosis resistance, finally leading to chronic

inflammation, can be blocked by anti-IL-6 receptor antibodies^[29].

IL-18

IL-18 is produced by intestinal epithelial cells and was originally identified as an IFN- γ inducing factor, shares similarities with the IL-1 family in terms of its structure, processing, receptor, signal transduction pathway, and pro-inflammatory properties^[30]. Recent studies have shown that the balance between this pleiotropic pro-inflammatory cytokine and its natural inhibitor, IL-18-binding protein (IL-18BP), may contribute to the pathogenesis of IBD^[31]. A local increase of IL-18 expression has been demonstrated in chronic lesions of CD compared with uninvolved areas or normal controls^[32], and an increase in IL-18 was also shown to be accompanied by marked increases in IL-18 receptor-positive immune cells as well as intense transcription of IL-18 induced by cytokines, such as IFN- γ , IL-1 β , and TNF- α ^[33]. In a recent study has been reported that IL-18 up-regulation may be found only in a minority of patients with CD^[34]. Furthermore, in the presence of IL-18, T cells from the inflamed CD tissue have been shown to produce less IL-10 than control tissue^[35]. Although recombinant IL-18 alone induces significant proliferative responses in freshly isolated mucosal lymphocytes from CD patients^[36,37], a synergy between IL-12 and IL-18 in activated macrophages may be a regulatory mechanism driving *lamina propria* lymphocytes toward a Th1 response in IBD^[38]. It has been reported that cytokine IL-12 may act in synergy with IL-18 to promote the induction of IFN- γ , leading to severe gut inflammation in mice^[39]. The development of Th1 CD4+ T cells in the intestinal mucosa is driven by IL-12, produced from activated macrophages, and IL-18, produced from activated macrophages and colonic epithelial cells. The synergistic effect is mainly caused by mechanisms involving the up-regulation of the IL-18 receptor by IL-12^[40].

ANTI-INFLAMMATORY AND IMMUNOMODULATORY CYTOKINES

IL-10

IL-10 is an anti-inflammatory cytokine that inhibits both antigen presentation and subsequent release of pro-inflammatory cytokines, thereby attenuating mucosal inflammation. The pivotal role played by IL-10 within the mucosal immune system has been extensively studied in the chronic ileo-colitis that develops in gene-targeted IL-10 knockout mice and by its therapeutic efficacy in several animal models of colitis^[41]. An inactivation of IL-10 in mice results in an increased production of IL-12 and IFN- γ ^[42,43]. Inflamed tissues and granulomas of CD show low IL-10^[44]. Melgar *et al*^[45] reported a highly significant increase in IL-10 mRNA levels in T lymphocytes and in IL-10-positive cells in the colons of UC patients. Recently produc-

tion of IL-10 by regulatory T cells has been implicated as important issue in IBD^[46]. Other regulatory cells that may participate in UC through the production of IL-10 are a regulatory B cells subtype called Bregs^[47]. The importance of IL-10 production by B cells has been evidenced in IBD models and in humans^[48,49], Mizoguchi *et al* showed that Bregs can be responsible for the suppression and/or recovery from acquired immune mediated inflammations by mechanisms that include IL-10 and TGF- β 1 in IBD^[47].

IL-4 and TGF- β

Overall, anti-inflammatory cytokines whose roles are less well characterized in IBD include IL-4 and TGF- β . IL-4 is a stimulatory molecule for B and T cells, and has known immunosuppressive effects in the intestine^[50]. T-cell receptor alpha chain-deficient mice (TCR -/-) treated with anti-IL-4 monoclonal antibody showed a decrease in Th2-type mRNA cytokine production and an increase in expression of IFN- γ , suggesting that IL-4 plays a major role in inducing Th2-type CD4+ cells in the gut to shift towards a Th1 response^[51]. Also another study showed that development of colitis in the TCR -/- mice depends on IL-4 rather than IFN- γ ^[52]. A study reported that the administration of IL-4 led to a significant reduction of the vascular endothelial growth factor (VEGF) production by peripheral blood mononuclear cells in active CD and UC patients^[53].

Similarly, TGF- β is an inhibitory cytokine recognized as a key regulator of immunological homeostasis and inflammatory responses. Reduced TGF- β activity is considered to be responsible for the development of autoimmune disorders in several pathologic conditions including IBD^[54]. Defective transforming growth factor TGF- β 1 signaling due to high levels of Smad7 is a feature of IBD^[55]. UC patients have exhibited increased production of TGF- β 1 by LPMC as compared with both CD patients and controls, highlighting that although TGF- β acts on the systemic immune system to promote a potent immunosuppressive effect, locally TGF- β may demonstrate pro-inflammatory properties^[56]. Evidence suggests that TGF- β can act in concert with epidermal, insulin-like, fibroblast growth factors, as well as VEGF to protect host tissue from luminal challenges and facilitate repair of mucosal injury in IBD^[57,58]. As future therapy, the inhibition of Smad7 may reestablish TGF- β 1 function and the suppression of colitis as proven in experimental models of colitis^[59].

IL-12 and related cytokines

IL-12 and IL-23 belong to the IL-12 family of pro-inflammatory heterodimeric cytokines and comprises IL-12p40/IL-12p35 and IL-12p40/IL-23p19 subunits^[60]. They are mainly produced by activated APCs and accessory cells such as DC and phagocytes^[61]. The receptors for these cytokines are also heterodimeric IL-12 binds an IL-12R β -IL-12R β 2 heterodimer, whereas IL-23 binds an IL-12R β 1-IL-23R heterodimer^[60]. The receptors for both IL-12 and IL-23 are mainly expressed on T cells,

NK cells, and NKT cells. However, low levels of the receptor for IL-23 are also expressed on monocytes, macrophages, and DCs^[61]. Both cytokines activate TYK2 and JAK2 as well as STAT1, STAT3, STAT4, and STAT5^[60]. Although IL-12 activates STAT4 most efficiently, IL-23 preferentially activates STAT3^[60]. Despite the similarities in receptor subunit and signaling, recent studies have shown that IL-12 and IL-23 drive divergent immunological pathways.

The expression of IL-12 is up-regulated in both active UC and CD biopsies and it correlates with activity index score^[62]. Levels of IL12p40 and IL12R β 2 are higher in early rather than in late CD suggesting that IL12-mediated modulation is strongly dependent on the stage of disease^[63]. In particular, to drive adaptive immune responses, DCs (that sense the nature of the microorganisms in the intestine) are key producers of IL-12 in IBD^[64].

In animal models, IL-23 showed to be essential for manifestation of chronic intestinal inflammation, whereas IL-12 is not. A critical target of IL-23 is a unique subset of tissue-homing memory T cells, which are specifically activated by IL-23 to produce the pro-inflammatory mediators IL-17 and IL-6^[65].

Recently, another IL-12-related cytokine, IL-27, was described. IL-27 consists of EBI3, an IL-12p40-related protein, and p28, a newly discovered IL-12p35-related polypeptide. Mucosal expression of IL-23p19 and IL-27p28 transcripts correlate with the inflammatory activity in IBD both CD and UC. Particularly, IL-27p28 transcripts and EBI3 transcripts were significantly elevated only in active CD^[66].

IL-17 and Th17 cells

Recently, a new T cell subset named "Th17", characterized by the production of IL-17, was identified as an important player in inflammatory responses^[67]. Sequencing the human genome resulted in the discovery of an additional five members of the IL-17 family that were consecutively named IL-17B to IL-17F. IL-17A is exclusively produced by Th17 cells^[68]. The production of IL-17 relies on STAT3 activation triggered by IL-23^[69]. IL-17 in general induces the recruitment of immune cells to peripheral tissues, a response that requires NF- κ B activation after IL-17 receptor engagement^[70,71]. IL-17 also leads to the induction of many pro-inflammatory factors, including TNF- α , IL-6, and IL-1 β , suggesting an important role for IL-17 in localizing and amplifying inflammation^[72-74]. Furthermore, TNF- α and IL-6, which are both produced by Th17 cells, not only support Th17 cell development but also synergize with IL-17 to enhance the production of pro-inflammatory mediators^[74]. Regulatory T cells CD4+CD25-Foxp3- could be a source of Th17 cells^[75]. In human cells, IL-1, IL-6, and IL-23 promote human CD4+ to Th17 differentiation, but TGF- β 1 is not needed like in mouse^[76]. IL-17 as well as Th17 cells have both been found to be elevated in serum and intestinal tissue of IBD patients. IL-17 was not detected in inactive patients tissue as well as other colitis^[77].

IL-13 and T cell response in UC

UC is characterized by a Th2 immune response in which IL-13, which is produced by specialized cells such as NK T-cells, was identified as an important effector cytokine^[78]. In UC, IL-13 may impair epithelial barrier function by affecting epithelial apoptosis, tight junctions, and restitution velocity^[79]. Both discoveries were made by determining the cytokine profile of LPMC isolated from tissue recovered from colonic resection from UC and CD patients. It was found that LPMC from UC patients secreted high amounts of Th2 cytokines IL-13 and IL-5^[78,79]. This research group found that the IL-13 and IL-5 LPMC cells bear NK specific markers CD161 and recognize CD1d, indicating that they are NK T-cells^[78]. These NK T-cells are considered "non-classical". The NK T-cells isolated from UC patients exhibited cytotoxicity towards an epithelial cell line (HT-29)^[78]. This cell population possibly could be the cells causing epithelial cell cytotoxicity in UC described in the 1980s^[80]. IL-13 signalling through the IL-13 α 2 receptor (IL-13R α) in general is involved in induction of TGF- β 1 production and fibrosis^[81]. The signalling through IL-13R α was important in the fibrosis caused by TGF- β 1 in an animal model^[82]. However, the extent to which this leads to the ultimate cascade of inflammation in UC remains to be determined.

NOVEL CYTOKINES INVOLVED IN IBD

Other cytokines like IL-21 and IL-22, which have been implicated in the pathophysiology of inflammatory and autoimmune diseases such as asthma, arthritis and lupus, play also an important role in IBD. IL-21 is a T cell derived cytokine member of the common gamma-chain-dependent cytokine family, which in general acts on intestinal epithelium helping to maintain the ongoing Th1 inflammation by inducing the production of IFN- γ ^[83,84]. IL-21 also has been shown to enhance the expansion of NK cells^[85]. IL-21 is expressed by immune T and B cells and non-immune cells like fibroblasts, where it activates the metalloproteinase 1 production, and signalling through its receptor IL-21R it activates STAT-3 in T cells^[86]. IL-21, like IL-6 and IL-23 is also involved in Th17 cell differentiation^[87] and it is over-expressed in both CD and UC, with higher levels being found in CD^[88].

IL-22 was originally described as an IL-9-induced gene and was named as IL-10-related T cell-derived inducible factor (IL-TIF)^[89]. This cytokine shows 22% amino acid identity with IL-10 and belongs to a family of cytokines with limited homology to IL-10. IL-22 binds at the cell surface to a receptor complex composed of two chains belonging to the class II cytokine receptor family (CRF2): IL-22R1 and IL-10R2^[90,91]. In the intestinal cells, particularly innate immune cells, the binding of IL-22 to its respective R1 chain induces a conformational change that enables IL-10R2 to interact with the newly formed ligand-receptor complexes. This in turn, activates a signal transduction cascade that re-

sults in rapid activation of several transcription factors, including STAT1/3 proteins^[91]. The principal sources of IL-22 are natural killer and activated T and B cells. Th17 has proven a very important role in this matter^[92]. IL-22 has proinflammatory functions in IEC and is upregulated in CD both in tissue and in serum^[93,94]. Surprisingly, in a murine model of UC, Sugimoto *et al* demonstrated a novel protective role for IL-22, in which IL-22 attenuates in the intestine inflammation by inducing mucin membrane bound production by goblet cells^[93,94]. Another recent paper showed that IL23R genotypes affect IL-22 serum concentrations, linking for the first time genetic CD susceptibility to Th17 cell function^[94].

POTENTIAL BIOLOGICAL THERAPIES DIRECTED TO CYTOKINES

Controlling the expression, production and activity of IL-23 as well as IL-17 is an approach that would allow the development of a novel treatment strategy with more anti-inflammatory efficacy and potentially with less suppressive effects on host defenses^[95]. There are different biologic therapies directed to several cytokines tested in patients with IBD: fontolizumab (anti-interferon γ) is a humanized monoclonal antibody to interferon gamma. A small phase 2 study of fontolizumab at subcutaneous doses of 10 mg/kg in patients with moderate to severe CD demonstrated efficacy and safety^[96]. A randomized clinical trial of 79 patients with CD receiving 1 mg or 3 mg of anti-IL-12 monoclonal antibody *versus* placebo demonstrated a response in 75% of CD patients compared with 25% in the placebo group^[97]. Other antibodies have been generated against to T-cell subsets blockade including CD3+ cells (visilizumab) and CD25+ cells (daclizumab and basiliximab) for UC. Pilot studies have shown promising results in steroid-resistant UC patients^[98]. IL-6 participates in a variety of critical functions, including T cell growth and differentiation, as well as B-cell proliferation. In a pilot study, where patients with active CD were treated with an antibody directed against the IL-6 receptor (Atlizumab), 80% responded at the full dose compared with 31% in the placebo group^[99]. IL-11 is produced by cells of mesenchymal origin. A placebo controlled trial of subcutaneous IL-11 in patients with active CD did not demonstrate clear efficacy^[100].

CONCLUSION

Cytokines are important in the pathogenesis of IBD and their manipulation has successfully reduced disease severity and maintained remission. Following the discovery of novel cytokines and the role they may play in gut mucosal immunity, as well as the emergence of new concepts and changing paradigms in IBD pathogenesis, the roles of several cytokines have been elucidated and tested in both preclinical animal models and clinical trials of patients with IBD. Complementary to this, proof of

concept for new cytokine targets is rapidly developing, with the possibility of future cytokine-based therapies that may offer greater specificity and decreased toxicity for the treatment of IBD. In addition, further applications of cytokine-based therapies in human clinical trials and preclinical animal studies are ongoing.

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