

# Pathophysiology and New Therapeutic Approaches in Inflammatory Bowel Disease

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Inflammatory bowel disease is the second most common chronic inflammatory disorder after rheumatoid arthritis [1]. While the prevalence of Crohn's disease has continued to rise over the last four decades, the prevalence of ulcerative colitis seems to remain relatively stable. The etiology of IBD is multi-factorial, consisting of a mixture of genetic and environmental factors that may serve as a trigger for disease initiation [1-3]. In contrast to the normal gut, the gut in IBD seems unable to shut off the activation of its immune system, resulting in an untrammelled inflammatory response.

The road leading to the development of new therapies in the last few years was paved by new insights on the pathophysiology of IBD, including the important role of pro- and anti-inflammatory cytokines. It was shown that T lymphocytes in the intestinal lamina propria of patients with CD and UC manifest abnormal proliferation and cytokine production, as well as decreased apoptosis [4]. During the inflammatory process, cytokines released from activated macrophages promote differentiation of T lymphocytes to CD4<sup>+</sup>/T helper1 or CD8<sup>+</sup>/T helper2 cells. Interleukin 12 and 18 were found to induce differentiation to Th1 cells, which are more abundant in CD. On the other hand, UC is associated with enhanced humoral immunity, but evidence for classical Th2 predominance (promoted by IL-4) is less secure [2]. IL-2 and interferon-gamma are cytokines secreted by Th1 lymphocytes, which play an important role in cell-mediated immunity, for instance autoimmune diseases, response against intracellular pathogens, and promotion of cytotoxic tissue damage. The cytokine profile of Th2 cells (IL-4, 5, 10 and 13) is primarily associated with allergic/atopic reactions and anti-extracellular pathogen defense, and is characterized by an antibody-mediated immune response [2].

IL-10 is an anti-inflammatory cytokine that affects T cells and macrophages by down-regulation of pro-inflammatory cytokine release, such as tumor necrosis factor, IFN- $\gamma$ ,

numerous interleukins and nitric oxide. IL-10 deficient ("knockout") mice showing an unregulated Th1 cytokine profile develop a disease similar to CD [2,5].

One of the recent and most extensively investigated pro-inflammatory cytokines is TNF- $\alpha$ . Produced by monocytes, macrophages and T cells, it affects proliferation, differentiation and function of most immune system cells. TNF- $\alpha$  plays an important role in the stimulation of acute-phase response, cytotoxicity, cachexia and shock. The molecular effects of TNF include stimulation of other cytokine production (such as IL-1 and 6), neutrophil recruitment and activation, expression of adhesion molecules, fibroblast proliferation, enhanced metalloproteinase production, and activation of the coagulation cascade [2,3,6]. It was recently suggested that TNF polymorphisms affect the susceptibility to CD and the disease location. Negoro et al. from Japan [7] reported on novel polymorphisms in the 5' region of the TNF gene (-1031C, -863A and -857T) that were positively associated with CD.

NF- $\kappa$ B is a nuclear transcription factor that plays a pivotal role in regulation of the pro-inflammatory process. Its nuclear translocation is promoted by TNF and lipopolysaccharides and is inhibited by IL-10, thalidomide and corticosteroids [2,3].

The contribution of the extracellular matrix to the disease process should not be ignored. In biopsy specimens from IBD subjects, the abundance as well as the activation of matrix metalloproteinases were significantly increased in the mucosa of CD and UC patients as compared to healthy controls [8]. These enzymes might serve as a target for the development of anti-IBD therapy investigations.

## New therapeutic approaches for IBD

The two main goals in the treatment of active IBD are the induction and maintenance of long-term remission. These goals can be achieved in less than one-third of IBD patients by mesalamine (5-amino salicylic acid). Steroids may induce remission in about 60% of patients, but prolonged therapy is not recommended. As many as 20% of CD patients are steroid resistant and up to 36% of the responders are steroid dependent [9]. Long-term remission can be maintained by immunosuppressive drugs such as azathioprine,

TNF = tumor necrosis factor

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IBD = inflammatory bowel disease  
 CD = Crohn's disease  
 UC = ulcerative colitis  
 Th1 = T helper 1  
 IL = interleukin  
 IFN = interferon

or its active metabolite 6-mercaptopurine (thioguanine derivatives), in up to 75% of CD and 60% of UC patients [3,5].

The role of cyclosporin in refractory IBD is currently being assessed. In a retrospective study reported here by Naftali et al. [10], 32 children and adults with severe steroid-refractory UC were treated with cyclosporin. Treatment was initially given intravenously, followed by oral administration to the responders for at least 5 months. As accepted in the literature, the dosage was 4 mg/kg and 5 mg/kg, respectively. The initial response rate was 78%, but at the end of up to 17 months of follow-up proctocolectomy was spared in only 37% of the patients. Although this study was retrospective and included a small number of subjects from six different hospitals, the results are similar to other reports. Cyclosporin acts through potent suppression of T cell proliferation and activation. It inhibits release of IL-2 by Th1 cells and down-regulates IL receptors on T cells [2,3,5]. In CD, uncontrolled studies have shown a benefit for both inflammatory and fistula disease, but the results of controlled trials are still controversial [2,5]. In a 12 month European study on 182 patients with chronic active CD, the rate of full remission induction and maintenance was similar with or without the addition of cyclosporin to low dose steroid therapy [11]. In severe refractory UC, intravenous cyclosporin was shown to achieve an initial response and spare urgent colectomy in 60–80% of the patients [2,3,5]. In a small pilot study from Spain [12], Ortiz et al. assessed the efficacy of oral microemulsion cyclosporin as the initial therapy for steroid-refractory UC. During 3 months of treatment oral cyclosporin controlled acute attacks and led to remission in four of the five patients treated. However, the benefits of cyclosporin therapy should be considered in light of its major toxic effects, such as nephrotoxicity, infections, hypertension, hyperlipidemia, neuropathy, seizures, and a possible risk of lymphoma after prolonged use [2,5]. Ongoing clinical trials are investigating cyclosporin as a means to avoid urgent colectomy and as a bridge to induce remission, but its current role as a long-term treatment is doubtful. In our experience the drug should be given for 7–10 days in continuous infusion at a dose of 8 mg/kg dissolved in 5% dextrose. After one week oral cyclosporin should be initiated at a dose of 4 mg/kg. Cyclosporin levels should be checked periodically. In patients treated concomitantly with steroids, prophylactic cotrimoxazole and trimethoprim should be given twice a week due to the immunosuppressed state.

Several new medical therapies consisting of immunomodulatory agents are currently being used for severe refractory IBD. As a typical Th1 cytokine, TNF plays a pivotal role in CD and therefore its blockade has been used as the first immune response modifier in IBD. Infliximab is a chimeric anti-TNF monoclonal IgG1 antibody that has been shown to neutralize TNF effects by blocking soluble TNF- $\alpha$  and binding to transmembrane TNF. It may also promote cell lysis through complement fixation or antibody-

dependent cell-mediated cytotoxicity [2,9,13,14]. In a single blinded trial, anti-TNF infusion yielded a clinical response in about two-thirds and a full remission in one-third of the patients at 4 weeks, but most relapsed after 3 months [13,15]. Clinical randomized controlled trials have shown that the use of multiple courses of intravenous infliximab in refractory CD patients led to a significant clinical, endoscopic and histologic improvement in induction and maintenance of remission [2,6,9,14]. The reported clinical response rates of re-treatment of refractory CD at 36 and 44 weeks were 72% and 53% in the infliximab group compared to 44% and 20% in the placebo group, respectively [9]. The median time to loss of clinical response was 48 weeks vs. 37 weeks in the placebo group ( $P=0.057$ ). For enterocutaneous fistula, the response rate measured by closure of >50% of fistulas was significantly higher with infliximab than with placebo (56–68% vs. 26%, respectively) [2]. At the molecular level of the mucosa, anti-TNF was also shown to cause a complete disappearance of neutrophils, reduction of monocytes towards normal levels, and normalization of the epithelial cell morphology with disappearance of signs of epithelial damage [6]. The levels of C-reactive protein and IL-6 were markedly reduced within hours after the injection. Although anti-TNF has been approved and used for moderate to severe Crohn's disease, the optimal indications, treatment duration and safety profile for prolonged use await the completion of further studies.

A second newly reported anti-TNF agent is thalidomide, which decreases TNF production, and inhibits activation of NF $\kappa$ B, neutrophil activity and angiogenesis [2,3,16,17]. Promising preliminary results in CD were recently published in two small open-label trials. Administration of thalidomide to refractory CD patients achieved clinical remission and response at 12 weeks in 41% and 64%, respectively [16]. The second trial [14] reported a 70% response rate and 20% remission induction in chronic active CD.

Antegren® (natalizumab, Elan Pharmaceuticals, USA) is a novel anti- $\alpha$ 4-integrin antibody that is presently being studied as an immunomodulator.  $\alpha$ 4-integrins are molecules expressed on the surface of leukocytes during recruitment from the circulation to the inflammatory sites. They are involved in attachment of these cells to the vascular endothelium, activation and diapedesis of leukocytes into the mucosa [2,3].  $\alpha$ 4-integrins may be of particular relevance to IBD since they confer selective homing of lymphocytes to the bowel mucosa. Small clinical studies on Antegren in CD patients reported 2 and 4 week response rates of 39–50% [2]. The initial suggested beneficial effect of anti- $\alpha$ 4-integrin antibody prompted a large ongoing case-controlled study on chronic active CD (Arber, personal communication).

Heparin was suggested to bind fibroblast growth factor, which promotes intestinal epithelial repair, and to reduce the recruitment of inflammatory cells. A preliminary study in

patients with mild to moderate UC has reported a beneficial effect with the administration of unfractionated heparin [2].

Notwithstanding the medical treatment, about 20–30% of UC subjects will require proctocolectomy, which is considered a definitive treatment for the intestinal manifestations of the disease [5]. Up to 70% of CD patients will be operated on at least once during their lifetime. The overall 5 year symptomatic recurrence rate of CD after surgery is 50–60%, and the histologic recurrence rates reach 70% and 85% by 1 and 3 years, respectively.

Another question addressed in the present issue of this journal is the treatment of severe pediatric UC [18]. In children, the gastrointestinal symptoms of IBD are similar to those of adults, but they may be overshadowed by more prominent systemic manifestations, such as growth failure, nutrition deficits and fever. Since an extensive involvement with pancolitis is more prevalent in children (up to 50%), the rate of colectomies is higher than in adults [5]. Steroids and immunosuppressive agents should be used cautiously in children because of the heavy burden they impose on the growth and development in childhood. In their article, Nagar et al. [18] retrospectively reviewed the post-proctocolectomy outcome of 11 children with UC. The follow-up period was at least 4 years. The overall complication rate was significant and comparable to the results published in the literature. The authors reported a good quality of life including physical and social activities in all the patients.

A new emerging surgical modality is laparoscopic colectomy. A recent case-matched study compared the efficacy of laparoscopic restorative proctocolectomy with the traditional open proctocolectomy [19]. Of the 40 patients enrolled, two-thirds had UC and one-third familial adenomatous polyposis. The median age was 25 (range 9–61 years). The patients were matched for age, gender, body mass index and disease severity. There were no conversions to open surgery in the laparoscopic group. The overall complication rates were similar in both groups. In the laparoscopic group the return of normal bowel function was significantly sooner, and the duration of hospitalization significantly shorter than in the open surgery group. Laparoscopic restorative proctocolectomy has the potential of becoming an appealing alternative to traditional open colectomy.

The fundamental question of medical vs. surgical treatment in severe refractory IBD and especially in children has still to be resolved. The newly developed immunomodulatory agents might give hope to some but not all of these patients. During the last few years the increased understanding of the pathogenesis of the disease has opened new avenues and established novel immunomodulatory therapies. However, these therapies have not yet been proven to provide long-term remission, and the indications, safety profile and treatment duration remain to be determined. Although the inflammatory puzzle of IBD is slowly being unraveled, the pathogenic enigma of the disease still remains and the ultimate therapy is yet to be defined.

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