During the past several years numerous studies have examined the immunology of inflammatory bowel disease (IBD). Recent major areas of focus are the role of T cells and cytokines. Genetically manipulated animal models (deficiency in several T cell receptor genes and cytokine knockouts) have facilitated the research of this field and provided the possibility of new therapy for IBD using monoclonal antibodies and cytokines. Surprising report showing remission of Crohn's disease after oc positive cells in mucosa have been reported in children with measured in tissues at the mRNA and protein levels and new ones are constantly being discovered. Cytokines can be distinguished from so-called "anti-inflammatory" cytokines. To date, over 100 individual cytokines have been identified and many of them have investigated the relationship between tissue levels of cytokines and the severity of mucosal inflammation, although conflicting results have been reported. IL-8 is a potent chemoattractant for polymorphonuclear cells and is a member of the chemokine family of pro-inflammatory cytokines. Pro-inflammatory cytokines are involved predominantly in the induction and perpetuation of inflammation. They include interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α). A number of studies have indicated increased expression of these cytokines in IBD, and some of them have investigated the relationship between tissue levels of cytokines and the severity of mucosal inflammation. Pro-inflammatory cytokines play a role in activating the immune system, stimulating TGF-β which inhibits lymphocyte function and has effects on multiple cytokines. Cyclosporin inhibits expression of T-cell cytokines such as IL-2, and INF-γ, and stimulates TGF-β which inhibits lymphocyte function.

Although the precise mechanism of mucosal inflammation in IBD has not been clarified, the recent development of monoclonal antibodies offers the possibility of therapeutic efficacy of IBD. Recently two monoclonal antibodies (anti-CD4 and anti-TNF-α) have been used for the therapy of IBD. A recent dose-escalating pilot study for steroid-refractory Crohn's disease using anti-CD4 monoclonal antibody has reported that the Crohn's disease activity index (CDAI) was significantly decreased at 10 weeks in the high dose groups. However, there was only a minor effect on the endoscopically evaluated disease activity. A more recent study concluded that intravenous infusion of anti-CD4 monoclonal antibody (B-F5) was not successful in 12 patients with severe refractory Crohn's, although four of 11 patients who received the complete course of treatment showed prolonged or partial improvement. A surprising report of TNF-α antibody treatment in Crohn's disease by Derkx et al. (9) showed that complete remission was achieved by intravenous infusion of anti-TNF-α (chimeric monoclonal antibody cA2) in 12-year-old girls with severe refractory Crohn's disease. Van Dullemen et al. have recently done a clinical study using the chimeric mouse/human monoclonal antibody cA2 in patients with steroid-refractory Crohn's disease, and have demonstrated that a single intravenous infusion of the antibody caused normalization of CDAI scores and healing of ulcerations as judged by colonoscopy within 4 weeks in 8 out of 10 patients (10). The unexpected effect of anti-TNF-α therapy of Crohn's disease is the long duration of clinical remissions, because the circulating half-life of the anti-TNF-α antibody is estimated at about 5–7 days. Moreover, a recent multicenter, double-blind, placebo-controlled trial of 108 patients with moderate-severe Crohn's disease has shown that 41% of the patients (34/83) went into remission by a single infusion of chimeric monoclonal antibody cA2 at 12 weeks, compared to 12% of the patients (3/25) given placebo (11).

Anti-inflammatory drugs such as sulphasalazine, 5-ASA, and corticosteroids are effective for initial or maintenance therapy in IBD, but none of these agents directly inhibits inflammatory cytokines including IL-1β, IL-6, IL-8, and TNF-α. On the other hand, immunosuppressive drugs, such as azathioprine and methotrexate, are expected to inhibit inflammatory cytokines or increase inhibitory cytokines including IL-10, TGF-β, IL-4, and IL-13. The new immunosuppressive agent, cyclosporin, has revolutionized organ transplantation, and has effects on multiple cytokines. Cyclosporin inhibits expression of T-cell cytokines such as IL-2, and INF-γ, and stimulates TGF-β which inhibits lymphocyte function.

Anti-inflammatory cytokine itself has been tried for therapy of IBD. IL-10, one of anti-inflammatory cytokines, inhibits the function of macrophages and monocytes and down-regulates...
the synthesis of proinflammatory cytokines such as IL-1α, IL-1β, IL-6, IL-8, TNF-α, and granulocyte colony-stimulating factor. In a study of three steroid-refractory patients with ulcerative colitis Schreiber et al have indicated topical IL-10 enema improved stool frequency and endoscopic findings, along with a dramatic decrease of TNF-α and IL-1β released by isolated mononuclear cells in the lamina propria of colonic mucosa (12). A recent multicenter, randomized, double-blind placebo-controlled study also has showed intravenous infusion of human recombinant IL-10 was effective for steroid-refractory patients with Crohn’s disease (13).

These new immunomodulatory therapies seem to be of potential interest to control IBD. Further long-term follow-up studies are required to clarify the long-lasting effect and the adverse effect of their drugs.

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References