IL-10 and its related cytokines for treatment of inflammatory bowel disease

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Abstract

Inflammatory bowel diseases (IBDs), including Crohn’s disease and ulcerative colitis are chronic inflammatory disorders of gastrointestinal tract. Although the etiology is incompletely understood, initiation and aggravation of the inflammatory process seem to be due to a massive local mucosal immune response. Interleukin-10 (IL-10) is a regulatory cytokine which inhibits both antigen presentation and subsequent pro-inflammatory cytokine release, and it is proposed as a potent anti-inflammatory biological therapy in chronic IBD. Many methods of IL-10 as a treatment for IBD have been published. The new strategies of IL-10 treatment, including recombinant IL-10, the use of genetically modified bacteria, gelatine microsphere containing IL-10, adenoviral vectors encoding IL-10 and combining regulatory T cells are discussed in this review. The advantages and disadvantages of these IL-10 therapies are summarized. Although most results of recombinant IL-10 therapies are disappointing in clinical testing because of lacking efficacy or side effects, therapeutic strategies utilizing gene therapy may enhance mucosal delivery and increase therapeutic response. Novel IL-10-related cytokines, including IL-19, IL-20, IL-22, IL-24, IL-26, IL-28 and IL-29, are involved in regulation of inflammatory and immune responses. The use of IL-10 and IL-10-related cytokines will provide new insights into cell-based and gene-based treatment against IBD in near future.

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INTRODUCTION

Inflammatory bowel diseases, including Crohn’s disease and ulcerative colitis are chronic inflammatory and frequently relapsing diseases of the gut that ultimately lead to destruction of the intestinal tissue. Over recent decades the incidence of IBD has been rising in the world, and IBD will become increasingly common in Asia, as it has been in the last fifty years in Europe and North America[1]. The pathogenesis of IBD likely involves multifactorial interactions among genetic factors, immunological factors and environmental triggers[2].

BIOLOGICAL CHARACTERISTICS AND FUNCTIONS OF IL-10

IL-10 was first identified in 1989 as a cytokine synthesis inhibitor produced by a subset of murine T lymphocytes termed T-helper-2 (Th2) cells. It is an 18.5 kDa cytokine with a broad immunoregulatory activity. It plays the role of a Th2 cell-derived cytokine, and is produced by several cell types, including monocytes, macrophages, T lymphocytes, B cells, dendritic cells, mast cells and various tumour cell lines. Its main biological functions seem to limit and terminate the...
inflammatory responses, block the proinflammatory cytokine secretion and regulate the differentiation and proliferation of several immune cells such as T cells, B cells, natural killer cells, antigen-presenting cells, mast cells, and granulocytes[9], IL-10 acts on specific IL-10 receptors that have now been cloned, although the signal transduction pathways and kinases that lead to the widespread anti-inflammatory actions of this cytokine are not yet well understood.

Human IL-10 binds as a 2-fold symmetric homodimer to a functional tetramer complex of two receptors[10], consisting of two α- or R1 chains which bind to IL-10, and of two CRF2-4 chains (β- or R2) which initiate the IL-10-induced signal transduction events. CRF2-4 is a member of the II cytokine receptor family (CRF2), which includes the IFN receptors and is encoded by the CRFB4 gene on chromosome 21[11]. IL-10R generates its signals through the JAK1-STAT3 pathway and activates the SOCS-3 gene (suppressor of cytokine signalling-3) of which the expression results in inhibition of JAK/STAT-dependent signalling and the expression of many genes in the cells[12]. Some of the actions of IL-10 can be explained by an inhibitory effect on the transcription factor nuclear factor-κB (NF-κB), but this does not account for all effects as IL-10 is very effective on inhibiting IL-5 transcription which is independent of NF-κB[13].

The immunoregulatory activity of IL-10 is based upon its ability to inhibit both cytokine synthesis and antigen presentation. IL-10 inhibits the synthesis of proinflammatory cytokines (IL-1β, TNF-α, IL-6), and the Th2 cell-derived cytokines (IL-4 and IL-5)[13]. IL-10 also inhibits chemokines such as monocyte inflammatory protein-1α (MIP-1α), RANTES, IL-8 and eotaxin[14], as well as the expression of inflammatory enzymes inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX-2) in macrophages, the proliferation of CD4+ T lymphocytes by inhibiting IL-2 release and reducing expression of major histocompatibility complex (MHC) class II molecules and the costimulatory molecules B7-1, B7-2, and low-affinity IgE receptors (CD23) in antigen-presenting cells, thus effectively blocking allergen presentation by mononuclear cells and dendritic cells to T cells. In addition, IL-10 also increases the expression of several anti-inflammatory proteins, including IL-1 receptor antagonist, soluble TNF-α receptor and tissue inhibitor of matrix metalloproteinases. Although many of the inhibitory effects of IL-10 on T lymphocytes are secondary to this reduction in monocyte-derived pro-inflammatory cytokines, it also has a direct regulatory effect on T-cell differentiation and proliferation by inhibiting IL-2 and IFN-γ release from activated T-cell clones[15].

However, the biology of IL-10 is highly complex. In addition to the down-regulation of immunity, both human IL-10 and murine IL-10 exert immunostimulatory effects by up-regulating MHC class II expression on B lymphocytes, and inducing cytotoxic T-cell differentiation. To complicate the issue, there is strong homology in the complementary DNA of human and murine IL-10 with an open reading frame sequence in the Epstein-Barr virus (human herpes virus type 4) genome, termed viral IL-10. Whereas viral IL-10 shares many of the immunoregulatory properties of human IL-10, it lacks immunostimulatory effects.

IL-10 THERAPY FOR IBD

Recombinant IL-10

The therapeutic experience of IL-10 in animal models of colitis is very encouraging. In vitro studies have shown that exogenous IL-10 can down-regulate the enhanced pro-inflammatory cytokine release from lamina propria mononuclear cells isolated from patients with Crohn’s disease. Early clinical studies in untreated, as well as steroid-refractory Crohn’s disease patients, suggested that IL-10 might have strong potential in the treatment of human diseases. Colombel et al[16] performed a double blind controlled trial to evaluate the safety and tolerance of recombinant human interleukin 10 (IL-10, Tenovil) in subjects operated on for Crohn’s disease. Tenovil treatment for 12 consecutive weeks in patients with Crohn’s disease after intestinal resection was safe and well tolerated. No evidence of prevention of endoscopic recurrence of Crohn’s disease by Tenovil was observed.

Unfortunately, this enthusiasm was dampened by the results of 2 multinational multicenter studies reporting the efficacy and safety of daily subcutaneous injections of recombinant human IL-10 (rhuIL-10) in patients with moderately active and steroid-refractory Crohn’s disease[17,18]. Fedorak et al[17] reported a 24-week double-blind placebo controlled study of 95 patients with moderately active Crohn’s disease randomized to receive subcutaneous rhuIL-10 at 1 of 4 doses (rhuIL-10:1, 5, 10, or 20 µg/kg) or placebo daily. After a 28-day treatment period, a modest response was seen in the group receiving the 5 µg/kg dose, whereby 23.5% of patients (n=17) showed improvement compared with 0% of patients treated with placebo (n=23). Interestingly, higher doses were less effective, although there was no difference in reported adverse events between doses. During the course of a 20-week follow-up period, disease recurrence requiring therapeutic intervention occurred in 70% of placebo-treated patients compared to 55% of the rhuIL-10-treated group[17].

In the study by Schreiber et al[18] involving 329 therapy refractory patients with active Crohn’s disease, no significant differences in the induction of clinical remission were seen between placebo and rhuIL-10 at any dose (1, 4, 8, and 20 µg/kg), although clinical improvement was achieved in 46% of patients in the 8 µg/kg group compared with 27% of patients receiving placebo (P=0.03). The authors also determined the nuclear levels of transcription factor NF-κB p65 and cytoplasmic concentrations of its inhibitor IκBα in ileocolonic biopsy specimens. They noticed significant differences between patients who responded to rhuIL-10 treatment and those who did not, implicating the inhibition of NF-κB nuclear translocation as one possible mechanism of the action of this therapy[18].

Recent studies linking high systemic concentrations of IL-10 with headache, fever[19], and anemia[20] have further aroused the enthusiasm for IL-10 as a therapeutic drug in treatment of IBD. Indeed, the biology of IL-10 is complex. In addition to its effects in down-regulating pro-inflammatory events, IL-10 has been shown to exert immunostimulatory effects by up-regulating MHC II expression on B lymphocytes and inducing cytotoxic T-cell differentiation. Clinical data support these immunostimulatory effects of IL-10 at high systemic doses. Tilg et al[21] reported that patients with Crohn’s disease receiving rhIL-10 at high doses experienced a significant increase in serum neopterin and phytohaemagglutinin (PHA) induced IFN-γ-gamma production from whole blood cells. This phenomenon may be responsible for the lack of efficacy of high doses of IL-10 in the treatment of Crohn’s disease[21]. In fact, the emerging picture regarding the in vivo effects of IL-10 is one of both the anti- and pro-inflammatory effects, depending on the local concentrations of IL-10 achieved, the types of antigens present in the microenvironment, and the activation state of the immune cells in the vicinity. It is possible that high systemic doses of IL-10 alter the balance between its immunoregulatory and immunostimulatory effects, which would explain the bell-shaped curve in therapeutic efficacy reported in the clinical trials. In addition, it is entirely possible that the pharmacodynamics of daily systemic IL-10 administration does not allow for efficient delivery of the cytokine to the local sites of inflammation. The serum half-life of IL-10 is between 1.1 and 2.6 hours, thus, the cytokine may be cleared before
Treatment by lactococcus lactis secreting IL-10

IBD in humans responds to high dose of intravenous interleukin 10, but this cannot be administered orally because stomach acid destroys it. Recently, studies have been published that looked at alternative methods of delivery of IL-10. The first study used the genetically engineered bacterium, Lactococcus lactis (L. lactis), as a delivery vehicle for IL-10. Steidler et al. hypothesised that an oral delivery system that effectively bypassed the stomach might provide a treatment which would cut the dose of IL-10 required and also reduce the risk of systemic side effects. Steidler and his colleagues[23] have engineered a non-pathogenic bacterium that produces interleukin 10, an anti-inflammatory cytokine that reduces inflammatory colitis. They then established two different mice models of inflammatory bowel disease. In the first model chronic colitis was induced by feeding dextran sulphate sodium to the mice over several weeks. When the recombinant bacteria were introduced into the mice stomachs, they survived the acid environment and released interleukin 10 in the colon. The second mouse model had its interleukin 10 gene knocked out. The resultant mice were shown to develop IBD spontaneously within 8 weeks of life. When the team administered the genetically engineered L. lactis to these mice at 3 weeks of age, colitis did not occur in the first place. They showed that daily intragastric administration of IL-10-secreting L. lactis caused a 50% reduction in colitis in mice treated with dextran sulfate sodium and prevented the onset of colitis in IL-10(-/-) mice. High serum concentrations of interleukin 10 were not found, despite good uptake by inflamed cells of the gut mucosa. This approach may lead to better methods for cost-effective and long-term management of IBD in humans. Because the genetically engineered bacterium survives stomach acid, the cytokine can be delivered directly to the inflammatory target in the colon. This could reduce the dose needed and any systemic effects.

However, the release of such genetically modified organisms through clinical use raises safety concerns. Steidler et al. replaced the thymidylate synthase gene thyA of L. lactis with a synthetic human IL10 gene to address this problem. This thyA-hIL10 L. lactis strain produced human IL-10 when infected, and when deprived of thymidine or thymine, its viability dropped by several orders of magnitude, essentially preventing its accumulation in the environment. The biological containment system and the bacterium’s capacity of secreting hIL-10 were validated in vivo in pigs. This approach is a promising one for transgene containment because, in the unlikely event that the engineered L. lactis strains acquired an intact thyA gene from a donor such as L. lactis subsp. cremoris, the transgene would be eliminated from the genome.

Two technical hitches must be ironed out, however, before human trials can be considered. Human interleukin 10 is slightly different from murine interleukin 10, so the L. lactis has to be re-engineered. The second obstacle is that human bile is stronger than mouse bile and is likely to kill the bacteria as they pass through the stomach and duodenum[23].

Gelatine microspheres containing interleukin-10

IL-10 is an anti-inflammatory cytokine that suppresses the T helper 1 immune response and down-regulates macrophages and monocytes. The therapeutic effect of systemic administration of IL-10 for patients with IBD, however, has not been satisfactory. Several studies have indicated that active monocytes, such as macrophages and T cells, play an important role in the pathogenesis of chronic human IBD, although the etiology remains unclear. Manipulation of these cells appears essential for the treatment of patients with IBD. Recently, considerable attention has been paid to the use of polymer microspheres for the sustained release of various drugs and the targeting of therapeutic agents to their sites of action.

Nakase et al.[24,25] developed gelatine microspheres(GM) containing IL-10(GM-IL-10), which can be released sustainedly to a local site without losing bioactivity. They administered these microspheres to IL-10 knockout mice rectally to investigate whether this treatment could ameliorate colitis. Colonic inflammation in mice treated with GM-IL-10 was remarkably reduced compared to those treated with IL-10 alone. Macroscopic and microscopic examination revealed marked improvement of colitis in IL-10(-/-) mice treated with GM-IL-10. mRNA expression of IL-12 in Mac-1-positive cells in GM-IL-10-treated mice was significantly decreased compared with that in the mice treated with IL-10 alone. CD40 expression in Mac-1-positive cells in GM-IL-10-treated mice was decreased more prominently than that in mice treated with IL-10 alone. The therapeutic effects of GM-IL-10 were associated with decreased expression of IL-12 mRNA and down-regulation of CD40 expression in Mac-1-positive cells. Additionally, intestinal administration of these microspheres significantly improved colitis with a decrease in histological score, myeloperoxidase activity, and nitric oxide production compared with those treated with free agents. Gene expressions of TNF-α, IL-1β, and IFN-γ were down-regulated in treated animals. Serum IL-10 levels and systemic macrophages were unchanged after treatment[26].

These data suggest that local macrophages in the intestine play a critical role in the initiation of chronic colitis in the animal model of IBD. A drug delivery system using these microspheres containing immunomodulatory IL-10(GM-IL-10) might be useful for treatment of patients with IBD.

Gene therapy

IL-10 is an endogenous anti-inflammatory and immunomodulatory cytokine that has been shown to prevent inflammation and injury in several animal studies, however clinical IL-10 treatment remains insufficient because of difficulties in the route of IL-10 administration and its biological half-life. It may be possible to use replication-deficient adenoviral vectors to deliver the IL-10 gene directly to gastrointestinal epithelial cells. This would lead to localized high level IL-10 release for a short duration that is determined by the lifetime of the infected cells. IL-10 adenoviral gene therapy has proved very successful in murine models of rheumatoid arthritis[27], a condition with many immunological similarities to Crohn’s disease. Previous studies have demonstrated that adenoviral vectors, when delivered by rectal infusion, could infect intestinal epithelial cells[28]. This approach may be limited by the host anti-adenoviral immune response, that has limited gene expression and prevented re-treatment with other adenoviral vectors[29]. However, there is evidence that the delivery of immunoregulatory genes, such as IL-10, would diminish both the cell-mediated and humoral anti-adenoviral responses[30]. Barbara et al.[31] reported that gene transfer was achieved by intraoperative injection of non-replicating human type 5 adenovirus bearing IL-10 gene, either 24 hours before or one hour after intrarectal administration of dinitrobenzene sulphonic acid in rats. Colonic damage and inflammation were assessed macroscopically and by measuring the myeloperoxidase activity and leukotriene B4 concentrations. Gene transfer increased IL-10 protein in serum for up to six days. IL-10 gene transfer prior to colitis improved colitis macroscopically and histologically, and significantly reduced colonic myeloperoxidase activity and leukotriene B4 concentrations. In contrast, IL-10 gene transfer after the onset of colitis had no beneficial effect. Lindsay et al.[32] showed that local adenoviral vectors encoding IL-10 (AdvmlIL-10) reverse
IL-10 compared with control colons of T cells, monocytes, and dendritic cells, all of which are key to be effective in patients with IBD? IL-10 certainly exhibits potent inhibitory effect on the activation and effector functions of immune-suppressor Treg known to be associated with high systemic levels and may prove to be a potent approach to the treatment of chronic inflammatory diseases such as Crohn’s disease.

Combining regulatory T cells and IL-10
T cells, and in particular, regulatory T(Treg) cells, play a pivotal role in the control of intestinal inflammation. Regulatory cells lacking anti-inflammatory cytokine IL-10 were unable to inhibit IBD, showing that IL-10 was required for the protective effects of lymphocytes in this setting. van Montfrans et al. presented a novel method of IL-10 delivery to intestinal mucosal tissue by the use of transduced T cells. In these studies, the authors demonstrated that T lymphocytes could be engineered by retrovirus construct transduction to express high levels of IL-10 upon activation. With the goal of providing long-term therapy for Crohn’s disease, peripheral blood mononuclear cells were obtained from healthy adults and transduced with a retroviral vector containing IL-10 and green fluorescent protein (GFP). These CD4+ T lymphocytes responded to CD3/CD28 stimulation with a 6-fold increase in IL-10 production that was shown to be biologically active. Transduced cells had high expressions of the mucosal integrin α4β7, and displayed efficient binding to MadCAM-1 expressing cells in vivo, suggesting that they would home to gut mucosa. Importantly, albeit in vitro, cells remained stably transfected for up to 4 months. In the classic CD45RBhigh model, these IL-10 transduced CD4+ cells were able to effectively prevent the development of colitis, even when given up 14 days after the transfer of CD45RBhigh cells. Although circulating levels of IL-10 were not detectable, IL-10-GFP encoding messenger RNA was detected in colons of mice 15 weeks after cell transfer, and IL-10 was detected in the intestinal draining lymph nodes, spleen, and colon, indicating that the IL-10-GFP transduced CD4+ cells persisted in vivo and migrated into the large intestine. The mice receiving IL-10 transduced CD4+ cells exhibited a decrease in the production of TNF-α in the colon and a decreased production of IFN-γ and/or TNF-α in the intestinal draining lymph nodes. These results indicate that the transferred CD4+ cells are stimulated in vivo and therapeutically effective.

One of the advantages of using T cells as delivery vehicles is the likelihood that the cytokine of interest, in this case, IL-10, would primarily be released only on activation in local sites of inflammation, which would avoid the side effects known to be associated with high systemic levels and may further induce the development of immune-suppressor Treg cells in the area of inflammation. Secondly, the use of ex vivo transduction methodology would prevent systemic exposure to the retroviral vector, but still ensure sustained gene expression. However, the question remains, will even local delivery of IL-10 be effective in patients with IBD? IL-10 certainly exhibits potent inhibitory effect on the activation and effector functions of T cells, monocytes, and dendritic cells, all of which are key players in intestinal inflammation. However, the colon from a patient with Crohn’s disease already secreted higher levels of IL-10 compared with control colonos and mononuclear cells isolated from the ileum of patients with Crohn’s disease appeared to be nonresponsive to IL-10. These findings suggest that even if IL-10 is delivered directly to the intestinal mucosa, it may not be therapeutic in Crohn’s disease. This is mirrored by effects both in the IL-10 gene-deficient mouse chronic colitis model and in the dinitrobenzene sulphonic acid model of colitis where IL-10 is able to prevent the development of colitis if given before inflammation develops, but is ineffective if given either exogenously or via gene transfer, once inflammation has become established. However, although IL-10 therapy may be ineffectual in treating active diseases, there may still exist a role for such therapy as maintenance treatment in Crohn’s disease. Low ileal IL-10 concentrations have been shown to predict relapse after ileocecal resection. In addition, it may be that only certain subgroups of Crohn’s disease patients respond to IL-10 therapy, whether it is delivered systemically or locally. It is clear that even among patients with similar clinical presentations, there exists a large diversity of patterns of immune responses to environmental and bacterial antigens. It is not known how patients with these types of immune reactivities respond to different therapies.

CONCLUSION AND PERSPECTIVES
IL-10 is a pivotal cytokine in the control of intestinal inflammation. Several clinical trials have demonstrated that daily systemic rhuIL-10 injections were safe and well tolerated with modest efficacy in Crohn’s disease, but clinical trials with rhuIL-10 in Crohn’s disease were disappointing, although some patients showed healing of intestinal mucosa. With the administered dose of IL-10 in the clinical trials, the ultimate local IL-10 concentrations in the intestine could be too low to result in downregulation of inflammation. Furthermore, higher doses of systemically administered IL-10 (which were also used in the clinical trials) might be detrimental rather than helpful. But it is possible that response to IL-10 is limited to a subgroup of patients, and perhaps delivering the IL-10 in a more sustained and focused manner would prove to be effective. These may be the several reasons why this is not the end of the road for rhuIL-10 therapy in Crohn’s disease. Recently, some novel alternative approaches, including the use of genetically modified Lactococcus lactis, gelatine microsphere containing IL-10, adenoviral vectors encoding IL-10 and combining regulatory T cells, may ensure that delivery of IL-10 is indeed local, tissue-specific, and therapeutic. These therapeutic approaches caused a significant reduction in intestinal inflammation in different mouse models, and they might be useful for treatment of human IBD. However, there is still a long way to go until these approaches can be evaluated in clinical studies.

New mammalian genes that encode IL-10-related cytokines have been described as the result of experiments using cdna subtraction cloning focusing on melanocyte differentiation (IL24), virus-induced T-cell transformation (IL26) or IL-9-mediated gene induction (IL22). The sequencing and annotation of the human genome could lead to the identification of five additional IFN- or IL-10-related genes. Similar to IL-10, these IL-10-related cytokines are α-helical proteins with similar cysteine localizations, whose amino acid sequences are about 20-30% identical. IL-19, IL-20, IL-22A (also known as IFNα2), IL-28B (also known as IFNα3) and IL-29 (also known as IFNα1). Similar to IL-10, these IL-10-related cytokines are α-helical proteins with similar cysteine localizations, whose amino acid sequences are about 20-30% identical. IL-19, IL-20, IL-22, IL-24, IL-26, IL-28A, IL-28B and IL-29 are grouped together on the basis of structural homologies, indicating that these genes are derived from common ancestors. All these new IL-10 superfamily member cytokines are strongly involved in immune regulation and inflammatory response, further studies will provide a better understanding of potential therapeutic utilities, some of them
may reduce adverse side effects and/or increase the efficacy typically seen in IL-10 therapy for IBD in the future.

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