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*Review*

# The Therapeutic Potential of Interleukin 10 in Infection and Inflammation

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**Abstract.** Interleukin 10 (IL-10), a cytokine with inhibitory activity on inflammation and cell-mediated immune responses, holds enormous potential for the treatment of inflammatory and autoimmune disorders. In addition, IL-10 has also been implicated in the immunopathogenesis of a number of infectious diseases through the use of IL-10 knock-out or IL-10 transgenic mouse models. In this review, we delineate infectious and inflammatory conditions in which IL-10 has shown potential for therapeutic manipulation. Specifically, we review the role of IL-10 in human endotoxemia/sepsis and in HIV infection, conditions for which preliminary phase I trials have recently been undertaken. It is suggested that the therapeutic potential of IL-10 to selectively ameliorate human infectious and inflammatory processes can be realized through a careful selection of the clinical conditions in which patients are undergoing concomitant treatment with anti-microbial regimens.

**Key words**: IL-10; IL-10 knock-out mice; infectious diseases; sepsis; HIV.

## Introduction

An appropriate balance of pro-and anti-inflammatory influences in the immune response is critical in the resolution of many pathological conditions. Over the past couple of decades, cytokines and lymphokines, which exert a wide variety of effects on growth, differentiation and inflammation, have been identified. Several cytokines (e.g., IL-2, IFN-α, IFN-γ and GM- CSF) have been evaluated in randomized controlled trials for the treatment of human diseases[8, 33, 76]. Interleukin 10 (IL-10), a cytokine with inhibitory activity on inflammation and cell-mediated immune responses (CMIR)[83], holds enormous potential for the treatment of inflammatory and autoimmune disorders. IL-10 has been used therapeutically in the recent past for the treatment of various autoimmune disorders, such as inflammatory bowel disease and rheumatoid arthritis, in phase II and phase III clinical trials[66, 106]. In addition, preclinical studies have implicated IL-10 in the pathogenesis of a variety of infectious diseases, and it is therefore important to delineate those infectious processes in which administration of IL-10 or its antagonist may be clinically beneficial. In this review, we will discuss the current state of knowledge regarding the role of IL-10 in the immunopathogenesis of a variety of infectious diseases and describe the potential for therapeutic manipulation of IL-10 in HIV infection and in endotoxemia/sepsis.

Abbreviations used: IL-10 – interleukin 10, CMIR – cell-mediated immune responses, IL-10KO – IL-10 knock-out, HIV – human immunodeficiency virus.

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## Molecular Biology and Biological Activities of IL-10

Human IL-10 (hIL-10) is an unglycosylated 18 kDa polypeptide. The hIL-10 gene is located on chromosome 1 [42] and bears >80% nucleotide sequence homology and >73% amino acid sequence homology with murine IL-10 (mIL-10), with both hIL-10 and mIL-10 encoding 178 amino acids in their open reading frame[83, 108]. In contrast to mIL-10, hIL-10, cDNA clones feature the insertion of Alu repetitive sequence elements in the 3' untranslated region[42]. Both mIL-10 and hIL-10 exhibit strong DNA and amino acid sequence homology (71%) to an open reading frame in the Epstein-Barr virus (EBV) genome, BCRF-1[83, 108], leading to the hypothesis that mIL-10 and hIL-10 evolved from a common ancestor. BCRF-1 in EBV also displays IL-10-like activity and has been designated viral IL-10 (vIL-10). The immunoregulatory properties of vIL-10 may confer a survival advantage to EBV through its inhibitory effects on host cell-mediated immunity.

IL-10, initially described as cytokine synthesis inhibitory factor[36, 83, 108], is a pleiotropic molecule whose effects include inhibition of antigen-presenting-cell (APC)-dependent cytokine synthesis by Th1 cells, costimulation of mast cell growth and costimulation of thymocyte growth in the presence of IL-2 and/or IL-4[36, 37, 83]. IL-10 is produced by a wide variety of cell types, including $CD4^+$ T cells, Th0, Th2, $CD8^+$ T cells and clones[34, 83], B cells[20, 47, 78, 93] and monocytes/macrophages[31, 36, 71]. IL-10 inhibits antigen-driven activity of both Th1 and Th2 subsets[34, 37, 83] and, hence, is not strictly a Th2-type cytokine, although it facilitates the induction of Th2 cell types. Treatment of anti-CD3--antibody-stimulated T cells with IL-10 induces long lasting anergy which is not mediated by endogenously produced cytokines such as IL-2, IL-4, IL-10, IFN-γ and TGF-β[21, 50]. However, anergic T cells obtained from mice rendered unresponsive to hemagglutinin antigen showed a 100-fold increase in IL-10 production[19], suggesting that T cells rendered anergic *in vivo* may have become regulatory T cells which influence neighboring immune responses through the release of IL-10[19]. IL-10 has also been suggested to regulate T cell maturation. In IL-10 knock-out mice, a blockade in T cell maturation was observed that could be abrogated by administration of anti-IL-10 antibodies[92]. These observations suggest that dysregulation of IL-10 expression can lead to T cell immunodeficiency[92].

IL-10 inhibits the synthesis of IL-1, IL-6 and TNF-α and inhibits the APC function of Langerhans cells[41], macrophage cell lines and primary monocytes[36, 37, 83]. The potent action of IL-10 on macrophages, particularly at the level of monokine production, supports an important role for IL-10 not only in the regulation of T cell responses but also on acute inflammatory responses[36, 37]. IL-10 has been shown to down-regulate the release of reactive oxygen and nitrogen intermediates and TNF-α[13]. Inhibition of these factors in macrophages by IL-10 results in macrophage deactivation[13], which may allow the growth of tumor cells and intracellular microbes[51]. IL-10 inhibits macrophage costimulatory activity, perhaps through inhibition of the expression of MHC class II[37] and the costimulatory molecule B7.2 on monocytes[28, 39]. Similarly, IL-10 has also been shown to inhibit the LPS-induced survival and cytokine release by eosinophils[101]. These observations suggest that IL-10 may also participate in the regulation of defense mechanisms in eosinophil-mediated parasitic and allergic diseases.

IL-10 exhibits stimulatory effects on B cell growth and differentiation[1, 15, 93]. Naive $IgD^+$ B cells, when activated with anti-CD40 antibodies, secrete IgG1 and IgG3 in the presence of IL-10[16], indicating a critical role of IL-10 in isotype switching and B cell differentiation. Similarly, IL-10 enhances the transcription and production of IgG4 and IgE by B cells[64]. IL-10 acts as an autocrine growth factor for $Ly\text{-}1^+$ B cells, which are important in murine models of autoimmune disease[63]. IL-10 is produced by a wide variety of $EBV^+$ B cell line[47] and B cells from systemic lupus erythematosus (SLE) patients, and IL-10 induces these B cells from SLE patients to secrete immunoglobulins[20, 78].

Studies on the kinetics of cytokine production have revealed that IL-6 and IL-12, along with IL-1, IL-2, TNF-α, GM-CSF, G-CSF and IFN-γ, are the first cytokines synthesized following activation of PBMC by mitogens[36, 96]. IL-10 is produced later and down-regulates the production of cytokines synthesized earlier as well as its own production[57, 96]. We and others have shown that IL-10 produced by different cell types is differentially regulated. IL-12 induces IL-10 production by T cells, whereas TNF-α induces IL-10 production in monocytes[31, 111].

## Molecular Mechanism for IL-10 Mediated Effects

IL-10 interacts with a single high-affinity receptor expressed on most hematopoietic cell types[102], following which it activates the Jak-STAT signalling pathway, specifically the phosphorylation of Jak 1 and Tyk 2 and activation of STAT 1 and STAT 3[90]. The ability of IL-10 to inhibit TNF-α production requires the

presence of STAT 3 and Jak 1[40]. In addition, cyclin D3, cdk6 and p27 play key roles in the IL-10-mediated human B cell differentiation[109]. The inhibitory effects of IL-10 in anti-CD3-antibody-stimulated lymphocytes has been suggested to be mediated by down-regulating the transcription factor NFκB[91] and by down-regulating the TAP 1 family of transporter proteins, which are responsible for transporting peptides from the endoplasmic reticulum to the cell membrane[117]. The complex interaction between signalling molecules with respect to IL-10 is not fully understood and needs further investigation.

## The Role of IL-10 in Inflammation and in Infectious Diseases: Results from Experimental Mouse Models

In general, the beneficial or harmful effects of a particular cytokine can be investigated through a) exogenous administration of the cytokine or its blocking antibody, or b) through the study of mice in which the gene has been selectively disrupted (knock-out models) or over-expressed (transgenic models). The global immunosuppressive effects of IL-10 have been demonstrated by administration of IL-10 to mice. In one study of footpad inoculation with alloantigens and sheep erythrocytes, IL-10 administration inhibited a number of immunologic effects, including delayed-type hypersensitivity, alterations in vascular permeability and increases in footpad cytokine production[75]. Conversely, IL-10 transgenic mice were unable to limit the growth of immunogenic tumor cells[54]. Administration of anti-IL-10 antibodies restored the anti-tumor responses, indicating that cell-mediated responses were globally suppressed in mice producing high levels of IL-10[54].

IL-10 knock-out (IL-10KO) mice demonstrate a state of chronic inflammation characterized by an over-expression of Th1 cytokines[115]. IL-10KO mice are growth-retarded and anemic and feature a form of enterocolitis which is similar to human inflammatory bowel disease and which can be partially ameliorated by exogenous administration of IL-10[70]. This finding has resulted in a great deal of experimental activity relating to cytokine expression and Th1/Th2 balance in the gut immune system in inflammatory bowel diseases. The role of IL-10 in the immunopathogenesis of other inflammatory and autoimmune diseases has also been studied using the IL-10KO mouse. These mice demonstrate more severe disease in experimental allergic encephalomyelitis[11, 29], in virus-induced encephalomyelitis[77], in hypersensitivity pneumonitis[53] and in silica-induced intrapulmonary inflammation[60], suggesting that IL-10 plays a beneficial role in controlling the harmful inflammatory response in the natural histories of these conditions.

The response of IL-10KO mice to infectious challenge depends upon the nature of the host immunologic response to the invading organism. In certain infections, such as *Listeria monocytogenes*[32], *Chlamydia trachomatis*[115] or *Candida albicans*[107], IL-10KO animals demonstrate improved survival compared with their wild-type littermates, suggesting a detrimental role for endogenous IL-10 in the natural histories of these infections. Similar results were obtained in other experimental conditions. Over-production of IL-10 by macrophages has been suggested to explain the increased susceptibility of neonatal mice to infection with *Listeria*[45]. Similarly, IL-10 transgenic mice are highly susceptible to *L. monocytogenes* or *Leishmania major* infection[54], and IL-10 administration abolished the innate resistance to *L. monocytogenes*[65]. In contrast, in infections such as *Toxoplasma gondii*[44], *Aspergillus fumigatus*[52], *Trypanosoma cruzi*[62] or *Schistosoma mansonii*[114], IL-10KO mice demonstrate increased mortality, suggesting a beneficial role of IL-10 in the immunopathogenesis of these infections in normal mice. The observed differences may relate to the relative importance of humoral versus cell-mediated immunity in the host clearance of these different pathogens.

Results for *Mycobacteria* and *Plasmodium* have been conflicting, perhaps relating to differences in the strains tested. In one study, *M. bovis*-infected IL-10KO mice showed lower bacterial burdens than control mice, possibly relating to increased IFN-γ production by macrophages[87]. In a similar study involving antimycobacterial immune responses, IL-10 transgenic mice were highly susceptible to infection with *Mycobacteria*[86]. However, IL-10KO mice infected with *Mycobacterium tuberculosis* did not demonstrate any differences in their course of pulmonary infection compared with their wild-type littermates[88]. Similarly in mouse models of malaria, IL-10KO mice infected with *Plasmodium chabaudi* demonstrated increased mortality[74], but another study using IL-10KO and IL-4KO mice did not demonstrate any differences in the time course of *P. chabaudi* or *P. yoelii* infection, while mice in which Th1-type cytokines had been targeted demonstrated a worse pathology[103].

## The Role of IL-10 in Human Infectious Diseases: Bacterial Sepsis and HIV Infection

In contrast to studies of autoimmunity and inflammation, relatively few clinical trials of IL-10 adminis-

tration in human infectious diseases have been performed to date. Currently, results of IL-10 administration in clinical trials of human infectious processes are limited to HIV and experimental endotoxemia/sepsis. Therefore we will limit our discussion to the role of IL-10 in the immunopathogenesis of sepsis and HIV infection.

*Bacterial sepsis*

Sepsis is a clinical diagnosis marked by a constellation of clinical and laboratory findings suggestive of detrimental immune activation by pro-inflammatory mediators associated with bacterial infection. Patients with bacterial sepsis may, therefore, benefit from the administration of IL-10, provided the triggering infectious pathogen has been eliminated through anti-microbial regimens. In animal models, IL-10 has been shown to elicit protective effects against endotoxic shock[46, 59]. Systemic administration of IL-10 reproducibly protected mice from a lethal intraperitoneal injection of endotoxin, and this protection could be reversed by prior administration of anti-IL-10 antibodies[59]. Furthermore, IL-10KO mice demonstrate increased mortality upon stimulation with endotoxin[58] or staphylococcal enterotoxin B[55] and show exaggerated production of pro-inflammatory Th1-type cytokines.

Numerous animal studies with widely varying models of sepsis have been performed. In general, animal models featuring inflammation in the absence of active infection (such as endotoxin administration) demonstrate benefit when IL-10 is present and detriment when IL-10 is antagonized[10, 46, 59, 99, 119]. In contrast, models using live pathogens, such as bacteremia[49, 65, 105], demonstrate a primarily harmful effect of IL-10 and a beneficial effect of its neutralization. Cecal ligation and puncture (CLP) is a model which mimics the human septic process of peritonitis, as necrotic tissue is present and endogenous gut organisms are released into the circulation. Several studies have demonstrated a beneficial role of IL-10 in this model[104, 110].

In adults with sepsis, IL-10 levels have been found to be elevated[80, 98] and have been correlated with levels of IL-6, IL-8 and TNF-$\alpha$[73]. Circulating IL-10 was found to be elevated in adults with shock of both septic and non-septic origins, but the levels were higher in patients with septic shock[79]. Adults with disseminated meningococcemia and shock have high levels of IL-10 in their serum[35, 73]. In children, high levels of circulating IL-10 were positively correlated with high levels of IL-12[56] and with mortality[69]. In meningococcal shock, levels of IL-10 and other pro- and anti-inflammatory mediators were found to be higher in non-survivors than in survivors[69]. Taken together, IL-10 has been found to be increased in patients with sepsis and septic shock in a similar manner to an acute phase reactant.

*HIV infection*

Several reports have suggested a constitutive production of IL-10 in HIV infection which is enhanced in patients with less than 400 $CD4^+$ T cells/$\mu$l[38, 71]. IL-10 concentrations were found to be increased in the serum of HIV-infected patients, with the highest levels being noted in AIDS patients, in patients with ongoing mycobacterial infection[100] and in patients with rapid HIV/AIDS disease progression compared with non-progressing patients[84]. In addition, patients undergoing therapy with anti-retroviral regimens displayed a significant gradual decrease in serum IL-10 concentrations[100]. Furthermore, high plasma IL-10 levels were correlated with high immunoglobulin levels in serum[85], and single bolus administration of intravenous immunoglobulin caused a further increase in IL-10 levels in plasma and PBMC cultures[85]. These results suggest that a vicious cycle may be operative, where high endogenous levels of immunoglobulin may enhance IL-10 production which, in turn, leads to higher immunoglobulin production[85]. Furthermore, B cell lines derived from AIDS patients are $EBV^+$ and constitutively secrete large amounts of IL-10[9, 81], raising the possibility that IL-10 may play a role in the development of B cell abnormalities in patients with AIDS.

Variable results have been reported regarding IL-10 production following PHA stimulation of PBMC from $HIV^+$ individuals. IL-10 production has been reported to be enhanced[27], to be unaltered[23, 48, 118] or to be decreased[30, 71, 82]. Increased IL-10 production by PHA--stimulated PBMC from $HIV^+$ individuals has been shown to be inversely associated with IL-2 production following stimulation with recall antigens[27]. The inverse correlation of IL-10 production with proliferative responses to recall antigens and anti-CD28 antibodies[27, 30, 71] and the observation that anti-IL-10 antibodies enhance CD28 mediated proliferation[71] suggest that IL-10 exerts immunosuppressive effects by inhibiting the CD28-B7 pathway in HIV infection[71]. Altered production of IL-10 in HIV infection may be of significance, since IL-10 has been demonstrated to inhibit HIV replication[4, 67, 68, 94] and to inhibit the expression on T cells of the chemokine receptor CCR-5[89], which may in turn restrict virus entry into the host cells. In addition, IL-10 has also been suggested as playing a vital role in inducing immune unresponsiveness[26, 27, 30, 71, 72, 95] and in HIV disease progression[25].

We have demonstrated a loss of IL-10 production in a subset of $HIV^+$ individuals which was caused by a defect in T lymphocyte function[71]. Similar results showing down-regulation of IL-10 production by $CD4^+$ T cells were obtained in humans[112] and in symptomatic rhesus monkeys infected with simian immunodeficiency virus[18]. The source of IL-10 production in $HIV^+$ IL-10 producers was within the $CD15^+$ monocytes. These results are in agreement with the observations that infection of monocytes from $HIV^-$ individuals, and of a monocytic cell line with HIV *in vitro*, induced IL-10 production[3, 68, 116]. The molecular mechanism by which HIV infection may induce differential IL-10 production by T cells and monocytes is not well understood. There is evidence to suggest that HIV *tat* antigen induces IL-10 expression in T cells/cell lines and B cells[12, 97]. In contrast, gp41/120 caused a rapid increase in IL-10 production by monocytes but not in T, B or NK cells[7, 14, 95]. HIV *nef* antigen has also been suggested as inducing IL-10 expression in monocytes[17]. Taken together, these findings suggest that the HIV antigens gp41, *tat* and *nef* differentially regulate IL-10 production in T cells and monocytes.

## Therapeutic Potential of IL-10 in Patients with Infectious Diseases

### *Healthy volunteers and patients with endotoxemia/sepsis*

A potentially beneficial role of IL-10 in the pathogenesis of various infectious diseases has been suggested by a number of studies using animal models. For example, in HIV infection, studies conducted to date indicate an important role for IL-10 and suggest a possible role for IL-10-related immunotherapy in combination with concomitant anti-retroviral therapy.

Preliminary studies have been performed in which IL-10 has been administered to healthy adult volunteers[22, 24, 43, 61], and a distinct pattern of alterations in cytokine production, immune responsiveness and immune cell numbers has emerged. The main immunologic effects have been consistent increases in neutrophils and monocytes and reduced lymphocyte counts[22, 24, 61]. In healthy volunteers subjected to experimental endotoxemia, IL-10 reduced LPS-stimulated *ex vivo* production of the pro-inflammatory cytokines TNF-$\alpha$[22, 24, 61] and IL-1$\beta$[22, 24, 61], IL-6[43] and IL-8[43], and also reduced IFN-$\gamma$ production following stimulation with PHA or phorbol esters[43]. Studies comparing IL-10 with corticosteroids, both alone and in combination, have demonstrated that even relatively low doses of exogenous IL-10 (8 $\mu$g/kg, within the dose range which is well tolerated) suppressed *ex vivo* pro-inflammatory cytokine production in a more prolonged and more efficacious manner than did exogenous corticosteroids[22]. IL-10 did not reduce production of the endogenous anti-inflammatory molecules soluble TNF-receptor p55 or IL-1ra[24]. In dose-response studies, adverse effects have been rare at 25 $\mu$g/kg, but higher doses (50 and 100 $\mu$g/kg) have been associated with mild to moderate flu-like symptoms characterized by fever with chills and myalgias[61].

### *HIV infection*

Experimental evidence suggests that administration of exogenous IL-10 to HIV-infected monocyte-derived macrophages results in a dose-related inhibition of HIV reverse transcriptase activity and inhibits TNF-$\alpha$-induced up-regulation of HIV proliferation. Also, exogenous IL-10 may inhibit viral assembly in HIV-infected macrophages. These observations strongly suggested that administration of IL-10 to HIV-infected individuals may have beneficial effects. Three phase I trials of recombinant human IL-10 in HIV infection have been reported[2, 5, 113], all of which reported that IL-10 was well tolerated. In one study, IL-10 transiently reduced HIV replication[2, 113]. In two other studies, however, no significant reduction in plasma HIV RNA levels or changes in $CD4^+$ T cell counts were observed[2, 5], although in several patients a one log decrease in plasma viremia was noted[5]. These divergent findings highlight the complexity of the immunopathogenesis of HIV/AIDS and the difficulty in selecting patients suitable for immunosuppressive therapy.

## Perspectives

IL-10 has shown promising therapeutic effects in many autoimmune and inflammatory disorders. However, in infectious processes, control of the relative balance of beneficial and harmful inflammation is critical. Studies of IL-10 manipulation in animal models have revealed a central role for IL-10 in the immunopathogenesis of a number of infectious diseases, which led to clinical trials of IL-10 administration to humans. Therapeutic administration of IL-10 is unlikely to be beneficial in circumstances where the infectious pathogen have not been eradicated. In humans with endotoxemia/sepsis, IL-10 administration has been shown to mediate a beneficial reduction in pro-inflammatory cytokine production and to ameliorate the harmful hemo-

dynamic and coagulopathic effects of endotoxemia. Demonstration of a beneficial anti-inflammatory effect of IL-10 in sepsis is critically dependent on the selection of patients in whom the infectious trigger has been controlled and the pro-inflammatory septic cascade is harmful rather than beneficial.

To date, phase I trials of administration of IL-10 to $HIV^+$ individuals have met with very limited success. In a manner similar to sepsis, IL-10 administration to $HIV^+$ individuals may be useful in arresting detrimental inflammatory processes, but may be ineffective when viral replication is ongoing. For example, IL-10 may have no beneficial effects when peripheral HIV viral loads remain high or when the virus has not been eradicated from the reservoir tissues and cells. In fact, IL-10 may have detrimental effects in this situation as it has been shown to enhance virus replication in cell lines chronically infected with HIV, a situation which may hold true in HIV-infected patients[6].

Overall, IL-10 holds great promise as a therapeutic anti-inflammatory agent in human and animal infectious diseases. IL-10 antagonists may be clinically useful in diseases which show protective Th1 responses such as lepromatous leprosy, tuberculosis and visceral leishmaniasis. However, to demonstrate the beneficial effects of IL-10, it is paramount that a proper set of patients are selected for analysis and that the immunopathogenesis of the condition under study be fully understood.

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