

Interleukin 10 (IL-10) Regulatory Cytokine and its Clinical Consequences

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Abstract

IL-10 involvement in disease progression continues to be evaluated. Through these studies it has become evident that the role of IL-10 in immunological conditions encompasses a large range of disorders. IL-10 deficiencies can lead to Th1 hypersensitivities i.e. Celiac's disease and autoimmune disorders i.e. type 1 diabetes (T1D). Conversely, increased IL-10 results in Th2 related hypersensitivities i.e. allergic dermatitis and autoimmune disorders i.e. systemic lupus erythematosus (SLE). These polar conditions are related to increases in either Th1 cytokines or Th2 cytokines respectively. With the dominant role of IL-10 being regulatory, clinical consequences can result from IL-10 related immuno-suppression. These enhanced IL-10 regulatory responses are related to improper clearance of pathogens and tumor cells, resulting in chronic infections and tumor development. Interestingly, HPV, HCV, HBV and other common chronic pathogens can persist even with normal levels of IL-10 but can be cleared by inhibiting IL-10 function.

Keywords: Inflammatory bowel disease (IBD); Collagen induced arthritis (CIA); Rheumatoid arthritis (RA); Type 1 diabetes (T1D); Nonobese diabetic (NOD); Systemic lupus erythematosus (SLE); Allergic dermatitis (AD)

Introduction

The Interleukin 10 (IL-10) cytokine is required for regulating immune functions by promoting the widespread suppression of immune responses through its pleiotropic effects. The autocrine/paracrine capabilities of IL-10 by direct binding to leukocytes and resultant containment of immune responses is considered the primary function of this cytokine. IL-10 secretion from CD4⁺CD25⁺FoxP3⁺ regulatory cells (Tregs), macrophages and other leukocytes followed by subsequent binding to IL-10 receptors on macrophages and dendritic cells (DCs) has been linked to reduced antigen presentation and increased T-cell energy [1,2]. The cytokine also functions to minimize the development of Th1 responses by decreasing Th1 related cytokines (IL-12 and IFN- γ) and encouraging Th2 responses by increasing levels of Th2 related cytokines (IL-4, IL-5 & IL-13) [3,4]. Furthermore, increased levels of IL-10 has been associated with increased activity of programmed cell death 1 (PD-1) protein and cytotoxic T-cell lymphocyte antigen 4 (CTLA-4) co-receptors on T-cell which function as negative regulators of T-cells, while also being associated with decreased CD28 co-receptor activity on T-cells, all of which are associated with reduced effector T-cell function [1,2,5]. Additionally, IL-10 is effective at decreasing levels of pro-inflammatory cytokines: IL-2, IL-6, IL-1 β , IL-12, GM-CSF, TNF- α and IFN- γ , in both stimulatory and naïve situations related to the presence or absence of sufficient antigen [1,6]. The reduction of these cytokines minimizes leukocyte maturation, recruitment and inflammation. Finally, IL-10 has been directly linked to reducing anaphylactic responses following antigen exposure and other potentially lethal inflammatory response i.e. hepatic acute phase responses [7].

While the majority of responses related to IL-10 signaling are classified as immune inhibitors, there are functions of IL-10 that are associated with pro-inflammatory responses. These are related to Th2 responses and are typically restricted to B-cells, granulocytes and NK cells [4,8,9]. IL-10 secreted from NK cells has been linked to increases in Th2 related autoimmune disorders [10,11]. Additionally, IL-10 has been shown to increase B-cell proliferation and development by functioning as a co-factor with IL-4 [12]. Interestingly, IL-10 secreted from DCs combined with IL-4 signaling enhances isotype switching

to IgE antibodies which directly affects granulocyte sensitization, while Treg derived IL-10 coupled with IL-4 function has been shown to prevent IgE switching and encourages production of IgG related isotypes and can specifically lead to the development of IgG4 which is associated Mikulicz disease [13-16]. The role of Treg derived IL-10 is related to minimizing the production of auto-reactive B-cells and involves the presence of PD-1 that is expressed at high level on Tregs. IL-10 secreted from Tregs, coupled with the presence of PD-1 ligand (PD-1L) preferentially selects the development of non-self reactive B-cells to become plasma cells which typically produce IgG isotypes. Interestingly, auto-reactive B-cells have decreased levels of PD-1L and may not require T-cell help [17,18]. Finally, there has also been evidence that IL-10 plays a role in CD8⁺ Cytotoxic T lymphocyte (CTL) induction in islet cell allografts [19].

While normal levels of IL-10 can lead to biological consequences like persistent infections, misregulation or abnormal levels of IL-10 can lead to other consequences: atypical innate immune response, autoimmune disorders, cancer development and allergic reactions. As will be discussed later, IL-10 promoter polymorphisms have been identified and attributed with a predisposition for autoimmune disorders and certain types of hypersensitivities [20]. Misregulation of IL-10 expression is a key factor in the development of immunological related conditions that can be linked to IL-10. IL-10 regulation is controlled by two events: Chromatin changes associated with histone modifications and transcription factor activation or silencing by DNA methylation. Additionally, protein can be differentially modified following translation to alter the functional capability of IL-10. Many cell types expression IL-10 and at different levels so factors that control IL-10 production vary [21].

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IL-10 Secreting Cells

Most leukocytes secrete IL-10 at some level. The majority of IL-10 secretion comes from monocytes and their common mature forms following differentiation: Macrophages and both plasmacytoid and myeloid dendritic cells [22]. Some specific granulocytes and Agranulocytes: eosinophils and NK cells, as well as the small lymphocytes: T and B cells, also secrete IL-10 but at a lower level [1,10]. Within the small lymphocyte group of cells types, the CD4⁺CD25⁺FoxP3⁺ regulatory T-cells produce a significant amount of IL-10 and are directly involved in developing T cell anergy and tolerance induction.

While IL-10 secretion is commonly thought of as being restricted to leukocytes, epithelial cells from mucosal surfaces particularly in the GI track can secrete IL-10 and have an important function in minimizing immune responses to commensal bacterial flora. Studies have shown that decreases in IL-10 in these cells can lead to colitis, Crohn's disease and other inflammatory bowel diseases [23].

IL-10 Effects on Leukocytes

Some of the more significant and well established IL-10 responses are on professional antigen presenting cells (APCs) which results in a decreased expression of MHC Class II molecules accompanied by a decrease in antigen presentation as well as decrease in B7 co-stimulatory molecules on macrophages [1]. In B-cells, IL-10 promotes B-cell proliferation, plasma cell development, and has differential responses related to isotype switching [13-16]. In T-cells IL-10 stimulates a shift towards Th2 response while minimizing Th1 response via the reduction of IL-12 and IFN- γ and the increase in IL-4, IL-5 and IL-13 [3,4]. Additionally, IL-10 is also associated with the development of Tregs from CD4⁺ T-cells [24]. IL-10 in NK cells increase proliferative response to IL-18 and also increase in the levels of major histocompatibility like molecules (MIC) A and B thereby increasing NK cell function. This direct role of IL-10 on MIC upregulation is suggested to be a regulatory response due to the ability of IL-10 induced NK cells function to kill autologous macrophages which minimizes antigen presentation [25,26].

Tolerance Induction

The development of CD4⁺CD25⁺Foxp3⁺ Tregs is associated with promoting activate tolerance to antigen exposure. It is not entirely clear how Tregs promote antigen tolerance but many factors have been established. One of those essential mechanisms is the production of IL-10. IL-10 secretion from Tregs is increased upon exposure to antigen and it is suggested that IL-10 secreted from Tregs helps facilitate tolerance by inducing T-cell anergy [27]. Additionally, studies in inflammatory bowel disease related to hypersensitivities have revealed decreased levels of IL-10 secretion from Tregs [28]. IL-10 has also been shown to be important for the development of Tregs. A common mechanisms for Treg development involves antigen presentation on tolergenic DCs coupled with IL-10 co-factor signaling in CD4⁺ T-cells to encourage the CD4⁺ T-cells to produce high levels of CD25⁺ and FoxP3 as well as IL-10 [29,30]. Tolergenic DCs typically have decreased levels of CD80 and CD88 while maintaining sufficient levels of MHC II for proper presentation to CD4⁺ to develop activate Tregs.

IL-10 Deficiency: Model for Hypersensitivity and Th1 Autoimmunity

Given that IL-10 is a critical regulatory cytokine, decreased levels have the potential to influence hyper immune situations. The

development of an IL-10 knock out mouse model has been a great tool for assessing IL-10 deficiencies and the potential for hypersensitive responses and autoimmunity. IL-10^{-/-} mice develop hyper Th1 responses like rheumatoid arthritis and other severe inflammatory conditions i.e. colitis [31]. In the rheumatoid arthritis model, IL-10 deficient mice were immunized with type II collagen. When compared to wild type (WT) mice, 20 days after immunization 100% of KO mice presented with arthritic symptoms while only 5% of the WT mice had similar symptoms. These symptoms were paralleled with a significant increase in Th1 cytokines (IFN- γ and IL-12) and a decrease in Th2 cytokines (IL-4, IL-5 and IL-13) [32]. Additionally there was a decrease in IgG1 and IgG2a specific collagen antibodies in the deficient mice. Colitis is a hallmark symptom in IL-10 KO and is developed spontaneously in these mice [31]. This severe inflammation in the GI track of IL-10^{-/-} mice are coordinated by an increase in Th1 related cytokines while Th2 related cytokines are not detectable [33,34]. These data clearly demonstrate an IL-10 deficiency results in the reduction of Th2 responses while encouraging a Th1 response and will increase the potential for Th1 related autoimmunity. Furthermore, cytokine profiles were measured from clinical samples taken from patients with Th1 Type IV hypersensitive to gluten which develops into Celiac's disease [35]. This cytokine profile indicates a decrease in IL-10 and Th2 related cytokines while presenting with an increase in Th1 cytokines. Additionally, an increase in antibody titers to gluten in hypersensitive patients could not be verified [36]. Interestingly, IL-10 promoter polymorphisms (-1082G/A, -819C/T, -592C/A), which results in decreased levels of IL-10 occur in higher frequency within individuals with a HLA-DQ2 haplotype which has been linked to a predisposition for development of Celiac's disease [37].

Early evidence from human subjects with Type I diabetes (T1D), rheumatoid arthritis (RA), psoriasis and other Th1 related autoimmune disorders showed decreased levels of serum IL-10, IL-4 and IL-5 paralleled with an increased level of Th1 related cytokines: IL-12 and IFN- α [38,39]. Using nonobese diabetic (NOD) mouse models with IL-10 deficiencies has revealed an increase in pancreatitis, decreased insulin production and increased blood glucose levels compared to normal NOD mouse models. Additionally, there was an increased shift to Th1 related responses in IL-10 deficient NOD mice. Curiously, there is no evidence of increases in Th1 responses in NOD mice with normal IL-10 levels when compared to non-diabetic control mice [40]. These data indicate that, at least in mouse studies, IL-10 deficiencies are required for the complete development of T1D related symptoms. Finally, evaluation of IL-10 promoter polymorphisms in symptomatic patients (-1082G/A, -819C/T, -592C/A) revealed a predisposition to RA that is not seen in T1D patients. These studies revealed a range of 26% to 58% frequency in RA patients while in the normal population the frequency is up to 5% [41-43].

IL-10 Upregulation, Cancer, Persistent Infections and Th2 Autoimmunity

While the role of IL-10 at preventing chronic immune responses is important in limiting the development of autoimmune and hyper immune responses, increased IL-10 regulation has a negative impact on the biological system, specifically with the increased chance of cancer development, chronic infections and Lupus (Th2 dependent autoimmune disorder). Viral infections can become chronic due to IL-10 upregulation [44-47]. A well developed immune system is required for proper clearance of pathogens, particularly ones that are adept at avoiding immune response: malaria causing *Plasmodium*, Hepatitis B and C Viruses (HBV, HCV), Epstein Barr Virus (EBV), Human

papilloma virus (HPV), Human Immunodeficiency Virus (HIV) and others. While increased levels of IL-10 can result in severe immune-suppression, even normal levels of IL-10 can allow for chronic infection due to decreasing levels of pro-inflammatory cytokines and promoting effector T-cell anergy [48]. Anti-viral medication has been shown to decrease levels of IL-10 thereby allowing the immune system to mount a stronger attack against the persistent viral infection [49,50]. Additionally some of the more common viruses associated with chronic infections like EBV encodes viral IL-10 to promote a tolerant environment which allows for prolonged infections [51]. The role of IL-10 in contributing to the persistence of pathogen infections was further established by infecting IL-10^{-/-} mice with common microorganisms associated with chronic infections in humans. These studies demonstrate that IL-10 deficiencies prevent persistent infection when compared to WT mice [52].

Increased levels of IL-10 secreted from macrophages have also been associated with certain types of cancers, particularly non-small cell lung cancers. Solid tumor masses consist of a range of cell types including both tumorigenic and non-tumorigenic cells which are composed of endothelial cells and fibroblasts. Additionally, there is sufficient amount of white blood cell (WBC) infiltration within tumors. Tumor associated macrophages (TAMs) make up a large portion of the WBC population in the tumor masses. The development of cancer antigen specific T-cell response is important in minimizing the progression of tumor formation. The TAMs play a crucial role in promoting cancer development due to their ability to minimize the production of T-cells that target tumor cells. Profiling TAMs revealed increased levels of IL-10 secretion as well as decreased levels of MHC molecules and B7 molecules [53,54]. Animal models revealed more evidence that IL-10 can promote cancer development. Macrophages were induced by IL-10 stimulation of monocytes and then transferred to mice that were implanted with tumor cells. Tumor pathology from these mice showed significantly larger tumors, increased angiogenesis and advanced metastatic tumor development compared to macrophages induced by either: IFN- γ , IL-12, IL-4 or IL-5 [55,56].

While deficiencies in IL-10 can lead to the development of Th1 related autoimmune responses, increases in IL-10 can lead to a development of Th2 responses. As previously mentioned, IL-10 activity promotes Th2 responses coordinated by an increase in IL-4, IL-5, IL-13 cytokines. Prolonged exposure to increases in IL-10 can lead to Th2 related autoimmune responses. This is evident in the evaluation of cytokines profiles in systemic lupus erythematosus (SLE) patients and studies in animal models. SLE is a categorized as a Th2 autoimmune disorder related to the production of autoreactive IgG antibodies [10,11]. The common SLE related self antigens are nuclear self antigens i.e DNA binding histones and rheumatoid factor. Studies linking IL-10 to SLE development have revealed that increased levels of IL-10 derived from NK cells and CD4⁺ cells with increased PD-1 are critical for the development of SLE in New Zealand Black (NZB) and New Zealand White (NZW) mixed strain [57]. These NZB/NZW mice develop spontaneous SLE symptoms. Additionally, studies evaluating systemic cytokine profiles as well as cytokines secreted from CD4⁺ cells isolated from peripheral blood mononuclear cells (PBMCs) isolated from SLE patients have been performed. These studies revealed an increase in IL-10 secreted from CD4⁺ cells as well as increased in Th2 related cytokines. A similar systemic cytokine profile was observed in these patients [58]. Additionally, evaluation of methylation profiles from CD4⁺ cells isolated from SLE patients revealed a decrease in methylation of the IL-10 promoter region which is associated with unregulated levels of IL-10 [59].

IL-10 in Th2 Related Allergic Responses

The development of immunological sensitization related to the increased production of IgE antibodies through Th2 responses is associated with increases in IL-4 and IL-5 cytokines. While this mechanism of type I hypersensitivity development is well known, the role of IL-10 has been less investigated. Studies using models related to Th2 allergic responses have been beneficial in establishing a definitive role of increased IL-10 in a pro-inflammatory setting. While several pro-inflammatory observations related to granulomas, B-cell proliferation, Th2 responses and systemic IgE isotypes have been linked to IL-10, it has only been until recently that direct roles of IL-10 in some of these immune responses could be verified [4,8]. Studies related to food allergies, eosinophilic esophagitis (EE), allergic dermatitis induced by eosinophil recruitment and asthma have been used to establish a definitive role of IL-10 as a potential inducer of Th2 hypersensitivities.

Clinical samples were taken from children with milk allergies or EE and compared to their asymptomatic siblings. The cytokine profile in dendritic cells (DCs), IgE receptor levels and IgE antibody crosslinking, as well as antigen stimulation revealed an increase in IL-10 in the affected patients that were assessed. First, when comparing DC between patients and sibling controls there was a significant increase in IgE receptors. When measuring cytokines secreted from unstimulated DCs isolated from peripheral blood there was an increase IL-10 but not IL-6, GM-CSF or TNF- α . When these pDCs were cross linked with non specific IgE antibody pools again only a significant increase in IL-10 was observed. Finally, when isolated DCs were stimulated with IgE antibody pools followed by the addition of crude milk extract allergens there was a significant increase in all cytokines. These data indicate that IL-10 may play a role in sensitization of Th2 related allergic response while IL-6, GM-CSF and TNF- α play a role in the hypersensitive response [60]. Similar results were observed when measuring cytokine production from PBMCs extracted from patients with severe allergic rhinitis and asthma, only patients exposed to allergens produced increased levels of IL-6, GM-CSF & TNF- α , while the IL-10 increase was observed in these patients prior to and after exposure of allergen [8].

Allergic dermatitis (AD) is a hypersensitive skin condition associated with dermal blistering, increased infiltration of eosinophils and elevated levels of IgE isotype antibody indicating a Th2 hypersensitive reaction. Many environmental allergens can cause the development of this hypersensitization. Additionally, when comparing industrialized regions to rural regions there is a 3-fold increase in cases of AD believed to be due to increased exposure to industrial related substances [61-63]. Studies in IL-10 deficient mice demonstrated the absence of IL-10 levels reduces dermal lesions, eosinophilic infiltration into dermal and subcutaneous layers following cutaneous sensitization with ovalbumin (OVA) coated dermal strips. Additionally, when evaluating OVA stimulated T-cell responses from WBCs isolated from draining lymph nodes and spleen, there was a decrease in Th2 related cytokines in the IL-10^{-/-} mice [4].

Mucosal IL-10 and Bacterial Flora

Maintaining tolerance to enteric flora within the GI tract is important in minimizing the development of inflammatory bowel disease (IBD). Epithelial derived IL-10 within the intestines is a critical factor for preventing inflammatory responses to commensal pathogens in the intestines [64]. IL-10 KO mice develop spontaneous IBDs and present with an abnormal bacterial flora profile; *Lactobacillus* strains

are common bacterial flora found with the GI track. IL10 KO mice present with decreased levels of *Lactobacillus* strains and increased levels of *Bacteriodes*. This shift in commensal bacteria in IL-10^{-/-} mice are believed to be due to the *Lactobacillus* being more sensitive to inflammatory condition which allows for *Bacteriodes* to supplant *Lactobacillus* in an IL-10 deficient environment. IL-10 deficiency coupled with abnormal bacterial flora contributes to abnormal digestion and the development of severe inflammation within the digestive system [65].

IL-10 Supplementation as a Therapy

Whether through direct injection of IL-10 or IL-10 gene delivery methods, the use of recombinant IL-10 (rIL-10) supplementation in autoimmune and hypersensitive disorders has been beneficial for minimizing these disorders. In addition to the delivery of rIL-10, biological IL-10 can be augmented in cases involving adoptive transfer of, or increasing levels of IL-10 secreting regulatory cells. IL-10 augmentation has been explored in many types of disorders: T1D, RA, IBD, asthma models and others.

Viral gene delivery studies to increase systemic levels of IL-10 have ameliorated T1D related symptoms in NOD mice. Intramuscular injections of an adeno-associated virus (AAV) encoding IL-10 results in increased levels of circulating IL-10. Following injection, the spontaneous development of T1D symptoms in NOD mice was prevented as seen by a decrease in pancreatitis, blood glucose, insulin autoantibodies and preservation of stable levels of insulin [66].

Viral gene delivery of IL-10 has also been used in models of RA, allergic responses & IBD. As previously mentioned, immunizing mice against collagen results in the development of RA like symptoms. Gene delivery of IL-10 prevented the development of RA in this collagen induced arthritis (CIA) mouse model [67]. Further studies in the CIA model used the adoptive transfer of hematopoietic stem cells that were transfected with a lenti viral vector encoding IL-10. These IL-10 enhanced stem cells increased the levels of IL-10 in recipient mice and prevented arthritic symptoms following collagen immunization [68]. Similar responses were observed following intra-articular infection of an adenoviral vector expressing IL-10 in the CIA model [69].

Inflammatory bowel disease (IBD) murine models have been established and IL-10 supplementation in these mice has been successful at minimizing IBD symptoms. The models for spontaneous development of colitis in IL10^{-/-} mice were utilized to test gene delivery of IL-10. An AAVrh10 vector, which has high tropic factors for intestinal epithelial cells, with an IL-10 transgene was infused by I.V infection in IL-10 KO mouse. Inflammatory scores were significantly reduced in the GI tract tissue sample following vector delivery expressing IL-10 [70]. While IL-10 deficient mice develop IBD symptoms, treatment of WT mice with trinitrobenzene sulphonic acid (TNBS) leads to disease symptoms in mice similar to Crohn's Disease. These symptoms could be reversed by intravenous (I.V.) delivery of an adenoviral vector encoding IL-10 [71].

The potential for IL-10 treatment to minimize T1D, RA & IBD symptoms in mouse models could not be replicated in clinical trials. The therapeutic regimen in these clinical trials has remained relatively constant in the different clinical trials. The rIL-10 administration protocol consists of I.V. or S.C (subcutaneous) injections at different dose cohorts 3 times a week for 4 to 6 weeks [72]. Gene therapy strategies which could lead to long term IL-10 supplementation have not been approved for clinical trial due to side effects of short

term IL-10 supplementation observed by the direct injection of IL-10 in patients. Many patients who received abbreviated IL-10 supplementation developed pre-anemic condition related to decreases in red blood cells (RBCs), while the level of RBCs stayed within the normal range following administration of rIL-10 in a clinical trial, the levels dropped in most patients and where borderline for anemic conditions. In addition to this concerning side effect the benefits to short-term administration of IL-10 were minimal. A mild reduction in systemic Th1 related cytokines has been observed. Some success was observed when the IL-10 treatment procedure was coupled with a steroid induced refractory period. The IL-10 treatment prolonged the relapse of GI track inflammation following steroid treatments [73].

Discussion

The balance of cytokines is critical for normal immune responses. Irregular cytokine levels can shift the immune responses from being beneficial to being harmful. IL-10 has a broad spectrum response in the immune system and is predominately involved in regulating immune responses which prevent hyper immunity. Still, roles of for IL-10 as stimulatory have been established adding to the breadth of IL-10 function within the immune system. Due to the widespread effects of IL-10, a large range of disorders has been reported due to the misregulation of IL-10. In situations of IL-10 deficiencies, Th1 hyper responses and autoimmune response can occur; conversely elevated levels of IL-10 can lead to a skewed Th2 response and hypersensitive responses. Increased Th2 cytokines lead to hyper production of antibodies and increase sensitization of granulocytes [8]. These IL-10 induced conditions result in increase allergic responses, asthma and Th2 related autoimmune disorders i.e. systemic lupus erythematosus (SLE). The presence of increased IL-10 levels in Th2 related immunological hypersensitivities suggests a pro-inflammatory role of IL-10. Still it cannot be ruled out that IL-10 in Th2 related allergic response may actually be a regulatory role by limiting the production of TNF- α and preventing anaphylaxis [7]. Cytokine profiling in models for anaphylaxis or evaluating clinical samples taken from patients with potentially fatal allergies such as type I hypersensitivity to peanuts may help verify that IL-10 functions regulate acute fatal responses in Th2 hypersensitive environments.

Since abnormal IL-10 levels commonly results in disorders of the immune system, IL-10 promoter polymorphisms have been thoroughly investigated. These studies have revealed predispositions to autoimmune and hyper immune disorders due to these genetic variations [40-42,74].

Increased levels of IL-10 can lead to other symptoms related to the reduction of T-cell responses. IL-10 is very effective at reducing antigen presentation by APCs and leading to T-cell anergy. This constitutes a significant immune suppressive response by IL-10. As a result of immune suppression, opportunistic consequences can occur. These include chronic infections and increased potential for developing certain types of cancers. Efforts to link IL-10 promoter polymorphisms to the development of cancer have been explored and no definitive connection has been established [75]. One expectation has been seen in the development of B-cell Hodgkin's Lymphoma [76]. Curiously, the incidence of Human Papilloma Virus (HPV) related cervical cancer has been linked to IL-10 promoter polymorphisms which contribute to an increased potential for prolonged infection [77].

Using IL-10 as a therapy, although effective in murine models, has not shown promise in clinical setting. Additionally, short term delivery of IL-10 in clinical trials results in a discouraging reduction in red

blood cells in most patients. While long term IL-10 treatment in mice using gene transfer strategies provided enthusiasm for this approach in patients, the consequences of long-term IL-10 in human could be dramatic and has precluded long-term IL-10 treatment in humans.

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