

REVIEW

Interleukin-10: an anti-inflammatory cytokine with therapeutic potential

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Summary

Inflammatory allergic disorders, such as bronchial asthma, allergic rhinitis and atopic dermatitis, are characterized by the production of numerous cytokines and chemokines by activated cells present in target tissues, including T cells, mast cells, macrophages and eosinophils. Among these cytokines, interleukin (IL)-4, IL-5, granulocyte-macrophage colony stimulating factor (GM-CSF) and tumour necrosis factor (TNF)- α , contribute directly and indirectly to the onset and the perpetuation of tissue eosinophilia, a hallmark of these diseases. IL-10 downregulates antigen-dependent activation of most of the cell types involved primarily in allergic reactions and prevents eosinophils homing to inflammatory sites, particularly the lung, in experimental models of asthma. Therefore, the exogenous administration of this cytokine, or the stimulation of its endogenous production, may represent a future objective in the treatment of the inflammatory component of allergic diseases. This review aims to summarize recent findings describing the anti-inflammatory profile of IL-10, particularly in the context of atopic diseases, and discuss its potential therapeutic use as an anti-allergic molecule.

IL-10: molecular aspects and cellular origins

Human IL-10 is a protein of 160 amino acids, with a molecular mass of 18.5 kDa, which contains two intramolecular disulphide bonds. The gene encoding IL-10 is located on chromosome 1 and contains several non-coding sequences which are involved in the regulation of its transcription and of the stability of the corresponding mRNA [1]. Previous findings have shown the involvement of cAMP in the intracellular signals linked to IL-10 gene activation. Accordingly, agents capable of increasing cAMP levels, such as prostaglandin E₂ or the phosphodiesterase type IV inhibitor, Rolipram, augment IL-10 gene transcription in monocytes and macrophages [2,3].

Human IL-10 receptor (hIL-10R) gene maps to chromosome 11q23.3 [4] and its expression have been associated mainly with haematopoietic cells [5]. The extracellular domain of hIL-10R is a monomeric glycosylated protein of 35–45 kDa, which binds hIL-10 to form a single complex involving two hIL-10 dimers [6].

IL-10 was characterized initially as a factor generated by mouse T-helper 2 (TH2) cells which prevent cytokine production by TH1 cells [7]. However, several other cell types have been further identified as a source of this cytokine, including CD4⁺ and CD8⁺ T lymphocytes, monocytes/macrophages, mast cells, keratinocytes, eosinophils, epithelial cells and various tumour cells [8,9]. Thus, IL-10 cannot be considered as a TH2-specific cytokine since its pattern of expression resembles IL-6 more than IL-4 or IL-5. In the majority of inflammatory disorders, cells of the monocytic lineage represent the major source of IL-10.

Most of the stimuli causing activation of monocytes/macrophages (bacterial wall components, parasites, HIV virus), of T cells (human T-cell leukaemia virus type 1) or of B cells (Epstein virus) promote IL-10 release. Furthermore, hormones, cytokines and lipid mediators generated during inflammatory reactions upregulate IL-10 synthesis in both T cells and macrophages [10]. Of interest, glucocorticosteroids, phosphodiesterase type IV inhibitors and the immunosuppressive compound cyclosporin A enhance IL-10 production both *in vitro* and *in vivo* [3,11–13]. To what extent this phenomenon contributes to the clinical efficacy of these drugs remains, however, to be determined.

Target cells for the biological activity of IL-10

Effect on inflammatory cells

The concept that IL-10 acts as an anti-inflammatory molecule was suggested primarily by studies showing inhibition of the synthesis of a large spectrum of pro-inflammatory cytokines by different cells, particularly of the monocytic lineage. Thus, IL-10 inhibits the production of IL-1 α , IL-1 β , IL-3, IL-6, IL-8, TNF α , G-CSF and GM-CSF and

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chemokines, including IL-8 and macrophage inflammatory protein (MIP)- α from lipopolysaccharide (LPS)-activated human monocytes [8,10]. These cytokines and chemokines play a critical role in the activation of granulocytes, monocytes/macrophages, NK cells, T and B cells and in their recruitment to the sites of inflammation. Collectively, these observations suggested that IL-10 plays a pivotal role in orchestrating the inflammatory reaction involving macrophage/monocyte activation in particular.

Addition of IL-10 to LPS-stimulated human mononuclear cells and neutrophils suppresses cytokine synthesis, mainly via the inhibition of the transcription of their corresponding genes [14,15]. IL-10 also prevents cytokine synthesis by post-transcriptional mechanisms, as shown in human macrophages where the inhibition of IL-1 α , IL-1 β and TNF α release induced by LPS is a direct consequence of mRNA degradation of their corresponding genes [16]. Since the protein synthesis inhibitor cycloheximide antagonizes the protective effects of IL-10, it was suggested that IL-10 may be responsible for the new synthesis of a ribonuclease acting on cytokine transcripts [16]. The ability of IL-10 to decrease mRNA stability has also been shown for a number of cytokines, including IL-6, IL-8, G-CSF, GM-CSF and IL-10 itself [14,15,17,18].

Endogenously produced IL-10 may also influence cell activation in an autocrine fashion, as in the case of human monocytes where IL-10 released upon activation down-regulates the generation of a large variety of cytokines as well as the expression of major histocompatibility complex (MHC) class II molecules [9]. Furthermore, monocyte activation in the presence of a neutralizing anti-IL-10 antibody increases proinflammatory cytokine production, suggesting that endogenous IL-10 may play a role in facilitating the resolution of the inflammatory response. IL-10 also prevents its own generation by LPS-stimulated monocytes, indicating an autoregulatory mechanism of IL-10 expression involving a negative feedback [8].

Interestingly, the anti-inflammatory properties of IL-10 are not linked exclusively to the inhibition of cytokine production, since its addition to purified monocytes or neutrophils promotes the release of the IL-1 receptor antagonist [19] which exerts anti-inflammatory activities on its own. IL-10 also prevents free oxygen radical release and nitric oxide-dependent microbicidal activity of macrophages and decreases their ability to generate prostaglandins [20].

Another important cell target for the anti-inflammatory activities of IL-10 is the neutrophil, which is deactivated in terms of cytokine, chemokine and mediator production in response to different stimuli, particularly LPS [21].

These findings indicate collectively that IL-10 down-regulates inflammatory reactions mainly by limiting the production of proinflammatory cytokines and mediators from monocytes and granulocytes.

Effect on cells involved in allergic reactions

Blood and tissue eosinophilia characterize atopic diseases, including bronchial asthma [22]. Histological analysis of bronchial biopsies from asthmatics showed the presence of degranulated eosinophils in the vicinity of zones of epithelial shedding, suggesting that their secretory products may play a crucial role in the development of tissue damage [22]. The infiltration and maintenance of eosinophils in the inflammatory sites is regulated mainly by TH2 cell-derived cytokines, as shown in asthmatic patients where bronchoalveolar T cells elaborate preferentially IL-4 and IL-5, but not IFN γ [23]. Studies on animal models have disclosed that IL-5 production by activated T cells is a crucial event in the onset of allergic eosinophilia [24,25]. These findings are compatible with the well-known ability of this cytokine to promote selectively eosinophil proliferation and differentiation, chemotaxis, priming and survival [26]. Accordingly, IL-5 is now considered an important and selective target for new therapeutic agents aimed at treating allergic eosinophilic inflammation. IL-10 prevents IL-5 production by human resting T cells [27] and by TH0 and TH2 clones [28]. In this case, the inhibitory effect of IL-10 relates to the functional deactivation of antigen-presenting cells (APCs), as shown by the strong downregulation of the expression of MHC class II molecules and of the two co-stimulatory molecules, B7 and intercellular adhesion molecule-1 (ICAM-1), on monocytes, macrophages and dendritic cells [10]. This observation can be extended to purified murine CD4⁺ T lymphocytes, where IL-10 suppresses IL-5 synthesis exclusively upon antigen stimulation in the presence of APCs, but not in response to solid-phase anti-CD3 monoclonal antibody [29]. These *in vitro* findings are corroborated by *in vivo* data showing suppression by IL-10 of antigen-induced eosinophilia and IL-5 generation in the peritoneal cavity of ovalbumin-immunized mice [29,30].

Besides IL-5 inhibition, the anti-allergic properties of IL-10 involve the blockade of other cytokines directly implicated in the homing and activation of eosinophils in inflamed tissues, such as IL-3 and GM-CSF [30,31].

More recently, another group of chemotactic cytokines, named chemokines, have emerged as important regulatory molecules in the context of allergic inflammatory processes. Chemokines are defined by the presence of four cysteine residues in highly conserved positions and classified as CC or CXC on the basis of the absence or the presence, respectively, of a single amino acid between the two cysteines nearest the N-termini [32,33]. Chemokines of the CC family are claimed to play an important role during allergic diseases, since they preferentially chemottract monocytes, eosinophils, basophils and T lymphocytes [32,33]. Among them, eotaxin, regulated upon activation in normal T cells expressed and secreted

(RANTES), monocyte–chemotactic protein (MCP)-3 and macrophage inflammatory protein (MIP)-1 α have gained particular attention in the context of allergic diseases, since their *in vivo* neutralization prevents antigen-induced eosinophilia both in the airways and in the skin of immunized mice [34,35]. MIP-1 α gene expression and protein generation are inhibited by IL-10 in human neutrophils, monocytes and alveolar macrophages [14,36]. Similarly, IL-10 diminishes MCP-3 production from human monocytes [37] and deactivates airway smooth muscle cells in terms of RANTES synthesis and release [38]. Collectively, these findings suggest that IL-10 may limit chronic airway inflammation, not only by preventing IL-5 production by T cells, but also by downregulating the synthesis and release of those chemokines essential for eosinophil, T cell and monocyte/macrophage chemoattraction and activation. To our knowledge, however, no data are currently available concerning the ability of IL-10 to interfere with eotaxin production in the context of allergic reactions. Preliminary results from our laboratory indicate that eotaxin release in the bronchoalveolar lavage fluid of antigen-challenged mice is unaffected by IL-10 under conditions of inhibition of airway inflammation, TH2 cytokine release and bronchopulmonary hyperreactivity (Pretolani *et al.*, unpublished results). This supports the concept that locally released eotaxin, probably by resident lung cells such as epithelial cells [39] and mast cells [40], does not represent a target for IL-10, at least in this experimental model of asthma. Further studies are nevertheless required to establish more precisely the potential interference of IL-10 with eotaxin synthesis and release, particularly from human cells.

IL-10 may also exert anti-allergic properties by deactivating directly eosinophil functions. Accordingly, stimulation with LPS or CD40 ligation on human eosinophils prolong their survival [41,42]. Both phenomena are prevented by IL-10, suggesting that this cytokine may accelerate eosinophil death, thus contributing to the resolution of eosinophilic inflammation.

Besides T cells and eosinophils, increasing evidence designates the mast cell as a multi-functional immune cell intimately associated with the pathogenesis of allergic disorders [43]. In particular, the production of IL-3, IL-4, IL-5, GM-CSF, but not IL-2 or IFN γ , by activated mast cells renders their functional profile closely related to that of TH2 T lymphocytes [43]. Mast cells also release TNF α following IgE-dependent stimulation [44]. This has major consequences on the emergence of leucocytic inflammation since TNF α may interfere directly with eosinophil chemoattraction, activation and survival, but also indirectly, by increasing the expression of specific adhesion molecules [45]. Although IL-10 has been shown to extend the viability of mouse mast cell lines *in vitro* and to influence mast cell development and differentiation [46], recent studies have

proposed important inhibitory activities of this cytokine on mast cell functions [30]. Accordingly, IL-10 reduces IgE-dependent TNF α and IL-6 generation from mouse bone marrow-derived mast cells and rat peritoneal mast cells, respectively [47,48]. This suggests that IL-10 may influence the antigen-driven mast cell activation, and thus interfere with early steps of the immune response.

In vivo effects of IL-10 compatible with its anti-allergic activity

As stated above, the preferential production of TH2-derived cytokines has been identified as the main mechanism involved in the development and maintenance of tissue inflammation characteristic of human asthma. Studies on murine models confirmed the critical role of IL-4 and IL-5 in the onset of pulmonary allergic eosinophilia [25,49,50]. TNF α also modulates eosinophil homing to the airways in response to antigen administration, as shown by *in vivo* neutralization studies [51]. IL-10, concurrently delivered with ovalbumin, protects immunized mice from allergic lung eosinophilia [51]. Of note, specific *in vivo* IL-10 neutralization intensifies the degree of antigen-induced eosinophil recruitment into the airways, supporting the concept that endogenous IL-10 plays a central role in the regulation of the inflammatory allergic processes within the lung. In this model, the inhibitory effect of IL-10 probably involves a blockade of the local formation of TNF α , since IL-10 administration 1 hour after antigen challenge, i.e. the time-point of the peak release of TNF α in the bronchial lumen, fails to display a significant protection [51].

Studies performed using mice with targeted disruption in the IL-10 gene also shed light on the involvement of this cytokine in inflammatory allergic disorders [52]. Thus, T-cell and eosinophil infiltration into the airways as well as IL-5 release in response to intranasally delivered *Aspergillus fumigatus* are aggravated in IL-10 gene knockout mice [53]. Mice lacking the IL-10 gene also show increased abnormal contact hypersensitivity responses [54], indicating that endogenous IL-10 acts as a natural immunosuppressant which controls and limits allergic inflammation both in the lung and in the skin. In support, IL-10 prevents IgE-dependent TNF α and IL-6 release from human keratinocytes, further indicating that this cytokine may regulate cutaneous allergic inflammatory responses [55].

The main effects of IL-10 compatible with its anti-allergic activities are summarized in Fig. 1.

IL-10 inhibits both TH1 and TH2 activation: two contradictory events?

Several observations indicate that the TH1-derived cytokine

IFN γ also downregulates allergic diseases. These include the inhibition of IL-4-mediated Ig isotype switching to IgE in murine and human B cells [56], the blockade of TH2 cell proliferation and the consequent TH0 cell differentiation into TH1 cells [57]. In murine models of allergic airway inflammation, systemic [58] or aerosol [59] administrations of IFN γ suppresses antigen-induced eosinophil infiltration into the airways. Based on these observations, it seems difficult to conciliate the anti-allergic activities of IL-10, which are largely due to its ability to dampen TH2 responses, with its well-known capacity to inhibit IFN γ production by TH1 cells. It should be mentioned, however, that IFN γ displays certain effects compatible with a pro-allergic activity, including the induction of eotaxin gene expression in endothelial cells [60], the increase in human eosinophil survival and cytotoxicity [61], as well as the upregulation of ICAM-1 expression on their surface [62]. Also, IFN γ is claimed to play a critical role in respiratory virus infection-induced asthma exacerbation [63], supporting the concept that blocking TH1 cell-derived IFN γ may not necessarily have negative consequences in the context of allergic inflammation.

Therapeutic perspectives

Correction of the TH1/TH2 imbalance and the subsequent blockade of TH2-derived cytokines on one hand, and downregulation of CC chemokine production and receptor interactions, on the other hand, may now be considered as the main objectives for the treatment of the inflammatory component of allergic disorders.

At present, the pharmacological treatment of allergic

asthma requires both bronchodilators to reverse airflow obstruction and anti-inflammatory agents, to prevent chronic airway inflammation. Glucocorticoids are potent anti-inflammatory drugs, with a prominent place in asthma therapy [64]. Although the mechanisms by which they exert anti-inflammatory activities remain to be elucidated fully, their ability to resolve eosinophilic inflammation is well established. This property relates to the inhibition of the synthesis of various eosinophilotactic cytokines, such as IL-3, IL-5 and GM-CSF [65] and to a direct pro-apoptotic effect exerted on mature eosinophils, both *in vitro* and *in vivo* [66–68]. However, the major drawback of these drugs concerns their local and systemic side-effects resulting mainly from long-term administration. Accordingly, the identification of new therapies allowing the doses of glucocorticoids to be reduced represents one of the future strategies to attenuate allergic inflammation. Due to its ability to downregulate APC, to exert immunosuppressive effects, to inhibit IL-5 as well as chemokine synthesis and to block certain functions on eosinophils and mast cells, IL-10 may represent one of these therapies (Table 1).

A single intravenous bolus injection of IL-10 to normal volunteers has been shown to be well tolerated and to exert a long-lasting inhibitory effect against LPS-induced IL-1, IL-6 and TNF α production from peripheral blood mononuclear cells [69]. A similar conclusion emerged from a pilot trial in which recombinant human IL-10 was administered intravenously to kidney transplant recipients receiving OKT3 induction therapy [70]. In these patients no adverse events were described and plasma levels of TNF α were decreased dramatically over 24 h. Although these

Fig. 1. Potential target cells involved in the anti-allergic activities of IL-10. IL-10 downregulates APC, CD4⁺ TH2 cells, mast cells and smooth muscle cells in terms of cytokine and chemokine synthesis and release. These include IL-3, IL-5, IL-6, GM-CSF, TNF α , RANTES and MIP-1 α which directly and indirectly promote eosinophil proliferation, differentiation, survival and chemoattraction of target tissues. By decreasing eosinophil survival, IL-10 also participate in their elimination thus facilitating the resolution of the inflammatory process.

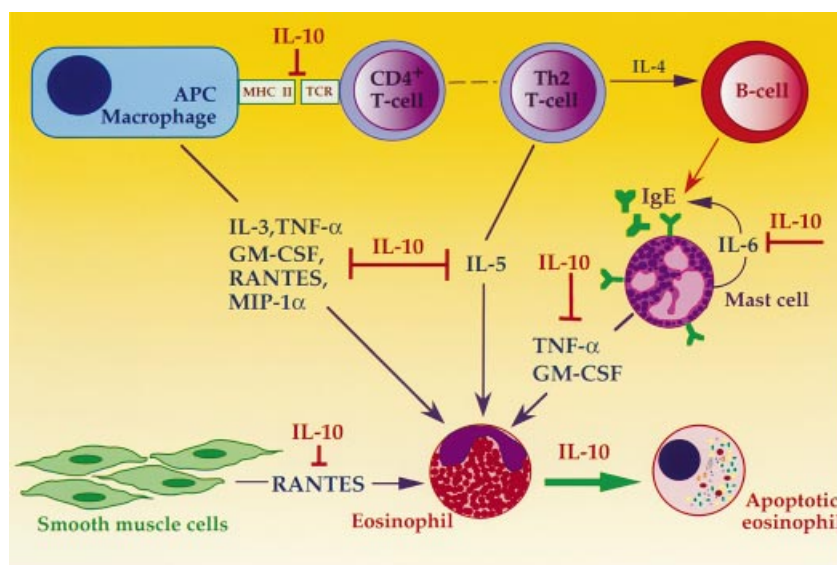


Table 1. Biological functions of IL-10 compatible with its anti-allergic activity*In vitro*

- Inhibition of IL-5 production by resting T cells and by TH0 and TH2 clones
- Downregulation of the expression of co-stimulatory molecules on APC
- Inhibition of IL-3 and GM-CSF synthesis and release from inflammatory cells
- Inhibition of IgE-dependent stimulation of mast cells and keratinocytes
- Downregulation of RANTES, MIP-1 α and MCP-3 synthesis and release from various cell types, including bronchial smooth muscle cells
- Decrease in LPS- and CD40-mediated eosinophil survival

In vivo (animal models)

- Suppression of antigen-induced eosinophilia and IL-5 release in the lung and the peritoneal cavity of immunized mice
- Enhancement of allergic lung eosinophilia after IL-10 neutralization
- Intensification of airway inflammation and local IL-5 release during allergic bronchopulmonary aspergillosis in IL-10 gene knockout mice

In vivo (humans)

- Decrease in the levels of proinflammatory cytokines in the plasma and inhibition of their release from activated monocytes after systemic IL-10
- Improvement of clinical parameters and local inflammation by subcutaneously-injected IL-10 during psoriasis

results are encouraging, further issues should be addressed in order to prove the benefit of IL-10 in human allergic diseases. These include the search for an optimum timing of administration, since in most animal models IL-10 is efficient exclusively when administered prophylactically, or concomitantly with the pro-inflammatory stimulus. Furthermore, animal models of asthma frequently reproduce artificially an acute and reversible, rather than an ongoing inflammatory process, indicating that a therapeutic rationale for treating patients with IL-10 should also consider potential drawbacks linked to its long-term administration.

Another critical point which deserves further investigation is the route of IL-10 administration, which should ensure good bioavailability, avoid potential side effects and target its activities. A relative deficiency in cutaneous IL-10 mRNA expression was detected in individuals with established psoriasis [71]. In these patients, the subcutaneous injection of IL-10 over 24 days improved clinical parameters and exerted immunosuppressive properties, indicating clearly that locally administered IL-10 represents a promising therapeutic approach for treating cutaneous diseases. Since alveolar macrophages from asthmatics also show a reduced ability to synthesize IL-10 [13,72], the inhalatory delivery would probably be the best strategy to compensate the defective production of IL-10 in the inflammatory airway environment. This possibility has already been tested successfully with IFN γ , since its administration by the inhalatory route to normal subjects over 12 days proved its clinical safety and represented an effective mode of delivery of this cytokine [73].

Whatever the therapeutic indications and the mode of administration, particular attention should be drawn to the potential side effects of IL-10 therapy, resulting mainly from its major impact on the immune system. These include (1) the increase sensitivity to pulmonary infections as a result of the impaired antimicrobial defence [74], (2) the potential enhancement of systemic autoimmunity, as shown in patients with lupus erythematosus where IL-10 increases the production of anti-DNA antibodies [75] and (3) the development of B-cell lymphoproliferative disorders, as IL-10 is a potent proliferation and differentiation factor for B lymphocytes *in vitro* [76]. Also, IL-10 administered repeatedly may act as a 'foreign peptide' and thus elicit allergic responses in susceptible individuals. Accordingly, the formulation of analogues devoid of undesired properties or of synthetic compounds able to promote selectively endogenous IL-10 synthesis, rather than the use of the recombinant protein itself, may represent a more promising strategy for the therapeutic management of inflammatory allergic disorders.

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