

The anti-inflammatory effects of interleukin-10 in allergic disease

Interleukin-10

Interleukin-10 was cloned as a murine Th2-derived factor, termed cytokine synthesis inhibitory factor, acting to inhibit activation of and cytokine production by Th1 cells [1,2]. Human IL-10 is produced by both Th1 and Th2 cells and acts more generally to reduce T-cell activation and cytokine synthesis [3]. Thus this cytokine was the first described with a potential anti-inflammatory action. In addition, IL-10 has been shown to be produced by a wide variety of cell types including monocytes, macrophages [4], B cells [5], mast cells [6] and eosinophils [7], and can inhibit pro-inflammatory cytokine production (IL-1, IL-6, GM-CSF, TNF α , IFN α , IL-8, Mip-1 α and IL-12) from these cells and CD80 expression by monocytes [2,8,9]. An important mechanism for the inhibition of T cell activation by IL-10 is this reduction in MHC class II expression by antigen presenting cells [10] and the molecular basis for this has been described as resulting from a block in MHC exocytosis and recycling [11].

The IL-10 gene is located on human chromosome 1, and the two receptor subunits have been described which interact through Jak1 and Tyk2 tyrosine kinases with Stat1, Stat3 and Stat5 [12,13].

Interleukin-10 production occurs late after T-cell activation relative to other cytokines, and this is thought to represent an autocrine negative regulation of T-cell responses [3]. The importance of IL-10 in immune regulation was demonstrated by generation of mice with targeted disruption of the IL-10 gene [14]. These animals develop spontaneous colitis to intestinal flora, and show growth retardation and anaemia. Further evidence for the role of IL-10 in immune regulation has come from the description of murine regulatory T-cell clones [Th3] generated after induction of oral tolerance to myelin basic protein [MBP], which produced IL-4 and IL-10 and could suppress experimental allergic encephalomyelitis induced by either MBP or proteolipid protein [15]. IL-10 is also involved in protection from T-cell-induced colitis in a mouse model by CD4⁺ CD45RB^{hi} CD38⁺ cells [16]. In addition Tr1 regulatory T cells were isolated from mice and human T cells grown in IL-10 [17]. These cells inhibit T-cell activation through mechanisms that depend, at least in part, on production of IL-10.

Potential for regulation of allergic inflammation by IL-10

In addition to the T-cell regulatory effect described above,

which might act to reduce activation of allergen-specific Th2 T cells, IL-10 has a number of other regulatory effects that may be relevant to allergic disease. It reduces macrophage production of pro-inflammatory cytokines. Although murine IL-10 was described as a mast cell growth factor [18], it also inhibits IgE-triggered mast cell cytokine production [9]. IL-10 reduces IgE production, tending to switch towards IgG4 production by B cells [19,20]. IL-10 also prevented eosinophil survival induced by lipopolysaccharide [21]. IL-10 also reduces chemokine production, and may thus reduce eosinophil recruitment to sites of allergic inflammation [22]. IL-10 inhibited TNF α and IFN γ -induced production of IL-8 and RANTES from human airway smooth muscle cells [23], and inhibited vascular smooth muscle proliferation [24]. Whether this might reduce airway remodelling in asthma remains to be established.

The factors involved in inducing IL-10 production from cells involved in innate immunity are uncertain, but hormones, lipid mediators and pro-inflammatory cytokine have all been implicated. It is of note that corticosteroids and cyclosporin A actually increase IL-10 production *in vitro* in some conditions [25]. If IL-10 were induced early during T-cell activation by allergen, this might favour the development of an allergen specific regulatory T-cell population: indeed there is some evidence that this may occur during allergen immunotherapy.

Evidence from animal models of allergic disease

Interleukin-10 'knockout' mice develop spontaneous colitis, confirming a role for IL-10 in immune regulation in health. Results of studies of IL-10 in animal models of allergic inflammation are varied. Grunig *et al.* [26] studied the effects of an *aspergillus* sensitization and inhaled challenge protocol in wild-type and IL-10^{-/-} mice, and showed an increase in airway eosinophilia and lung methacholine responsiveness to inhaled challenge in the absence of IL-10, although this varied with the genetic background and route of priming used. Similarly, an animal model of contact dermatitis revealed an exaggerated inflammatory response in the absence of IL-10 [27]. Zuany-Amorin [28] administered IL-10 to Balb/c mice sensitized and then challenged with ovalbumin and showed reduced antigen induced airway eosinophilia. In the current issue of *Clinical and Experimental Allergy* Tournoy *et al.* [29] report a similar sensitization model in C57BL/6 IL-10^{-/-} mice, where they

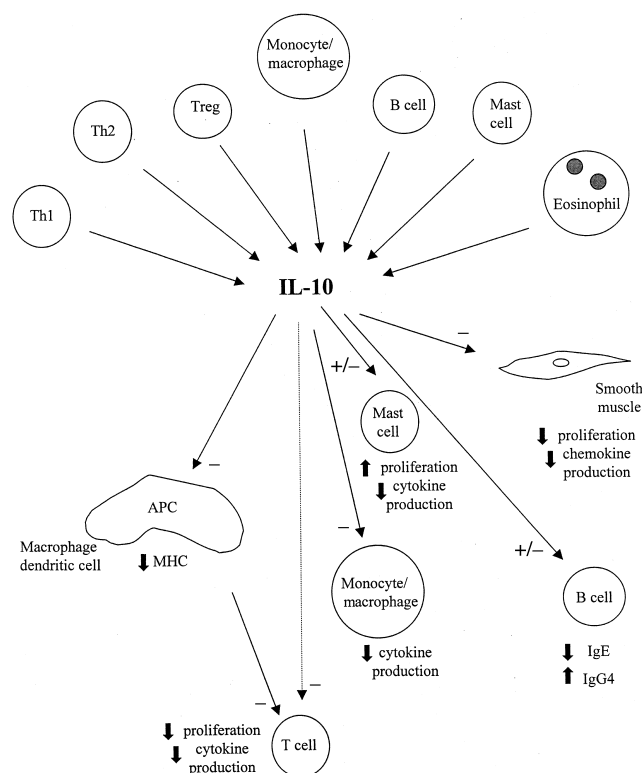


Fig. 1. Potential actions of IL-10 in allergic inflammation.

describe an increase in antigen-induced airway eosinophilia. However, these investigators went further to measure airway responsiveness and failed to detect a significant increase of antigen-induced AHR in IL-10-deficient animals. Whilst animal models of AHR can give apparently contradictory results [30,31] and measurement of airway responsiveness in mice is some way from the situation in human asthma, a number of recent results also raise the possibility of dissociation of airway eosinophilia and antigen-induced AHR. In particular in an IL-5-deficient Balb/c model blockade of IL-4-reduced antigen-specific IgE and airway eosinophilia but did not completely abolish AHR [32], whilst blockade of IL-13 or IL-4R-reduced AHR without significantly affecting IgE or eosinophilia [33,34]. In addition recent data suggest a direct effect of cytokines such as IL-5 on human airway smooth muscle [35], and an early report of a dose-finding trial of anti-IL-5 in asthmatics suggested reduction in blood eosinophils without significant effects on baseline AHR or allergen induced late responses [36]. Although such data is intriguing, the majority of data still suggests a link between eosinophils and AHR in asthma, and at the very least a link between Th2 T cell activation and AHR. Thus the potential for IL-10 in reducing airway inflammation, AHR and asthma symptoms remains worthy of exploration.

IL-10 in human asthma and allergic disease

Reports in human asthma are at first sight contradictory, with an increase in numbers of cells expressing mRNA at baseline in bronchial biopsies reported, with a further increase in T cell IL-10 signal following allergen inhalation challenge [37]. In contrast, stimulated macrophage IL-10 production was reported to be deficient in asthma by one group [38] but spontaneous AM IL-10 production was reported by others [39]. It is possible that IL-10 production from T cells is unregulated in asthma, with further auto-regulatory IL-10 being produced after allergen challenge, but that induced macrophage IL-10 production is reduced. Furthermore, IL-10 promoter polymorphisms are reported [40], and it is possible that IL-10 effector functions are reduced in atopic asthmatic subjects.

Inhaled steroids were reported to increase AM IL-10 production *ex vivo* [41] and this might partly explain the reduction in IL-4 and IL-5 mRNA expression with increase in IFN γ mRNA-expressing cells seen after oral prednisolone treatment of asthma [42].

Given the description of regulatory T-cell subsets which may suppress T-cell activation and cytokine production by mechanisms involving IL-10, together with TGF β and contact-dependent signals, there is clear potential for inducing a T-regulatory response to allergen. Indeed, data from Akdis and Blaser [43] suggest that this may be one mechanism for allergen injection immunotherapy, since allergen-specific T-cell anergy evoked by such therapy was shown to depend, at least in part, on IL-10.

Potential for IL-10 in treatment of atopic allergic disease

Whilst it may prove possible to give exogenous IL-10 by either inhaled or intravenous routes, and indeed such an approach appeared to reduce lesional activity in patients with psoriasis, cytokine therapy is fraught with technical difficulties. More attractive would be the possibility of administration of IL-10 as an adjuvant to induce T-cell anergy or regulatory T-cell subsets, or stimulation of natural IL-10 production. IL-10 remains an attractive potential modulator of atopic allergic disease (Fig. 1).

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