

EDITORIAL

Microenvironmental influences in atopic disease

Introduction

The principal feature that distinguishes atopic subjects from nonatopics is their capacity to develop a sustained immunoglobulin (Ig) E response to environmental allergens. The resulting release of pharmacological mediators by IgE-sensitized mast cells produces an acute inflammatory reaction, release of preformed mediators notably histamine, and the synthesis and secretion of cytokines of the Th2 type that attract and activate inflammatory cells. The elevated levels of IgE produced by B cells in atopic disease are initiated and sustained by the Th2 cytokines IL-4 and IL-13, and inhibited by the Th1 cytokine interferon (IFN)- γ [1,2].

In atopic disease, the activated T cells driving the immune response are predominantly of the Th2 subset, as they produce higher levels of IL-4 and lower levels of IFN γ than healthy control subjects [2–6]. The low levels of IFN γ have also been shown to negatively correlate with serum IgE levels [7]. This observation has been confirmed in this issue by Matsui *et al.* [8]. They find that PBMCs from atopic patients stimulated with IL-12 produce less IFN γ than PBMCs from healthy subjects. Moreover, after challenge with the aero-allergen Der f 1, PBMCs from atopic patients produce less IL-12 than healthy subjects. In both subject groups the serum IgE level negatively correlated with the levels of IL-12 and IFN γ produced by the PBMCs. They suggest that the elevated levels of serum IgE observed in individuals with atopic disease results from an abnormality in the production of IFN γ and/or IL-12 by PBMCs.

Regulation of IFN γ production by IL-12

Differentiation of naive T cells into Th1 and Th2 cells is strongly influenced by cytokines. IL-12, IL-18, and IFN γ promote Th1 differentiation, whereas IL-4 efficiently promotes Th2 differentiation. In addition to the direct influences of IFN γ and IL-4 on Th1 and Th2 cells, respectively, there also exists the phenomenon of reciprocal regulation of the T-helper cell populations which further reinforces the deviation of these subsets. IFN γ is predominantly produced by activated CD4⁺ T cells of the Th1 subset and inhibits both the differentiation and effector functions of Th2 cell. Conversely the Th2-cell cytokines IL-4 and also IL-10 prevent Th1-cell proliferation by inhibiting IL-12 produced by antigen-presenting cells (APCs) and counteract the effects of IFN γ [9].

IL-12 is probably the most important of the cytokines involved in skewing the immune response towards a Th1 phenotype and promoting IFN γ production by activated Th1

cells. IL-12 is a heterodimeric cytokine produced by a number of cell types including activated macrophages, monocytes and dendritic cells (DCs) [10]. IL-12 is composed of two disulphide-linked subunits designated p35 and p40 that are biological inactive monomers [11]. However, binding of the 70 kDa dimer (IL-12 p70) to the IL-12 receptor (IL-12R) expressed on activated T cells of the Th1 subset, induces the production of IFN γ [11–13]. The receptor for IL-12 consists of the β 1 and β 2 subunits [11], which when coexpressed confer high-affinity binding. IL-12R β 2 contains conserved tyrosine residues in its cytoplasmic portion and may be involved in signal transduction [14]. Recent studies in both mouse and humans have shown that Th2 cells do not express IL-12R β 2 on their surface, possibly due to downregulation by IL-4, TGF- β 2 and IL-10 [12,13,15,16]. This may explain the unresponsiveness of Th2 cells to IL-12.

IL-12 and IFN γ in atopic disease

The importance of IL-12 and IFN γ in atopic disease has been examined using animal models. The presence of recombinant murine IL-12 during priming and re-challenge with ovalbumin [17] or sheep erythrocytes [18] has been shown to abolish eosinophilia and airway hyperresponsiveness. These effects of IL-12 were shown to be influenced by IFN γ , as the therapeutic effects were partially abrogated by treatment with anti-IFN γ antibodies [18]. Mucosal IFN γ gene transfer has also been shown to result in a similar reduction in antigen- and Th2-induced eosinophilia and hyperresponsiveness [19].

In humans, monocytes from atopic patients can have reduced IL-12 levels [6,20]. In this issue Matsui *et al.* suggested that the elevated levels of IgE characteristic of atopy may be due to an abnormality in production of IFN γ and/or IL-12 [8]. However, the low IFN γ production by T cells from atopic patients can be restored to normal levels following culture with IL-12 [21]. This suggests that the low level of IFN γ seen in atopy, may not solely be an inherited abnormality but also an effect of the atopic environment.

The role of the microenvironment

There is now good evidence that factors in the tissue microenvironment play a critical role in defining the immune response by acting on immature antigen presenting cells (APCs), such as dendritic cells. Following encounter with pathogen-derived or induced factors in the peripheral

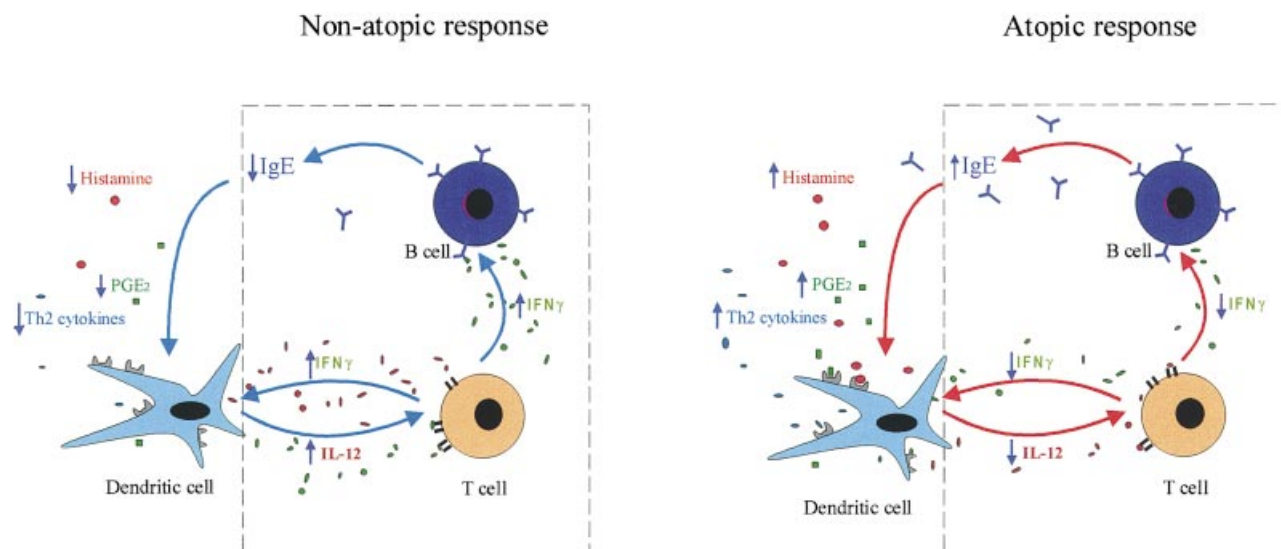


Fig. 1. The interactions between IL-12, IFN γ and various aspects of the microenvironment in the nonatopic and atopic immune response.

tissue, the immature DC matures and starts to migrate towards regional lymph nodes where it then presents antigen to naive T cells. Although there is evidence that the surface molecule repertoire on DCs can direct T-cell development [22,23] it is believed that soluble molecules derived from DCs skew T-cell differentiation more efficiently. As such, the level of IL-12 produced by APCs during antigen presentation has been shown to be of particular importance for directing T-cell differentiation *in vitro*. Microenvironmental factors that influence IL-12 production by APCs, including PGE₂, histamine, IL-10 and interferons, may therefore have T-cell skewing potential (Fig. 1).

To support this, evidence has shown that human monocyte-derived dendritic cells (Mo-DCs) stimulated *in vitro* with prostaglandin E₂ (PGE₂) have reduced IL-12 production [24]. Coincidentally, these Mo-DCs also stimulate naive T cells to differentiate into a Th2 phenotype producing high levels of IL-4 and IL-5 and low levels of IFN γ [24]. In addition, monocytes from atopic subjects have increased PGE₂ production [25,26], and it is known that PGE₂ can act directly on T cells to decrease their IFN γ production [27].

Histamine, produced during immediate hypersensitivity reactions by mast cells and basophils, may also be involved in determining T cell outcome. It has been shown to reduce IL-12 p70 levels by *Staphylococcus aureus* Cowan strain I (SAC)-stimulated monocytes, and could therefore lead to preferential Th2 cell differentiation [28].

IL-10 has also been suggested to influence APC-driven Th2 differentiation. Mo-DCs exposed to IL-10 in combination with IL-1 β and TNF- α have reduced IL-12 p70 production [29], and murine DCs treated with IL-10 have been

demonstrated to induce Th2 differentiation [30]. However, IL-10-treated Mo-DCs are more commonly regarded to be involved in tolerance induction as immature Mo-DCs exposed to IL-10 show a reduced capacity to stimulate CD4⁺ T cells in an allogeneic mixed lymphocyte reaction [30,31].

Type I interferons, including IFN α and IFN β , inhibit Mo-DC p40 IL-12 secretion leading to reduced T-cell IFN γ production and a possible consequent increase in differentiation to Th2 cells [32]. In contrast, the presence of IFN γ during LPS- or IL-1 β /TNF α -induced maturation of Mo-DCs has been demonstrated to enhance IL-12 production following CD40 ligation [33]. IFN γ -treated Mo-DCs may therefore promote Th1 differentiation.

The current literature suggests that the APC may direct the appropriate immune response towards a cell-mediated (Th1) or humoral (Th2) immune response, by responding to pathogen-derived, or -induced IL-12-promoting or IL-12-inhibiting factors. However, as Mo-DCs recently have been shown to produce IL-4 in response to Rauscher Leukaemia Virus (RLV) with a concomitant reduction in IL-12 production [34], it is possible that pathogen derived, or induced factors are regulating levels of IL-4 as well as IL-12 produced by the DC.

While there is no doubt that there is an inherited component to atopic disease [35,36], supported by the results presented by Matsui *et al.* [8], it cannot be excluded that the interpretation of the data presented has been biased by the selection of their subjects. Atopic patients are known to have elevated levels of allergic mediators, including PGE₂, histamine and IgE, as well as having a Th2-skewed immune response. The reduced levels of IFN γ and IL-12 produced

by PBMCs from atopic patients may therefore be as a result of unresponsiveness of the Th2 cells to IL-12, perhaps through a defect in the IL-12 receptor, and the effects of allergic mediators on APCs with consequent influence on T-cell differentiation. The increased levels of serum IgE, representing the allergic environment, may therefore account for the reduced IFN γ and IL-12 detected. While studies like Matsui *et al.* [8] provide valuable information on an individual area (Fig. 1, enclosed square), the relative contributions and complex relationships of all the disease components should not be overlooked in the attempt to further our understanding of atopy.

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