

Peripheral blood mononuclear cells from house dust mite allergic patients produce IL-2 in response to specific allergen challenge

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Summary

Proliferative responses and production of IL-2 by peripheral blood mononuclear cells of patients with *Dermatophagoides pteronyssinus* rhinitis $\pm$ asthma were measured at up to 24 hr intervals from 1–8 days, after stimulation with mitogen (PHA), antigen (SKSD) and specific allergen (*D. pteronyssinus*). IL-2 was measured in culture supernatants using the murine CTLL cell line bioassay. Compared to non-atopic controls, patients had significantly higher proliferative responses to *D. pteronyssinus* and SKSD but similar responses to PHA. In patients, maximal proliferative responses to PHA, SKSD and *D. pteronyssinus* were at 3, 6 and 7 days, respectively. IL-2 levels in response to stimulation with *D. pteronyssinus* were significantly higher in patients than controls, where only background levels were found ($15.4, 7.9\text{--}30.7 \times 10^{-2}$ U/ml [mean, range] $n=11$; vs $2.2, 0.1\text{--}8.4 \times 10^{-2}$ U/ml, $n=6$; $P<0.05$). In contrast, IL-2 production to PHA and SKSD, although higher in patients, was not significantly different than controls. These results suggest allergic patients possess a population of T cells expandable by specific allergen which are induced to secrete IL-2.

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Introduction

Understanding of the role of cytokines in the regulation of the immune responses involved in allergic disease is at an early stage. It is still unclear whether atopic individuals have fundamental genetic defects in the regulation of cytokines required for immune effector cell activation and differentiation and for IgE production. However, it is apparent that many cytokines are involved both in regulation of IgE responses and in the inflammatory processes characteristic of allergic disease and that T cells are central to this process.

Recent opinion supports the hypothesis that there are discrete helper T cell subsets in man [1,2], distinguished by their cytokine secreting profiles, similar to the established T_H1/T_H2 categories in mice [3]. In the murine model T_H1 cells exclusively secrete IL-2 and IFN- γ whereas the T_H2 subset produces IL-4, IL-5 and IL-6, amongst others. The role of IL-2 is well established as an early signal for T and

B cell proliferation and as an inducer of IFN- γ . IL-4 is a critical cytokine in the development of human and murine IgE responses, promoting IgE isotype selection in IgM and IgD expressing B cell precursors [4] and also acting as a homeostatic regulator of IL-2 induced IFN- γ production [5]. IFN- γ , on the other hand, has been demonstrated to down regulate the effect of IL-4 [6] and it is a defect in this regulation which has been suggested as a cause of the exaggerated IgE responses characteristic of atopic conditions [1,6–9].

There has been much work on the cytokine secreting profiles of antigen-specific T cell clones and T cell lines derived and expanded from various shock organs [1,9–12]. Since clones and cell lines are usually derived from one or a few patients, it is not possible to know whether they are representative of the overall T cell response. There is also limited information concerning the cytokine profiles occurring at target organs in specific allergic disorders. Recovering and culturing sufficient numbers of responsive cells from shock organs such as the nose or skin is impractical, although important progress in this area has been made by the methods of *in situ* hybridiza-

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murine studies that the bulk would be derived from responding T cells and that it would be directed towards the same or other expanding T cells [20]. IL-2 also acts in conjunction with other cytokines on many other cell types. The major functions of IL-2 are recognized as the induced proliferation of T cells, the enhancement of B cell survival and immunoglobulin production, the generation of lymphokine activated killer cells [21] and the induction of various other cytokine responses, particularly IFN- γ and TNF [22,23] in those cells. Paradoxically, in mice IL-2 also induces apoptosis of mature, antigen-activated T lymphocytes and may thus be an important regulator of T cell interactions [24]. The rapid induction of IL-2 production by PHA, the somewhat slower induction by SKSD and the delayed induction by *D. pteronyssinus* in house dust mite-allergic subjects could be explained by the relative number of responsive cells and their expected exponential expansion. It might also reflect the requirement or otherwise for antigen processing before efficient presentation, particularly with the more complex stimuli such as SKSD and *D. pteronyssinus* extract.

The presence of a subset of mononuclear cells (T cells) capable of producing IL-2 in atopic donor PBMC cultures after specific allergen challenge suggests the presence of memory T cells. It has recently been demonstrated that memory T cells (CD45 RO+) are the predominant T cells infiltrating biopsies of late cutaneous reactions in atopic subjects after specific antigen challenge [25]. It is probable that with such specific recruitment the local production and effects of cytokines in shock organs such as the nose, lungs or skin may be enhanced at or near sites of antigen challenge over those detected in PBMC culture.

We are unable to assess the responsive functional phenotype of T_H subsets present in our cultures, based on the measurement of IL-2 alone. However, it is of interest to consider our findings in the light of other data and current concepts of T_H cytokine phenotype in allergy, where allergic subjects are considered to have an impaired T_H1-type response (reduced IFN- γ production [7,8]) or an enhanced T_H2-type response (increased IL-4 and IL-5 [26]). Our data is consistent with that of others who have detected low levels of IL-2 secreted by *D. pteronyssinus* allergen-specific T cells, characterized as T_H2 cells on the basis of the secretion of IL-4 and IL-5 [26]. However, IL-2 production has traditionally been associated with T_H1 cells: in the mouse IL-2 secretion is restricted to T_H1 cells [3] and in man the response to non-allergenic antigens is typically T_H1 in type, with high levels of IL-2 production [11]. Further, certain murine and human T cell clones, which simultaneously secrete T_H1 and T_H2 cytokines, have been established [27,28], demonstrating that there can be heterogeneity in this system.

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