Allergic Rhinitis: Basic Mechanisms and Influence of Treatment

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The classical mechanism of induction of immediate symptoms following allergen exposure involves the IgE dependent activation of mast cells and basophils. Another feature characteristic of allergic rhinitis is local eosinophilia. Recent data suggests that local mechanisms of IgE regulation and tissue eosinophilia depend upon release of cytokines particularly from T lymphocytes, but also from alternative cells including mast cells. This brief review of studies from our own and other groups evaluate the evidence for a putative role for cytokines, their cell source and the influence of treatment including immunotherapy and topical corticosteroids.

MAST CELLS

Immediate symptoms of itching, sneezing, watery nasal discharge and nasal congestion following both natural and experimental allergen exposure occur as a consequence of the IgE - dependent activation of nasal mucosal mast cells. Mast cell degranulation has been observed directly in biopsy specimens following local provocation [1], epithelial mast cell numbers increase following seasonal grass polen exposure [2] and epithelial mast cell numbers are reduced by treatment with corticosteroids [3] and following allergen specific immunotherapy. [4] Mediators released following mast cell degranulation include histamine, tryptase and bradykinin. Newly formed, membrane-derived mediators include LTC4, LTB4 and prostaglandin D2. A further potent lipid mediator released is platelet activating factor. The known biological properties of these mediators include vasodilation, increased vascular permeability, chemotaxis for inflammatory cells and induced neural reflexes, all of which may contribute to the development of immediate nasal symptoms following allergen exposure. Mediators of hypersensitivity are detectable in nasal washings during both immediate [5] and late-phase responses [6] following allergen provocation. The identification of both histamine and the mast cell-specific prostaglandin D2 during immediate responses confirms mast cell involvement. The release of histamine but not prostaglandin D2 at 3-11 hr after challenge implies basophil participation during late-phase responses. [6,7] The contribution or otherwise of mediators in the production of clinical symptoms is reflected by the therapeutic response to specific mediator antagonists. The efficacy of oral (and topical) antihistamines in suppressing itch, sneezing and discharge (but not nasal blockage) confirms a primary role for histamine. Recent studies suggest that leukotriene antagonists and lipoxygenase inhibitors may also be effective, although specific bradykinin antagonists (now available) have yet to be tested.

EOSINOPHILS

A characteristic feature of allergic rhinitis is local eosinophilia which is evident in nasal lavage [8] and in nasal biopsies [9] although the mechanism remains unclear. Tissue eosinophilia may result from increased eosinophil chemotaxis or vascular adhesion, increased bone marrow production of eosinophils or prolonged survival of eosinophils in tissues. Recent evidence strongly supports a role for so called "Th2-type" cytokines as originally defined in murine studies [10] and recently confirmed "*in vitro*" [11] and "*in vivo*" [12] in studies of human T lymphocytes.

CYTOKINES IN ALLERGIC RHINITIS

Cytokines, originally described as products of T lymphocytes, are now known to be produced by a wide variety of cells including macrophages, eosinophils, mast cells, basophils and epithelial cells. By use of nasal biopsy and the combined techniques of immunohistology and *in situ* hybridisation we have examined the role of T lymphocytes and cytokines during natural exposure [13] and following local provocation [14, 15] and have examined the influence of treatment with immunotherapy [16] and topical corticosteroids. [17]

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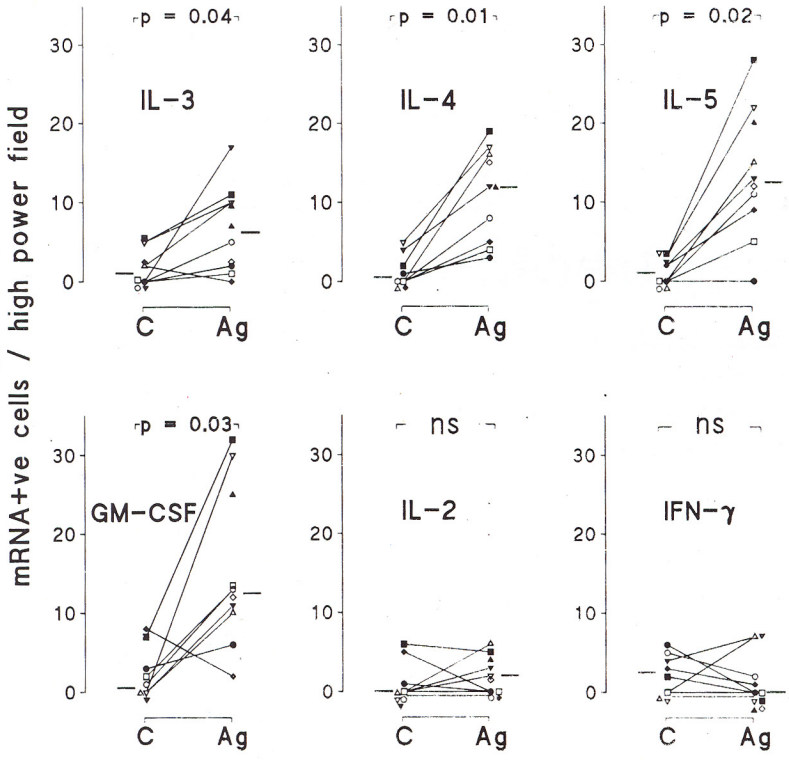
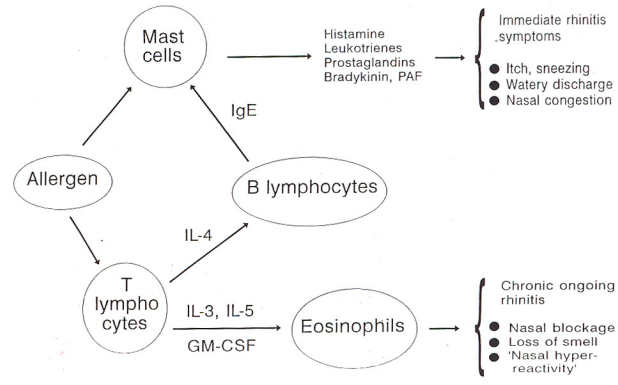


Figure 1 *- In situ hybridization of nasal biopsies using rioprobes for IL-3, IL-4, Il-5, GM-CSF, IL-2 and IFN-y. The cytokine mRNA profile of cells infiltrating biopsy sites 24 h after local allergen provocation (Ag) and after challenge with a control solution (C). the symbols identify values from the same individual patients, in two subjects (A), biopsies for in situ hybridization were obtained only after allergen. Median values are represented by the solid bars. Comparisons were made using the Wilcoxon matched pairs signed ranks test.*

During natural grass pollen seasonal exposure, the characteristic findings on immunohistology of nasal biopsies was tissue eosinophilia (with an increase in both total and "activated" EG2+ cells and the epithelial migration of tryptase-only (but not tryptase + chymase positive) mast cells. [13] At 24 hr after local grass pollen provocation we observed an increase in CD4+ helper T lymphocytes, an increase in CD25+ (interleukin 2 receptor bearing) cells and elevations in both eosinophils and neutrophils [14]. *In situ* hybridisation studies demonstrated preferential mRNA expression for IL-4 and IL-5 during the late phase at 24 hr. [15] Elevations in IL-3 and GM-CSF were also observed but not increases in IL-2 or IFNg. There was a close correlation between "Th2-type" cytokine mRNA expression and the number of activated (EG2+) eosinophils, particularly IL-5 (Fig. 1).

Taken together these observations support CD4+ T lymphocyte recruitment and activation and the release of Th2-type cytokines "*in vivo*" contributing to the development of late nasal responses and associated tissue eosinophilia. The precise cell(s) of origin of these cytokines is yet to be determined, although our preliminary data suggests the principal cellular source (at least at mRNA level) to be T lymphocytes, with a contribution from mast cells. [18, 19] (Figure 2).



INFLUENCE OF TREATMENT ON CELLS AND CYTOKINES

More recently we have examined the effect of treatment on these cellular findings. Briefly, both immunotherapy [16] and prolonged (6 weeks) treatment with topical corticosteroids [17] inhibit both early and late phase nasal responses after allergen (grass pollen) challenge. Both forms of treatment also inhibit local numbers of T lymphocytes and eosinophils. [16, 17]

Our hypothesis was that immunotherapy and corticosteroids may act by distinct mechanisms inhibiting local recruitments of activated, CD25+, CD4+ T lymphocytes and eosinophils. We have performed two large prospective double blind placebo controlled trials each involving over 40 patients. Following one year treatment with immunotherapy a repeat nasal allergen provocation demonstrated inhibition of both early and late nasal responses. There was a non-significant reduction in IL-4 and IL-5 mRNA+ cells during the late phase response. [20] The striking finding was a significant increase in allergen induced cells mRNA+ for interferon gamma. This suggested a "switch" in favour of an additional TH1 response following successful immunotherapy. [20, 21] In contrast six weeks pretreatment with topical corticosteroids (Fluticasone proprionate, when compared to placebo treatment) resulted in selective inhibition of cells mRNA+ for IL-4. No significant decrease in IL-5 mRNA+ cells was observed after challenge and no increase in interferon gamma. [22] Thus topical corticosteroids act by supressing TH2-type res-ponse whereas immunotherapy may act by modulating T lymphocytes in favour of an additional TH1 response characterised by local increases in interferon gamma.

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