

Perennial allergic rhinitis and keratoconjunctivitis

J P Rihoux

There are many studies dedicated to the allergic nose, but most of them deal with seasonal allergic rhinitis and particularly with acute experimental situations. Perennial allergic rhinitis is less well documented.

When studying the allergic nose, several aspects must be taken into consideration: the genetic background of the patient, various environmental factors (antigens, air pollution, climate), and the peculiar characteristics of the nose itself including its anatomy—total surface area: 150 cm², volume: 15 ml—and histology—epithelium (ciliated, non ciliated, pseudostratified, columnar, goblet cells), mucus, immunocompetent cells, lamina propria, basement membrane, blood supply, and nerves and neurotransmitters.¹

It is well recognised that the symptoms of perennial allergic rhinitis are caused by overproduction of different families of chemical mediators. These mediators are produced by migrating or resident inflammatory cells, by resident cells, or by inflammatory cells produced locally from progenitors—for example, T cells, mast cells, eosinophils, neutrophils, epithelial cells, endothelial cells, and antigen presenting cells (APCs). This review focuses on some recent aspects of perennial allergic rhinitis which cast new light on the pathophysiology of this common disease.

Cytokine profile in perennial allergic rhinitis

Since the description by Mosmann² of the dichotomy of the murine T cell, a Th2/Th1 imbalance has been described in allergic conditions in humans. The nasal mucosa in perennial allergic rhinitis is characterised by the presence of a high percentage of activated Th2 cells accompanied by high levels of Th2 cytokines, increased expression of leucocyte endothelial adhesion molecules, and accumulation of activated eosinophils.³ As a result there is a significant increase in eosinophil cationic protein (ECP) levels in the nasal lavage fluid of patients with perennial allergic rhinitis compared with controls (± 85 ng/ml versus 32 ng/ml).⁴

Nasal biopsy specimens taken from patients with perennial allergic rhinitis and measurements of cytokine mRNA expression show a significant increase in interleukin (IL)-5 expressing cells and a significant decrease in IL-2 expressing cells.⁵ In recent experiments attention has focused on the epithelial cells as regulators of airway inflammation. Several mediators are released by these cells including lipid mediators, cyclo-oxygenase derivatives, peptides (endothelin, vasopressin, substance P, CGRP), oxygen products, peptidases, and cytokines.⁶ Although keratinocytes, fibroblasts,

Langerhans' cells, and mast cells seem to be prominent sources of stem cell factor (SCF), epithelial cells of patients with perennial allergic rhinitis also show increased expression of SCF mRNA.⁷ This increased expression is correlated with the number of mast cells and the histamine content.

It is known that several elements may play a role in the differentiation of Th0 cells into Th2 cells including the nature of the antigen itself, its concentration, the route of its administration, the CD40-CD40 ligand interaction, the costimulatory molecules CD80 and CD86 and their contrareceptor CD28, and the cytokine milieu but, in patients with perennial allergic rhinitis, it has been shown that CD86 (B7-2) expression on B cells and monocytes shows selective upregulation on in vitro challenge with house dust mite antigen which suggests a major role for CD86 in this differentiation.⁸

Interestingly, in 1997 Meissner *et al*⁹ reported the presence of a subset of CD8+ T cells producing IL-4 and stimulating IgE production in vitro in the peripheral blood of cat sensitive patients with rhinitis or asthma. In this study the frequency of IL-4+ CD8+ T cells correlated with serum IgE levels. Also of interest is the presence of activated Th2-like $\gamma\delta$ T cells in the nasal mucosa of patients with perennial allergic rhinitis as shown by Pawankar *et al* in 1996.¹⁰ It therefore seems likely that at least three types of Th2-like cells may coexist in the nose of subjects with perennial allergic rhinitis: $\alpha\beta$ Th2, $\gamma\delta$ Th2, and CD8+ Th2 cells. The situation could be even more complex since it is now possible to identify Th1, Th2, Th0, TC2 CD8+ (producing IL-4 and IL-5), Th3 CD4+ (producing TGF- β), Th3 CD8+ (producing TGF- β), Tr1 CD4+ (producing IL-10, IL-5, TGF- β) and so on.¹¹ Allergy could also represent a pathological aberration of mucosal tolerance leading to the production of “helper” Th2 cells instead of “regulatory/suppressor” Th2 cells.¹² Clearly the concept of murine T cell dichotomy must be questioned.

This review of the probable complexity of cytokine and T cell profiles in patients with perennial allergic rhinitis is substantiated by Metz *et al*¹³ who showed that the cytokine profiles of patients with chronic allergic keratoconjunctivitis are characterised by increased expression of IL-5 together with interferon (IFN)- γ in T cells recovered from the conjunctiva—that is, a Th0 type rather than the expected Th2 type.

Another interesting observation is that the eosinophils of patients with allergic keratoconjunctivitis appear to be highly activated and to have a significantly higher expression of cytokines such as IL-4, GM-CSF, and IL-8.¹⁴

UCB SA, Chemin du
Foriest, 1420 Braine
l'Alleud, Belgium
J P Rihoux

Correspondence to:
Dr J P Rihoux
jean-pierre.rihoux@
UCB-group.com

This pattern differs from that observed in patients with giant papillary conjunctivitis and vernal keratoconjunctivitis, suggesting the existence of different "populations" of eosinophils. Hingorani *et al* concluded that the profiles may depend on the duration and stage of the disease: acute, subacute, chronic; existence of remodelling. There are probably similarities between allergic tissues (eyes, nose, bronchi, and skin), but there are also differences and the pattern of cells and cytokines in patients with perennial allergic rhinitis may be quite different from those in the eyes of patients with allergic keratoconjunctivitis.

Histamine in perennial allergic rhinitis

Histamine has long been considered to be the mediator of the acute type 1 allergic reaction. Accordingly, the H₁ antihistamines were also considered to be the ideal symptomatic treatment for pruritus, sneezing, and runny nose. Banu and Watanabe¹⁵ recently reported that T cells deficient in H₁ receptors (histamine H₁R knockout mice) have a low proliferation response to anti-CD3 ϵ cross linking or antigen stimulation *in vitro*. A similarly deficient response was observed in B cells. This suggests that histamine may play a part in regulating some fundamental steps of the antigen-antibody conflict. It also means that the H₁ antihistamines are probably more than symptomatic approaches to the allergic conditions.

It has also been recently reported that H₁ receptor expression is increased in the nasal mucosa of patients with perennial allergic rhinitis.¹⁶ Moreover, it has been shown that histamine decarboxylase mRNA is significantly increased while histamine N-methyltransferase mRNA is decreased.¹⁷

Timmerman and coworkers recently presented some interesting preliminary data to the annual meeting of the European Academy of Allergology and Clinical Immunology held in Brussels on 3–7 July 1999. They showed that some H₁ antagonists behave as inverse agonists, in the same way as H₂ antagonists.¹⁸ These recent data cast a new light on histamine, on histamine H₁ receptors, on H₁ antagonists, and

on therapeutic approaches with compounds of this family which appear rather heterogeneous. Much remains to be done, of course, to elucidate the pathophysiology of perennial allergic disease and the mechanisms of action of the drugs commonly used to treat it.

- 1 Van Cauwenberge P, Watelet JB, Verhoye C, *et al*. The clinical expression of allergy in the nose. *Allergy* 1999;54:93–102.
- 2 Mosmann T. Actions and interactions of T cells and their lymphokines. In: *Proceedings of the Satellite Symposium, Fourth International Conference on Immunopharmacology, Osaka Japan*, 16 May 1988, 5–16.
- 3 Montefort S, Feather IH, Wilson SJ, *et al*. The expression of leukocyte-endothelial adhesion molecules is increased in perennial allergic rhinitis. *Am J Respir Cell Mol Biol* 1992;7:393–8.
- 4 Rasp G, Thomas PA, Bujia J. Eosinophil inflammation of the nasal mucosa in allergic and non-allergic rhinitis measured by eosinophil cationic protein levels in native nasal fluid and serum. *Clin Exp Allergy* 1994;24:1151–6.
- 5 Varga EM, Jacobson MR, Till SJ, *et al*. Cellular infiltration and cytokine mRNA expression in perennial allergic rhinitis. *Allergy* 1999;54:338–45.
- 6 Polito AJ, Proud D. Epithelial cells as regulators of airway inflammation. *J Allergy Clin Immunol* 1998;102:714–8.
- 7 Otsuka H, Kusumi T, Kanai S, *et al*. Stem cell factor mRNA expression and production in human nasal epithelial cells: contribution to the accumulation of mast cells in the nasal epithelium of allergy. *J Allergy Clin Immunol* 1998;102:757–61.
- 8 Nakada M, Nishizaki K, Yoshino T, *et al*. CD86 (B7-2) antigen on B cells from atopic patients shows selective, antigen-specific upregulation. *Allergy* 1998;53:527–31.
- 9 Meissner N, Kussebi F, Jung T, *et al*. A subset of CD8⁺ T cells from allergic patients produce IL-4 and stimulate IgE production *in vitro*. *Clin Exp Allergy* 1997;27:1402–11.
- 10 Pawankar RU, Okuda M, Suzuki K, *et al*. Phenotypic and molecular characteristics of nasal mucosal $\gamma\delta$ T cells in allergic and infectious rhinitis. *Am J Respir Crit Care Med* 1996;153:1655–65.
- 11 Thomas MJ, Kemeny DM. Novel CD4 and CD8 T cell subsets. *Allergy* 1998;53:1122–32.
- 12 Umetsu DT, DeKruyff RH. Updates on cells and cytokines. *J Allergy Clin Immunol* 1997;100:1–6.
- 13 Metz DP, Hingorani M, Calder VL, *et al*. T-cell cytokines in chronic allergic eye disease. *J Allergy Clin Immunol* 1997;100:817–822.
- 14 Hingorani M, Calder V, Jolly G, *et al*. Eosinophil surface antigen expression and cytokine production vary in different ocular allergic diseases. *J Allergy Clin Immunol* 1998;102:821–30.
- 15 Banu Y, Watanabe T. Augmentation of antigen receptor-mediated responses by histamine H₁ receptor signaling. *J Exp Med* 1999;189:673–82.
- 16 Iriyoshi N, Takeuchi K, Yuta A, *et al*. Increased expression of histamine H₁ receptor mRNA in allergic rhinitis. *Clin Exp Allergy* 1996;26:379–85.
- 17 Hirata N, Takeuchi K, Ukai K, *et al*. Expression of histidine decarboxylase messenger RNA and histamine N-methyltransferase messenger RNA in nasal allergy. *Clin Exp Allergy* 1999;29:76–83.
- 18 Smit MJ, Leurs R, Alewijnse AE, *et al*. Inverse agonism of histamine H₂ antagonists accounts for upregulation of spontaneously active histamine H₂ receptors. *Proc Natl Acad Sci USA* 1996;93:6802–7.