The epidemic of **allergy and asthma**

Stephen T. Holgate

Allergic diseases, such as asthma, rhinitis, eczema and food allergies, are reaching epidemic proportions in both the developed and developing world. Key factors driving these rising trends are increased exposure to sensitizing allergens and reduced stimulation of the immune system during critical periods of development. In allergic disease, there is a polarization of T-lymphocyte responses, and enhanced secretion of cytokines involved in regulation of immunoglobulin E, mast cells, basophils and eosinophils, ultimately leading to inflammation and disease. A clear understanding of the cellular and molecular mechanisms of allergic disease and the complex interplay between genetic and environmental factors will undoubtedly create new opportunities for public health and therapeutic interventions.

The foundations of *allergy** have evolved slowly, beginning with John Bostock's description of *catarrus aestivus* or hay fever (1819), Charles Blackley's recognition of pollen grains as causative agents (1873), the discovery of a transferable tissue-sensitizing factor in the serum by Prausnitz and Küstner (1921) and, finally, the identification of this factor as an immunoglobulin subclass (*immunoglobulin E* or IgE) by Johansen in Sweden and the Ishizakas in the United States (1967)[1]. The past 30 years has witnessed a spectacular increase in our knowledge of the cellular and molecular mechanisms of allergic disease (Fig. 1), which has been paralleled by the rising trends in the incidence and health impacts of these diseases worldwide[2]. Whereas in Bostock's and Blackley's day hay fever was a rare disorder restricted to the privileged class, as we approach the millennium almost half the population of the West demonstrates sensitization to one or more environmental *allergens*. In countries such as Britain or Australia, this translates to 1 in 4 children under the age of 14 years having *asthma* and 1 in 5 having *eczema*[3]. Added to this is the occurrence of serious allergic disorders caused by new allergens such as nuts, soya and latex.

At one extreme, *anaphylaxis* and asthma can be life threatening and every year there occur deaths often in young people that are avoidable. Fortunately, most allergic disorders are not life threatening, but they all cause distress and misery for millions — often at a time in their lives when they should be most active. *Allergic rhinitis*, asthma and eczema all interfere with sleep, intellectual functioning and recreational activities, whereas food allergy leads to considerable anxieties for fear of inadvertently ingesting the offending allergen.

The basis of allergy

With the exception of insect anaphylaxis, the process of sensitization usually results from contact of allergens with mucosal surfaces. In the case of respiratory allergy, it is exposure to aeroallergens that is important, asthma being associated more with indoor allergens derived from dust mites, pets and fungi, whereas seasonal rhinoconjunctivitis requires exposure to grass and tree pollens. The nature of the allergen itself seems important, with many inhalant allergens exhibiting enzymic activities (for example, *Der* P_1 and *Der* P_9 from dust mites[4]). In an experimental setting, simultaneous exposure to allergen and proteolytic activity enhances sensitization, possibly by disrupting epithelial tight junctions. This might in turn allow greater access of allergen to *dendritic cells* or interrupt critical molecules involved in IgE regulation such as the low-affinity receptor for IgE (CD23) and the interleukin (IL)-2 receptor (CD25)[4,5]. In the case of food allergens, the biological challenge for the allergens is to survive digestion.

Communication between allergens and T cells occurs through *antigen*-processing cells, such as dendritic cells. A major breakthrough in our understanding of the pathophysiology of allergy, irrespective of the organ in which the phenotype is expressed, has been the discovery that, in response to allergens, T lymphocytes produce a restricted array of *cytokines* encoded in a small cluster on the long arm of chromosome 5 at bands 31–33 (chromosome 5q31–33), which has been shown to be the IL-4 gene cluster. The proinflammatory cytokines are produced in particular by a subtype of T helper cells known as *Th2*. The other T helper subtype, *Th1*, tends to antagonize the allergic response (Fig. 1). Factors that select for Th2 responses include low-affinity binding of the allergen peptide to the groove of major histocompatibility complex (MHC) class II, selective use of co-stimulatory molecules (for example, engagement of T-cell CD28 by CD86 in preference to CD80) and reduced dendritic cell secretion of IL-12. The microenvironment in which the dendritic cell finds itself is also emerging as an important determinant of the balance between interferon-γ (IFN-γ)-producing Th1 cells and proallergic Th2 cells. One suggestion is that prostaglandin E_2 produced by epithelial cells, inhibits IL-12 production by dendritic cells, thereby favouring a Th2 response. The property of dendritic cells to acquire a phenotype that is capable of directing T-cell cytokine polarization has led to the suggestion that there are two types of dendritic cell designated DC_1 and DC_2 (ref. 6). But in mice, lung tissue *macrophages* with some properties of dendritic cells are capable of shutting down local T-cell responses, a mechanism that may help explain why all individuals testing positive for an allergic reaction are not asthmatic[7].

*Terms in italic are defined in the glossary on p. B39.

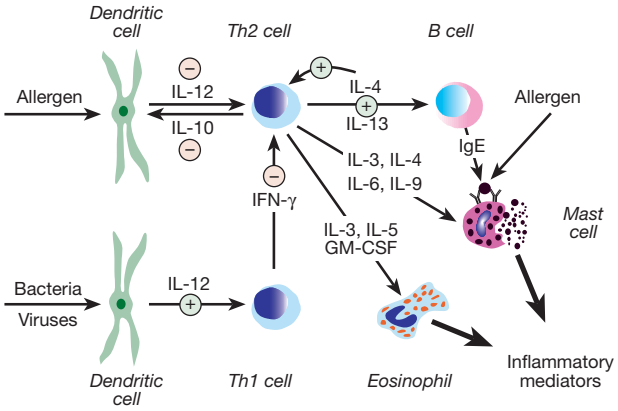

Figure 1 **Proposed cellular and molecular mechanisms of allergy. Both soluble mediator and cognate interactions between dendritic cells and naive CD4$^+$ T cells direct their differentiation to the Th2 phenotype with the capacity for enhanced secretion of cytokines encoded in the IL-4 gene cluster on chromosome 5q31–33. Th2 polarization is effectively suppressed if T cells are driven along the Th1 pathway by IL-12 to produce increased IFN-γ. It is suggested that exposure to bacterial and possibly viral 'danger' signals at a critical time during immune development in childhood enhances Th1 at the expense of Th2 polarization producing protection against allergy.**

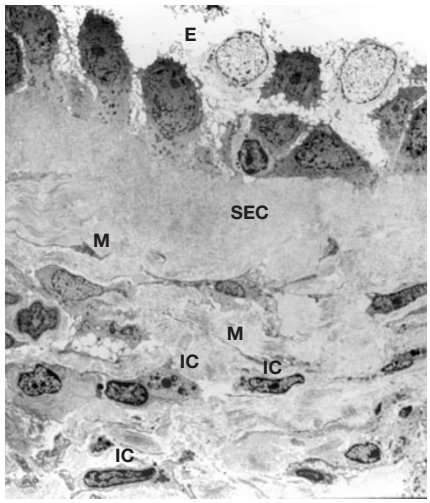

Figure 2 **Transmission electron micrograph of allergic asthmatic bronchial mucosa showing epithelial disruption (E), subepithelial collagen deposition (SEC), myofibroblasts (M) and inflammatory cell infiltrates (IC) (×1,060).**

Helper T cells are not the only source of proallergic cytokines. *Mast cells*, *basophils*, *eosinophils*, CD8$^+$ T cells and, under certain circumstances, bronchial epithelial cells, fibroblasts and smooth muscle can all produce cytokines encoded by the IL-4 gene cluster[8].

IgE as the allergic trigger

Both asthma and eczema are considered to be primarily T-cell-mediated disorders with IgE serving as an important trigger. In asthma, this view is supported by the efficacy of a humanized blocking antibody directed against T cells[9]. Detailed knowledge of the site of molecular interaction between IgE and the high-affinity IgE receptor (FcεR1) has also enabled mouse monoclonal antibodies to be developed that selectively bind to the relevant IgE *epitopes*. By splicing sequences encoding the antigen-binding regions of one of these monoclonal antibodies into a human IgG framework, a therapeutic antibody (MAb E-25) has been developed[10]. Administration of MAb E-25 to allergic asthmatic subjects led to rapid elimination of circulating IgE to almost undetectable levels and was paralleled by a marked reduction in FcεR1 expression. Over a period of 9 weeks, this treatment markedly attenuated the early-phase (mast-cell dependent) and late-phase (inflammatory) bronchoconstriction to inhaled allergen. The efficacy of MAb E-25 in treating chronic asthma and rhinitis is evidence for a key role of IgE in chronic allergic inflammation, although not all patients responded equally well[9].

The effectors of allergic disease

Although IgE production is associated closely with allergic *hypersensitivity* responses, a wide range of cellular responses underlies chronic allergic disease, including the production of inflammatory *mediators*. Release of histamine and cysteinyl leukotrienes account for most of the early- and late-phase responses, although the cellular origin of these mediators may differ — mast cells in the early phase and eosinophils, basophils and macrophages in the late phase.

The discovery of histamine by Dale and Laidlaw in 1911 created a new science — immunopharmacology. Histamine H1-antagonists are first-line drugs for the treatment of anaphylaxis, rhinoconjunctivitis and *urticaria* but are singularly ineffective in asthma and eczema. The discovery of slow reacting substance by Feldberg and Kellaway in 1938 and its subsequent chemical characterization in 1979 by Bengt Samuelsson's group as a mixture of three cysteinyl leukotrienes — LTC_4, LTD_4 and LTE_4 — has stimulated the development of antagonists for this class of lipid mediator[11]. It seems that this new asthma treatment is especially effective in a sub-population of asthmatics who are intolerant of aspirin and other non-steroidal anti-inflammatory drugs and who exhibit enhanced LTC_4 synthase activity[11,12]. Understanding the factors that regulate the synthesis and release of these mediators from mast cells, eosinophils, macrophages and *monocytes*, as well as understanding genetic variants of the cysteinyl-LT_1 receptor and its promoter, will create an opportunity for using genetic screening as a method for predicting drug responsiveness (pharmacogenetics).

Human mast cells can be classified on the basis of their granule content of neutral proteases. All mast cells contain the unique four-chained neutral protease tryptase, but only those located in connective tissue are enriched with chymase and carboxypeptidase A. The high content of neutral proteases in mast-cell granules implies important mediator functions. For example, tryptase can activate one of the protease-activated receptors (PAR-2) expressed on the surface of endothelial and epithelial cells. This leads to enhanced cytokine production, and the expression of adhesion molecules that selectively recruit eosinophils and basophils[13]. Although mast cells contribute to chronic airway inflammation, it is activated eosinophils that are considered to mediate most of the disordered airway function characteristic of this disease. Their selective recruitment and activation is a characteristic feature of asthma, whether allergic or non-allergic. Until recently, relatively little was known about how eosinophils released their mediators in allergic tissue responses. The recent recognition that, in the presence of IL-4 or IL-13, tissue but not circulating eosinophils express FcεR1 provides one mechanism whereby the local cytokine milieux is able to create allergen-responsive cells, while cleavage of eosinophil PAR-2 receptors by mast cell tryptase offers another.

Eosinophil recruitment from the circulation into a tissue subjected to an allergic response requires signals to reach the bone marrow. IL-5 is highly effective at releasing eosinophils and their precursors from the bone marrow[14]. Thus, in allergic asthma, both the circulating and sputum eosinophilia before and after allergen exposure were effectively suppressed by a single injection of a humanized blocking anti-IL-5 monoclonal antibody[15]. A similar effect has been observed with human recombinant IL-12, in this case operating by the suppression of IL-5 and other Th2 cytokine production by INF-γ (Fig 1). In contrast to similar experiments conducted in animal 'models' of

asthma, neither of these treatments affected the early or the late bronchoconstriction responses, nor *bronchial hyperresponsiveness* in humans. These highly selective interventions in allergic asthma not only question the interpretation of relatively acute animal models, but also the primacy of eosinophils as mediator-secreting cells in asthma. One interpretation for the findings is that reducing circulating and sputum eosinophils may not reflect a parallel reduction in primed eosinophils already resident in the airways, especially as in asthma protection of tissue eosinophils from apoptosis is at least as important as new cell recruitment[16]. In this regard, granulocyte-macrophage colony-stimulating factor (GM-CSF) produced by the epithelium and subepithelial myofibroblasts as well as eosinophil contact with matrix proteins are especially relevant.

Allergy: nature or nurture

Asthma clusters in families. The role of genetic factors as important determinants of allergic disease is revealed in studies of mono- and di-zygotic twins and in highly inbred populations such as those living in Tristan da Cunha where asthma affects up to 40 per cent of the population. Genetic factors operate at two levels determining: (i) allergen recognition through MHC class II haplotypes; and (ii) the organ localization and response. Although genetic factors may explain at least part of the wide intercountry differences in disease incidence, they do not explain the rising disease trends. The hypothesis that currently finds most favour is the influence of hygiene in western society that deprives the developing immune response of important signals for Th1 development, especially in children born of atopic parents and who at birth exhibit impaired IFN-γ production[17].

The hygiene hypothesis best accommodates the link between allergy and social class, the urban to rural gradient, infant diet, over-use of antibiotics and the East to West gradient of disease. It involves the concept of faulty programming of the mucosal immune system *in utero* and during a critical period of childhood up to five years of age. However, these environmental influences best fit the rising trends in *atopy*, rather than asthma. Since the reunification of Germany in 1989, the prevalence of atopy in east Germany has almost caught up with that in the western half of the country and yet the prevalence of asthma has not changed. Similarly, over the past two decades, atopy has increased markedly in Nigeria, Ethiopia and the Gambia, but the prevalence of asthma and bronchial hyperresponsiveness has failed to parallel this. It would seem that factors other than atopy are required for the expression of the more chronic allergic disorders and that they are likely to have their origin in the organ itself as revealed in asthma by lung transplantation[18].

In all types of asthma, fragility and activation of the bronchial epithelium, proliferation of the underlying myofibroblasts and the laying down of 'repair' collagens (types I, III and V) in the *lamina reticularis*, which causes thickening of the sub-basement membrane region, are as characteristic of the disease as the presence of activated mast cells and eosinophils (Fig. 2). These unique pathological features of asthma indicate strongly that reactivation of the epithelial–mesenchymal trophic unit occurs which, in the fetus, is involved intimately in lung growth and branching[19]. In asthma, the same morphogenetic signalling molecules, including the epidermal growth factor family, transforming growth factors, basic and acidic fibroblast growth factors, nerve growth factors, vascular endothelial growth factor and keratinocyte growth factor and their respective receptors, are either over-expressed or exhibit evidence of activation. This suggests that epithelial–mesenchymal signalling is enhanced, and may account for some of the airways smooth muscle hypertrophy and other features of the remodelling of the airway wall in this disease[20].

Key questions to answer are whether epithelial–mesenchymal signalling is a primary or acquired abnormality and how these morphogenetic changes interface with the Th2 cytokine response. Epithelial cells and fibroblasts express receptors for IL-4 and IL-13 as well as signal transducer and activator of transcription 6 (Stat-6) and insulin-receptor substrates (IRS-1 and IRS-2) and respond to these Th2 cytokines with phenotypic responses that are compatible with observations in asthma (for example, *goblet cell* metaplasia[21,22], the enhanced secretion of the eosinophil chemoattractant eotaxin, and differentiation of fibroblasts to myofibroblasts[23]). Functional *polymorphisms* of the relevant genes will not only impact on Th2 and IgE responses but will also influence the organ phenotype upon which these immune responses act.

Conclusions

In this supplement, the up-to-date set of reviews by a group of international experts covers the spectrum of knowledge of allergy and asthma, from epidemiology to molecular mechanisms and future therapies. The recognition that most atopic disorders have their origins in childhood, are increasing in incidence in developed and developing countries and have strong links to the environment suggests that solutions to stop the epidemic are more likely to come from public health than pharmacological interventions[22]. The challenge for the new century is to understand how environmental factors interact with the human genome to reveal the atopic state, its organ specificity and the associated diseases.

Stephen T. Holgate is in the Respiratory, Cell & Molecular Biology Research Division of the School of Medicine, University of Southampton, Mail Point 810, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK.
e-mail: sth@soton.ac.uk

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