

Atopic allergy and other hypersensitivities

Allergy, a disease of the internal and external environments

Editorial overview

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Abbreviations

AD	atopic dermatitis
AID	activation-induced deaminase
DC	dendritic cell
DH site	DNase I hypersensitive site

About 20% of the population in Western countries suffer from allergic diseases, which include asthma, rhinitis, atopic dermatitis (AD) and food allergy. This prevalence is steadily rising and the rise correlates with improvement in living standards and better control of infectious diseases in childhood. The series of reviews in this section illustrate the fact that allergic diseases are environmental diseases, not simply because they are triggered by environmental allergens but also because they arise in an abnormal internal molecular and cytokine environment that influences the decision of immune T cells to differentiate into allergy-promoting Th2 cells.

It has been known for close to 15 years that, upon encounter with antigen, naive T cells can differentiate along one of two pathways to become Th1 or Th2 helper T cells, which differ by the profile of their secreted cytokines. Th2, but not Th1, cells secrete cytokines that promote eosinophil mediated (IL-5 dependent) and IgE mediated (IL-4 and IL-13 dependent) allergic inflammation whereas Th1, but not Th2, cells secrete IFN- γ , which inhibits the actions of IL-4 and IL-13.

Avni and Rao (pp 654–659) dissect the mechanisms of T cell differentiation into Th1 and Th2 cells. Their review delineates three stages of cytokine expression: an initiation phase that is highly dependent on antigen, cytokines and cytokine-induced STAT factors; a commitment phase, mediated by subset-specific transcription factors such as GATA3 and cMaf in Th2 cells, and T-bet and ERM in Th1 cells, in which the differentiated phenotype is stabilized and maintained in the absence of further stimulation; and a phase of acute gene transcription, elicited by secondary contact of differentiated T cells with antigen, that requires the antigen-induced transcription factor NFAT.

Naive T cells exhibit only two DNase I hypersensitive sites (DH sites) in a ~43 kilobase interval spanning the IL-4

and IL-13 genes. Stimulation with antigen in the presence of IL-4, which induces STAT6, results in the appearance of ten clusters of Th2-specific DH sites and in the induction of the Th2-specific nuclear factor, GATA3. This factor, which perpetuates its own expression, binds to at least one of the DH sites and 'fixes' the chromatin in an 'open', accessible conformation, most probably by recruiting chromatin-remodeling complexes and histone acetyltransferases. This commits the T cell to the Th2 lineage. In the case of Th1 cells, IL-12 and STAT4 induce the transcription factor T-bet, which, in a similar fashion to GATA3, commits the T cell to the Th1 lineage. Restimulation of committed Th2 or Th1 cells with antigen induces NFAT, which now can access the regulatory regions of the cytokine genes to cause high-rate transcription and secretion of cytokines.

A major effect of IL-4 and IL-13 is the induction of IgE class switching in B cells. Oettgen (pp 618–623) reviews the molecular mechanisms of IgE class switching. Binding of IL-4 or IL-13 to their receptors on B cells causes signaling via the IL-4-receptor α chain, common to both receptors, and leads to the induction of 'germline' transcription at the C ϵ locus. The C ϵ transcripts consist of the I ϵ exon, the downstream switch S ϵ region and the C ϵ exons but the transcripts are sterile due to the presence of stop codons in I ϵ . The S ϵ region of the RNA, which contains abundant guanosines, hybridizes to the cytidine-rich S-region of the DNA strand. The RNA–DNA hybrid then serves as a nuclease substrate, giving rise to double-strand DNA breaks, which can then be annealed by DNA end-joining. The recombination process requires signaling via CD40 and induction of a cytidine deaminase, activation-induced deaminase (AID). This molecule has homology to APOBEC-1 — an RNA-editing enzyme whose substrate is the mRNA for apolipoprotein B — and, like APOBEC-1, is implicated in changing cytidine to uracil. Through RNA-editing of an as-yet unidentified substrate, AID may generate an enzymatic activity that is essential for the cutting of DNA, a process central to switch recombination. Deficiency of CD40 ligand or of AID results in failure of class switching in patients, giving rise to type I (X-linked) or to type II (non-X-linked) hyper-IgM syndrome, respectively.

Mast cells and basophils are not only important effector cells in acute IgE-associated allergic reactions but also may contribute to the late-phase reactions (LPRs) that develop hours or days following exposure to allergen. Mast cells and basophils express the high-affinity receptors for IgE (Fc ϵ RI). It has been now clearly established that IgE upregulates the expression of Fc ϵ RI, most probably by

protecting it from internalization and degradation. This has important clinical implications because mast cells that express high numbers of FcεRI release mediators at lower concentrations of antigen and secrete greatly enhanced amounts of histamine, leukotrienes and Th2 cytokines. Much of the efficacy observed in recent trials of humanized mouse anti-human-IgE monoclonal antibodies may be related to the decrease in FcεRI expression on basophils and mast cells, subsequent to the drastic drop in circulating free IgE. Because IgE deficient mice develop allergic inflammation in their lungs that is indistinguishable from wild-type controls, the role of mast cells in allergic inflammation has been put in doubt.

On the basis of study of mast cell deficient mice with mutations in c-kit, Wedemeyer, Tsai and Galli (pp 624–631) present evidence that mast cells contribute significantly to three cardinal features of airway allergic inflammation: allergen-induced hyper-reactivity to cholinergic stimulation; eosinophilic infiltration; and proliferation of airway epithelium. A role for mast cells in innate and in adaptive immunity is suggested by the increased susceptibility of mast cell deficient mice to TNF-α-dependent death (following cecal ligation) and to infection with *Strongyloides*. Finally, and importantly, the ability to grow relatively simply mast cells from bone marrow progenitors, and recently from embryonic stem cells, is opening new frontiers in the investigation of mast cell biology and particularly of FcεRI signal transduction that will have an important impact on the treatment of allergic diseases.

The 'hygiene hypothesis' contends that better standards of living contribute to the increase in allergic diseases. Recent studies indicate that infections with viruses and especially bacteria early in life may help to inhibit allergic Th2 responses by skewing the immune response towards Th1, possibly by activating macrophages and NK cells to release IL-12. However, the situation is not so simple because several studies suggest that viral/bacterial infections exacerbate allergic diseases, for example bronchial asthma, airway hyper-responsiveness and AD.

Herz *et al.* (pp 632–640) review the effect of infections on the allergic response. Epidemiological evidence shows a negative association between infection with measles or hepatitis A viruses and allergy. Experimental evidence suggests that influenza A viruses and respiratory syncytial virus (RSV) decrease the eosinophilic inflammation in a mouse model of asthma. However, both viruses exacerbated established asthma, possibly because IL-4 produced during the allergic response may switch the normally predominantly Th1-biased T cell response against the virus towards a Th2 response. The resulting tissue eosinophilia would play a critical role in the virus-induced airway hyper-responsiveness. Even the Th1 component of the antiviral response may exacerbate the allergic disorder by increasing an influx of inflammatory cells into the airways through the induction of proinflammatory cytokines

and chemokines such as the eosinophil attractant, RANTES. Infection with *Mycobacterium tuberculosis* and vaccination with BCG are negatively correlated with allergy. In contrast, the use of antibiotics during infancy has been correlated with an increased risk of developing asthma. CpG-motif-containing oligonucleotides — found in the DNA of many different types of organisms — and lipopolysaccharides are potent inducers of IL-12 and IFN-γ secretion, leading to inhibition of allergic airway inflammation. The mechanisms by which helminthic infections promote allergic responses are not clear but probably include mechanical injury, which is known to play a critical role in the Th2 response introduced through injury to the skin.

AD affects 5% of children and is characterized by infiltration, predominantly in the dermis, of activated memory CD4⁺ T cells and eosinophils. In acute lesions of AD, there is significant increase in cells expressing IL-4, IL-5 and IL-13 mRNA and protein, suggesting preferential accumulation of Th2 cells. In the chronic skin lesions of AD, cells containing IFN-γ mRNA and protein predominate over those containing IL-4 and IL-5.

Several observations suggest that allergens play an important role in AD. Approximately 80% of patients with AD have elevated levels of serum IgE and evidence of IgE antibody to a variety of foods and inhaled allergens. T cells isolated from AD skin lesions have been shown to proliferate and secrete IL-4 in response to dust-mite antigen. Injury plays an important role in AD; simple occlusion and restraining from scratching results in healing of the skin. The role of injury in the induction of the allergic response in AD is dual: it allows the penetration of protein antigen and it skews the response towards Th2, via the induction of cytokines such as IL-10 that favor the differentiation of dendritic cells (DCs) towards DC2 cells that induce Th2 differentiation. Injury is also likely to play a similar role in allergic diseases such as asthma and food allergy (see below). Indeed, in experimental models of mouse asthma, simple inhalation of recombinant allergen is not sufficient to induce an allergic response; however inhalation of a crude extract from *Aspergillus fumigatus* does.

Akdis *et al.* (pp 641–646) address in their review an important issue regarding AD: what makes the Th2 cells home to the skin? Once activated in the regional lymph nodes following contact with antigen-laden DCs, allergen-specific T cells enter the blood then, upon re-exposure to antigen, home back to the skin. There is strong evidence that skin-homing T cells in humans express the CLA antigen, which is a post-translationally modified P-selectin glycoprotein ligand 1 (PSGL-1). Circulating CLA⁺ T cells are increased in AD and express activation markers. Recently, cutaneous attracting chemokine, CTACK/CCL27, and its receptor, CCR10, were shown to play a role in the preferential accumulation of CLA⁺ T cells in the skin.

However, other mechanisms of chemoattraction must exist because CTACK is constitutively expressed in mouse skin. In contrast, in a mouse model of AD, the Th2-selective chemokine TARC is selectively induced by mechanical injury. Furthermore, following epicutaneous (EC) sensitization with the allergen ovalbumin (OVA), Th2 cells are recruited to the lung upon OVA inhalation. This cross-circuitry between skin and lung (and possibly gut) may be governed by chemokine–chemokine-receptor pairs and may underlie the clinical observation that the majority of children with AD go on to develop asthma. One of the important aspects of AD is marked keratinocyte pathology. Akdis *et al.* discuss their recent work, which shows keratinocyte apoptosis in AD that is dependent on Fas expression; Fas is induced by IFN- γ , which is secreted by Th1 cells present in the chronic lesions of AD. This is consistent with the finding of attenuated skin thickening observed in IFN- $\gamma^{-/-}$ mice following EC sensitization with allergen. Recent evidence indicates that Th2 cells induce IL-12 secretion by macrophages, which then induces the differentiation of Th1 cells locally.

Helm and Burks (pp 647–653) have reviewed the complex and little-investigated, but important, field of food allergy. This field will assume a forefront in the debate regarding the introduction and marketing of transgenic foods. Allergy to food affects 1–2% of the population. Allergic sensitization via the gastrointestinal tract is probably facilitated by injury. Indeed the only models of inducing IgE antibody responses to allergens rely on

concomitant feeding of cholera toxin. The end-organ manifestations of fluid loss and epithelial injury are dependent on T cells and eosinophils. The latter are recruited to the gut under baseline conditions, increasingly so after allergic challenge in an eotaxin–CCR3 dependent manner. The involvement of Th2 cells is demonstrated by the protective effect of anti-IL-4 monoclonal antibody and by the requirement for STAT6. As in AD and in asthma, chemokines play an important role in lymphocyte homing to the gut. CTACK is highly expressed in the gut and mesenteric lymph nodes. This may explain the frequent association of food allergy and AD. Intriguingly, a Th2 response predominates in ulcerative colitis (UC), whereas a Th1 response predominates in Crohn's disease, suggesting that allergic sensitization plays an important role in UC. Thus, an understanding of the mechanisms of allergic sensitization to foods has probably important implication for inflammatory bowel disease.

The impact of allergic diseases on mortality, morbidity and on the economy is staggering. The past decade has seen important advances in our understanding that there are these environmental diseases and whether they are caused by a Th2 cell response to allergens. The basic reason why 20% of individuals have an internal environment conducive to a Th2 response to allergens is not understood. However, there is reason to hope that the sequencing of the human genome will help solve the mystery at the molecular level and will eventually help devise better preventive and curative therapies for these afflictions.