

A New Paradigm for Immunoglobulin E in Allergic Diseases

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Current Allergy and Asthma Reports 2005, 5:227–232
Current Science Inc. ISSN 1529-7322
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Recent observations at the level of the antigen presenting cell, as well as the T cell, point toward a pivotal role for interleukin (IL)-10 in the control of immunoglobulin E (IgE)-mediated allergic diseases, such as asthma and rhinitis. This has led to restructuring of the Th1/Th2 paradigm with IL-10 acting to modulate Th2-driven IgE antibody (Ab) responses. The modified Th2 response to cat allergen is associated with high-dose allergen exposure and the presence of high titer IgG and IgG4 Ab; however, IgE Ab and allergic symptoms are absent. Characteristics of this immune response indicate that it is a variant of the allergic response, which develops in an IL-10–dependent manner, but it is distinct from other types of nonallergic or tolerant responses. These observations point toward a new paradigm for the development of IgE-mediated responses. This may be important for advancing our understanding of the response to immunotherapy and anti-IgE, and for defining immune mechanisms that drive allergic responses.

Introduction

The association between immunoglobulin E (IgE) antibodies (Ab) and allergic disorders such as asthma and rhinitis is well established. However, the mechanisms whereby IgE Ab contribute to the pathogenesis of allergic disease and to allergic symptoms are yet to be elucidated. IgE antibodies likely play a multi-faceted role in the development and persistence of the allergic phenotype. Definition of the modified Th2 response to cat allergen, which is not associated with IgE Ab to cat allergen or allergic symptoms, despite the presence of high levels of circulating IgG Ab, has highlighted the pivotal role of IgE Ab in the development of allergic disease. In vitro and in vivo studies suggest a central role for regulatory T cells or inhibitory factors such as interleukin (IL)-10 in the control or suppression of

Th2-driven IgE-mediated responses. This represents a shift in the Th1/Th2 paradigm but is likely an overly simplistic view. For example, definition of the modified Th2 response, which is distinct from other nonallergic responses, illustrates how the immune response to allergens cannot be segregated solely based on the presence or absence of IgE. Furthermore, it is increasingly apparent that multiple factors influence immune regulation, including properties of the allergen itself, the environment, and genetics. This article assesses how IgE- and non-IgE-mediated responses may develop in light of recent observations in both murine and human systems. The distinction between different types of nonallergic responses is highlighted, and a new paradigm is presented to explain how the modified Th2 response may arise as a variant of the allergic phenotype.

The Link Between Immunoglobulin E and Allergic Symptoms

Immunoglobulin E antibodies directed against allergens from diverse sources play a multi-faceted role in the pathogenesis of allergic disease. Cross-linking of IgE bound to its high affinity receptor, FcεRI, on mast cells and basophils triggers the release of mediators that orchestrate allergic inflammatory processes. Elaboration of IL-4, IL-5, and IL-13 by T helper (Th)2 cells, the principal effector T-lymphocyte population in the allergic response, may also be enhanced by IgE. Specifically, IgE antibodies facilitate receptor-mediated uptake of allergen by antigen-presenting cells such as dendritic cells and B cells, thereby enhancing antigen presentation to Th2 cells [1,2]. Despite recent advances in defining IgE antibody-mediated processes at the cellular and molecular level, the mechanistic link between IgE and allergic symptoms remains elusive. Epidemiology studies have yielded findings that support an etiologic role for IgE in symptomology. Notably, sensitization to indoor allergens is a major risk factor for perennial asthma, and the prevalence of both asthma and airway hyperresponsiveness are correlated with serum IgE levels [3–5]. The association between elevated serum IgE levels and allergen sensitization with persistent wheeze in early childhood suggests that IgE is a prerequisite for the devel-

opment of allergic symptoms [6]. This statement is supported by the high prevalence of allergic rhinitis (~50%) and asthma (>60%) in atopic dermatitis patients who exhibit markedly elevated levels of total IgE in serum [7]. The strongest evidence of a direct role for IgE in the pathogenesis of allergic disease is provided by the efficacy of anti-IgE therapy in patients with asthma and rhinitis based on improvement in symptoms and decreased airway reactivity [8,9]. In asthmatic subjects, treatment with omalizumab was associated with attenuation of both early- and late-phase responses in the lung [8]. Similarly, inhibition of nasal responses to allergen challenge was observed in patients with allergic rhinitis after treatment [9]. Such changes were associated with decreases in sputum eosinophils, reductions in inflammatory cytokines, and downregulation of FcεRI expression on a variety of cell types [8–10]. Although the development of IgE Ab-mediated, immediate-type hypersensitivity to allergens is frequently associated with allergic symptoms such as wheezing, rhinitis, and hives, sensitization to allergens without symptoms is also observed. Adding to the complexity, there is no clear correlation between serum titers of IgE Ab to a specific allergen and symptomology, with some patients exhibiting low levels of IgE Ab, despite the presence of severe asthma. With this in mind, local production of IgE Ab within the upper or lower respiratory tract, as has been demonstrated in murine models, may also contribute to allergic inflammatory processes at the site of allergen encounter [11].

Murine models of asthma have been invaluable in dissecting the relative contributions of different cell types and molecular mediators associated with this complex disease. Sensitization to antigen in these models is typically carried out using an intraperitoneal route of immunization. In a murine system that attempted to mimic human asthma by sensitization with aerosolized allergen, administration of anti-IgE was associated with decreased lung eosinophilic inflammation and airway mucosa pathology [12]. These observations point to a pivotal role for IgE Ab in the development of lung eosinophilia. The debate regarding the role of eosinophilia in the development of airway hyperreactivity and symptoms is ongoing [13,14]. The ability to induce allergic inflammatory changes in the lungs of mice, independent of IgE Ab, adds another layer of complexity to the mechanistic link between IgE and symptoms. There is no doubt that IgE Ab play a critical role in the initiation of allergic inflammatory processes—*ie*, the early phase of the allergic response. Unraveling the contributions of IgE Ab to persistence of asthma and rhinitis symptoms will prove more challenging, given that murine models of chronic allergic disease have not been successfully developed.

Determinants of the Allergic and Nonallergic State

It is clear that genetics and the environment are major contributing factors to the development of IgE Ab-mediated

responses. Each of these factors encompasses a multiplicity of putative determinants of disease that make it difficult to predict allergic phenotype. For example, exposure to environmental allergens, which is an established risk factor for sensitization, is dependent upon multiple variables, including the type of allergen encountered, the timing (*ie*, early life), and the dose (and route) of allergen received. In addition, co-exposure to infectious organisms, as well as the degree of exposure to bacterial products such as lipopolysaccharide (LPS), may influence the development or persistence of allergic responses through adjuvant effects [15–17]. Similarly, genetic studies have identified numerous genetic loci and polymorphisms in candidate genes that are linked to IgE levels and allergic diseases, including asthma and atopic dermatitis [18]. Taking these observations into account, it is not surprising that minor manipulations, even within the same murine model of asthma (*ie*, change in allergen-dosing regimen) can lead to differential involvement of immune pathways (*ie*, IgE-dependent and IgE-independent) that mediate allergic responses [12].

A pivotal role for Th2 lymphocytes in IgE Ab-mediated disease is well established. However, there is evidence to suggest that, at the T-cell level, the development of allergic disorders is not an “all-or-none” phenomenon. Just as the allergic phenotype encompasses a broad spectrum of clinical entities, it is increasingly apparent that complex immune mechanisms govern both allergic and nonallergic responses and that development of the allergic state cannot simply be explained by induction of a Th2 response. Indeed, the Th1 cytokine, interferon (IFN)- γ , may be a prominent feature of allergen-specific T-cell responses in allergic individuals [19,20]. In some allergen systems, there is evidence of T-cell priming, irrespective of allergic phenotype, as judged by *in vitro* assessment of T-cell recall responses. This observation is arguably not surprising, given the ubiquitous nature of certain environmental allergens. The key question is: If circulating allergen-specific T cells are present in nonallergic individuals, why does this not result in manifestation of allergic disease? In recent years, much emphasis has been placed on a protective role for Th1 cells in the nonallergic state based on the mutually inhibitory effects of Th1 and Th2 subsets. Although in some studies there is evidence of increased induction of IFN- γ in T cells derived from nonallergic subjects compared with their allergic counterparts, evidence of a clear-cut distinction based on Th1 and Th2 cytokines is lacking. Instead, differences appear to be subtle and suggest a delicate interplay between distinct T-helper subsets, with the frequency or ratio of Th1 and Th2 cells determining immune outcome [21••]. The renewed interest in regulatory T cells has advanced this viewpoint. Specifically, regulatory T cells may play a pivotal role in controlling the interplay between Th1 and Th2 cells such that an increase in Th2 responses induces an allergic response while a shift in favor of Th1 responses could induce the nonallergic state. An attractive feature of this model is that it does not

preclude a role for Th1 cells in allergic disease. Indeed, there is emerging evidence to suggest that Th1 cells may actually be required for optimal Th2 priming [22]. Moreover, it offers an alternate explanation of the hygiene hypothesis. Thus, rather than increased microbial burden leading to direct enhancement of Th1 responses, the effect of microbial products on Th1 effector cells may be indirect, mediated through regulatory T cells [23].

It is clear that bacterial products such as LPS can modulate allergen-specific T-cell responses both in vitro and in vivo, and these effects appear to be mediated by dendritic cells (DC). For example, in a murine system, co-administering low-dose inhaled LPS with antigen preferentially induced a Th2 response, whereas inhalation of high-dose LPS favored a Th1 response [15]. The effects of LPS were shown to be dependent on signaling via Toll-like receptor 4 (TLR4) and DC activation. Consistent with this, inhalation of "low-dose" endotoxin (10,000 endotoxin units) by nonallergic subjects was associated with increased IL-13 and decreased IFN- γ in sputum [24]. The implication is that co-exposure to bacterial adjuvants is a pre-requisite for mounting a Th2-type allergic response. Moreover, it is the degree of "microbial education" experienced by the DC that dictates immune outcome. In keeping with this, a TLR4 polymorphism associated with asthma has recently been described [25]. In that study, peripheral blood mononuclear cells (PBMCs) derived from children with the TLR4 polymorphism exhibited decreased production of the Th1-polarizing cytokine IL-12 after stimulation with LPS. Thus, altered responsiveness to innate immune signals may contribute to the development of allergic disease.

Control of Distinct Immune Responses: Role of the Dendritic Cell

Dendritic cells have been shown to play a pivotal role in both the initiation and effector phases of allergic inflammatory processes in murine models [26••]. However, establishing a definitive role for DCs in nonallergic responses could prove more difficult. There is evidence to support a role for IL-10-producing DCs or plasmacytoid DCs in tolerance to inhaled antigen through the induction of T cells with suppressive activity [27,28]. It is possible that distinct immune mechanisms operate through the same type of dendritic cell to generate different forms of nonallergic responses, which are mediated by regulatory T cells. Consistent with this, a model has been proposed whereby allergen exposure in conjunction with exposure to different doses of bacterial products (pathogen-associated molecular patterns [PAMPs]) results in the development of nonallergic responses mediated by two distinct immune pathways. In this model, high-dose PAMPs facilitate DC maturation and IL-12 production with subsequent generation of Th1 effector cells in parallel with regulatory T cells. In contrast, in the absence of PAMPs, DCs fail to mature, and, as a consequence, such immature DCs preferentially induce regulatory T cells without effector T cells, thereby

leading to tolerance [29••]. One drawback of this model is that it fails to explain observations in human systems that implicate involvement of regulatory T cells not only in nonallergic responses, but also in allergic responses. An alternate possibility is that different DC types are integral to both allergic and nonallergic responses and that the "balance" between immunogenic and tolerogenic DC subsets dictates immune outcome. In keeping with this, in a murine model, depletion of lung plasmacytoid DCs, but not myeloid DCs, during inhalation of normally inert antigen led to allergic inflammatory changes within the lungs [28]. Thus, cooperation between specific DC types after allergen encounter may be critical to regulation of the allergic response.

Revisiting the Th1/Th2 Paradigm

Regulatory T cells have become a focus of vigorous study in the allergy field, largely as a result of their resurgence in other immune-mediated disorders. Consequently, the regulatory cytokine, IL-10, has emerged as a central regulator of the allergic response, acting to influence the "balance" between Th1 and Th2 subsets. In a murine model, respiratory exposure to high-dose antigen induced IL-10-producing DCs and expansion of T cells that secreted high levels of IL-10 [27]. In humans, IL-10 has been implicated in tolerance induction in allergic patients injected with high doses of the major bee-venom allergen, PLA2, or grass pollen extract, during immunotherapy [30–32]. Notably, in patients with seasonal pollinosis, local increases in IL-10 were observed in the nasal mucosa after 2 years of immunotherapy, but only during the pollen season [32]. These changes were associated with blunting of seasonal increases in allergen-specific IgE and marked enhancement of IgG Ab. Furthermore, these IgG Ab blocked IgE-facilitated binding of allergen-IgE complexes to B cells in vitro. Consistent with the seasonal increases in IL-10 observed in that study, Ling *et al.* [33] reported diminished suppression of allergen-specific T-cell responses in grass pollen-allergic subjects who were currently experiencing symptoms, compared with atopic subjects without symptoms. When considering these studies collectively, the phenotypic characteristics of regulatory T cells described in relation to immunotherapy and control of allergic responses under "steady state" conditions were different. As a consequence, the nature of regulatory T cells involved in the allergic response remains controversial, particularly with regard to antigen specificity. This is perhaps not surprising, given that regulatory T cells constitute a highly heterogeneous T-cell population. Indeed, CD4⁺ T cells that secreted IL-10 were recently shown to suppress T-cell responses in an allergen-specific manner through a variety of mechanisms, including soluble factors (*ie*, IL-10 and TGF- β) and cell-surface molecules (CTLA-4 and PD-1) [21••]. Such regulatory T cells appear to incorporate features of distinct regulatory T-cell subsets, thereby highlighting the complexity of regulatory mechanisms involved in human systems [34].

Role of Immunoglobulin E: A New Paradigm?

The complex patterns of sensitization observed in humans are difficult to explain based on models described in relation to a single allergen. Each atopic individual exhibits a unique allergen-specific IgE Ab profile that reflects the impact of both host (*ie*, genetics) and environmental factors. Co-existence of sensitization and tolerance to different allergens, such as dust mite and cat, is a frequent observation. Such findings suggest that allergen-specific factors are critical determinants of atopic status. In humans, different types of nonallergic responses can be defined on the basis of serum antibody profile [35••]. Thus, the nonallergic response is not a homogeneous entity. For example, subjects who are not sensitized to cat allergen fall into two distinct categories: those with IgG and IgG4 Ab to the major cat allergen, Fel d 1, and those with no evidence of a serologic response [35••]. A notable feature of the IgG^{pos}IgE^{neg} serum antibody profile to cat (modified Th2 response) is the lack of allergic symptoms, despite exposure to high levels of Fel d 1 in the environment. This immune response may be viewed as a form of high-dose immunologic tolerance. It is tempting to speculate that such distinct nonallergic states involve different DC-driven immune pathways that are analogous to those described earlier in relation to bacterial co-exposure. Based on this premise, high-dose exposure to cat allergen in the absence of endotoxin or other environmental adjuvants would be predicted to induce tolerance (*ie*, modified Th2 response), whereas co-exposure to high levels of endotoxin may protect against allergy to cats (*ie*, no serum antibodies). Interestingly, levels of endotoxin in houses with a cat are comparable with those in houses with no animals present but significantly lower than in houses with dogs (Platts-Mills J *et al.*, Unpublished data). These observations indicate that nonallergic responses to cats do not arise by virtue of high co-exposure to PAMPs, or by co-exposure to PAMPs at levels low enough to prevent DC maturation. In our experience, endotoxin levels are readily detectable under normal living conditions. Thus, if we assume that bacterial products act as adjuvants, even at very low levels, then development of tolerance in the absence of PAMPs seems unlikely. Standardization of techniques for measuring environmental endotoxin is sorely needed to determine "threshold" levels that may be relevant to generation of distinct allergic phenotypes.

An alternate explanation for development of the modified Th2 response to cat allergen is that intrinsic properties of the allergen, coupled with genetics of the host, are critical to immune outcome. At the T-cell level, the modified Th2 response to cat allergen is associated with enhanced T-cell reactivity to two overlapping immunodominant epitopes of Fel d 1 that selectively induce IL-10 and IFN- γ [20]. These epitopes map to the amino-terminal region of polypeptide chain 2 of the molecule and are predicted to bind to the major histocompatibility class (MHC) II molecule, *0701. Interestingly, more than half of patients with a modified Th2 response express the major HLA-DRB1

allele, *0701, and increased induction of IL-10 and IFN- γ to chain 2 epitopes is restricted to modified Th2 subjects who are DR7-positive [20]. Despite evidence of increased T-cell reactivity to putative regulatory epitopes of Fel d 1 in patients with a modified Th2 response, strong T-cell reactivity to these epitopes is also a feature of low-to-moderate titer IgE Ab responses. Furthermore, T cells derived from subjects with no evidence of an active serologic response exhibit strong T-cell reactivity to this region of the molecule. This may be explained by the ability of regulatory epitopes to bind to multiple HLA-DR molecules. By contrast, T cells derived from allergic patients with high-titer IgE Ab to cat who have atopic dermatitis exhibit diminished reactivity to these epitopes [36]. Thus, altered T-cell recognition of regulatory epitopes is associated with aberrant production of IgE Ab.

Enhanced T-cell recognition of chain 2 regulatory epitopes in DR7-positive subjects could result from increased affinity and/or stability of chain 2 peptide binding to DR7 coupled with increased density of DR7-peptide complexes on the surface of the antigen-presenting cell. Such molecular interactions could result in optimal generation and activation of regulatory T cells. A key question that remains is how the modified Th2 response fits within the framework of allergic and nonallergic responses. We propose that the modified Th2 response is a variant of the allergic phenotype that develops as a result of high-dose environmental exposure to cat allergen. This premise is based on several observations: 1) production of Th2 cytokines in T-cell cultures from modified Th2 responders but not those from subjects without detectable serum antibodies; 2) enhanced T-cell recognition of regulatory epitopes in parallel with marked elevations in circulating Fel d 1-specific IgG Ab in cat-allergic subjects receiving immunotherapy; and 3) numerous anecdotal reports of the development of symptoms after change from high-dose cat exposure to low-dose cat exposure (*eg*, after removal of cat from the home).

Restructuring of the Th1/Th2 paradigm in the context of regulatory T cells has led to the view that development of allergic responses is dependent on the capacity of regulatory T cells to influence the proportion of Th1 and Th2 effector cells. The effect on Th2 cells could be indirect (*eg*, decreased Th1 responses with a concomitant Th2 skewing) or direct (*eg*, diminished capacity for regulatory T cells to suppress Th2 cells). In either case, enhanced Th2 responses would result. An attractive feature of this model is that it implicates regulatory T cells in both allergic and nonallergic responses and suggests that different allergic phenotypes arise from different degrees of control mediated by regulatory T cells. In the immune response to cat allergen, allergic (IgE^{pos}) and nonallergic (IgE^{neg}IgG^{neg}) responses are associated with increased Th2 cytokines (albeit at low levels) and increased Th1 cytokines, respectively. Interestingly, IL-10 is a prominent feature of both types of immune response. Furthermore, IL-10 appears to suppress T-cell

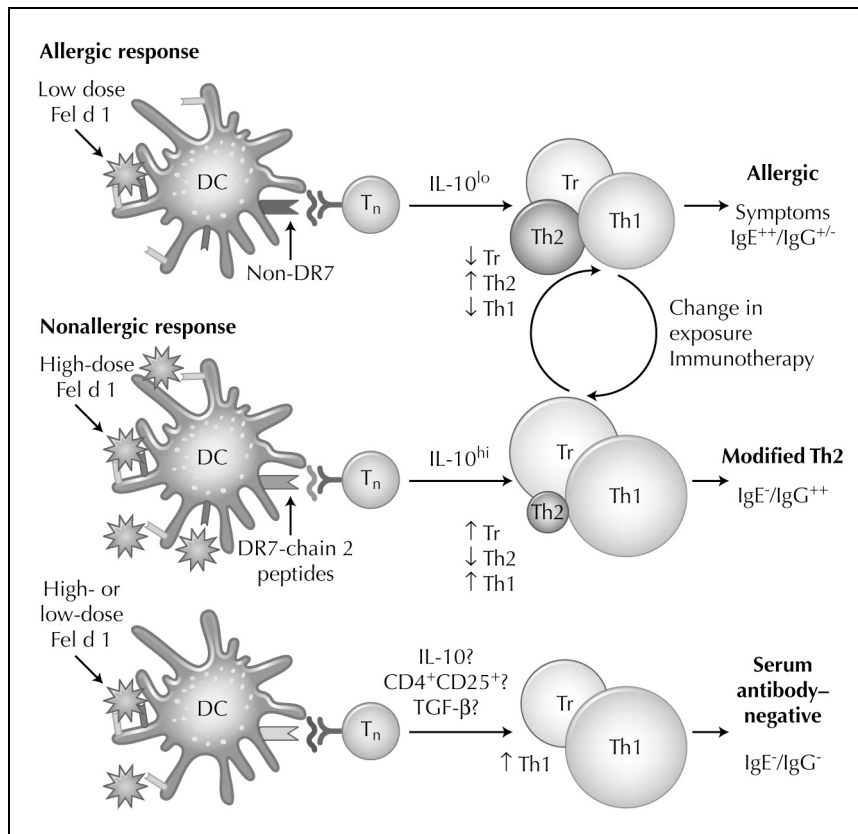


Figure 1. The immune response to cat allergen: development of different allergic phenotypes. Low-dose exposure to cat allergen in the absence of HLA-DR7 leads to suboptimal T-cell recognition of regulatory epitopes of Fel d 1, low levels of IL-10 production, and increased Th2 responses that drive IgE-mediated responses. In contrast, high-dose exposure to cat allergen in conjunction with expression of DR7 expands T cells that are specific for regulatory epitopes within the allergen-specific T-cell repertoire. As a consequence, production of IL-10 and IFN- γ is increased, Th2 responses are suppressed, and the modified Th2 response develops. The modified Th2 response is a variant of the allergic response, and transition from one type of response to the other can occur with change in exposure to allergen, either as a result of change in the environment or via systemic exposure during immunotherapy. IL-10 is a feature of all types of immune response; however, serum antibody-negative responses are not associated with enhanced IL-10 production, suggesting that alternate mechanisms are involved in generating these responses. HLA—human leukocyte antigen; IFN—interferon; IgE—immunoglobulin E; IL—interleukin; Th—T helper.

reactivity to cat allergen, irrespective of allergic phenotype. Despite this, a role for IL-10 in mediating IgE^{neg}IgG^{neg} nonallergic responses has not been demonstrated. A model to explain how IgE-mediated responses and distinct types of non-IgE-mediated responses may develop is shown in Figure 1. This model integrates genetics as well as intrinsic properties and dose of the allergen. A distinction between this model and previous models is that IL-10 is a major feature of all types of immune responses to cat allergen. Furthermore, different types of nonallergic responses develop through discrete immune pathways and, unlike classic immunologic tolerance, T-cell activation appears to be a prerequisite. Another novel aspect of this model is that it links genetics to immunoregulation, thereby explaining how the modified Th2 response develops as a variant of the allergic phenotype.

Why some individuals fail to mount a serologic response despite high levels of exposure to cat allergen is not clear. Furthermore, it is not known why T cells from a subset of individuals with a modified Th2 response fail to produce IL-10 [20]. Thus, at this point, a role for adaptive regulatory T cells (CD4⁺CD25⁺ T cells) or other inhibitory cell types and mediators in nonallergic responses to cat allergen cannot be excluded. In terms of future studies, the effects of regulatory T cells on Th1 cells in the context of IgE-mediated responses should not be overlooked in humans. Indeed, we have shown that

IFN- γ is a feature of both allergic and nonallergic responses and that IL-10 acts preferentially on this cytokine, an effect that could indirectly alter Th2-driven responses [20]. Finally, an important consideration is whether the paradigm presented here is applicable to other allergens. There is convincing evidence that IgE Ab production to cat allergen is downregulated compared with IgE Ab directed against other allergens, most of which are encountered at much lower levels in the environment [37]. These observations highlight the complex regulatory mechanisms that govern allergen-specific responses as well as the necessity for detailed studies of allergens relevant to human disease.

Conclusions

IgE antibodies play a critical role in the development of allergic disease such as asthma and rhinitis. The decision to mount IgE-mediated immune responses versus non-IgE-mediated responses is dictated by genetics of the host as well as the level of environmental allergen exposure and intrinsic properties of the allergen itself. Nonallergic responses may be mediated by distinct immune pathways that act to suppress Th2-driven responses. The ability to enhance such regulatory pathways may be a critical determinant in the successful treatment of rhinitis and other IgE-mediated disorders.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. van der Heijden FL, Joost van Neerven RJ, van Katwijk M, *et al.*: Serum-IgE-facilitated allergen presentation in atopic disease. *J Immunol* 1993, 150:3643–3650.
 2. Maurer D, Fiebiger E, Reininger B, *et al.*: Fc epsilon receptor I on dendritic cells delivers IgE-bound multivalent antigens into a cathepsin S-dependent pathway of MHC class II presentation. *J Immunol* 1998, 161:2731–2739.
 3. Custovic A, Simpson A, Woodcock A: Importance of indoor allergens in the induction of allergy and elicitation of allergic disease. *Allergy* 1998, 53:115–120.
 4. Burrows B, Martinez FD, Halonen M, *et al.*: Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med* 1989, 320:271–277.
 5. Sears MR, Burrows B, Flannery EM, *et al.*: Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *N Engl J Med* 1991, 325:1067–1071.
 6. Martinez FD, Wright AL, Taussig LM, *et al.*: Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995, 332:133–138.
 7. Spergel JM, Paller AS: Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003, 112:S118–S127.
 8. Chung KF: Anti-IgE monoclonal antibody, omalizumab: a new treatment for allergic asthma. *Expert Opin Pharmacother* 2004, 5:439–446.
 9. Bush RK: Etiopathogenesis and management of perennial allergic rhinitis: state-of-the-art review. *Treat Respir Med* 2004, 3:45–57.
 10. Prussin C, Griffith DT, Boesel KM, *et al.*: Omalizumab treatment downregulates dendritic cell FcepsilonRI expression. *J Allergy Clin Immunol* 2003, 112:1147–1154.
 11. Beier KC, Hutloff A, Lohning M, *et al.*: Inducible costimulator-positive T cells are required for allergen-induced local B-cell infiltration and antigen-specific IgE production in lung tissue. *J Allergy Clin Immunol* 2004, 114:775–782.
 12. Tumas DB, Chan B, Werther W, *et al.*: Anti-IgE efficacy in murine asthma models is dependent on the method of allergen sensitization. *J Allergy Clin Immunol* 2001, 107:1025–1033.
 13. O'Byrne PM, Inman MD, Parameswaran K: The trials and tribulations of IL-5, eosinophils, and allergic asthma. *J Allergy Clin Immunol* 2001, 108:503–508.
 14. Kay AB, Phipps S, Robinson DS: A role for eosinophils in airway remodeling in asthma. *Trends Immunol* 2004, 25:477–482.
 15. Eisenbarth SC, Piggott DA, Huleatt JW, *et al.*: Lipopolysaccharide-enhanced, toll-like receptor 4-dependent T helper cell type 2 responses to inhaled antigen. *J Exp Med* 2002, 196:1645–1651.
 16. Barends M, Van Oosten M, De Rond CG, *et al.*: Timing of infection and prior immunization with respiratory syncytial virus (RSV) in RSV-enhanced allergic inflammation. *J Infect Dis* 2004, 189:1866–1872.
 17. Kondo Y, Matsuse H, Machida I, *et al.*: Effects of primary and secondary low-grade respiratory syncytial virus infections in a murine model of asthma. *Clin Exp Allergy* 2004, 34:1307–1313.
 18. Wills-Karp M, Ewart SL: Time to draw breath: asthma-susceptibility genes are identified. *Nat Rev Genet* 2004, 5:376–387.
 19. Byron KA, O'Brien RM, Varigos GA, Wootton AM: Dermatophagoides pteronyssinus II-induced interleukin-4 and interferon-gamma expression by freshly isolated lymphocytes of atopic individuals. *Clin Exp Allergy* 1994, 24:878–883.
 20. Reefer AJ, Carneiro RM, Custis NJ, *et al.*: A role for IL-10-mediated HLA-DR7-restricted T cell-dependent events in development of the modified Th2 response to cat allergen. *J Immunol* 2004, 172:2763–2772.
 21. Akdis M, Verhagen J, Taylor A, *et al.*: Immune responses in healthy and allergic individuals are characterized by a fine balance between allergen-specific T regulatory 1 and T helper 2 cells. *J Exp Med* 2004, 199:1567–1575.
- This research article presents evidence that different ratios of distinct T-cell subsets corresponding to allergic and non-allergic responses in humans are controlled by regulatory T cells.
22. Bocek P, Foucras G, Paul WE: Interferon gamma enhances both in vitro and in vivo priming of CD4+ T cells for IL-4 production. *J Exp Med* 2004, 199:1619–1630.
 23. Romagnani S: The increased prevalence of allergy and the hygiene hypothesis: missing immune deviation, reduced immune suppression, or both. *Immunology* 2004, 112:352–363.
 24. Alexis NE, Lay JC, Almond M, Peden DB: Inhalation of low-dose endotoxin favors local Th2 response and primes airway phagocytes in vivo. *J Allergy Clin Immunol* 2004, 114:1325–1331.
 25. Fageras Bottcher M, Hmani-Aifa M, Lindstrom A, *et al.*: A TLR4 polymorphism is associated with asthma and reduced lipopolysaccharide-induced interleukin-12 (p70) responses in Swedish children. *J Allergy Clin Immunol* 2004, 114:561–567.
 26. Lambrecht BN, Hammad H: Taking our breath away: dendritic cells in the pathogenesis of asthma. *Nat Rev Immunol* 2003, 3:994–1003.
- A detailed overview of the evidence of a role for dendritic cells in the initiation and effector phases of allergic inflammatory responses in murine models.
27. Akbari O, DeKruyff R, Umetsu DT: Pulmonary dendritic cells producing IL-10 mediate tolerance induced by respiratory exposure to antigen. *Nat Immunol* 2001, 2:725–731.
 28. de Heer HJ, Hammad H, Soullie T, *et al.*: Essential role of lung plasmacytoid dendritic cells in preventing asthmatic reactions to harmless inhaled antigen. *J Exp Med* 2004, 200:89–98.
 29. Herrick CA, Bottomly K: To respond or not to respond: T cells in allergic asthma. *Nat Immunol* 2003, 3:405–412.
- This article presents a model to explain the role of high- and low-dose PAMPs in generation of allergic and non-allergic responses.
30. Akdis CA, Blesken T, Akdis M, *et al.*: Role of interleukin-10 in specific immunotherapy. *J Clin Invest* 1998, 102:98–106.
 31. Francis JN, Till SJ, Durham SR: Induction of IL-10/CD4+CD25+ T cells by grass pollen immunotherapy. *J Allergy Clin Immunol* 2003, 111:1255–1261.
 32. Nouri-Aria KT, Wachholz PA, Francis JN, *et al.*: Grass pollen immunotherapy induces mucosal and peripheral IL-10 responses and blocking IgG activity. *J Immunol* 2004, 172:3252–3259.
 33. Ling EM, Smith T, Nguyen XD, *et al.*: Relation of CD4+CD25+ regulatory T-cell suppression of allergen-driven T-cell activation to atopic status and expression of allergic disease. *Lancet* 2004, 363:608–615.
 34. Akbari O, Stock P, DeKruyff RH, Umetsu DT: Role of regulatory T cells in allergy and asthma. *Curr Opin Immunol* 2003, 15:627–633.
 35. Platts-Mills T, Vaughan J, Squillace S, *et al.*: Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet* 2001, 357:752–756.
- This epidemiology study describes the modified Th2 response. The dose-response relationship between exposure to cat allergen and the development of IgE and IgG antibodies is examined.
36. Carneiro R, Reefer A, Wilson B, *et al.*: T cell epitope-specific defects in the immune response to cat allergen in patients with atopic dermatitis. *J Invest Dermatol* 2004, 122:927–936.
 37. Erwin EA, Wickens K, Custis NJ, *et al.*: Cat and dust mite sensitivity and tolerance in relation to wheezing among children with high exposure to both allergens. *J Allergy Clin Immunol* 2005, 115:74–79.