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The Immune Response to Intrinsic and Extrinsic Allergens: Determinants of Allergic Disease

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Abstract
A central role for Th2 effector cells in IgE-mediated allergic disease is well established. However, the question of why some individuals develop allergic disease and others do not remains largely unanswered. Until recently, the prevailing view was that the allergic response reflected a shift in the Th1/Th2 'balance' to favor production of Th2 cytokines and IgE antibody isotype switching. Evidence is now emerging to suggest that distinct allergic responses cannot be distinguished simply on the basis of type 1 and type 2 cytokine profiles. For example, delayed-type hypersensitivity responses to intrinsic allergens derived from the dermatophyte fungus *Trichophyton* are associated with a paradoxical increase in Th2 cytokines compared with immediate hypersensitivity responses. In contrast, analysis of 'tolerant' responses to extrinsic allergens which are induced by specific immunotherapy or high-dose natural exposure to inhaled allergen (the modified Th2 response) supports a role for both the Th1 cytokine IFN-γ and the regulatory cytokine IL-10. However, IL-10 may also be a critical mediator in the allergic response. In this article, we examine how analysis of epitope-specific T cell responses may lead to an understanding of how T lymphocyte cytokines relate to distinct allergic phenotypes. The relevance of Th1/Th2 and regulatory cytokines to development of new allergen-specific therapies is also discussed.

Introduction

Recognition of Th2 cytokines including IL-4 and IL-5 as the effector molecules of allergic disease has led to the view that treatment with Th2 'inhibitors' or induction of Th1 responses could be beneficial therapies for allergic disease. Indeed, there is some evidence that amelioration of allergic disease resulting from conventional immunotherapy (IT) is associated with altered cytokine profiles [1–5]. Recently, the 'Th1/Th2 balance' model has been revisited owing to renewed interest in the regulatory cytokine IL-10 and its role in inflammatory disease. To date, most studies on T cell responses to allergens have focused on animal models of asthma or on allergic humans. However, definition of immune mechanisms governing non-allergic responses may hold the most promise for understanding development of allergy and for identifying new targets for therapy. In this article we discuss the immune response to intrinsic and extrinsic allergens, both of which

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induce distinct immune responses related to different allergic phenotypes in man. Specifically, we explore the characteristics of different types of nonallergic responses with a view to understanding the determinants of allergic disease.

Trichophyton: A Model for Examining the Relevance of the Th1/Th2 Paradigm to Man

The dermatophyte fungus, *Trichophyton*, induces distinct skin test reactions in different individuals. Immediate hypersensitivity (IH) to *Trichophyton* is associated with chronic infections of the skin and/or nails and the presence of serum IgE and IgG antibodies (Ab) to *Trichophyton* antigens [6–9]. The ability of *Trichophyton* proteins to elicit specific bronchial hyperreactivity in asthmatic subjects with chronic dermatophytosis coupled with improvement of asthma after systemic antifungal therapy, provides strong evidence that exposure to *Trichophyton* contributes to allergic disease [10–12]. *Trichophyton* has been described as an 'intrinsic allergen' based on the presence of an IH skin test in the absence of positive skin tests to common inhalant allergens. Historically, intrinsic allergens have also been described according to their ability to colonize humans; however, in contrast to other well recognized intrinsic allergens such as those derived from *Aspergillus* [13], there is no evidence that *Trichophyton* can be cultured from the lungs. Thus, it has been proposed that the route of exposure to allergen results from fungal colonization at sites remote to the lung. In keeping with this, it is tempting to speculate that asthma associated with *Trichophyton* infection results from an inflammatory response generated in the absence of local antigen, a process which could be considered analogous to an id reaction. Dermatophytids, or id reactions, are cutaneous inflammatory lesions which occur at a different site to that of the primary infection; a characteristic feature is that the organism cannot be isolated from these secondary lesions. Delayed-type hypersensitivity (DTH) skin tests to *Trichophyton* are common in the general population and have not been associated with disease of the respiratory tract [14]. Subjects with DTH typically have acute infections which tend to resolve spontaneously and they do not have IgE Ab to *Trichophyton* antigens [8, 15–17]. Based on the distinct serologic profiles and different clinical manifestations associated with IH and DTH reactions, it has been proposed that cell-mediated responses to *Trichophyton* play a role in the eradication of infection, while serum antibodies including IgE are nonprotective.

The Th1/Th2 paradigm has provided a framework for evaluating protective or cell-mediated (Th1) and nonprotective humoral (Th2) responses to antigens from diverse sources. Outside the field of allergy, it is well established that the same microbial stimulus, which elicits DTH responses, can also induce serologic responses. For example, infection with the intracellular pathogen *Mycobacterium leprae* can result in Th1-mediated tuberculoid leprosy which is associated with DTH to *M. leprae*. In contrast, Th2-mediated lepromatous leprosy is associated with strong antibody responses without DTH [18–21]. However, type 2 responses to such pathogenic organisms are not associated with IgE Ab or allergic disease [22]. With regard to inhalant (extrinsic) allergens, though there are rare anecdotal reports of DTH, cell-mediated immunity is not a feature of the immune response. Thus, *Trichophyton* provides a unique system for studying the relevance of Th1 and Th2 cells to the allergic and nonallergic state in humans.

T Cell Repertoires Mediating DTH and IH Responses to *Trichophyton* Do Not Fit the Classical Th1 and Th2 Profiles

In any given individual who has been exposed to allergen, the allergen-specific T cell repertoire consists of a population of CD4+CD45RO+ (memory) T lymphocytes which recognize one or more T cell antigenic determinants or peptide epitopes generated from the same molecule. Major or immunodominant T cell epitopes of allergens can be identified by stimulating T cells in vitro with synthetic peptides spanning the amino acid sequence of the allergen. Using this approach, work by our group showed that different patterns of T cell epitope recognition of the *Trichophyton* allergen, Tri r 2, were associated with IH and DTH responses [23, 24]. Specifically, recognition of an amino-terminal immunodominant epitope, as judged by strong T cell-proliferative responses in peripheral blood mononuclear cell (PBMC) cultures, was associated with DTH but not IH skin tests. By applying novel statistical approaches, 6 peptide markers spanning two regions of the molecule were identified, which distinguished different skin test groups. Thus, cells with distinct specificities constitute the population of T lymphocytes which mediate DTH and IH to the same *Trichophyton* allergen. However, analysis of cytokine responses in these cultures yielded surprising results; responses stimulated by Tri r 2 were dominated by the Th1 cytokine IFN-γ both in DTH *and* in IH responders. Paradoxically, the

DTH-associated epitope, P5, induced IL-5 and IL-10 production in DTH but not IH responders; furthermore, production of Th2 cytokines was not a feature of P5-specific responses in IH subjects [25]. Another important observation in this system was that cytokine profiles induced by whole allergen and by allergen-derived peptides were different, even in cultures established from the same individual. The implication is that the allergen-specific T cell repertoire contains a heterogeneous population of CD4+ T lymphocytes with Th1/Th0 and Th2 phenotypes, independent of the allergic status of the host. So while differences in the allergen-specific T cell repertoire were identified in patients with allergic and nonallergic responses to the intrinsic allergen, *Trichophyton*, when considered together these observations do not support a simple relationship between Th1 and Th2 cytokines and dichotomous immune responses to the same allergen.

Definition of the Nonallergic Phenotype: Evidence for Distinct Immune Mechanisms

In order to understand the immunologic mechanisms which govern allergic and nonallergic responses, classification of subjects is paramount. One advantage of studying the immune response to *Trichophyton* is the well-defined distinction between two biological outcomes, namely IH and DTH skin responses. When comparing allergic and nonallergic responses to extrinsic allergens, classification of subjects is more complex. Nonallergic responses to extrinsic allergens are typically defined on the basis of lack of measurable serum IgE or negative skin test reactivity because DTH is not a feature of the response to these allergens. However, in contrast to most extrinsic allergens including mite, serum antibody profiles to the major cat allergen, Fel d 1, are heterogeneous in nonallergic subjects (i.e. those with negative skin tests to cat extract). Indeed, both the presence and absence of Fel d 1-specific IgG Ab, without IgE, are common in nonallergic subjects. The modified Th2 response is a term used to describe a serologic profile characterized by high titer Fel d 1-specific IgG Ab including IgG4 without serum IgE in non-cat-allergic subjects. This immune response was first defined based on an increased prevalence of IgG/IgG4 Ab without IgE Ab in children exposed to high-dose allergen [26]. Subsequent studies showed that IgG/IgG4 Ab titers associated with the modified Th2 response were strongly correlated with levels of Fel d 1 present in house dust. However, a subset of nonallergic subjects had no serologic evidence of an immune response to cats, despite a wide range of allergen exposure [27]. We propose that, among indoor allergens, development of the modified Th2 response is unique to cat allergen based on the very high levels of allergen which can be measured in houses (for example, levels of airborne cat allergen may be up to 100-fold higher than for mite allergen). Thus, the modified Th2 response could reflect a form of high-dose tolerance induced by natural allergen exposure. However, further epidemiologic studies of the relationship between allergen dose and immune response are required to determine whether this phenomenon is restricted to cat.

It is well established in rodent models that repeated exposure to respiratory antigen (OVA) results in antigen-specific T cell hyporesponsiveness coupled with suppressed production of IgE [28, 29]. These changes have been associated with protection against allergen-induced airway hyperreactivity [30]. An interesting feature of this 'aerosol-induced' IgE tolerance in animal systems is the selective suppression of IgE (and IL-4 production) despite induction of IgG Ab [28, 29, 31–34]. Thus, parallels can be drawn between murine models of respiratory tolerance and the modified Th2 response to Fel d 1 in humans. The lack of a humoral response in other nonallergic individuals points to an alternate immunologic mechanism governing the nonallergic phenotype. It is possible that the modified Th2 response develops in individuals with a genetic predisposition to develop allergic disease and that IgE Ab production is suppressed as a result of high-dose allergen exposure. In contrast, nonallergic subjects without serum antibodies may represent a distinct population of individuals without a propensity to develop allergies. Obviously, understanding the immune mechanisms which govern distinct nonallergic responses to inhalant allergens is fundamental to developing new approaches to treatment.

The Goal of Allergen-Specific Therapy: Th1 Skewing or Immune Regulation?

Allergic disease is associated with elevated IgE and eosinophilia, the hallmarks of a Th2 (i.e. IL-4, IL-5) cytokine response. Thus, many investigators have focused on defining a relationship between atopy and production of Th2 cytokines, either at sites of allergic inflammation or by circulating allergen-specific T cells. In the early 1990s, several groups reported the isolation of allergen-specific T cell clones from atopic donors which produced Th2 cytokines and which exhibited distinct cytokine profiles compared with T cell clones specific for bacterial antigens or

allergen-specific clones derived from nonatopic individuals [35, 36]. However, during the last decade, clones specific for a variety of allergens have been described, often with heterogeneous cytokine profiles (i.e. Th1, Th2, Th0) [35–43]. Indeed, in keeping with our studies on *Trichophyton*, induction of the Th1 cytokine, IFN-γ, is common for a variety of allergens or allergen-derived peptides [35, 37, 42–46]. In our experience, there is tremendous heterogeneity of cytokine responses for patients with the same allergic phenotype and evidence for a clear association between Th1 and Th2 responses with nonallergic and allergic states, respectively, is weak. And though several studies, including our own, have reported increased production of IL-4, IL-5 or IL-13 in cultures of PBMC derived from allergic compared with nonallergic subjects, immune responses to extrinsic allergens cannot simply be ascribed to Th2 responses since other cytokines, including IFN-γ, often dominate the response. These observations raise the important question of whether or not induction of a Th1 response should be the appropriate goal of IT. Indeed, by definition, Th1 cytokines are proinflammatory and there is evidence to suggest that Th1-type mediators including IFN-γ and the chemokine IFN-γ-inducible protein 10 (IP-10 or CXCL-10) which attracts activated Th1 lymphocytes may in fact be deleterious to the lung [47, 48].

In the past, studies of patients receiving conventional IT provided an avenue for defining protective allergen-specific immune responses. There is no doubt that IT for certain allergens (those derived from grass, bee venom and cats) is efficacious, as judged by decreased allergic symptoms. While it is well recognized that injection of allergen is associated with marked increases in allergen-specific IgG Ab of the IgG4 isotype, there is conflicting data regarding the changes which occur at the T cell level [49–54]. In patients receiving preparations containing whole antigen, T cell hyporesponsiveness, as judged by decreased proliferation or decreased production of Th2 cytokines, has been reported [1–4, 55, 56]. Increased IFN-γ both in vivo (cutaneous late phase reactions) and in vitro (cultures of PBMC or T cell clones) has also been observed [1–5]. However, other studies have reported a decrease in both Th1 *and* Th2 cytokines, and either selective inhibition or no change in Th2 cytokines [5, 55–58]. It seems likely that these disparities reflect, at least in part, the different experimental systems used. However, despite the lack of a consensus regarding the mechanisms of immune modulation resulting from conventional IT, new vaccine preparations have been designed with a view to enhancing Th1 cytokine production, based on the premise that Th1 responses to allergens would confer protection. Immunostimulatory sequence (ISS) DNA derived from bacteria is a potent stimulator of proinflammatory cytokines including IFN-γ and the Th1-differentiating cytokine, IL-12. Administration of ragweed allergen, Amb a 1, covalently linked to ISS DNA has been shown to enhance IFN-γ production in PBMC cultures from treated patients [59]. However, it is now becoming apparent that ISS DNA and other 'Th1-skewing' adjuvants such as heat-killed *Mycobacterium vaccae* can inhibit allergic inflammation by mechanisms independent of IFN-γ or IL-12 [60, 61].

Studies of patients receiving conventional IT along with some of our recent findings (see below) suggest that induction of regulatory cytokines, as opposed to upregulation of Th1 responses, might be a more appropriate goal of treating allergic disease. Indeed, there is strong evidence that subcutaneous administration of whole allergen induces IL-10. In the mid-to-late 1990s Akdis et al. [56, 62] demonstrated diminished allergen-specific T cell proliferation in patients receiving rush IT for bee venom allergy. This T cell 'anergy' was attributed to induction of IL-10-producing CD4+CD25+ T cells. In that system, both allergen-specific PBMC proliferation and production of Th1 and Th2 cytokines were enhanced in the presence of monoclonal antibody to IL-10. Work by Bellinghausen et al. [63] yielded similar findings with one notable difference; blocking IL-10 had no effect on allergen-stimulated IL-4 production. As a result of the latter studies it was proposed that venom IT induces IL-10-producing regulatory T cells which inhibit the potential proinflammatory effects of enhanced Th1 cytokines stimulated by IT. Most recently, increased expression of IL-10 mRNA in the upper respiratory tract and recruitment of regulatory T cells to the skin have been reported in patients receiving allergen-specific IT [64, 65].

Given the complexity of T cell responses induced by IT, we recently undertook prospective studies aimed at monitoring changes in allergen-specific T cell responses which occur during conventional IT using cat extract [27]. For the in vitro studies, peptides as opposed to whole allergen were used in order to evaluate the effect of injection of a preparation containing whole allergen on epitope-specific T cell responses. To date, patients have been monitored at monthly intervals for up to 7 months. Results showed that subcutaneous injection of cat extract was associated with marked fluctuations in T cell proliferation and cytokine responses and that changes in the pattern of epitope-specific T cell responses within each patient were unique. Though diminished proliferative

responses occurred within 2 months, T cell hyporesponsiveness did not persist. However, IT resulted in activation of T cells which targeted epitopes associated with production of IL-10 and IFN-γ; furthermore, increases in Th2 cytokines to major epitopes mapping to different regions of the molecule were also observed. Overall, IT was associated with increased production of both IL-10 and IFN-γ to both major and minor epitopes of Fel d 1. Our results suggest that injection of whole allergen induces selective expansion of Fel d 1-epitope-specific T cell populations including those with a Th1, Th2 and regulatory phenotype, but with a predominance of IFN-γ- and IL-10-producing T lymphocytes.

The Immune Response to Cat: A Central Role for IL-10 in Distinct Allergic Phenotypes

During the last few years, evidence has emerged to support a role for IL-10 in the development and/or maintenance of allergen-specific tolerance not related to IT. For example, increased IL-10 production in cultures stimulated with antigens derived from the parasite, *Schistosoma haematobium*, has been associated with decreased prevalence of positive skin tests in infected children [66]. Other studies showed that nickel-specific T cell clones generated from nonsensitized individuals produced higher IL-10 compared to those from subjects with sensitivity [67]. In addition to its inhibitory effects on both Th1 and Th2 cytokines, a variety of other immunologic properties point to the regulatory effects of IL-10 in allergic responses; these include inhibition of activation of human lung mast cells and selective enhancement of IgG4 Ab with suppression of IgE [62, 68, 69]. As alluded to earlier, IgG4 Ab production has been associated with systemic tolerance induced by injection of allergen and the modified Th2 response to cat resulting from high-dose natural exposure. Taken together, these observations support an immunoregulatory role for IL-10 both during development of the nonallergic response and in modulation of an established allergic response.

We recently analyzed T cell responses to the major cat allergen, Fel d 1, in three groups of individuals with distinct serum antibody profiles: allergic ($IgG^{pos}IgE^{pos}$), modified Th2 ($IgG^{pos}IgE^{neg}$) and controls ($IgG^{neg}IgE^{neg}$) [27]. The primary goal of these studies was to examine the relevance of Th1 and Th2 responses to allergic and nonallergic phenotypes and to determine the effects of IL-10 on distinct allergen-specific responses. Interestingly, strong T cell-proliferative responses to Fel d 1 and to Fel d 1-derived peptides were measurable irrespective of allergic phenotype. Thus, in contrast to tolerance induced by injection of allergen during IT, T cell anergy was not a feature of tolerant responses to cat associated with IgG Ab (modified Th2) or not associated with IgG Ab (controls). It is clear that circulating allergen-specific memory T cells are present in both groups of nonallergic subjects. This raises the question of why allergen-specific effector T cells do not induce B cell responses in serum antibody-negative nonallergic individuals.

Analysis of T cell cytokine responses to cat allergen showed that induction of Th2 cytokines localized to major epitopes of chain 1 of the Fel d 1 molecule, while major epitopes of chain 2 selectively stimulated IL-10 and IFN-γ. In keeping with a role for Th2 cytokines in allergic disease, in vitro responses to the IL-5-inducing major epitope, P1:2, were associated with the allergic but not the nonallergic state. However, only low levels of IL-5 were induced in this system and epitope-specific T cell responses were dominated either by IFN-γ or IL-10, independent of allergic phenotype. Allergic and nonallergic patients could not be distinguished based on recognition of major epitopes which stimulated IL-10 and IFN-γ. Furthermore, IL-10 was the dominant cytokine in cultures stimulated with whole allergen irrespective of allergic status. Blocking IL-10 enhanced Fel d 1-specific T cell proliferation and production of IFN-γ but did not increase IL-5 or IL-13. However, this pattern was not restricted to nonallergic responses. It was confirmed that Fel d 1 stimulated IL-10 production in both monocytes and CD4+ T lymphocytes; thus, the findings implicate IL-10-producing CD4+ regulatory T cells in the control of both nonallergic and allergic responses to an important inhalant allergen.

As already mentioned, work by Bellinghausen et al. [63] showed that, similar to our observations with cat, blocking IL-10 did not enhance production of Th2 cytokines in cultures from patients receiving bee venom IT. It is tempting to speculate that the same action of IL-10 in individuals with distinct allergic phenotypes may have different clinical outcomes; for example, in nonallergic subjects, IL-10 could abrogate the potential proinflammatory effects of Th1 responses while in allergic individuals, IL-10 could actually contribute to allergic inflammation by blocking the Th2 inhibitory effects of Th1 cells within the allergen-specific T cell repertoire. Consistent with this, we have observed an increased ratio of IL-10 to IFN-γ in Fel d 1-stimulated cultures and increased spontaneous production of IL-10 in the absence of antigen by both CD4+ T cells and monocytes derived from allergic individuals. An alternative explanation for these findings

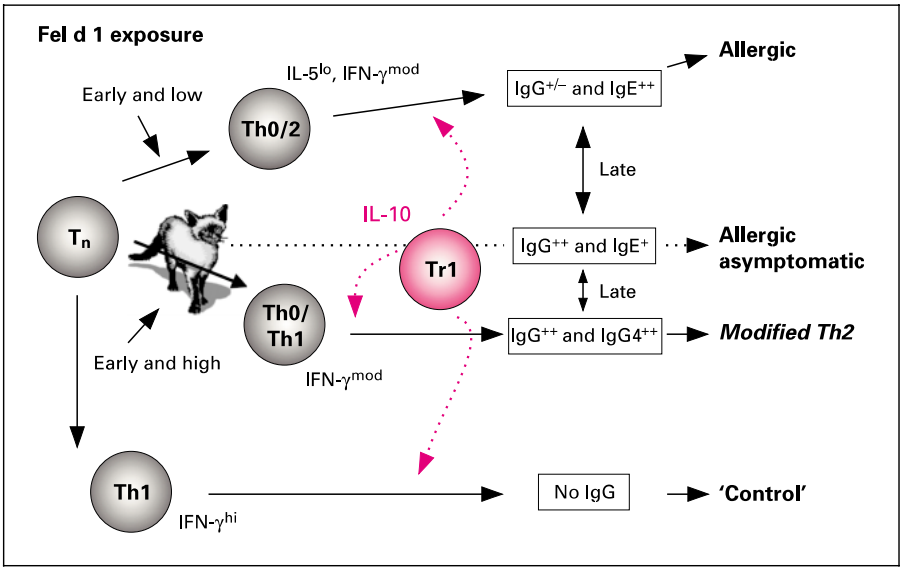

Fig. 1. Development of distinct immune responses to cat and plasticity of an established response. The modified Th2 response to cat develops as a result of high-dose allergen exposure during early life. In contrast, the allergic response is more common with moderate or low-dose exposure. The modified Th2 and allergic response are not fixed but are susceptible to modulation dependent upon change in allergen exposure. The nonallergic phenotype characterized by lack of a serologic response represents a separate immune pathway which may develop independently of allergen exposure.

is that IL-10 gene expression is dysregulated in allergic disease; indeed, overexpression of IL-10 has been proposed to contribute to the pathogenesis of atopic dermatitis, a disease associated with very high levels of total IgE [70]. However, the ability for IL-10 to suppress IgE Ab would appear to be at odds with this explanation. Yet another possibility is that IL-10 acts on different cell subsets and/or different molecular pathways in diverse immune responses to the same allergen. Clearly, more work is required in order to determine whether B cells or T cells are the primary target for IL-10 in allergen-specific responses; however, the pleiotropic effects of IL-10 make this a challenging prospect.

Plasticity of the Immune Response to Allergens

The question of how distinct immune responses to the same allergen develop, and how allergic and nonallergic responses relate to each other is highly relevant to understanding the immunopathogenesis of allergic disease and to the design of new treatments. We previously speculated that development of tolerant and allergic responses to cat allergen represented divergent immune pathways in which high- and low-dose exposure to Fel d 1 induced T helper cells with distinct phenotypes. In that model, low- or moderate-dose exposure to cat (e.g. 0.5–8 μg/g Fel d 1) induces a Th0 or Th2 response with elaboration of IL-4 and IL-5 and help for IgE and IgG4 Ab production culminating in the allergic phenotype. In contrast, high-dose allergen exposure could induce T cells with distinct cytokine profiles and increased IL-10 production. In that model, serologic profiles associated with the modified Th2 response reflected differential regulation of IgE and IgG4 Ab isotypes by IL-10. In light of our recent findings, this model has been revised to account for a central role for IL-10 in both allergic and nonallergic responses to cat allergen (fig. 1). We propose that development, or persistence, of the allergic and nonallergic state is dependent, at least in part, upon the actions of IL-10. It seems likely that the timing and dosage of allergen exposure is critical to the type of immune response induced during childhood and subsequent later life. This may in turn influence the timing of actions of critical mediators, including IL-10. Indeed, induction of IL-10 after B cell commitment has occurred may actually drive IgE Ab production thereby contributing to an allergic outcome [71].

Based on IT studies, it is reasonable to conclude that an established allergic response is not fixed, but can be altered. There are several lines of evidence to suggest that such effects could also result from change in natural exposure. First, there are many anecdotal reports of patients experiencing a change in allergic status after change in exposure; second, heterogeneity of T cell and serologic responses to Fel d 1 in tolerant and allergic responders is consistent with a 'disease spectrum' relating to allergen exposure. Inherent to this premise is the view that the modified Th2 response develops in subjects exposed to high-dose allergen who might otherwise be allergic at low levels of exposure. Finally, we have recently studied a

group of allergic subjects, each of whom live with a cat, but report no allergic symptoms. The serum antibody profile in these individuals is remarkably consistent (IgG^{high} and IgE^{low}) and could represent a 'transitional' phenotype intermediate to the allergic and modified Th2 response. Thus, we propose that a reversal of allergic phenotype can result from a change in natural exposure from low- to high-dose allergen in susceptible individuals.

Adding to the complex picture is the fact that exposure to a given allergen does not occur in isolation but in the context of multiple allergens. Indeed, the lower levels of total serum IgE in modified Th2 subjects compared with allergics beg the question of whether the immune response to one allergen can influence the response to another [27]. In Sweden, where mite exposure is absent, a decreased prevalence of sensitization to birch and dog is present in children living with a cat and this relationship is restricted to non-cat-allergic individuals [72]. However, in New Zealand, where exposure to high levels of mite allergen is common and is thought to occur early in life, there is no evidence of decreased prevalence of IgE or IgG Ab to mite in children living with a cat [73]. In the United States, Ownby et al. [74] showed that children living with 2 or more animals had a decreased prevalence of positive skin prick tests to *any* allergen (15% compared with 33.6% for children living without animals). One interpretation of these observations is that exposure to animal allergens creates a 'suppressive milieu' which downregulates the allergic response in general, and that high-dose exposure to mite allergen overrides this effect.

Concluding Remarks

It is clear for both intrinsic and extrinsic allergens that different allergic phenotypes cannot be defined simply on the basis of type 1 and type 2 cytokines. Our studies have shown that analysis of epitope-specific T cell responses is essential for defining the nature of T cells which mediate allergic and tolerant responses. However, differences between allergic and nonallergic subjects are often complex and do not fit within the framework of the Th1/Th2 paradigm. While it seems that altering the Th1/Th2 cytokine balance may be relevant to induction of tolerance, it is clear that multiple mechanisms, which have yet to be defined, may be involved. The heterogeneity of T lymphocyte subsets within the allergen-specific T cell repertoire makes the design of new therapies a challenge. In addition, the potentially important role, which IL-10 fulfils in both allergic and nonallergic responses, adds another layer of complexity to the problem. Understanding the mechanisms of action of IL-10 will likely be a key factor in understanding the pathogenesis of allergic disease and in determining new approaches to treatment.

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