

Benign T_H2 immunity in children: A fresh perspective on control of the allergic response



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As the complexity of allergic disease continues to evolve, the role of T_H2-driven IgE responses remains at the forefront. The ability for ligation of IgE by allergen to trigger mast cell and basophil activation and to facilitate allergen uptake and antigen presentation to T cells provides a cellular basis for the pathogenic effects of IgE in patients with allergic disease. On the other hand, a variety of immune mechanisms counterbalance IgE-mediated processes. Arguably, those that have gleaned the most attention involve IL-10 and IgG antibodies.

If we first consider IL-10, convincing evidence of its protective role came from a landmark article published in 1998 by Akdis et al.¹ In that study, subjects who received high-dose rush immunotherapy for bee venom allergy developed T-cell anergy toward the major bee venom allergen phospholipase A₂, which was associated with enhanced induction of IL-10 in *in vitro* cell cultures stimulated with allergen. Neutralization of IL-10 in these cultures restored T-cell responsiveness to phospholipase A₂. Furthermore, addition of exogenous IL-10 inhibited phospholipase A₂-specific IgE production while augmenting IgG₄. These findings implied that IL-10 opposed T_H2 responses and differentially regulated IgE and IgG₄ antibodies in the context of high-dose allergen tolerance.

Around the same time, work by a separate group demonstrated the ability of IL-10 to inhibit IL-4-dependent IgE class-switching while promoting IgG₄ antibody production in cultures from dust mite allergic subjects.² Since that time, an increase in serum specific IgG levels coupled with induction of IL-10 in allergen-stimulated culture systems has been widely reported in patients who receive allergen-specific immunotherapy administered through both the subcutaneous and sublingual routes.³ Further evidence that this immune profile might be protective came from observations in beekeepers exposed naturally to high-dose phospholipase A₂ through repeated bee stings,⁴ as well as environmental exposure to high-dose cat allergen (Fel d 1) among asymptomatic subjects living with a cat.⁵

Although the mechanisms whereby IL-10 and IgG suppress allergic inflammation have been widely debated, their importance as molecular sentinels in the context of high-dose allergen exposure is not in dispute. Both IL-10 and IgG act in a multifaceted fashion. In the case of IL-10, this mediator is produced by a variety of immune cell types, including peripheral regulatory T cells (regulatory T type 1 cells) and regulatory B cells, which act to suppress a variety of T-cell and non-T-cell types.⁶ On the other hand, IgG antibodies block IgE-mediated pathways by binding allergen or triggering inhibitory signaling pathways, thereby reducing allergen uptake by antigen-presenting cells and preventing activation of basophils and mast cells.⁷⁻⁹

An important consideration is whether immunoregulatory processes mediated by IL-10 and IgG translate to beneficial clinical outcomes. Although this relationship is apparent for clinical interventions involving high-dose allergen administration, it is less obvious for environmental exposures, which constitute a much lower cumulative allergen dose. Among inhalant allergens, the major cat allergen Fel d 1 is unique, given its propensity to remain airborne for long periods and to accumulate in house dust at levels that far exceed those of other perennial inhalant allergens, including those derived from house dust mite. Indeed, high-dose exposure to Fel d 1 induces high levels of Fel d 1-specific IgG and IgG₄ in the serum of subjects who lack specific IgE and allergic symptoms. This characteristic profile was termed the “modified T_H2 response” because of the presence of IgG₄ without the hallmarks of atopy.^{5,10} The terminology used embodies the concept that T_H2 cytokines are necessary for isotype switching to IgG₄. Consistent with this, IgG₄ antibodies are readily detected among subjects sensitized to common allergens; however, IL-10 preferentially skews switching to IgG₄ over IgE.^{2,3}

Since the modified T_H2 response was first described, other groups have sought to identify markers of immune regulation in childhood that might modify the risk of allergic disease. Such studies are challenging because they require a large sample size, well-defined cohorts, and meticulous assay design. In 2011, Custovic et al.¹¹ reported an association between specific IgG, but not IgG₄, and a decreased risk of wheeze in 2 population-based cohorts of schoolchildren in the United Kingdom and Australia. The interpretation was that IgG₁, the most abundant IgG isotype, exerts a protective effect.

In this issue of the *Journal*, the same group explored whether IgG-dependent “control” might explain why a subset of children who are atopic do not manifest allergic symptoms.¹² Such “benign T_H2 immunity” constitutes a common clinical phenotype that can be readily exploited to investigate regulation of the allergic response. An intriguing aspect of this response is that although production of IgE is not constrained, its pathogenic effects are attenuated *in vivo*. The current work focused on

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prototypical allergen sources with established links to asthma and rhinitis (house dust mite and grass, respectively) and capitalized on existing independent population samples of children from the United Kingdom and Australia. Major findings included associations between increased allergen-specific IgG/IgE ratios and reduced symptoms and negative skin test results among sensitized children. The ability for sera from donors with high IgG/IgE ratios to inhibit IgE-dependent activation of basophils by allergen provided proof of concept for IgG-mediated modulatory effects. Perhaps the most interesting facet of this article is the strategy used to identify T-cell markers that could yield mechanistic insight into the relationship between allergen-specific IgG/IgE ratios and benign Th₂ immunity. For these experiments, house dust mite-stimulated CD4⁺ T cells obtained from atopic children who had moderate- to high-level sensitization were subjected to global gene expression analyses. Higher IgG/IgE ratios were associated with reduced expression of genes that were integral to an atopy-associated Th₂ module that was previously characterized. Using an algorithm designed to predict the upstream biological causes for a given gene expression profile, the authors were able to link increased IL-10 signaling, coupled with decreased signaling through Th₂ cytokine and Toll-like receptor pathways, to high IgG/IgE ratios. Importantly, the relationships between cytokines, serum antibody profile, and clinical phenotype were borne out at the protein level, as judged by cytokine responses to house dust mite evaluated across the entire Western Australia Pregnancy Cohort. The implication is that allergen exposure in asymptomatic subjects who are nonetheless sensitized, triggers signaling networks involving the upstream regulator IL-10, which act to attenuate pathogenic Th₂ responses.

The key question is how this mechanistic insight could inform the design of new treatments for allergic disease. As the authors point out, induction of IgG₁ antibodies might be beneficial for blocking IgE-mediated acute-phase responses, and the consequent T cell-mediated late events. Going forward, it will be important to solidify the functions of IgG₁ versus other antibody isotypes, most notably IgG₄, in different types of “benign” responses to allergens and to assess whether antibody affinity is a contributing factor. In keeping with the fundamental tenets of immunology, the resulting serum antibody profile will be dictated by the nature of the allergen, the route of exposure, and the dose of allergen received. Thus, antibody isotypes and their proportions relative to each other might be strikingly different depending on the context of allergen exposure.

There are also important experimental considerations when evaluating serum antibody profiles. Recent evidence suggests that the ratio of specific IgG to IgE might be artificially enhanced by using the Immuno Solid-phase Allergy Chip compared with

ImmunoCAP (Phadia, Uppsala, Sweden) because of reduced IgE signals in the presence of high IgG when the amount of allergen is limiting.¹³ The current study design used different assay platforms (including Immuno Solid-phase Allergy Chip and ImmunoCAP) to measure serum antibodies in each cohort, as well as cohort samples of different ages, thereby precluding a rigorous comparison of IgG/IgE ratios at different ages.

An obvious next step is to examine how serum antibody responses evolve in relation to symptoms throughout childhood to address the durability of benign Th₂ immunity. This aspect has important clinical implications, not only for identifying those who might be at risk for later-onset allergic disease but also for identifying early windows for intervention that could mitigate this risk.

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