

Role of IgG₄ in IgE-mediated allergic responses

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B cells have been classically involved in immune responses through antigen presentation to T cells, secretion of cytokines, and differentiation to plasma cells for immunoglobulin production. Human B cells express 4 subclasses of IgG (IgG₁, IgG₂, IgG₃, and IgG₄), and each subclass has different biological functions. The structure and biological functions of IgG₄ are less well understood, in part because of the lack of a functional correlate in mice. IgG₄ is the least abundant subclass of IgG in serum, accounting for approximately 4% of total IgG, whereas its levels can reach up to 75% of total IgG after chronic exposure to antigen, such as allergen immunotherapy.^{1,2} Because of its unique structural features in the hinge region, IgG₄ has several noninflammatory properties, which are listed below (Table I).

IgG₄ has low affinity for the classical activating Fcγ receptors, except FcγRI. It can form bispecific and functionally monovalent antibodies through half-molecule exchange, also called Fab arm exchange.³ Two heavy chains of IgG₄ separate to form half-molecules comprising just 1 heavy and 1 light chain. After this, half-molecules of any different specificity can recombine and create bispecific antibodies. Bispecific antibodies lack the ability to cross-link allergens and do not form immune complexes. An additional mechanism through which specific IgG can downregulate the activation of mast cells and basophils is by cross-linking of FcεRI and FcγRIIb with allergen-complexed specific IgE and IgG.⁴ A third noninflammatory role of IgG₄ results from the disrupted C1q binding site, leading to the inability to activate complement.⁵ A fourth role of specific IgG₄ to hinder mast cell and basophil degranulation is competition with specific IgE for allergen binding as a “blocking antibody.”² Increased serum allergen-specific IgG₄ levels are associated with allergen immunotherapy and healthy subjects who have been exposed to relatively high doses of allergens, such as nonallergic beekeepers and cat owners.¹

In contrast, recent evidence has also revealed a deleterious role for IgG₄ in antitumor responses in patients with malignant

melanoma by hindering IgG₁-mediated antitumor immunity.⁵ Furthermore, a variety of inflammatory diseases have now been classified under the term IgG₄-related disease in which IgG₄ serum levels are often increased and IgG₄-positive plasma cell infiltrates are found.⁵ However, the contribution of IgG₄ to the pathogenesis of these diseases still remains unclear.

There is limited information from detailed analyses of multiple allergen sources on early development of allergen-specific IgG and IgG₄ antibodies and the route of sensitization. The study by Schwarz et al⁶ in the current issue of the *Journal* investigated whether the route of exposure can affect IgG responses to environmental allergens in early childhood. The authors examined the sera of 148 children at age 2 and 7 years participating in the German Multicentre Allergy Study, a birth cohort born in 1990. Specific IgG and IgG₄ were tested against 91 molecules of 42 different allergen sources in a multiplex microarray. The allergenic molecules categorized by route of exposure (animal foodborne, vegetable foodborne, and airborne allergens) were studied at a molecular and source level. The authors demonstrated that IgG responses in infancy to environmental noninfectious antigens are associated with the oral route of exposure and the IgE sensitization status of the subjects to the same allergens. In contrast to the current knowledge on induction of IgG₄ by high-dose allergen exposure, the contribution of IgG₄ in natural induction of total IgG was found to be relatively small and infrequent. An important finding was the higher IgG prevalence in IgE-sensitized children at 2 years of age spread over the 91 molecules and was not strictly limited to an antigen that specifically induced the IgE-sensitization.

The study by Schwarz et al⁶ also contributes to the previously introduced concept that the “physiologic/natural/default” IgG response is directed mainly to ingested, noninfectious antigens.⁷ Five cow’s milk proteins were ranked as the top most prevalent antigens to which specific IgG antibodies were detected. In contrast, airborne allergens were at the lower half of the prevalence spectrum at the age of 2 years. Children with IgE sensitization at the age of 7 years already had high prevalence of IgG at age 2 years.

Although multiple cellular and molecular factors contribute, tolerance to allergens essentially results from increased IL-10 secretion from allergen-specific regulatory T and regulatory B cells. The production of allergen-specific IgG₄ has been linked to another important cell that plays a role in allergen tolerance, namely the regulatory B cell. IgG₄-expressing B cells specific for the major bee venom allergen phospholipase A₂ were isolated from healthy nonallergic beekeepers, who displayed tolerance to bee venom antigens. In addition, the frequency of IL-10⁺ regulatory B cells was increased in allergic patients after 3 months of allergen-specific immunotherapy.⁸ Furthermore, IL-10 alone was shown to play a major role in the induction of IgG₄ and suppression of IgE.^{8,9}

It is not clear thus far whether physiologic/natural/default IgG₁ or IgG₄ is linked to the development of tolerance to certain allergens or whether it might be an epiphenomenon with no functional

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TABLE I. Anti-inflammatory features of IgG₄

Fab arm exchange leads to functionally monovalent antibodies. This prevents formation of immune complexes.
Low affinity for activating Fcγ receptors.
Does not fix complement.
Acts as a blocking antibody to compete with IgE for allergen binding.
Direct mast cell and basophil suppression by cross-linking of FcεRI and FcγRIIb with IgE and IgG ₄ .

relevance.⁶ It is generally known that weak IgE responses in infancy can be transient and that a high percentage of them can fade away after a few years. As Schwarz et al⁶ have pointed out in the discussion, there are some limitations of the study, such as not analyzing the whole cohort, limit of detection of specific IgG in the microarray, and missing detection of specific IgG₁, IgG₂, and IgG₃. Further studies are now needed to define how “default and healthy” versus “preatopic” IgG, IgG₁, and IgG₄ responses can be better discriminated because high levels of specific IgG to some allergens early in life might predict the development of IgE sensitization later in life.

Eosinophilic esophagitis (EoE) has emerged in the past decade as a chronic esophageal disorder and the second most common cause of chronic esophageal symptoms after gastroesophageal reflux disease. The study by Wright et al¹⁰ in the October 2016 issue of the *Journal* suggests a role for food-specific IgG₄ in the pathogenesis of EoE. Increased levels of esophageal intrasquamous IgG₄ deposits associated with EoE were recently reported.¹¹ The authors performed a case-control study of 20 adults with EoE and 10 control subjects without EoE using biobanked specimens and investigated levels of total IgG₄ and several food-specific IgG₄ in esophageal homogenates and plasma. It was observed that total and food-specific IgG₄ levels were increased in the esophagi of patients with EoE compared with those of control subjects without EoE. They found that when food triggers are eliminated for 6 weeks in an elimination diet of egg, wheat, soy, peanut/tree nuts, and seafood, esophageal total and food-specific IgG₄ levels decreased in responders. In contrast, this decrease was not observed in plasma, suggesting local production of IgG₄ and its relationship to local inflammatory cell infiltrates. There was a significant correlation between esophageal and plasma levels of peanut-, soy-, egg-, casein-, and wheat-specific IgG₄, whereas total IgG₄ levels did not show any correlation. Presented as a “Letter to the editor” in the October 2016 issue of the *Journal*,¹⁰ this study has certain limitations, such as low sample numbers, missing IgE analyses, missing immunohistology, and use of only adult samples. Nevertheless, the demonstration of food-specific IgG₄ in the esophagus proposes a role for IgG₄ in

the pathogenesis of EoE. Overall, the 2 studies bring novel information on IgG and IgG₄ sensitization and open a new window into future research on the roles of “physiologic/natural/default” IgG sensitization and intrasquamous esophageal IgG₄ deposits in patients with EoE.

Overall, IgG₄ responses will antagonize effector functions mediated by other antibody classes by means of competition and neutralization of the corresponding allergens.

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