Published in final edited form as:

Ann Allergy Asthma Immunol. 2019 June ; 122(6): 563–564. doi:10.1016/j.anai.2019.03.024.

Food Allergy, Eosinophilic Esophagitis and the Enigma of IgG4

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Keywords

IgG4; food allergy; eosinophilic esophagitis; immunotherapy; tolerance

The recognition that IgE, formerly known as reagin, is central to the pathogenesis of allergic disease dates back nearly a century to the seminal work of Prausnitz and Kustner. By contrast, IgG4 represents an antibody subclass that is often increased in the setting of allergic disease but whose role in disease pathogenesis is less clear¹. Reports in the 1980s suggested that allergen-specific IgG4 could play a role as an anaphylactic antibody, but subsequent research cast significant doubt on this possibility. Instead, IgG4 is most widely viewed as a marker of tolerance in allergic disease as evidenced by high levels of: i) venom-specific IgG4 in non-allergic bee workers, ii) cat-specific IgG4 in non-allergic cat owners, and iii) allergen-specific IgG4 in subjects who undergo various forms of immunotherapy. The term ‘modified Th2 response’ has been used to reflect this state of high-titer allergen-specific IgG4 that is present during states of tolerance¹. As an additional example, IgG4 to food antigens appears to be particularly common in the community. In support of this we recently reported that many children in a birth cohort who regularly consume milk had moderate-high levels of IgG4 to milk components². When thinking about IgG4 and its putative role in allergic tolerance it is helpful to consider several features that could explain anti-inflammatory effects³. These include the fact that IgG4 has relatively low affinity for

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Trial Registration: Not applicable

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complement (C1q) and Fc γ receptors, and that IgG4 can undergo 'Fab arm exchange' which contributes to functional monovalency and poor antigen cross-linking. On this backdrop, an association with elevated titers of allergen-specific IgG4 has emerged with another form of food allergy, eosinophilic esophagitis - a finding that challenges the dogma that IgG4 mediates allergic tolerance.

Eosinophilic esophagitis (EoE) is a clinicopathologic condition that has been rapidly increasing in prevalence in recent years⁴. Although multiple lines of evidence point away from specific IgE as being causal in disease, the success of food elimination diets and the central role of type 2 immune cells and mediators in pathogenesis suggest that EoE is a form of food allergy. In 2014, Clayton *et al* published a landmark study in which the authors first suggested that IgG4 might be a relevant feature of this disease⁵. Since this time, the central findings of Clayton *et al* have been replicated and extended, and our group recently found that children with EoE have significantly higher serum levels of IgG4 to milk-specific proteins than unselected controls². While studies to date have not defined a clear role for IgG4 in the pathogenesis and diagnosis of EoE, there are many similarities between EoE and another disease that features high levels of IgG4, IgG4-related disease (IgG4-RD). Similar to EoE, IgG4-RD is a progressively fibrosing condition with localized inflammation characterized by infiltration of IgG4-producing plasma cells. Thus, the possibility that IgG4 could play a role in EoE pathogenesis is a critical question in the field and an area of active investigation.

A possible mechanism by which IgG4 could be involved in the pathophysiology of EoE is through the generation of immune complexes. Although the dogma is that IgG4 has limited ability to form immune complexes because of functional monovalency, there are reasons to think that under some circumstances immune complexes could form. Because Fab arm exchange typically occurs over hours to days, it is possible that IgG4 produced locally in large quantities could rapidly form immune complexes prior to arm exchange. This would additionally be favored when a source of relevant antigens, such as cow's milk, is present in high amounts, as is likely the case in EoE because of local barrier dysfunction. Although this mechanism is currently just conjecture, it is supported by two studies that demonstrated granular IgG4 immunostaining and electron-dense immune deposits in esophageal biopsies of patients with EoE, findings which are suggestive of immune complex deposition^{5,6}. Whether these complexes are directed to foods or other antigens, and whether these immune complexes decrease with disease remission is currently unknown.

On the other hand, there are also explanations for the elevated titers of food-specific IgG4 that are consistent with the supposition that IgG4 is not causally-related to EoE. For example, high titers of IgG4 to food could represent an antigen-specific compensatory immune response, albeit inadequate, to the food-antigen driven local inflammation. Alternatively, IgG4 could represent an epiphenomenon that is linked to the immune response that is causal in the inflammatory pathogenesis, but where the IgG4 itself does not play a central role in promoting or controlling inflammation. Such a situation could result if dysregulated regulatory T cells (Treg) were important contributors to EoE pathogenesis, as some data has suggested. The connection with Tregs (or possibly regulatory B cells [Breg])

comes, in part, from our understanding that IL-10 plays a central role in driving IgG4 class-switch, though eosinophils could also be a source of the IL-10.

Putting it together

Viewed simplistically, high-titer IgG4 in situations of both antigen-specific tolerance and food-antigen mediated inflammatory disease represents a conundrum. However, this apparent paradox could provide important insights into the role of IgG4 in allergic disease. Our framework for thinking about this is that IgG4 induction, like IgE, requires type 2 immune mediators to promote B-cell class-switch, most critically IL-4³. Thus, most often IgG4 is observed concomitant with IgE, as we have reported for EoE. The fact that IgE can be low titer in part reflects the dominant role of IL-10, which is also requisite for IgG4 class-switch (see Fig 1). Levels of IL-10 tend to be high in situations of chronic antigen stimulation, particularly stimulation that occurs in gastrointestinal mucosa. In this lens, it is not surprising that high-titer IgG4 would result from an allergic epithelial barrier disease of the esophagus, i.e. EoE. The question of whether IgG4 is pathogenic in EoE is important and warrants further investigation, but it is important to consider that a pathogenic role in EoE does not discount the possibility that under most other situations high-titer IgG4 contributes to allergic tolerance and not disease. Thus, while there may be merit in assessing tissue IgG4 and/or measuring serum food-specific IgG4 as part of an evaluation for EoE, the existing data do not support such a role in traditional IgE-mediated food allergy, as a positive result is best interpreted to reflect ongoing exposure and tolerance.

Acknowledgments

Funding: This work was funded by the NIH through the following grants: 1K23-AI-123596 (ECM), T32-AI-007496 (JW), R21-AI-138227 (TPM) and R37-AI-20565 (TPM)

Disclosure of Potential Conflicts of Interest: E. McGowan has received grants from the National Institutes of Health (NIH), the American Academy of Allergy, Asthma and Immunology (AAAAI), and Food Allergy Research and Education (FARE), and served as a consultant for Shire. T. Platts-Mills has a patent on an IgE assay to α -Gal and has received assay support from Phadia/Thermo-Fisher. J Wilson has no disclosures.

Abbreviations/Acronyms

Breg	Regulatory B cell
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
EoE	Eosinophilic esophagitis
Treg	Regulatory T cell

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Model of IgE and IgG4 induction related to allergen exposure

Fig 1.

Model to show relationship between IgE and IgG4 in allergic disease. IL-4 and/or IL-13 are important for both IgE and IgG4 class-switch. IL-10, which can result from Treg but also eosinophils, increases under situations of chronic antigen stimulation and favors IgG4. Th2 – T helper 2 cells, Treg – regulatory T cell, Tfh – T follicular helper cell.