Review Article

The Contribution of Allergen-Specific IgG to the Development of Th2-Mediated Airway Inflammation

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In both human asthmatics and animal models of allergy, allergen-specific IgG can contribute to Th2-mediated allergic inflammation. Mouse models have elucidated an important role for IgG and Fc-gamma receptor (FcγR) signaling on antigen presenting cells (APC) for the induction of airway inflammation. These studies suggest a positive feedback loop between IgG produced by the adaptive B cell response and FcγR signaling on innate immune cells. Studies of IgG and FcγRs in humans with asthma or allergic lung disease have been more controversial. Some reports have identified associations between allergen-specific IgG and severity of allergic responses, while other studies have found associations of IgG subclass IgG4 with allergic tolerance. In this paper, we review the literature to help define the nature of IgG and FcγR signaling on innate immune cells and how it contributes to the development of allergic immune responses.

1. Atopic Asthma Is Commonly Associated with Th2 Responses

Asthma is a chronic inflammatory disease of the lungs marked by recurrent episodes of airway hyperresponsiveness resulting in chest tightness, wheezing, and shortness of breath. Allergic or atopic asthma is the most common form of asthma, and allergic sensitization occurs in about 80% of asthmatic children and 60% of asthmatic adults [1]. Although there are now multiple phenotypes for atopic asthma, it has been classically associated with an excessive Th2-driven inflammatory response [2]. Development of an aberrant Th2 response leads to production of several cytokines including IL-4, IL-5, IL-9, and IL-13 that results in eosinophilia, goblet cell hyperplasia, mast cells activation, and smooth muscle hypertrophy [3]. In addition to these cellular effects, there is an important humoral response generated during primary sensitization that leads to production of allergen-specific IgE and IgG1. Much of the interest in dissecting the pathogenesis of asthma has focused on allergen-specific IgE which is well known to induce allergic hypersensitivity [4]. However, it was found that IgE−/− mice were still able to develop anaphylaxis and airway hyperreactivity suggesting that other mediators including allergen-specific IgG could be playing an important role in disease pathogenesis [5, 6]. Moreover, the total allergen-specific IgG response is greater in magnitude and has a significantly increased half-life compared to the total allergen-specific IgE response [7]. The complex nature of IgE in promoting allergy can be reviewed in a variety of recent articles [8–10]. In this review, we discuss current research on IgG, FcγRs, and allergy in order to better identify the role of IgG during allergic airway inflammation.

Based on research discussed in this paper, we propose a model whereby allergen-specific IgG promotes the expansion of secondary Th2 responses through ligation of FcγRs on innate immune cells (Figure 1). Allergen-specific IgG can be detected in the airways of sensitized individuals, and we propose that during secondary exposure to inhaled allergens, immune complexes (ICs) consisting of antigen and allergen-specific IgG are formed. These ICs can interact with both activating and inhibitory FcγRs on innate immune cells and...
2. FcyR Expression and Function on Hematopoietic Cells

FcyRs have emerged as an important bridge between the innate and adaptive arms of the immune system as they are primarily expressed on innate cells and their function can be altered by IgG ligation of FcyRs. Thus far, there have been four FcyRs identified in mice: FcyRI (CD64), FcyRII (CD16), FcyRIII (CD16-2), and FcyRIIB (CD32) [11]. The family of FcyRs is more complex in humans because multiple isoforms exist: FcyRI, FcyRIIA, FcyRIIB, FcyRIC, FcyRIIIA, and FcyRIIIIB [12]. In mice, FcyRI, FcyRIII, and FcyRIV are activating receptors that signal primarily through the Fc common γ-chain (FcγR, noted as γ2 in Figure 2), and in humans, FcyRI, FcyRIIA, FcyRIIC, and FcyRIIIA are activating Fc receptors although only FcyRI and FcyRIIA use FcγR [13]. FcγR contains immunoreceptor tyrosine-based activation motifs (ITAMs) that allow Syk kinases to dock and become activated [14]. In contrast to mice, human FcyRIIA and FcyRIIC contain an inhibitory ITAM, and human FcyRIIB is a GPI-linked receptor only expressed on human neutrophils [12]. On the other hand, FcyRIIB in both humans and mice is an inhibitory receptor with an immunoreceptor tyrosine-based inhibitory motif (ITIM) that allows Syk to dock and become activated [15]. A schematic of both mouse and human receptors along with their signaling chains is shown in Figure 2.

In addition to the numerous FcyRs, there are four IgG subclasses present in mice (IgG1, IgG2a, IgG2b, and IgG3) and humans (IgG1, IgG2, IgG3, and IgG4). Each FcyR has a varying affinity for the monomeric IgG subclasses. FcyRI in mice and FcyRI in humans have the highest affinity for IgG and can bind monomeric IgG2a in mice or IgG1 and IgG3 in humans [17, 18]. The other FcyRs have a significantly
lower affinity for IgG and primarily bind to IgG-ICs [16]. In mice, FcγRIIB and FcγRIII are able to bind IgG1, IgG2a, and IgG2b while FcγRIV has been shown to bind IgG2a, IgG2b, and IgE [19–22]. In humans, IgG1 and IgG3 can be found bound by all the FcRs; IgG2 binds to allelic variants of FcγRI and FcγRIII; IgG4 binds to FcγRI, the FcγRII family, and an allelic variant of FcγRIII [12]. In both mice and human, IgG1 and IgG2 are found in the highest abundance in the serum. Human IgG4 is found at very low concentrations and is the only IgG subtype unable to form immune complexes or activate complement through binding C1q [23, 24]. Differences between IgG subtype expression and their affinity for activating or inhibitory FcγRs may be important mechanisms for the regulation of allergic disease.

Both activating and inhibitory FcγRs can be expressed on hematopoietic cells, primarily innate immune cells, and the expression patterns of these receptors vary between mice and humans as highlighted in Figure 3. Most of the innate immune cells express both activating and inhibitory FcγRs resulting in a certain threshold that will lead to the activation or inhibition of the immune response based on the ratio of these receptors and which IgG subclasses are present. This added level of control allows antibodies generated by the humoral immune system to play a critical role in affecting activation of innate immune cells through ligation of specific FcγRs to induce immunogenic or tolerogenic responses, which will be discussed below.

### 3. Murine Models of Allergy Suggest an Important Role in IgG Signaling in the Development of Allergy

Preliminary studies investigating the contribution of FcγRs in IgG-mediated disease models demonstrated that they helped regulate the immune response. The first knockout mouse model developed to address the role of IgG and activating FcγRs in inflammatory responses was the FcγRIγ−/− mouse which had an attenuated Arthus reaction, an IC-mediated type III hypersensitivity response [25]. These results were confirmed in several other studies highlighting that FcγRIγ−/− mice had significantly decreased IgG-mediated cellular responses [26–28]. However, the specific FcγRs involved in mediating this response could not be identified because the FcγRIγ−/− mouse lacked all activating FcγRs, so other studies developed specific FcγRI−/−, FcγRII−/−, and FcγRIV−/− mice to further clarify their role during in vivo immune responses. Studies in mice deficient for activating FcγRs, particularly FcγRI and FcγRIII, showed decreased IgG-mediated responses in the knockout mice in several

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**Figure 2:** Mouse and human FcγR structure diagram. Receptors are labeled as “activating,” “inhibitory,” or “unknown.” Relative affinity of each receptor to monomeric (free) IgG is listed below each receptor [12, 16]. Signaling chains associated with each receptor are labeled; beige diamonds represent ITAMs, green box represents ITIM, and grey box represents cell membrane.

| Mouse | Human |
|-------|-------|
| FcγRI (CD64) | FcγRI (CD64) |
| FcγRII (CD16-2) | FcγRIIA (CD16A) |
| FcγRIII (CD16) | FcγRIIA (CD32A) |
| FcγRIIB (CD32B) | FcγRIIC (CD32C) |
| FcγRIIB (CD32B) | FcγRIII (CD16B) |
| FcγRIIB (CD32B) | FcγRIIB (CD32B) |
| Activating | Activating |
| Activating | Activating |
| Activating | Activating |
| Activating | Unknown |
| Activating | Inhibitory |
| High affinity | High/low affinity |
| Low affinity | Low affinity |

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Figure 3: Human and murine FcγRs are expressed on a variety of hematopoietic cells. Cells of the innate immune system express both activating and inhibitory FcγRs: monocytes, macrophages, DCs, basophils, eosinophils, neutrophils, NK cells, and mast cells. On the other hand, B cells uniquely express FcγRIIb both in mice and humans. * denotes that expression can be induced upon activation.
IgG-ICs [50]. These results indicate that allergen-specific IgG resolved by 24 hours suggesting an immediate response to that peaked one hour after antigen administration and had resolved by 24 hours suggesting an immediate response to IgG-ICs [50]. These results indicate that allergen-specific IgG could exacerbate allergic lung diseases by forming allergen-specific IgG-ICs that promote activation of innate immune cells through interactions with FcyRs. Although several innate cells contribute to allergic lung disease, there has been a great deal of interest in understanding how DCs contribute to this process. It is well established that DCs are important in promoting Th2 inflammation in the lungs and can direct differentiation of CD4+ T cells into specific T cell lineages, and FcyRs on DCs have been identified as being a potential mediator in affecting DC and Th2 responses in the lungs [49, 51–54]. Studies in our lab highlighted a role for FcyRIII in regulating Th2 responses; we demonstrated that when TLR4-stimulated DCs received an additional signal through FcyRIII, it led to augmented Th2 responses in murine models of allergic airway inflammation in an IL-10-dependent manner [53]. Our studies are supported by the finding that activation by IgG-ICs on macrophages and neutrophils results in heterodimerization of TLR4 and FcyRIII [55]. These conclusions suggest that IgG-ICs could provide a link between the adaptive and innate immune responses by modulating TLR signaling. Thus, a positive feedback loop between allergen-specific IgG and FcyRs on DCs could drive established Th2 responses and exacerbate the development of allergic lung diseases. However, it should be noted that several studies have recently argued that free IgG1, not in immune complexes, and IVIg can bind FcyRIII and induce “inhibitory” ITAM signaling [56, 57]. The relevance of this effect may not be applicable to the development of allergic lung diseases because during secondary responses, ICs that bind to FcyRIII at a much higher affinity than free monomeric IgG are formed [16]. Other studies investigating the role of FcyRIIB on APCs have pointed to an inhibitory role for FcyR in Th2 responses. Sensitized wild-type mice receiving an intranasal aerosol antigen challenge had an increase in FcyRII expression on respiratory CD14+/MHCIi+ mononuclear cells and CD11c+ cells [44]. Furthermore, another study suggested that FcyRIIB on DCs contributed to tolerance induction against mucosal antigens [58]. One possible mechanism by which FcyRIIB on DCs ameliorates allergic airway inflammation is through inhibition of antigen uptake and DC activation [45]. Collectively, the studies in mice suggest that allergen-specific IgG generated during primary sensitization complexes with inhaled antigen during secondary responses and depending on the balance of FcyRs signaled on DCs, can either positively or negatively affect the development of Th2 inflammation in the lungs.

4. FcyR and IgG in Human Allergy and Asthma

The complexity of the IgG subclasses and FcyRs in humans has made it more difficult to determine the effect of allergen-specific IgG on the development of Th2 responses in allergic diseases. Most studies in humans have investigated the correlation between different IgG subclasses, their specificities, and association with allergic phenotypes, while only a few studies have investigated the role of IgG signaling and their receptors in human allergic disease. Correlations between atopy and FcyR expression levels have provided conflicting results yet overall suggest that increased expression of activating FcyRs is augmented in allergic individuals [59–62]. Interestingly, one study investigating the ability of human FcyRIII− and FcyRIII+ monocyte-derived DCs (mDCs) to reactivate memory responses found that FcyRIII+ mDCs stimulated stronger T cell responses in vitro [63]. In general, determining the function of human FcyRs has proven difficult as there are limited reagents and variable populations being studied. Currently, studies have utilized transgenic mice overexpressing human FcyR genes to study function, but these studies are often limited by cell expression and binding affinity to mouse IgG. To examine the role of human FcyRs in models of allergic disease, human FcyRIIA which binds mouse IgG1, IgG2a, and IgG2b was overexpressed in an FcyR−/− mouse and assayed for anaphylactic responses. Expression of only human FcyRIIA in mice was sufficient to induce both active and passive anaphylaxis, as well as acute allergic responses [64]. Similarly, an FcyR humanized mouse that expresses the entire human FcyR family and lacks all mouse FcyRs was generated. These mice were able to mount comparable immune responses to wild-type mice during immune-complex mediated anaphylaxis, NP-OVA sensitization and challenge, FcyRIIB-dependent vaccination, and antitumor immunity; thus, they could prove to be a valuable tool in clarifying the role of human FcyRs [65]. While these studies utilized human FcyRs expressed in mice, together they confirm the hypothesis that FcyRs contribute to the development of allergic disease and demonstrate that human receptors display similar phenotypes to their murine counterparts.

Several studies have found a contributing role for antigen-specific IgG in the pathogenesis of asthma in humans. Notably in 2005, the German Multicentre Allergy Study published results from a longitudinal study of cat exposure and asthma development in children from age 6 months to 10 years. As expected this study found that cat Fel d 1 antigen-specific IgE levels were associated with increased asthma risk but surprisingly found that children with both antigen-specific IgE and IgG antibodies showed the greatest risk for asthma. This study and other studies did not find a correlation between allergen-specific IgG alone and increased asthma risk [66]. A similar study investigated childhood exposure and antibody responses to both house dust mites (HDM) and cats and determined that both total antigen-specific IgG and IgG4 to cat Fel d 1 and HDM Der f 1 paralleled the level of total antigen exposure. Analysis of these populations showed a strong association with HDM-specific IgG, but not cat-specific IgG, for increased risk of asthma.
Levels of IgG4 had no effect on IgE levels quickly following the end of therapy without a loss of tolerance [79]. Further, it is well known that IgG4 is unable to form immune complexes, activate complement, nor does it have a high affinity for FcyRs. Together, these findings suggest that even though IgG4 is induced in response to constant antigen exposure, it may act as a bystander and not a bona fide mechanism for mediating allergic tolerance. Overall, data has suggested that IgG in some context may be capable of overlapping epitope binding with IgE responses in order to dampen allergic sensitivity; however, it appears that it may not be a common mechanism and more research will be needed to elucidate these contradicting results.

One mechanism of immune regulation that might reconcile the seemingly contradictory findings presented above is recent studies suggesting a role for regulatory T cell populations (Treg or Tr1) in the development of both tolerance and allergen-specific immunotherapy [80–82]. Treg-produced IL-10 may contribute to the effects of immunotherapy by enhancing the survival and proliferation of previously differentiated IgG4 B cells [81]. Additionally, IL-10 treatment of IL-4-treated peripheral blood mononuclear cells (PBMCs) can promote the production of IgG4 and decreased IgE antibodies from peripheral B cells [81]. Finally, purified IL-10-producing Tr1 cells or Treg cells co-cultured with PBMCs from allergic individuals can modulate the B cell response to HDM antigen Der p 1 away from IgE and towards IgG4 [82]. Together, these human studies identify an important role for regulatory T cell subsets in the development of tolerance in allergy. Importantly, these results suggest that the correlation of elevated levels of IgG4 with tolerance during immunotherapy may actually be a side effect of increased IL-10 in the serum and not a direct effector mechanism.

5. Discussion

Although the mechanisms by which IgG contributes to the pathogenesis or tolerance of allergic responses remain controversial, we believe that the evidence from both mouse and human studies points towards an important role for IgG in the regulation of allergic phenotypes. Clinical studies have demonstrated that in addition to elevated levels of allergen-specific IgE, allergic individuals also have elevated levels of allergen-specific IgG. Our previously published results showed that the activating receptor FcγRIII was necessary for potent induction of Th2 responses [53]. Further we found that FcγRIII is able to modulate TLR signaling on DCs in order to drive Th2 responses [53]. Based on these results and the data presented above, we propose a model (Figure 1)
whereby primary sensitization to an allergen results in B cell class switching and the production of allergen-specific IgG1. IgG1 can be found present in the lungs of sensitized individuals and will be able to complex with inhaled allergens during secondary responses. Allergen-ICs in the lung can signal through the activating FcγRs on innate immune cells, in particular FcγRIII. We have found that signaling through this receptor induces DC that specifically augments Th2 development through the expression of multiple genes. These migratory respiratory DCs can provide a milieu supportive of allergic responses in the airways thereby providing a positive feedback loop between the development of B cells that produce allergen-specific IgG, and the innate response of the respiratory DCs in the lungs. While we propose a positive feedback of allergen-specific IgG, the expression pattern and affinity of different FcγRs on innate cells in the lungs may explain the differential results found between some studies. The presence of different FcγRs and different types of innate cells in normal versus atopic individuals could determine whether antigen-specific IgG contributes to the development of allergy or tolerance. Specifically, inhibitory FcγR receptors may explain how in some murine studies FcγRIIB seems to be able to overcome the activating FcγRs to ameliorate disease. It is known that FcγRIIB has lowered affinity to IgG compared to the activating receptors, therefore suggesting that results studying FcγRIIB in mice may not be the same in human allergy. Thus to thoroughly understand the importance of the IgG response in allergy, questions remain such as the differential expression of IgG subtypes, differences in IgG-affinity, and expression levels of FcγRs on innate cells between allergic and nonallergic individuals.

Authors’ Contribution

J. W. Williams and M. Y. Tjota contributed equally to this work.

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