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Potential Mechanisms for IgG4 Inhibition of Immediate Hypersensitivity Reactions

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Published online: 18 February 2016
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Abstract IgG4 is the least abundant IgG subclass in human serum, representing less than 5 % of all IgG. Increases in IgG4 occur following chronic exposure to antigen and are generally associated with states of immune tolerance. In line with this, IgG4 is regarded as an anti-inflammatory antibody with a limited ability to elicit effective immune responses. Furthermore, IgG4 attenuates allergic responses by inhibiting the activity of IgE. The mechanism by which IgG4 inhibits IgE-mediated hypersensitivity has been investigated using a variety of model systems leading to two proposed mechanisms. First by sequestering antigen, IgG4 can function as a blocking antibody, preventing cross-linking of receptor bound IgE. Second IgG4 has been proposed to co-stimulate the inhibitory IgG receptor FcγRIIb, which can negatively regulate FcεRI signaling and in turn inhibit effector cell activation. Recent advances in our understanding of the structural features of human IgG4 have shed light on the unique functional and immunologic properties of IgG4. The aim of this review is to evaluate our current understanding of IgG4 biology and reassess the mechanisms by which IgG4 functions to inhibit IgE-mediated allergic responses.

Keywords IgG4 · Hypersensitivity · Blocking antibodies · Allergy · Allergen immunotherapy · IgE

Introduction

The identification of four distinct subclasses of human IgG was first described during the 1960s, when they were designated as IgG1, IgG2, IgG3 and IgG4, based on their relative concentrations in human serum [1–3]. IgG4 was notable as the least abundant IgG subclass with an average serum concentration of 0.4 mg/ml, compared to 8 mg/ml for IgG1. In addition, unlike the other IgG subclasses, IgG4 is unable to fix complement or precipitate antigens. IgG4 is comprised of two identical 50-kDa heavy chains each consisting of four distinct immunoglobulin domains (VH, CH1, CH2 and CH3) and two identical 25-kDa light chains each consisting of two immunoglobulin domains (VL and CL). The 12 amino acid hinge region between CH1 and CH2 provides mobility of the variable Fab regions in relation to the Fc region, facilitating binding of antigen. All of the IgG subclasses share a high degree of sequence homology, but key differences in the hinge region and Cγ2 domain give rise to important variations in effector function.

IgG antibodies interact with immune cells through binding to Fcγ receptors expressed on cell surfaces [4•]. With the exception of the neonatal Fcγ receptor (FcγRn), which binds at the Cγ2–Cγ3 interface and functions primarily to transport IgG across placental and mucosal surfaces, all Fcγ receptors bind at the N-terminus of Cγ2. There are seven Fcγ receptors in humans (Table 1); FcγRI has the highest overall affinity for IgG and can bind monomeric antibody. This high affinity...
means that FcγRI is saturated with IgG, although similar to
the high affinity IgE receptor FcεRI, signaling only occurs
following antigen cross-linking [5]. The other Fcγ receptors
generally have lower affinity (100–1000-fold less) for IgG
 subclasses and hence bind only to immune complexes and
not to monomeric antibody.

IgG4 binds to all of the Fcγ receptors with the exception of
FcγRIIIB (Table 1), which contains a membrane anchored
GPI domain and thus cannot induce intracellular signaling
[6]. FcγRI and FcγRIIa both associate with the common γ
chain, which contains an intracellular immunoreceptor
tyrosine-based activation motif (ITAM), driving cellular acti-
vation upon receptor engagement. FcγRIIa and FcγRIIc
are single-chain activating receptors and also possess an ITAM
in their intracellular domains. Signaling through activated Fcγ
receptors promotes a range of effector functions including
internalization of Fc-bound immune complexes, enhanced
antigen-presentation, antibody-dependent cell-mediated cyto-
toxicity (ADCC) and cellular activation [7•, 8]. In contrast,
FcγRIIIB is a single-chain inhibitory receptor, the only inhibi-
atory Fcγ receptor in humans, possessing an immunoreceptor
tyrosine-based inhibition motif (ITIM) in the intracellular
domain. IgG4 is the only IgG subclass that can bind with equal
affinity to both FcγRIIb and the activating receptors.

Co-ligation of FcγRIIb with activating Fcγ receptors results
in inhibition of effector cell responses [9]. FcγRIIb also plays
an important role in regulation of B cell activity and plasma
cell survival [10].

The crystal structure of human IgG4 Fc was first solved in
1997 in complex with an IgM rheumatoid factor [11]. More
recently, a higher resolution structure of IgG4-Fc was solved,
providing further insights into the unique structural features of
IgG4 compared to IgG1. In particular, the crystal structure
of IgG4 Fab has been determined in complex with the
complement component C1q [18].

**Fab Arm Exchange**

Cysteine residues in the hinge region of IgG4 result in
intra-heavy chain disulphide bonds, as opposed to the
inter-heavy chain bonds present in the other IgG subclasses.
In addition, a key amino acid substitution in the Cγ3-Cy3
interface weakens the domain interactions. Under reducing
conditions, the combined effect allows dissociation of the
two heavy chains of human IgG4 into half-molecules [13].

Re-association of half-molecules originating from different
IgG4 antibodies results in ‘bi-specific’ monovalent antibodies.

IgG4 antibodies that have undergone this process are conse-
quentially unable to undergo antigen cross-linking to form im-
une complexes. Analysis of serum from healthy human sub-
jects revealed that 20–30 % of monomeric IgG4 contained
both κ and λ light chains within the same molecule, demon-
strating that Fab arm exchange occurs in vivo in a substantial
fraction of IgG4 [14•].

**IgG4 Production**

Naïve B cells express IgM as a monomeric membrane-bound
B cell receptor (BCR). Activation of naïve B cells through the
BCR can lead to rearrangement of the immunoglobulin heavy
chain locus through class switch recombination. This results
in the expression of a different ‘switched’ isotype (IgG, IgA or
IgE), dependent on additional signals provided by cytokines.

Class switch recombination to IgG4 depends on the produc-
tion of the Th2 cytokines IL-4 and IL-13, along with ligation
of CD40 [15, 16]. These same signals (IL-4 plus CD40L)
classically drive class switch recombination to IgE, the prima-
ry effector antibody involved in allergic disease [17]. There is
a clear biological relationship between IgG4 and IgE produc-
tion, although the molecular mechanisms that dictate recom-
bination to IgG4 versus IgE have yet to be fully elucidated
[18]. The addition of IL-10 [19] or IL-21 [20] to in vitro

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**Table 1** Cellular expression and relative binding affinities of human Fcγ receptors

| Receptor  | Cellular expression                  | IgG1 | IgG2 | IgG3 | IgG4 |
|-----------|-------------------------------------|------|------|------|------|
| FcγRI/CD64| Monocytes, macrophages, DC, neutrophils*, mast cells* | +++++ | –    | ++++ | ++++ |
| FcγRIIa/CD12a | Monocytes, macrophages, DC, basophils, mast cells, eosinophils, platelets | ++++ | ++ | +   | +   |
| FcγRIIb/CD32b | B cells, DC, basophils, neutrophils subsets of monocytes and macrophages | + | – | ++ | + |
| FcγRIIc/CD32c | NK cells, monocytes, macrophages and neutrophils | + | – | ++ | + |
| FcγRIIa/CD16a | Natural killer (NK) cells, monocytes and macrophages | +++ | +/- | ++++ | +/- |
| FcγRIIb/CD16b | Neutrophils subsets of basophils | +++ | – | +++ | – |
| FcyRn | Monocytes, macrophages, DC, neutrophils, epithelial cells, endothelial cells | ++++ | ++++ | ++++ | ++++ |

There are two polymorphic variants of FcγRIIa (131H and 131R) with similar binding properties. FcγRIIa has two polymorphic variants (158V and 158F). IgG2 and IgG4 bind only to FcγRIIa158V and only as immune complexes, whereas IgG1 and IgG3 bind to both variants with high affinity [6].

*Induced following activation
IgG4 and the Modified Th2 Response

An important feature of IgG4 production is the association with high-dose chronic antigen exposure. The production of allergen-specific IgG4 is linked to the 'modified Th2 hypothesis', whereby an allergen-driven Th2 response in which IgG4 dominates and IgE is absent results in protection from immediate hypersensitivity [24]. This was first described by Platts-Mills and colleagues who demonstrated that children exposed to high concentrations of the major cat allergen, Fel d 1, had high titers of Fel d 1-specific IgG4 and were clinically tolerant (ie not cat allergic) [25]. Similarly, high titers of allergen-specific IgG4 are observed following chronic exposure to other exogenous allergens including occupational allergens [26] and bee venom [27]. Thus, the balance between IgG4 and IgE production appears to critically influence the development of allergen-induced hyporesponsiveness versus immune tolerance. Importantly, studies of IgG4-induced antibody responses in allergen immunotherapy (AIT) demonstrate that IgG4 is capable of directly inhibiting the activity of IgE.

IgG4 and Allergen Immunotherapy

AIT is an effective treatment for IgE-mediated allergy and induces long-term clinical tolerance, associated with increases in IL-10-producing T regulatory cells and reductions in basophil reactivity [28]. The observation that IgG4 responses are associated with chronic high-dose natural allergen exposure is consistent with the effect of AIT—including repeated administration of high-dose subcutaneous, sublingual or oral allergen over years—in inducing allergen-specific IgG4 [29–31]. The concept that treatment-induced IgG antibodies could provide protection from immediate hypersensitivity emerged early in the history of AIT. Pre-dating even the discovery of IgE, Cooke and Loveless demonstrated that post-immunotherapy serum could inhibit in vivo Prausnitz-Küstner reactions [32]. In 1982, Golden et al. demonstrated that titers of venom-specific IgG were significantly higher in patients who were successfully treated with venom immunotherapy, whereas treatment failure was associated with lower levels of specific IgG [33]. This led to the theory that specific IgG levels could correlate with the clinical response to treatment. During this time, it was established that despite initial low levels in serum, AIT appeared to stimulate marked increases in allergen-specific IgG4 [34]. However, data from certain clinical trials raised doubts regarding the relevance of allergen-specific IgG4 to the clinical benefit of AIT since high levels of allergen-specific IgG4 were associated with treatment failure rather than success [35].

Inhibition of IgE Activity by IgG4

Definitive evidence that IgG is able to inhibit IgE activity was provided by Van Neerven and colleagues who reported that AIT-induced IgG could inhibit IgE-facilitated allergen presentation (IgE-FAP) by B cells to T cells in vitro [36]. Later similar studies went on to show that this ‘blocking activity’ co-eluted with IgG4 [37, 38]. IgE-FAP depends on the binding of immune complexes formed of allergen and specific IgE to the low-affinity IgE receptor CD23 (FεRII). Capture of IgE-allergen complexes by CD23-expressing antigen-presenting cells results in internalization and processing of the allergen-IgE-receptor complex with subsequent presentation of allergen-derived peptides to T cells [39]. The ability of IgG4 antibodies to inhibit this process relies entirely on the affinity, specificity and quantity of the blocking antibody, regardless of isotype or subclass [40, 41]. Conventional subcutaneous immunotherapy induces significant increases in allergen-specific IgG4 6–8 weeks following the start of treatment [29]. This corresponds with the appearance of IgE-FAP inhibitory activity in serum but is preceded by increases in allergen-driven IL-10 production by peripheral blood mononuclear cells. The functional inhibitory activity of IgG4 appears to relate more closely to the clinical efficacy of AIT than absolute levels in serum, which may explain why levels of IgG4 often correlate poorly with clinical responses. In a randomized double-blind placebo controlled trial of subcutaneous grass pollen immunotherapy, continued clinical remission 2 years after treatment withdrawal was accompanied by persisting inhibitory antibody activity in serum against IgE-FAP [38]. Although the levels of serum allergen-specific...
IgG4 fell to near pretreatment values during the 2 years of treatment withdrawal, depletion experiments identified IgG4 as the main source of the continuing inhibitory activity. This study indicates that the activity but not quantity of IgG4 antibodies per se is the main determinant of clinically relevant IgE inhibition (Fig. 1).

In addition to inhibiting CD23-dependent IgE activity, IgG4 can also block the effects of IgE signaling through FcεRI, and in turn inhibit immediate hypersensitivity. For example, IgG4 purified from the serum of an immunotherapy-treated individual inhibited IgE-mediated basophil degranulation, which depends on cross-linking of high-affinity IgE receptor (FcεRI)-bound IgE [42]. The ability of IgG4 to inhibit FcεRI-dependent activity of IgE has been proposed to arise through two possible mechanisms; either through direct competition for allergen with receptor-bound IgE and/or through simultaneous binding of IgG4 to the inhibitory FcγRIIb. A high-affinity monoclonal IgG4 antibody specific for the grass pollen allergen Phl p 7 was able to inhibit IgE-mediated basophil degranulation in vitro [43]. In order to determine whether this activity was subclass-dependent, a panel of antibodies with identical specificity but different subclasses, namely IgG1, IgG2, IgG3, IgA1 and IgA2, was generated [41•]. The antibody specificity was found to be the critical determinant of the inhibitory activity, since each subclass was able to block basophil activation to an equal degree. Thus, any antibody isotype with sufficient affinity for allergens has the potential to effectively prevent cross-linking of IgE receptors through competition with IgE for allergen binding.

**IgG4 and FcγRIIb-Mediated Inhibition of IgE**

Using a bi-specific antibody, Kepley and colleagues demonstrated that cross-linking of FcγRIIb and FcεRI inhibits IgE-mediated basophil activation [44]. The role of FcγRIIb in the inhibitory effect of AIT serum on basophil degranulation has been the subject of conflicting reports in the literature. In two independent studies using similar methodologies, the inhibitory activity of AIT serum on basophil activation was investigated by pre-incubation of basophils with antibodies to block human FcγRII. Whereas one study found that pre-incubation attenuated the inhibitory effect of AIT serum leading to increased basophil activation [45], the other study reported that FcγRII blockade had no effect on the inhibition of IgE-mediated basophil degranulation by AIT serum despite successful inhibition of IgG complex binding [46]. These two studies used different anti-FcγRII antibody clones, although neither was able to discriminate between the activating (FcγRIIa) and inhibitory (FcγRIIb) receptors expressed by human basophils. The direct effects of these antibodies on basophil function, e.g. activation by signaling through FcγRIIa, were not investigated but may have influenced the experimental outcomes. A further single report used two monoclonal antibodies selective for FcγRIIa and FcγRIIb, respectively, to assess the role of these receptors in IgG-mediated inhibition of basophil reactivity [47]. Intriguingly, the authors found
that blocking either FcγRIIa or FcγRIIb attenuated the inhibitory activity of IgG from AIT serum, although as with previous studies, the direct effect of these monoclonal antibodies on basophil activation was not assessed [47].

The potential for interaction of allergen-specific IgG4 and FcγRIIb to result in effective inhibition of FcεRI signaling remains uncertain. Using surface plasmon resonance, Bruhns and colleagues found that IgG4 bound to FcγRIIb with moderate affinity (Kₐ = 2 × 10⁵ M⁻¹) and when IgG4 antibodies were aggregated as F(ab)² complexes, binding to FcγRIIb was detected on cell surfaces [6]. However, human IgG4 does not precipitate antigen and forms only small immune complexes compared to IgG1 [48], likely due to the dynamic process of Fab arm exchange [49]. This may have significant functional consequences for interactions between IgG4 and FcγRIIb, which have yet to be examined experimentally. Furthermore, the potential biological relevance of this pathway must also be considered, since although FcγRIIb is constitutively expressed by basophils, expression on mast cells is variable depending on tissue distribution; while peripheral blood [50], cord-blood derived [51] and synovial mast cells [52] all express FcγRIIb, expression has not been demonstrated on human skin mast cells [53] or intestinal mast cells from most individuals [54]. Therefore, at least in the skin and intestine, the potential relevance of IgG-mediated inhibition of mast cell activation through FcγRIIb pathways must be questioned.

**Conclusions**

IgG4 is closely associated to the production of IgE and therefore has relevance to the study of allergic disease. Absolute levels of IgG4 often fail to correlate with clinical tolerance, although absolute levels of IgE are similarly poorly predictive of disease severity. Nonetheless, the biological activity of IgG4, in particular the potent inhibition of IgE-mediated basophil/mast cell activation and antigen presentation, suggest that this unique subclass is indeed relevant to disease expression. IgG4 has a long association with tolerance to aeroallergens, both in studies of allergen immunotherapy and the so-called modified Th2 response. An accumulating body of literature also supports a potential wider role for IgG4 in oral immunotherapy studies of food allergy [55] and also in natural tolerance to food allergens [56–59]. Experimental approaches need to be developed to address unresolved questions concerning IgG4 biology, such as identification of factors that regulate IgG4 versus IgE responses. Understanding the precise molecular determinants that control the fate of IgG4 versus IgE switching could highlight therapeutic targets for prevention of allergy and promotion of clinical tolerance.

**Compliance with Ethical Standards**

**Conflict of Interest** Drs. Till and James declare no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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