On the role of antibody affinity in the IgE mediated allergic response

Monique Vogel[1], Martin Bachmann[1], Mona O. Mohsen[1], Matthias Kramer[2], Sviatlana Starchenka[3], Piers Whitehead[2], and Matthew Heath[3]

[1]Universitat Bern
[2]Bencard Allergie GmbH
[3]Allergy Therapeutics Plc

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Abstract

Type I hypersensitivity, also known as classical allergy, is mediated via allergen-specific IgE antibodies bound to type I FcR (FcεRI) on the surface of mast cells and basophils upon cross-linking by allergens. This IgE-mediated cellular activation may be blocked by allergen-specific IgG through multiple mechanisms, including direct neutralization of the allergen or engagement of the inhibitory receptor FcγRIIb which blocks IgE signal transduction. In addition, co-engagement of FceRI and FcγRIIb by IgE-IgG-allergen immune-complexes causes down-regulation of receptor bound IgE, resulting in desensitization of the cells. Both, activation of FceRI by allergen-specific IgE and engagement of FcγRIIb by allergen-specific IgG are driven by allergen-binding. Here we delineate the distinct roles of antibody affinity versus avidity in driving these processes and discuss the role of IgG subclasses in inhibiting basophil and mast cell activation.

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Martin F. Bachmann[1,2,3*], Monique Vogel[1,2], Mona O. Mohsen[1,2,6], Matthias F. Kramer[5], Sviatlana Starchenka[4], Piers Whitehead[5] and Matthew D. Heath[4]

[1]Department of Immunology, University Clinic for Rheumatology and Immunology, Inselhospital, Bern, Switzerland;[2]Department of Biomedical Research Bern (DBMR), University of Bern, Bern, Switzerland. [3]Nuffield Department of Medicine, The Jenner Institute, University of Oxford, Oxford, UK; [4]Allergy Therapeutics (UK) Ltd., Worthing, UK; [5]Bencard Allergie GmbH, Munich, Germany;[5]SeromYx Systems, Cambridge, United States.[6]Saiba AG, Bahnhofstr. 13. CH-8808 Pfaeffikon Switzerland.

*Corresponding author: Martin F Bachmann**,** Department of Immunology, University Clinic for Rheumatology and Immunology, Inselhospital, Bern, Switzerland. E-mail: martin.bachmann@dbmr.unibe.ch

Abstract

Type I hypersensitivity, also known as classical allergy, is mediated via allergen-specific IgE antibodies bound to type I FcR (FcεRI) on the surface of mast cells and basophils upon cross-linking by allergens. This IgE-mediated cellular activation may be blocked by allergen-specific IgG through multiple mechanisms, including direct neutralization of the allergen or engagement of the inhibitory receptor FcγRIIb which blocks IgE signal transduction. In addition, co-engagement of FcεRI and FcγRIIb by IgE-IgG-allergen immune-complexes causes down-regulation of receptor bound IgE, resulting in desensitization of the cells. Both, activation of FcεRI by allergen-specific IgE and engagement of FcγRIIb by allergen-specific IgG are driven by allergen-binding. Here we delineate the distinct roles of antibody affinity versus avidity in driving these processes and discuss the role of IgG subclasses in inhibiting basophil and mast cell activation.

KEYWORDS

Allergy, affinity, antibody, IgE, IgG.

1 Introduction

The discovery of IgE-mediated allergic disease as an indication of hay-fever, or allergic rhinitis, was first described in 1819 by John Bostock, a medical doctor who himself suffered from hay fever[1]. He called the disease catarrhus aestivus, summer catarrh, as it was invariably absent in winter time. Catarrhus aestivus was a rare disease in the early nineteenth century, and after reporting his own case, it took him more than nine years to identify another 28 cases for publishing a second article [2]. At the beginning of the 20th century, allergens were considered being toxins [3]. Only with the discovery of IgE antibodies [4,5], it became evident that allergen-specific antibodies are the reason for the aberrant response of the body against pollen.

In clinical practice, there are several possibilities to avoid the activity of IgE and many pharmaceutical interventions aim to prevent IgE production and/or make the immune system more tolerant to allergens by inducing a shift in Th cell responses from Th2 to Th1 or regulatory T cells [6,7]; more recently, the concept of mAbs targeting and blocking IgE directly has been introduced[8]. Alternatively, it may be possible to block the action of IgE indirecty by induction of allergen-specific IgG through passive [9] or active vaccination[10,11]. This approach is supported by the clinical observation that successful specific immunotherapy may correlate with an increase of the IgG/IgE ratio, and more recently, that polyclonal and monoclonal allergen specific IgG antibodies were able to curb allergic immune responses both in mice and humans as a form of passive vaccination [12-14]. Hence, it seems reasonable to conclude that the overarching goal of immunotherapy should be the induction of allergen-specific IgG antibodies.

This raises the question of antibody specificity and quality. Which are the key parameters driving or inhibiting allergic responses? As outlined below, the answer is complex and different for IgE mediated activation by allergen versus IgG mediated neutralization of allergen versus FcγRIIb-mediated inhibition of allergic responses (Figure 1). The same is true for antibody specificity, as rules for IgE-mediated activation versus IgG-mediated blockade or FcγRIIb-mediated inhibition are fundamentally different. Perhaps unexpectedly, the role of IgG subclasses plays only a minor role in inhibiting the allergic response.

2 Low affinity IgE antibodies suffice to drive the allergic responses: avidity provides the key

Antibody affinity, also known as binding affinity and defined by its equilibrium constant, is the strength of the interaction between the antigen-binding site on an antibody and a specific epitope on an antigen (monovalent binding) and can be defined by its equilibrium constant (Figure 2A). Antibody avidity represents the overall strength of the antibody-antigen interactions and is influenced by several factors in particular multivalent binding (Figure 2A). In essence, the greater an immunoglobulin's valency (number of antigen binding sites), the greater it's potential avidity as it can bind multiple epitopes on a single antigen – provided the antigen is multivalent [15].

Most classical physico-chemical analysis is performed in solution, in part to avoid the effects of multivalent binding. Nevertheless, standard antibody binding assays, such as ELISA, surface plasmon resonance and Biolayer Interferometry are performed with antibodies in solution; their ligands are, however, typically bound to two-dimensional surfaces. This opens the possibility of antibodies to bind their ligands with 2 arms, a problem that is typically avoided by complicated coating techniques, including coating at low density to avoid avidity effects (caused by multivalent binding), as affinity (referring to monovalent binding) is much better defined by classical binding models than avidity. However, and a notion often overseen is that most pathogens i) are recognized on 2 dimensional surfaces and ii) are highly polyvalent and therefore prone to bind antibodies in a multivalent fashion. Indeed, natural IgM antibodies bind viral particles with great efficiency due to decavalent binding which makes many antibodies stick like glue even if the binding affinity of an individual variable region is low and barely measurable[16]. Hence, avidity may be more important in the real-life setting. In the case of IgE bound to FcεRI on the surface of effector cells, nature adds one level of complexity: lateral diffusion. While in ELISA plates, ligands are fixed on plastic, IgE molecules bound to FcεRI can rapidly diffuse along the cell surface membrane, a process that is strongly facilitating multivalent,

high-avidity binding of IgE antibodies to allergens (Figure 2B). In this context, it is interesting to note in this context that the restriction of the movement of receptor-bound IgE within the 2 dimensions of the cell membrane results in high local concentrations of the IgE molecules as well as allergens bound to IgE. Indeed, 10'000 molecules bound to the cell surface of regular sized cells may exhibit a local concentration of $>10^{-6}$ M within the membrane[17]. In addition, membrane bound molecules diffuse on the cell surface with a high velocity, allowing to circle around the cell once every second [18]. Hence all these properties foster multivalent binding of single allergens to membrane bound IgE recognizing different epitopes on the allergen. Indeed, we could show that IgE antibodies exhibiting an affinity as low as 10^{-6}M for the allergen Fel d 1, were nevertheless able to bind multivalently to FcεRI bound IgE on mast cells and cause degranulation of the cells [19]. This was not possible if the membrane was brought below the Krafft point, the temperature at which cholesterol in membranes freezes, not allowing for lateral diffusion of molecules (Figure 2C). Thus, lateral diffusion of IgE allows for multivalent binding of allergen, causing high avidity interactions and consequently, low affinity IgE antibodies can trigger cellular activation. This effect may be particularly pronounced for dimeric allergens. Indeed, a case in point is the cat allergen Fel d 1, which is naturally dimeric and causes particularly strong allergies. These data may also explain the often unexpectedly high cross-reactivity between structurally unrelated allergens such as birch allergens and latex.

3 High affinity antibodies are required for allergen-neutralization

The most straight-forward way for IgG antibodies to inhibit activation of basophils and mast cells by allergens is direct neutralization of the allergen in competition with allergen-specific IgE[10,20]. This mechanism, now, corresponds to the above discussed and by physico-chemists preferred interaction of antibodies with ligands; it happens in solution, or at least within tissue fluids and antibodies typically bind with one arm only. Hence, because this epitope-specific interaction is a competitive one, it is largely promoted by high affinity and monovalencys, in contrast to avidity that only plays a minor role. Indeed, low affinity IgG antibodies failed to neutralize allergens and did not block basophil/mast cell activation both *in vitro* as well as *in vivo* [21]. As a further restriction, neutralizing antibodies must recognize the same allergen as the IgE and preferably even the same epitope. This contrasts with interaction mediated via FcγRIIb, as described below. Indeed, low affinity IgG antibodies fail to neutralize the allergen but may efficiently block cellular activation by engaging FcγRIIb.

4 Λοω αφφινιτψ αντιβοδιες συφφιςε το ενγαγε ΦςγPIIβ: αβρογατινγ IγE σιγναλλινγ φορ σινγλε αλλεργενς

Using Fel d 1 as a model antigen, we have shown that low affinity IgG antibodies fail to neutralize the allergen but nevertheless can efficiently block mast cell/basophil activation [21,22]. This unexpected finding was entirely FcγRIIb dependent. Furthermore, the low affinity antibodies must have a different epitope specificity than the IgE, as only in this case, low affinity IgG could block mast cell activation by interaction *with* FcεRI-bound IgE and engagement of the inhibitory FcγRIIb. Again, it is likely that lateral diffusion and avidity stabilization is important in the process, as low affinity IgG may need to rapidly engage with and be stabilized by FcγRIIb for effective inhibition of cellular activation. Thus, in this way, also low affinity IgG antibodies can "poison" IgE-signalling by engaging FcγRIIb. There is an interesting analogy from enzyme kinetics for the two types of inhibition. Allergen neutralization corresponds to competitive inhibition, requiring high affinity ligands for effective competition. In contrast, engagement of FcγRIIb corresponds to con-competitive inhibition, rather independent of high affinity[23].

5 ΦςγPIIβ σηοως ινηιβιτορψ αςτιιτψ αςροσς επιτοπες ανδ αλλεργενς ιν αλλεργεν-μιξτυρες: αβρογατινγ IγE σιγναλλινγ φορ μυλτιπλε αλλεργενς

A key difference between allergen neutralization and engagement of FcγRIIb is the breadth of activities, not only in terms of affinity but also in terms of specificity. As discussed above, neutralization is only possible for a given epitope on a given allergen. Unexpectedly, engagement of FcγRIIb not only blocks activation of IgE antibodies with a different epitope than the IgG exhibits, but is also effective for entirely different allergens as long as the allergen recognized by the IgG antibody is present in the mixture. Specifically, peanut-allergic

local and systemic responses against whole peanut allergen extract could be blocked by immunization against a single allergen, specifically Ara h1 or Ara h2 [13,24]. Even though mice were allergic against multiple peanut allergens, immunization against a single allergen was sufficient to block allergic responses. Furthermore, polyclonal antibodies against Ara h 1 or Ara h2, as well as a mAb against Ara h 2 were able to abrogate allergic responses induced the peanut extract [25], confirming earlier data for allergy against Fel d 1 , an allergy which is, however, mostly driven by a single allergen [26]. This protective effect of Ara h 1 and Ara h 2 antibodies was again strictly dependent on the presence of functional FcγRIIb. In absence of the inhibitory receptor, no reduction in allergic symptoms could be observed. Hence, IgG complexes with a single allergen are able to abrogate IgE-signalling induced by complex allergen mixtures.

6 Role of the IgG subclass

Clinical efficacy of allergen-specific immunotherapy or vaccination best correlates with increased levels of IgG4 over IgG1 in human. Hence, it is generally assumed that IgG4 is the key IgG subclass for clinical outcome. However, as pointed out previously, the correlation between clinical efficacy and IgG4 may simply be due to the fact that the way we are currently performing immunotherapy is preferentially inducing IgG4 rather than other subclasses [27]; mostly due to the absence of strong toll-like receptor or other innate ligands in the formulations. It should be noted that a correlation between clinical outcome and allergen-specific IgG4 has been reported in some but not all studies. IgG4 is not a validated biomarker [28]. Negative results may in part be due to suboptimal designs of conventional immunotherapy. However, more recently, it was demonstrated that IgG1 and IgG4 appeared in mucosal fluids after AIT with genetically modified allergens, an active area of ongoing clinical research[29].

We compared the ability of 3 different mAbs against Fel d 1 expressed in a IgG1 or IgG4 format (exhibiting identical epitope specificities despite expressed as IgG1 and IgG4) for their ability to block primary human basophil activation via allergen-neutralization or engagement of FcγRIIb [27]. Indeed, both antibody subclasses had the same ability to block basophil activation in a quantitative manner. These observations were confirmed when the affinity of the antibodies for recombinant FcγRIIb was assessed by Biolayer Interferometry showing similar affinities for IgG1 and IgG4. Hence, it seems that different IgG subclasses – at least IgG1 and IgG4 – are capable of allergen neutralization and FcγRIIb engagement. It is now planned to further assess the diversity and functionality of antibody profiles in response to a vaccine against peanut allergy which is in clinical development (PROTECT trial; ClinicalTrials.gov Identifier: NCT05476497).

7 TLR7 triggering broadens antibody repertoire and affinity

Despite the above-described ability of low affinity allergen-specific IgG antibodies to block type I hypersensitivity responses, it remains common thinking that high affinity antibodies would be more effective to also neutralize the allergen. In addition, induction of high affinity antibodies continues to be a general and common goal in vaccinology. For that, induction of germinal centres (GC), also known as secondary follicles, is a key goal, as GCs are the anatomical location of hypermutation and antibody affinity maturation. Induction of GCs is driven by antigen deposition on follicular dendritic cells (FDCs) and effective stimulation of B cells. Repetitive display of antigens in general and allergens specifically has been found to induce strong and rapid B cell responses due to effective B cell receptor cross-linking as well as engagement of the innate immune system [30]. Indeed, natural IgM recognizes repetitive epitopes on viruses and virus-like particles (VLPs), causing activation of the classical pathway of complement (C1q), leading to the deposition of these particles on FDCs and to GC-reactions [16]. In addition, VLPs may package RNA from *E. coli* during VLP production, when assembling inside bacteria. This RNA has not only been observed to effectively drive class switching to IgG and IgA, but also to increase the affinity of the induced antibodies as well as to facilitate maintenance of a broad immunoglobulin repertoire against both VLPs as well as displayed allergens [31]. Furthermore, in a preclinical model of peanut-allergy, presence of RNA in VLPs displaying Ara h 2 proved essential for induction of protective IgG responses against peanut allergy. Hence, repetitive display of allergens on VLPs packaged with RNA appears an attractive way to increase induction and maintenance of high affinity antibodies (Figure 3). In studies on VLPs with Fel d 1 and peanut allergens, a substantially reduced interaction with IgE bound to mast cells has been shown and a failure to significantly activate the

FcεRI mediated signalling cascade. Hence, under conditions where similar or higher amounts of allergen were bound to IgE on mast cells, free allergen induced strong cellular activation while allergens on VLPs failed to do so [13,14]. Together, it was therefore an attractive choice to bring Ara h 2 displayed on VLPs (VLP-peanut) into clinical development [24].

8 Conclusions

The affinity as well as the avidity of IgE-allergen interactions play critical roles for activation of effector cells and allergic reactions. It is well accepted that specific allergen-binding of antibodies is required for cellular activation. However, the low affinity of IgE binding to FcεR on the cell surface can be compensated for by bivalent, high avidity binding to multiple epitopes on allergens. This appears to be the mechanism responsible for the often not expected allergen cross-reactivity which may be driven by low affinity but high avidity interactions. Similarly, IgG antibodies with low affinity for the allergen were also sufficient to inhibit mast cell activation by engaging the inhibitory FcγRIIb. Furthermore, polyclonal and monoclonal antibodies specific for a single allergen were able to block allergic symptoms mediated by whole allergen extract. This effect was also mediated by FcγRIIb and was rather independent of the affinity of the antibodies for the allergen as low affinity antibodies were also effective. Interestingly, comparison of two different IgG subclasses, IgG1 and IgG4 showed the same capacity to block mast cell activation and to bind to FcγRIIb, suggesting similar clinical efficacy for both antibody subclasses. Finally, even if FcγRIIb-mediated inhibition can be triggered by low affinity IgG antibodies, allergen neutralization still requires high affinity antibodies which are generated in the germinal centres. The generation of such antibody responses has been shown to be optimized by repetitive display and TLR signalling in B cells which can be triggered by immunization with virus-like particles packaged with RNA and displaying antigens in a repetitive fashion.

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Author contributions

M.F. Bachmann, M.O. Mohsen, M.F. Kramer, S. Starchenka, M. Vogel, P. Whitehead, M.D. Heaths wrote, revised and approved this manuscript.

Competing Interests

M.F. Bachmann, M.O. Mohsen, M. F. Kramer, S. Starchenka, M.D. Heath are involved in the development of allergen-specific immunotherapies within Allergy Therapeutic LTD and Saiba AG.

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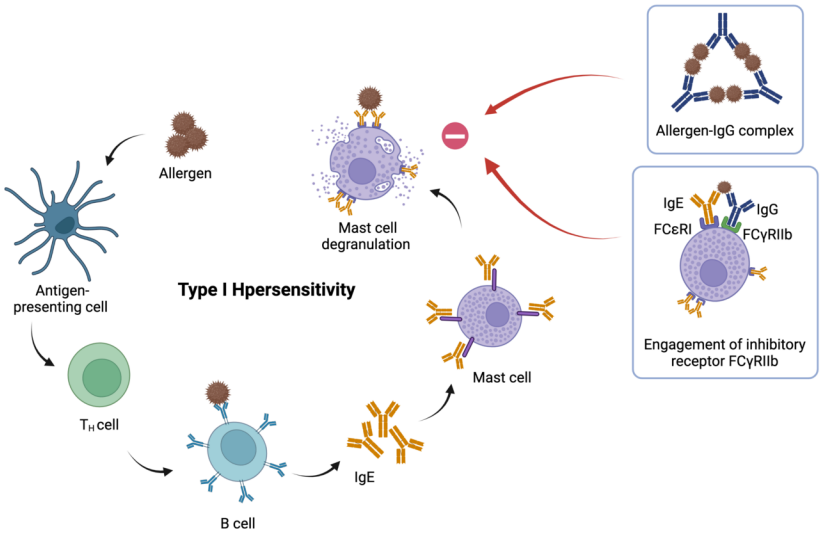

FIGURE 1. Model illustrating the impact of IgG antibodies on Type I hypersensitivity . Allergens are taken up by antigen presenting cell which present processed antigen to T_H cells. T_H cells help B cells to produce IgE which binds to FcεRI on the surface of mast cell and sensitize them. Subsequent production of allergen-specific IgG antibodies which neutralizes allergens and/or engage the inhibitory receptor FcγRIIb.

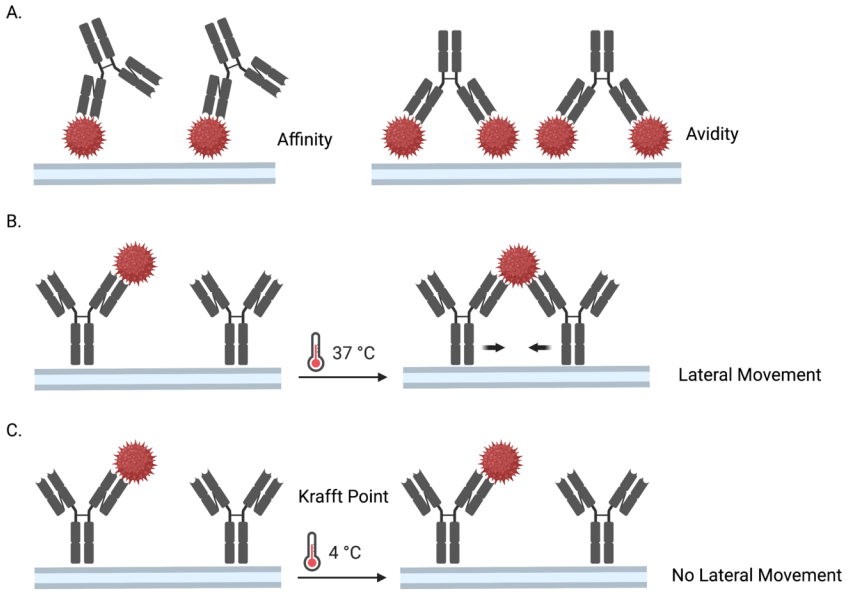

FIGURE 2. Strength of interaction between antibody and antigen. A) Difference between antibody affinity and avidity. B-C) Lateral movement at 37°C facilitating multivalent and high-avidity binding of IgE antibodies to allergens, while temperatures below the Krafft point at (e.g. 4°C) inhibits lateral movement and multivalent binding.

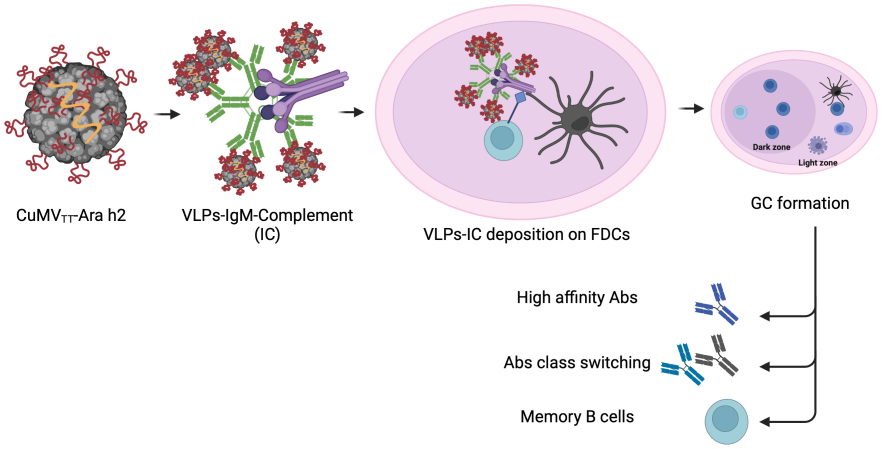

FIGURE 3. A cartoon illustrating a VLP nanoparticle-based vaccine against peanut allergy. The nanoparticles are packed with ssRNA, a TLR7/8 ligand, and display Ara h2 antigen. The natural pentameric IgM antibody can bind the VLPs with low affinity/high avidity. Such interaction contributes to the activation of classical complement cascade and binding of the formed immune-complex on FDCs for effective formation of GCs. This vaccine may induce high-affinity antibodies, drive antibody class-switching and establish long-lived memory. Abs; antibodies.