

Is IgE-mediated hypersensitivity an autoimmune disease?

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Introduction

It is now well established that IgE plays a key role in the complex interaction between humoral and cellular components of the hypersensitivity response in allergy. A pre-requisite to such a role is the binding of IgE to high-affinity Fc-receptors (Fc_εR) on mast cells and basophils and the subsequent cross-linking of receptor-bound IgE molecules with the allergen (antigen). Cross-linking of membrane-bound IgE antibodies can also be effected *in vitro* with allergen, concanavalin A (binds to the carbohydrate moieties of IgE) and heterologous anti-IgE antiserum. The pharmacokinetics and dynamics of mediator production by anti-IgE or its F(ab')₂ fragment are relatively comparable to release induced by allergen (for review see 17). Particularly striking is the overlap between the concentrations of antigen (1-3 µg/ml) and anti-IgE (3 µg/ml) required for optimum release of histamine from human basophils. Cross-linking of mast cell- and basophil-bound IgE by a specific ligand (allergen or anti-IgE) initiates a chain of events culminating in mediator release. These include activation of proteolytic enzymes, rise in cAMP concentration, increased phospholipid metabolism, mobilisation and influx of calcium ions, generation of arachidonic acid metabolites and protein phosphorylation. Anti-IgE antisera have, therefore, been extensively utilised in elucidating the mechanism of IgE-dependent mediator release from basophils

and mast cells. Injection of anti-IgE antibody into human skin produces a mast cell-dependent weal and flare response followed by a late-phase response mediated by eosinophils and neutrophils. That these inflammatory cells are activated (i.e. show enhanced receptor expression and effector function) by histamine and leukotrienes (LTB₄) liberated by an IgE-dependent mechanism has been clearly demonstrated using an *in vitro* system in which basophils were challenged with anti-IgE and changes in the activity of bystander eosinophils and neutrophils were recorded (17).

It is, therefore, not surprising that there has recently been a surge of interest in elucidating the pathophysiological role of autoantibodies to IgE (for a thorough review see 22). The demonstration of these autoantibodies in the sera of allergic patients raises some very important questions, the most critical of which is whether IgE-mediated hypersensitivity can be caused by autoimmunity. The purpose of this contribution is to bring into focus the biological significance of circulating autoanti-IgE antiglobulins and their clinical implications. Data from experimental animal models will also be incorporated where appropriate.

Antigenic specificity

Human autoantibodies to IgE have been detected in all major immunoglobulin classes. In

terms of specificity, at least two distinct populations of anti-IgE antibodies can be recognised (12, 15).

Antibodies in the first group react with non- ϵ -chain-specific epitopes found on individual IgE myeloma proteins. These are low-affinity antiglobulins belonging to IgM, IgG and IgA, and are thought to be directed against carbohydrate-associated epitopes. The ϵ -chain oligosaccharide specificity of these antibodies is further exemplified by the finding of this antibody activity in IgG2 (28), a subclass normally elicited by polysaccharide antigens. Their heat-resistant (30 min at 56°C) determinants are found on the pepsin F(ab')₂ piece and not on the papain Fab_c or Fc_c fragments. However, unlike the so-called "pepsin agglutinators", these antiglobulins are also reactive with intact IgE. It is doubtful whether these autoantibodies are biologically important, therefore they will not be discussed any further.

Autoanti-IgE antibodies in the second group mainly belong to the IgG isotype and are directed against heat-labile determinants in the D_c2 region. These are high-affinity antibodies reactive with both recombinant Fc_c* (i.e. lacking carbohydrate groups) and papain-produced Fc_c. The high binding affinity of IgG anti-IgE is demonstrated by its potent biological activity, which will be discussed shortly. Similar IgG autoanti-IgE antibodies have been deliberately induced in rodents (2) and, as we shall see later, these animals are proving to be invaluable experimental models for studying the *in vivo* effects of anti-IgE autoantibody.

There have so far been no studies concerning the nature of the stimulus for anti-IgE production in allergic individuals but a conformationally altered (i.e. immune complexed) IgE is the most likely trigger. Thus, for instance, IgG anti-IgE autoantibody is found in high titre mostly in individuals with exaggerated IgE response to environmental allergens (i.e. atopics) and in patients undergoing allergen-specific desensitization. In both of these situations large amounts of allergen-IgE complexes are generated, and recent molecular studies have reinforced the traditional view that anti-IgG antiglobulins (known collectively as rheumatoid

factors or RF) are stimulated by an antigen-driven (i.e. IgG complexed to antigen) mechanism (26).

Prevalence

For obvious reasons most studies of the distribution of IgG anti-IgE antibodies, measured by enzyme linked immunosorbent assay (ELISA), have so far focused on conditions characterised by excessive IgE production (for review see 9, 14). For instance, IgG anti-IgE was detectable in the sera of 95.5% of patients with atopic asthma, 72.2% of those with non-atopic (so-called 'intrinsic') asthma and 86.7% of patients with atopic dermatitis (or atopic eczema). In all these conditions there were particularly good correlations between IgG anti-IgE titres and total IgE levels. Other conditions with high prevalence of IgG anti-IgE include parasitic infestations (e.g. paragonimus and hookworm), hyper IgE syndrome, allergic rhinitis and urticaria (with or without vasculitis), rheumatoid arthritis (RA), food-induced arthralgia and systemic lupus erythematosus (SLE).

Gruber (9) detected IgG anti IgE in 34% of a group of 67 patients with SLE, and in a similar proportion of those with RA. One of the remarkable features of these studies was the close correlation between the presence of this autoantibody and the development of vasculitis lesions in SLE and RA. Vascular lesions are thought to play a central role in the pathogenesis of rheumatoid synovitis and subcutaneous nodules. These findings are particularly significant in view of the tendency of IgG anti-IgE to form complexes with IgE (see below).

Before we go on to discuss the biological role of IgG anti-IgE, it is important to reflect on its prevalence within the four IgG subclasses, since these exhibit considerable variation in their molecular structure and effector functions (23). The general consensus (14, 27) is that IgG anti-IgE antibody activity is found in IgG₁, IgG₃ and IgG₄, but not in IgG₂; with IgG₄ displaying a disproportionately high percentage of the autoantibody activity. However, this is not a unique situation since most protein anti-

gens elicit antibody responses in IgG₁ and IgG₃ with a subsequent shift to IgG₄ (i.e. upon chronic antigenic stimulation). IgG₂, on the other hand, is most prominent in antibody responses to polysaccharide antigens (23).

Interference in antibody assays

The demonstration that IgG anti-IgE is detectable in a very large proportion of allergic patients' sera (9, 14, 27) raises an important, if not a worrying, question concerning the possible effect of anti-IgE on IgE assays. Most *in vitro* assays for total and allergen-specific IgE rely on the use of a heterologous anti-IgE reagent for detection. The co-existence in the reaction mixture of an endogenous autoanti-IgE antibody of similar specificity would provide unexpected competition for the binding sites on IgE, and those already occupied by autoanti-IgE would no longer be accessible (Fig. 1). These concerns have now been justified by Paganelli et al. (19) who investigated the ability of an affinity purified IgG anti-IgE preparation to inhibit IgE recognition by heterologous anti-IgE antibody in two widely used methods – paper radioimmunosorbent test (PRIST) for total IgE and radioallergosorbent test (RAST) for specific IgE. The addition of IgG anti-IgE autoantibody to the PRIST system (at IgE : anti-IgE ratio of 1:1 to 1:100) has drastically influ-

enced the diagnostic value of this assay by producing falsely low (i.e. 10–90 % reduction) total IgE levels. However, no such reduction in total IgE values were seen at higher IgE : anti-IgE ratios (i.e. 1:1 to 12:1). In the RAST system, the addition of autoanti-IgE had little influence on sera with high dust mite-specific IgE (i.e. RAST class 3 or 4), but its inhibitory effect was most noticeable on sera containing moderate amounts of specific IgE (i.e. RAST class 2 or 1). It is, therefore, very tempting to speculate that the apparent failure of laboratory procedures to confirm a seemingly IgE-mediated allergic disorder (e.g. idiopathic asthma) is a direct result of the type of interference discussed above. Efforts are now being made to address this problem and the adoption of alternative IgE assays and new monoclonal anti-IgE production strategies are to be anticipated.

Most sera obtained from allergic patients, particularly those who have been desensitized or who are undergoing such immunotherapy, have large amounts of both IgE and IgG antibodies to the same allergen(s). The simultaneous presence of IgG anti-IgE autoantibody in these sera will no doubt pose serious problems for allergen-specific IgG measurements too. Thus, the secondary antibody employed for IgG detection will react with both allergen-specific IgG and IgG directed against IgE; the latter becomes immobilised on the solid-phase by reacting with allergen specific IgE (Fig. 2).

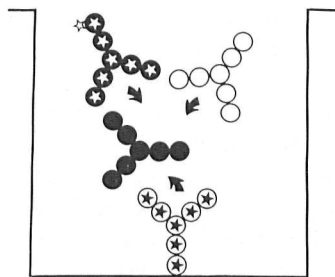


Fig. 1. Interference of IgG anti-IgE autoantibody with IgE measurement in a typical sandwich technique. Serum IgE (●) is first captured by a solid phase-bound heterologous anti-IgE (⊗) and the sandwich is completed by adding a labelled second heterologous anti-IgE (⊗*). A smaller proportion of the labelled anti-IgE will bind to IgE in the presence of IgG anti-IgE autoantibody (○).

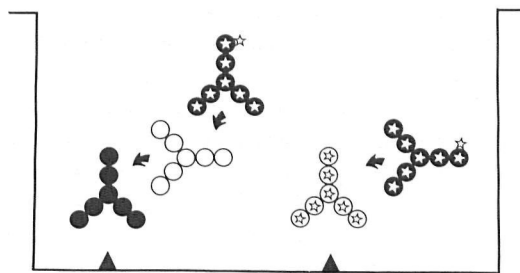


Fig. 2. Interference of IgG anti-IgE autoantibody with allergen-specific IgG measurement. The allergen (▲)-coated solid phase will bind allergen-specific IgG (⊗) from serum, which is then detected by a labelled anti-IgG (⊗*). The labelled anti-IgG will also react with IgG anti-IgE autoantibody (○) bound to solid phase-captured allergen-specific IgE (●).

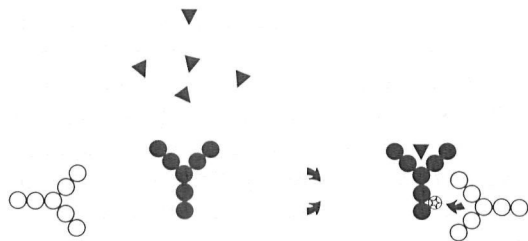


Fig. 3. Allergen-induced conformational changes in the IgE molecule. The binding of allergen ($\blacktriangle$) to IgE ($\bullet$) will allosterically reveal the IgG anti-IgE autoantibody ($\circ$) reactive site ($\odot$).

Unlike its effect on IgE RAST and PRIST, IgG anti-IgE autoantibody produces falsely high allergen-specific IgG values.

Biological effects

Immune complex formation. As would be anticipated a proportion of IgG anti-IgE would become bound to IgE and circulate as an immune complex, therefore escaping detection by anti-IgE antibody assays. The presence of these complexes in atopic patients was originally suspected when heating sera at 56°C for 30 min resulted in a striking increase in the IgG anti-IgE titre (11). This effect was interpreted to be due to disruption of the heat-labile D_e2 antigenic site and the consequent detachment of the IgG anti-IgE molecule. Since then the presence of such complexes in the sera of atopic, parasitic and hyper-IgE syndrome cases has been confirmed using a range of chromatographic procedures (18). The gel-filtration profile of the IgG anti-IgE activity found in atopic patients' sera revealed a single peak corresponding to 600 kDa, whereas the IgE protein was detectable in two peaks, a major peak of monomeric IgE and a minor peak of IgE (about 5% of total) complexed to anti-IgE. The proportion of IgG anti-IgE circulating in immune complex form will no doubt depend on its affinity and the relative concentration of IgE, but as we have just seen, values as high as 100% can occur. IgE-IgG anti-IgE complexes may also contain exogenous antigens bound to the Fab arms of IgE, particularly in atopic patients with food-specific IgE.

Such food antigens may indeed encourage the formation of large antiglobulin-containing complexes by inducing conformational changes in the IgE molecule, rendering the autoantigenic site more accessible. In other words, prior occupancy of the Fab portions of IgE by the antigen might allosterically reveal the anti-IgE reactive site on the Fc_e (Fig. 3). This suggestion, although speculative at the moment, would have important pathological implications, and we are currently pursuing this problem experimentally.

Circulating IgG anti-IgE antibody may have an important physiological function in atopic individuals in whom the exaggerated IgE response to environmental allergens puts the body under a heavy burden of potentially pathogenic immune complexes. Clearance of immune complexes from the blood is a direct function of their molecular size and lattice formation as well as their ability to activate complement and bind to Fc-receptors on monocytes. IgE is neither complement fixing nor has high-affinity Fc-receptors on phagocytic cells, therefore allergen-IgE complexes cannot be removed by the mononuclear phagocyte system or by the CR1 receptors on platelets. The interaction of IgG anti-IgE with allergen-IgE complexes would, therefore, not only increase the size of the complexes but also endows them with effector function triggering sites (i.e. Fc_e). It has been shown in an experimental model that the presence of RF has a differential effect on the clearance kinetics and organ localisation of passively transferred or *in vivo* formed IgG-antigen complexes (7). Immune complexes formed in antibody-excess or slight antigen-excess were cleared rapidly from the blood to the liver and spleen, and RF significantly enhanced removal from the blood and uptake by the liver. RF have, therefore, a protective effect and their formation in healthy individuals is probably a physiological component of the secondary immune response. It remains to be seen experimentally whether IgG anti-IgE has a similar beneficial effect on the clearance of IgE-containing immune complexes.

Mast cell and basophil activation. The potential pathological importance of circulating autoanti-

IgE antibody, which is the theme of this review, stems from the well documented *in vivo* and *in vitro* effects of heterologous anti-IgE on mast cells and basophils, and the consequent release of inflammatory mediators (see Introduction). The pressing question here, therefore, is whether mast cells and basophils can be activated by autoanti-IgE too.

Cutaneous mast cell reactivity to isolated IgG anti-IgE autoantibody preparations from atopic (14) and SLE (9) patients has been convincingly shown by the demonstration of weal and flare responses at the injection sites. A similar immediate skin response was observed in a rodent model using purified, deliberately induced IgG autoanti-IgE (but not control IgG) (2). Histological examination of the injection sites revealed evidence of connective tissue mast cell degranulation. An autoanti-IgE-containing serum incubated with leukocytes of healthy individuals produced modest histamine release (8–30%) from 5 out of 22 cases tested. The histamine releasability was due to IgG anti-IgE, since absorption of the serum with IgE- or anti-IgG-coupled Sepharose abolished the activity (9). However, as we have just seen from the low incidence (5/22) of positive histamine release, basophil activation by affinity purified IgG anti-IgE isolated from rheumatoid (9) and atopic (12) patients' sera is by no means always successful. Failures may possibly be attributed to the fact that IgG anti-IgE is often IgG₄ (14, 27),

a subclass thought to be functionally monovalent (1) and, therefore, incapable of cross-linking. However, in a situation like this, it should still be possible for IgE to be cross-linked by a second antibody directed against or reactive with IgG₄. There is a precedent for this possibility in that some individuals whose leukocytes do not release histamine when challenged with mouse monoclonal anti-IgE, will do so after subsequent addition of a goat anti-mouse IgG (8). That a similar situation can arise *in vivo* is inferred (24) from experiments (25) in which RF and RF-like (i.e. isolated from atopic patients) IgM anti-IgG preparations were shown to be capable of inducing significant (10–74.1%) histamine release from leukocytes of atopic (asthma and eczema) patients *in vitro*. In retrospect, these positive releases were most likely due to multivalent cross-linking of cell bound IgE through IgG anti-IgE (24) (Fig. 4). The *in vivo* implications of these observations are extremely significant particularly in the pathogenesis of atopic and rheumatoid disorders where both anti-IgE and anti-IgG (RF) antiglobulins are frequently present together (9, 25).

It is highly relevant in this connection that anti-IgG RF activity has also been demonstrated in the IgE class in rheumatoid patients' sera (16–90% prevalence rate) and joint fluids (i.e. locally synthesized) (9). The binding of such IgE anti-IgG antibody molecules to Fc_εR on basophils and synovial tissue mast cells and their subsequent interaction with antigen (i.e. self IgG) will result in the release of inflammatory mediators (Fig. 5). One pathological con-

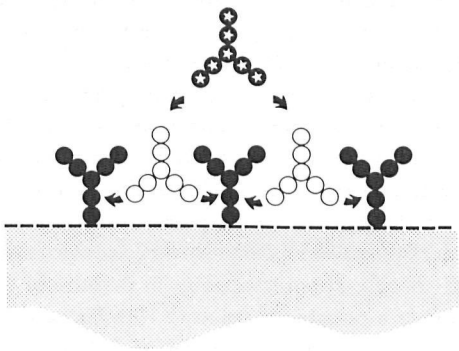


Fig. 4. Multivalent cross-linking of mast cell- and basophil-bound IgE through IgG anti-IgE autoantibody. The process of cross-linking of cell-bound IgE (●) by IgG anti-IgE autoantibody (○) is enhanced when the IgG molecules themselves become cross-linked by rheumatoid factor (⊙).

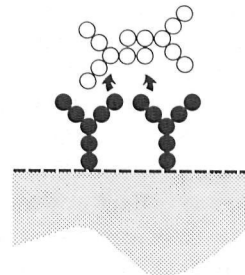


Fig. 5. Activation of mast cells and basophils by self-associated IgG. Cell-bound IgE anti-IgG molecules (●) are cross-linked by aggregated IgG (○).

sequence of this activation process happening in the circulation is enhanced vascular permeability and deposition of antiglobulin-containing immune complexes at tissue sites. That this mechanism of vascular injury is important in the development of synovitis and subcutaneous nodules is underlined by the finding that IgE RF are particularly prevalent in RA patients with vasculitis and other extra-articular manifestations (9). Furthermore, in a series of six experiments passive sensitization of isolated synovial tissue mast cells with serum containing IgE RF followed by exposure to aggregated human γ -globulin resulted in histamine release (9). The specificity of the histamine release process was ascertained by showing that IgE depletion of the sensitizing serum by absorption with Sepharose-coupled anti-IgE abrogated its activity.

Studies with a rat model are beginning to throw some light on the *in vivo* effect of chronic exposure of mast cells to anti-IgE autoantibodies (2). For instance, deliberate autoanti-IgE induction, by immunization with alum-precipitated myeloma IgE, decreased the number of safranin-staining connective tissue mast cells in the tongue and skin by 50 %. The decrease in the number of mast cells could have been the result of chronic degranulation and/or lysis (i.e. cytotoxicity); the latter mechanism is particularly likely with a complement-fixing IgG anti-IgE subclass. It is interesting in this connection that the local injection of purified autoanti-IgE 24 h prior to passive sensitization of the same skin site with IgE anti-ovalbumin has partially suppressed the cutaneous anaphylactic response to intravenous ovalbumin administration (2). This was interpreted as being due to mast cell granule depletion following degranulation with autoanti-IgE.

Perhaps one of the most remarkable biological effects of anti-IgE autoantibody recorded so far is the accelerated elimination of the nematode *N. brasiliensis* from the rat intestine (initially transmitted by s-c injection of larvae) (2). Thus, by day 6 following a secondary worm infection more than 95 % of the worms had disappeared from auto-anti-IgE producing rats whereas 40 % of the infecting dose remained in control rats. It is tempting to attribute this effect to an autoanti-IgE triggered mast cell degranulation, mediator

secretion and release of toxic granules from eosinophils (2). Eosinophils have low-affinity Fc-receptors for IgE (Fc_εR_{II}) and can be activated either by autoanti-IgE (i.e. through surface bound IgE) or by mast cell secretion products (e.g. PAF and LTB₄).

Admittedly, the above studies were mainly designed to explore the triggering effect of autoanti-IgE on mast cells and basophils. It remains to be seen whether such triggering action is a property of all IgG anti-IgE autoantibodies. For instance, it is not inconceivable that some populations of IgG anti-IgE, depending on their subclass nature and epitope location within the Fc_ε, would interfere with the binding of IgE to its Fc_εR on mast cells and basophils. This has already been demonstrated in the case of IgE binding to Fc_εR_{II} on human B-cells (see further below).

Interaction with Fc_εR_{II}-bearing cells. In recent years heterologous anti-IgE reagents have been employed to show low-affinity IgE receptors (Fc_εR_{II}) on a variety of cells including B-cells, T-cells, macrophages, eosinophils, platelets, neutrophils and skin dendritic (Langerhans') cells (5). These cells are known to participate in inflammatory responses and the Fc_εR_{II} could be a target for the activation mechanism. For instance, macrophages treated *in vitro* with goat IgG anti-IgE or its F(ab')₂ fragment released β -glucuronidase (20) and were shown to become cytotoxic for schistosomula (4, 13). If autoanti-IgE activates macrophages and eosinophils by a similar mechanism *in vivo*, IgG anti-IgE autoantibody, could play a significant part in the host defence against invasion.

Apart from the cross-linking effect, anti-IgE autoantibody could quite possibly block IgE binding to a variety of molecules, including Fc_εR_{II} and regulatory IgE-binding factors. The demonstration that complexes containing human IgE and mouse anti-IgE could activate IgE-specific suppressor T-cells in human (10), point to a possible regulatory role for auto-anti-IgE in the feedback control of IgE synthesis. Thus, purified IgG anti-IgE autoantibody (but not control IgG) was shown to significantly inhibit IgE binding to the cultured human B-cell line, RPMI-8866, and to reduce, in a dose-

dependent manner, the interleukin-4 (B-cell growth factor) - induced expression of Fc ϵ RII (CD23) on peripheral B-lymphocytes (14). These are interesting observations and further work in this area will no doubt provide more insights into the intricate relationship between autoanti-IgE and IgE production.

Exploration of this area of enquiry has already started by Bell and colleagues using an experimental model system (2). The *in vivo* effects of autoanti-IgE induction were investigated in two rat strains - a conventional PVG. RT1^u strain and a high IgE-producing BN strain. In the PVG. RT1^u strain, autoanti-IgE induction was accompanied by a significant decline in total serum IgE level. This effect was not due to peripheral neutralization of IgE by anti-IgE and the subsequent enhanced removal of complexes, since the half-life of an injected radiolabelled IgE was the same in anti-IgE producing and control rats. Immunofluorescence studies of Fc ϵ RII positive B-cells in mesenteric lymph nodes have also shown a reduction from about 4 to 2% by anti-IgE induction. Furthermore, the pre-induction of autoanti-IgE in rats produced a significant reduction in ovalbumin-specific IgE synthesis in both low and high IgE-producing strains (16). The reduction was IgE-specific because the IgG anti-ovalbumin response remained intact. Autoanti-IgE production had no effect, however, on ongoing IgE antibody response to ovalbumin. Earlier reports have shown that neonatal injections of heterologous anti-IgE suppress serum IgE levels in mice and rats (3, 6), and rats treated in this way fail to mount specific IgE responses following challenge with castor bean allergen (3) and ovalbumin (6). It would, therefore, be particularly interesting to find out if these effects can also be produced by placentally transferred IgG anti-IgE, since studies of this sort might offer new therapeutic strategies for neonates at risk of developing allergic disease.

Concluding remarks

Under conditions which are neither complement-fixing nor cytotoxic antibodies can stimu-

late cells to perform their normal functions. The best *in vitro* examples of such stimulatory effect are mast cell and basophil mediator release by anti-IgE, B-lymphocyte activation by antibody to immunoglobulins, T-lymphocyte transformation by monoclonal antibody to the CD3 antigen, and the induction of pinocytosis by anti-macrophage serum. There is no reason to believe that cell activation, as opposed to cell lysis, can not be effected by an autoantibody of appropriate specificity. In fact this mechanism is well documented in patients with autoimmune thyrotoxicosis (Graves disease) where an IgG autoantibody directed against a thyroid cell surface antigen stimulates thyroxine secretion. Excessive thyroxine production in this so-called "stimulatory hypersensitivity" (21) is likely to be caused by the binding of the autoantibody to the receptor for thyroid stimulatory hormone and the induction of membrane changes necessary for adenyl cyclase activation.

Several types of immunologically active cells bear IgE receptors and as such they are potential targets for IgG anti-IgE autoantibody. From a clinical point of view the most important of these cells are mast cells and basophils, which are the key cellular components of the IgE-mediated hypersensitivity events. IgG anti-IgE mimics the allergen by utilising a standard reaginic pathway (i.e. mediated by membrane-bound IgE) to trigger the release of pharmacologically active mediators from mast cells and basophils. This is clearly a novel anaphylactic mechanism and it remains to be seen to what extent such autoimmunity contributes to the development of allergic symptoms. At the mechanistic level, however, it would seem possible that the IgG anti-IgE acts in concert with the allergen. That is to say, the binding of IgG anti-IgE to the Fc ϵ -autoreactive site may require the prior engagement of the IgE Fab arms with the allergen. Such conformationally induced unveiling of the Fc ϵ -autoantigenic region and its consequent receptivity to anti-IgE is not an unreasonable proposition particularly if we consider that the same mechanism may have led to the formation of IgG anti-IgE in the first place. Thus, the binding of the allergen to IgE serves as a molecular switch for autoanti-IgE, turning

on both its production and action. IgG anti-IgE may, therefore, have a synergistic effect on IgE cross-linking by the allergen by simply making the process a lot more efficient. In this case, however, unlike the classical allergen-triggered cell activation, the allergen need not cross-link IgE molecules (i.e. a monovalent allergen will suffice). Therefore, by parting with the requirement that the allergen must be at least divalent, IgG anti-IgE enables a fragment of the allergen (e.g. a digestion product comprising a single epitope) and small organic molecules taken as medicament to trigger IgE-mediated reactions. Fc ϵ RII-bearing cells like eosinophils and neutrophils, which are important in late-phase allergic complications may similarly be activated by this alleged co-operative interaction between antigen (of parasitic origin for example), IgE and IgG anti-IgE. Thus, only cells that come in contact with the antigen are activated by IgG anti-IgE.

Although these suggestions are purely speculative, they provide an interesting framework within which the question of the interplay between IgE, allergen and IgG anti-IgE can be addressed experimentally.

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