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REVIEW

The anti-IgE/anti-FcεRIα autoantibody network in allergic and autoimmune diseases

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Summary

Basophil granulocytes and tissue mast cells and their mediators play a role in the pathogenesis of several immune and inflammatory disorders. Human basophils and mast cells (FcεRI$^+$ cells) can be activated through immunological interaction with the IgE-FcεRI network. FcεRI$^+$ cells can be triggered by cross-linking between the Fab portions of IgE and multivalent antigens (direct anaphylaxis). 'Reverse type' anaphylaxis can occur through three distinct mechanisms: antibodies against the Fcε portion of IgE (anti-IgE), antibodies against epitopes of the α chain of FcεRI (anti-FcεRIα) and anti-IgG acting on IgG–IgE complexes bound to FcεRI. Anti-IgE autoantibodies are occasionally present even in normal donors and more frequently in a variety of allergic (chronic urticaria, atopic dermatitis and bronchial asthma) and autoimmune disorders (rheumatoid arthritis, lupus erythematosus and systemic sclerosis). IgG anti-IgE from a small percentage of patients induces the release of mediators from human FcεRI$^+$ cells. Some of the anti-IgE autoantibodies present in allergic patients are non-anaphylactogenic, thus representing a possible protective mechanism preventing the association of IgE with FcεRI. Anti-FcεRIα autoantibodies also occur in a significant percentage of patients of chronic urticaria and probably non-allergic asthma and some autoimmune diseases. Although anti-IgE and anti-FcεRIα autoantibodies, present in a percentage of patients with immune disorders, are relevant to the pathogenesis of these conditions, much remains to be learnt about their immunochemistry, their prevalence and precise role in various inflammatory diseases.

Introduction

In 1966 Ishizaka *et al*. opened a new era in the pathophysiology of immunological disorders when they identified and purified IgE from the serum of allergic patients [1]. It became evident immediately that human IgE molecules, unlike other immunoglobulin classes, bind specifically and with very high affinity ($K_a \approx 10^9$ M^{-1}) to receptors (FcεRI) on the surface of human basophils and mast cells [2]. IgE cross-linking on FcεRI$^+$ cells by specific antigens results in the release of a variety of preformed (e.g. histamine, etc.) and *de novo* synthesized chemical mediators (e.g. peptide leukotrienes, prostaglandins, etc.) [3–5], and cytokines [6–9] that exert their effects by interacting with specific receptors on target organs [10,11]. Receptors of lower affinity ($K_a \approx 10^7$ M^{-1}) for IgE (FcεRII/CD23) have been found on human B lymphocytes and monocytes [12], and on platelets [13], and eosinophils [14]. More recently, it has been demonstrated that Langerhan's cells [15,16], dermal dendritic cells [16,17], peripheral blood monocytes of atopic patients [18] and eosinophils [19] express FcεRI and that this structure functions as an IgE binding moiety and can mediate IgE-dependent allergen presentation [20]. Recent evidence suggests the existence of two isoforms of human FcεRI. The tetrameric complex ($\alpha\beta\gamma_2$) exists on human basophils and mast cells, whereas the trimeric complex ($\alpha\gamma_2$) is present on human monocytes, dendritic cells and Langerhan's cells [21].

Human basophils and mast cells can be triggered by cross-linking of IgE interacting with multivalent antigens (direct anaphylaxis) [22] or by a 'reverse type' anaphylactic reaction [23]. The latter mechanism could involve

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antibodies directed against the Fcε chain of IgE (anti-IgE) [23], antibodies against epitopes of α chain of FcεRI (anti-FcεRIα) [24] or anti-IgG acting on IgG–IgE complexes bound to FcεRI [25]. Figure 1 illustrates schematically four possible mechanisms of activation of human basophils and mast cells by cross-linking the IgE-FcεRI network.

There is compelling evidence that activation of human FcεRI$^+$ cells through cell-bound IgE is central to the pathogenesis of allergic diseases [26]. Several observations have extended the possible role of the IgE antibody system. High serum IgE levels have been found not only in patients with allergic diseases [27,28], but also in patients with hyper-IgE syndrome (Buckley's syndrome) [29], in patients infected by parasites [30], in some patients with immune deficiencies of the T-cell system [31,32], Hodgkin's disease [33], AIDS [34–36] and bone marrow-transplanted patients during the acute phase of graft vs host disease (GVHD) [37]. Finally, basophils and mast cells probably participate in the pathogenesis of such immune disorders of connective tissues as rheumatoid arthritis [38–40], systemic sclerosis [41,42] and systemic lupus erythematosus [43]. FcεRI$^+$ cells are found in delayed-type immune reactions in the lung [44,45], in the skin [46,47], in inflammatory reactions to tumours [48,49] and GVHD [50].

These observations suggest that the IgE–FcεRI network and FcεRI$^+$ cells might participate in a variety of immune reactions associated not only with allergic disorders, but also with immune deficiencies, tumour growth and autoimmune diseases. It is therefore possible that IgE might be the effector molecule not only through the classical interaction of the Fab portion with allergens, but also through alternative site(s) on the IgE molecule.

Anti-IgE autoantibodies in allergic disorders

Six years after the identification of IgE, Williams *et al.* reported the occurrence of anti-IgE antibodies of the IgM class in sera obtained from various groups of patients, the

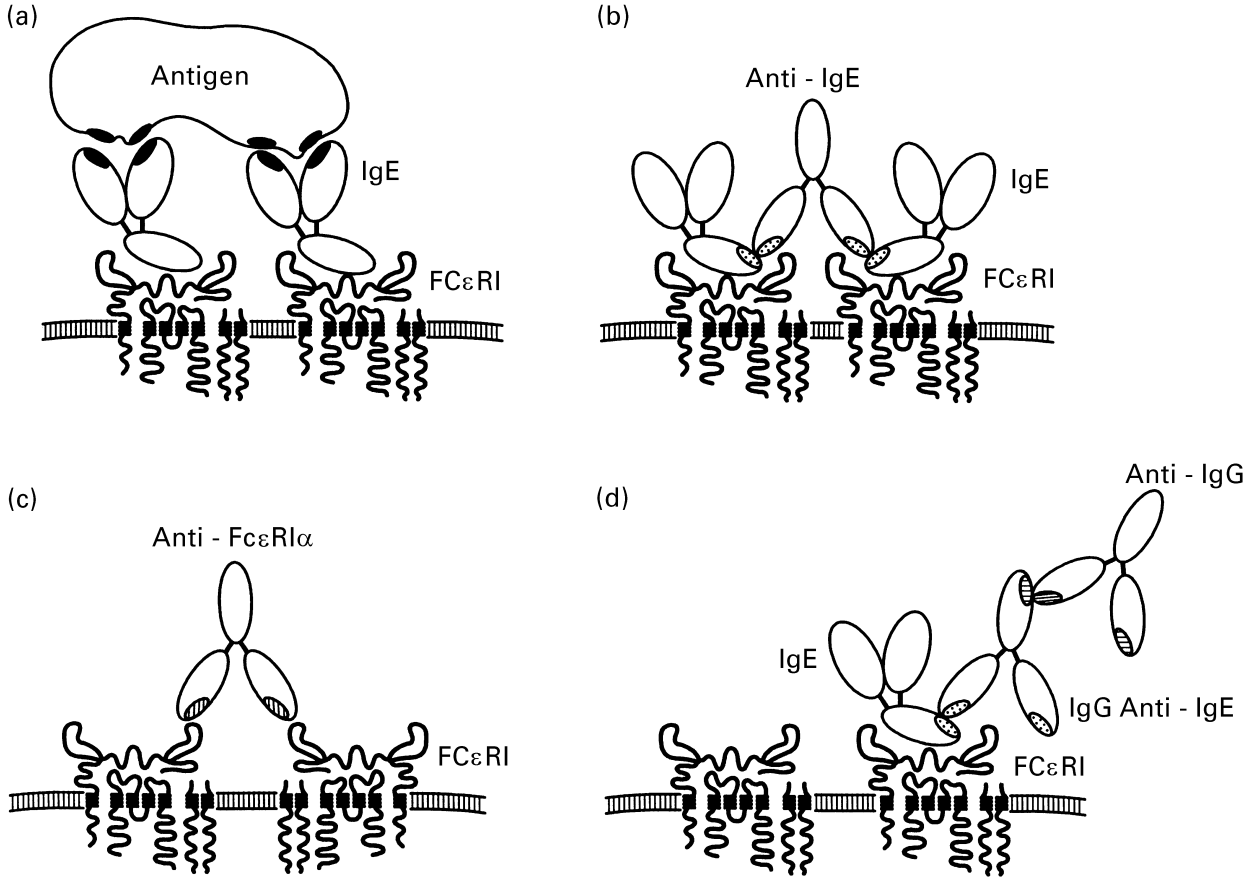

Fig. 1. Schematic representation of the mechanisms by which human basophils and mast cells can be activated through immunological interaction with the IgE–FcεRI network. (a) FcεRI$^+$ cells can be triggered by cross-linking between the Fab portions of IgE and multivalent antigens (direct anaphylaxis). 'Reverse type' anaphylactic reactions can occur through three distinct mechanisms: (b) antibodies against the Fcε chain of IgE (anti-IgE); (c) antibodies against epitopes of the α chain of FcεRI (anti-FcεRIα); and (d) anti-IgG acting on IgG–IgE complexes bound to FcεRI.

highest incidence being among patients with allergic and parasitic diseases [51]. Although this observation evoked considerable interest, attempts to prove a pathophysiological role for IgM anti-IgE autoantibodies were unsuccessful. In fact, these anti-IgE antibodies did not release histamine from basophils [51]. Several groups have confirmed the presence of anti-IgE in some conditions, mostly related to atopy [52–58]. Depending on the techniques used (haemoagglutination, radioimmunoassay, enzyme immunoassay, etc.), autoantibodies of one or more immunoglobulin isotypes have been detected [59]. The majority of IgG anti-IgE autoantibodies found in allergic disorders belongs to the IgG1 and IgG4 subclasses [60–62]. In several studies a significant correlation was observed between the levels of anti-IgE autoantibody and serum IgE levels [54,61–63]. However, the presence and the levels of anti-IgE autoantibodies did not always correlate with the disease activities [63], presumably because of the epitope heterogeneity of the human anti-IgE [62]. The relevance of epitope heterogeneity on human IgE has been investigated in a study in which the epitope specificity of the cloned antibody was found to be directed against the Cε2 domain of the IgE heavy chain [64]. This is in agreement with an earlier finding by Shakib and Powell-Richards that IgG anti-IgE in human serum was directed against two epitopes located within the Cε2 and the Cε4 domains [65].

Obviously, the main interest in such autoantibodies derives from their potential triggering of the release of proinflammatory and immunomodulatory mediators from mast cells and basophils and, therefore, their participation in the pathogenesis of immune disorders. Initial attempts to induce mediator release from basophils *in vitro* by affinity-purified IgG anti-IgE were unsuccessful [51]. Swainson *et al.* [66] demonstrated the presence of IgE-containing immune complexes in patients with atopic dermatitis. Nawata *et al.* [54,56] reported the presence of IgG anti-IgE autoantibodies in sera from patients with bronchial asthma and showed that these autoantibodies induce a reverse-type immediate skin reaction. This group also reported the occurrence of IgG anti-IgE autoantibodies in approximately 80% of patients with atopic dermatitis [56]. Quinti and coworkers [57] defined the specificity of the anti-IgE, demonstrating that IgM anti-IgE activity could be abrogated by Fab immune absorption, but that IgG anti-IgE was not affected. Moreover, the ε chain specificity of IgG anti-IgE was demonstrated by showing the reactivity of the autoantibody with the protein backbone of the Fcε of IgE synthesized from a fragment of the cloned gene of the heavy chain of human myeloma IgE (ND). Gruber and coworkers [67] found that IgG anti-IgE from one of six patients with urticarial symptoms induced histamine release from human basophils. Although the most interesting feature of anti-IgE antibodies is that they may induce mediator release from human FcεRI$^+$ cells, it is important to remember that these autoantibodies might modulate a variety of immune and inflammatory functions [68–71]. It is also important to note that anti-IgE antibodies can interfere with the immunoassay of serum IgE since IgE might be hidden within IgE/anti-IgE immune complexes and, therefore, not be detectable *in vitro* [72–76].

In collaboration with Quinti and Paganelli, we demonstrated that IgG anti-IgE isolated by affinity chromatography from one of six patients with atopic dermatitis-activated human basophils and mast cells [77,78]. There was an excellent correlation between the maximum percentage of histamine release from basophils induced by rabbit anti-IgE

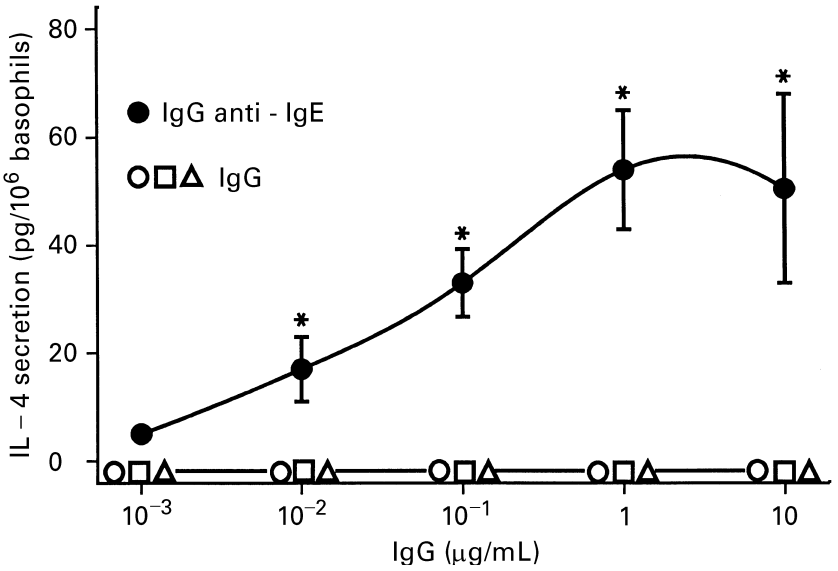

Fig. 2. Effect of increasing concentrations of a preparation of IgG anti-IgE isolated from a patient with atopic dermatitis (closed symbols) [78] and IgG isolated from three normal donors (open symbols) on IL-4 secretion from human basophils. Each point indicates the mean ± SEM. *$P < 0.001$ when compared with the corresponding concentration of IgG isolated from normal donors.

(R–aIgE) and human anti-IgE (H–aIgE). In addition, human anti-IgE specifically desensitizes basophils to a subsequent challenge with both H–aIgE and R–aIgE. Furthermore, removal of IgE from basophils by lactic acid treatment blocked the releasing activity of H–aIgE. Passive sensitization with polyclonal or monoclonal IgE proteins restored the response of basophils to H–aIgE. Preincubation with IgE purified from three myeloma patients (PS, ADZ and PP) concentration-dependently blocked the histamine-releasing activity of both R–aIgE and H–aIgE. More recently we have also demonstrated that this IgG anti-IgE autoantibody induces IL-4 release from basophils purified from peripheral blood (Fig. 2). The specificity of this observation is supported by the lack of effect of IgG purified from normal donors on IL-4 secretion from basophils. These results demonstrate that IgG anti-IgE from some patients with atopic dermatitis induces the release of proinflammatory mediators and cytokine from human basophils by interacting with membrane bound IgE.

We also demonstrated that H–aIgE not only activated basophils, but also mast cells isolated from skin and parenchymal lung tissue. Furthermore, the naturally occurring H–aIgE is a complete secretagogue, capable of releasing not only preformed mediators (histamine), but also of inducing the *de novo* synthesis of peptide leukotriene C_4 from human basophils and lung mast cells. These results demonstrated conclusively that in some patients with atopic dermatitis IgG anti-IgE can induce mediator release from FcϵRI$^+$ through the interaction with cell-bound IgE.

The prevalence of naturally occurring autoantibodies directed towards IgE in allergic patients and in normal donors has been evaluated extensively. There is convincing evidence that anti-IgE autoantibodies occur in the sera of some normal donors [74,79]. IgG anti-IgE are also commonly detected in cord serum [80,81]. Anti-IgE autoantibodies occur also in normal children and in young patients with asthma [75]. The same group extended their observation of the occurrence of immune complexes containing IgG anti-IgE in the sera of adults with allergic disorders [76]. The biological relevance of the latter observation was supported by the demonstration of binding of IgG–IgE complexes attached to the basophil through IgE bound to FcϵRI [25].

Taken together these findings provide evidence that naturally occurring autoantibodies directed toward IgE are heterogeneous immunochemically and functionally. In particular, Stadler and his collaborators [64,82,83] have emphasized the biological and clinical relevance of the heterogeneity of anti-IgE autoantibodies detected in the sera of allergic patients. The different releasing activity of anti-IgE antibodies might be due to a different affinity for IgE, epitope specificity and subclass composition [64,65]. Although the affinity for IgE of naturally occurring anti-IgE antibodies in humans has not been studied, Nisonoff and coworkers [84] have provided evidence of heterogeneity of anti-IgE antibody affinity by immunization of inbred mice with syngeneic IgE. Whatever the mechanism(s), it is becoming clear that at least in some patients with atopic dermatitis or urticarial symptoms, naturally occurring anti-IgE autoantibodies act as complete segretagogues by interacting with IgE on basophils and mast cells. Some of these autoantibodies are anaphylactogenic and can trigger IgE-mediated activation of FcϵRI$^+$ cells [77,78], whereas others are not [82,83]. In particular, naturally occurring anti-IgE autoantibodies can inhibit the binding of IgE to the low affinity receptor for IgE or even remove surface-bound IgE, and may thereby exert a regulatory function on the immune system [85].

The latter observation is of great relevance, because humanized anti-IgE antibodies have been used with success to remove surface-bound IgE on human FcϵRI$^+$ cells and may therefore exert a regulatory function on the IgE immune system [86,87]. Anti-human IgE antibodies are in clinical evolution as therapeutic agents against atopic diseases [88]. Thus, the possibility cannot be excluded that some of the naturally occurring non-anaphylactogenic anti-IgE autoantibodies, represent a protective mechanism capable of preventing the association of IgE with its FcϵRI on human basophils and mast cells.

The groups of Kinet and Stingl [89] have recently found IgG anti-IgE in 69% of patients with chronic urticaria and 73% with atopic dermatitis as well as in 26% of controls. In this study not all the anti-IgE autoantibody-containing IgG fractions induced histamine release from basophils, thus confirming previous observations [78].

Recently, Kaplan and coworkers [90] found that approximately 50% of the IgG fractions purified from the sera of patients with chronic urticaria possessed histamine-releasing activity directed against IgE or an epitope on the α chain of FcϵRI. This confirms the observations that autoantibodies in patients with allergic diseases can be directed toward different epitopes of the IgE/FcϵRI network.

Anti-IgE antibodies in autoimmune diseases

Mast cells may subserve a pathogenetic role in systemic autoimmune diseases (e.g. rheumatoid arthritis) via the modulation of a variety of proinflammatory, fibrogenic and immunological processes. The role in connective tissue remodelling is suggested by the ability of mast cell products (tryptase, histamine, LTC_4, chymase, etc.) to activate fibroblasts [91–93], to stimulate and activate latent collagenase *in vitro* [94], and by their appearance at the site of fibrosis [95,96].

Williams *et al.* [51] first reported IgM anti-IgE in approximately 10% of patients with rheumatoid arthritis in their first description of anti-IgE autoantibodies. Several studies have confirmed the presence of IgE antiglobulins in the sera or

synovial fluid of a significant number of patients with rheumatoid arthritis and rheumatoid vasculitis [97–101]. The presence of IgE-containing immune complexes might interfere with the quantitative determination of IgE levels in patients with rheumatoid arthritis [72]. IgE-containing immune complexes isolated from patients with rheumatoid arthritis can stimulate human neutrophils to produce superoxide anion [71]. In addition, Gruber *et al*. [102] have shown that IgE-containing immune complexes from patients with rheumatoid arthritis can sensitize synovial mast cells to release histamine when challenged with aggregated gammaglobulins. These observations suggest the possibility that IgE rheumatoid factors secreted by synovial plasma cells may bind to the FcεRI of neighbouring mast cells [38–40]. Exposure to an antigen complex, such as self-aggregating IgG, might activate synovial mast cells and so lead to mediator release. In addition, IgE rheumatoid factors might sensitize circulating basophils that in turn might contribute to the extra-articular features of rheumatoid arthritis, as suggested by an increased incidence of IgE rheumatoid factors in rheumatoid vasculitis [102].

IgM anti-IgE and IgG anti-IgE autoantibodies were also detected in 26% and 34%, respectively, of 67 patients with SLE [102]. The biological relevance of these autoantibodies obviously extends beyond their presence in the circulation. In fact, the mechanism by which organ damage occurs in SLE is believed to be due in part to the deposition of immune complexes within small blood vessels — a process that leads to complement activation and vascular damage [103]. This cascade of events is dependent on an increase in vasopermeability, which may result from the activation of circulating basophils or tissue mast cells. Anti-IgE autoantibodies might interact with membrane-bound IgE, so causing degranulation of these cells. Indirect evidence in support of basophil and IgE involvement in SLE is the observation that patients with active disease appear basopenic, presumably secondary to degranulation [104].

Recent studies have focused attention on the potential role of mast cells and their mediators in the pathogenesis of systemic sclerosis [41,95]. Serum IgG anti-IgE antibodies were detected in 21% of patients with systemic sclerosis, whereas IgM anti-IgE were found in 14% of patients [105]. Although attempts to demonstrate mediator release from basophils *in vitro* by using serum samples of these patients were unsuccessful, the possibility exists that anti-IgE autoantibodies may represent an additional mechanism for activation of mast cells and their subsequent interaction with fibroblasts [91–96] in scleroderma.

In conclusion, the possibility exists that anti-IgE autoantibodies in sera of some patients with rheumatoid arthritis, SLE and systemic sclerosis may contribute to the pathogenesis of the vascular and articular lesions characteristic of these disorders.

Anti-FcεRI antibodies in allergic disorders

In 1991 Greaves and coworkers [106] reported that intradermal injection of autologous sera obtained from 25 patients with chronic urticaria caused a weal in 20 donors.

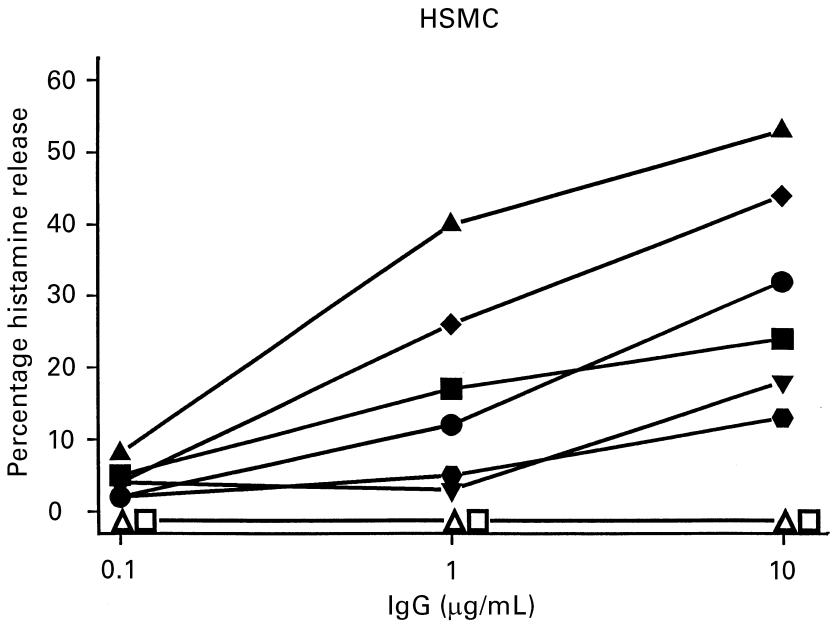

Fig. 3. Effect of increasing concentrations of IgG anti-FcεRI isolated from eight patients with chronic urticaria on histamine release from human skin mast cells. Each symbol represents the results for a different donor. Each point indicates the mean of duplicate determinations.

There was no response in 10 healthy controls or five patients with dermographism. Fourteen chronic urticaria sera elicited histamine release > 10% above basal levels from leucocytes of at least one of seven healthy donors. The latter *in vitro* response was present in the IgG fraction and was, at least in part, mediated by IgE bound to FcεRI on human basophils. These results extended the original observation of Gruber and coworkers [67], suggesting that histamine-releasing autoantibodies are presumably important in the pathogenesis of some patients with chronic urticaria.

The same group of investigators extended the initial observation demonstrating the presence of autoantibodies against the FcεRI as a cause of histamine release from basophils and skin mast cells in chronic urticaria [107]. Histamine-releasing activity was found in the IgG fraction and was neutralized by a recombinant preparation of the extracellular domain of the α subunit of FcεRI. In this study a positive control was provided by a monoclonal antibody (6F7), which reacts specifically with an epitope of the α subunit of FcεRI. This important observation provided the first demonstration that histamine-releasing IgG autoantibodies against the α subunit of FcεRI are present in some patients with chronic urticaria. This represented a novel and potentially important mechanism in the pathogenesis of chronic urticaria and possibly of other diseases mediated by mast cell/basophil activation.

Fig. 4. Effect of intradermal injection of saline (A), histamine (B) and of increasing doses (10–50–100 μl) of autologous plasma (C, D and E) in a patient with chronic urticaria. Venous blood was withdrawn with an anticoagulated syringe. Plasma was separated by centrifugation (2×) (1000 ***g***, +4°C, 10 min). Aliquots of autologous plasma were injected intradermally with a 27-G needle.

Several groups have recently confirmed and extended the original observation of Greaves and coworkers. The groups of Kinet and Stingl [89] have demonstrated that 37% of IgG isolated from chronic urticaria patients exhibited autoreactivity against FcεRIα. No anti-FcεRIα reactivity was observed in IgG fractions from atopic dermatitis or healthy control individuals. Not all the autoantibodies induced histamine release from basophils. We have purified the IgG fractions from the sera of eight patients with severe chronic urticaria. Increasing concentrations of IgG from patients with chronic urticaria were incubated with mast cells isolated from skin tissue. In four of eight preparations there was a concentration-dependent histamine release (> 20%) from human skin mast cells. Two preparations caused a histamine release of less than 20%, whereas two preparations were apparently devoid of histamine-releasing activity *in vitro* (Fig. 3). Interestingly, a preparation of IgG causing histamine release from basophils *in vitro* also caused a weal when injected intradermally in their donor skin (Fig. 4). To determine whether the histamine-releasing activity detectable in the IgG fraction was directed against FcεRI or IgE we used two approaches. First, removal of IgE from human skin mast cells by brief exposure to lactic acid treatment did not abolish the releasing activity of IgG fractions. Furthermore, preincubation with a soluble fragment of α chain blocked the histamine-releasing activity of IgG. Thus, IgG purified from some patients with chronic urticaria induces mediator release from human mast cells *in vitro* and *in vivo* interacting with an epitope on the α chain of FcεRI.

In a recent study performed on 163 patients with chronic urticaria it was reported that intradermal injection of autologous serum caused a skin reaction in 60% patients, whereas anti-FcεRI autoantibodies were detected in 23% of chronic urticaria patients [108]. Using a different technical approach (RBL cells transfected with α chain of FcεRI) Kaplan and coworkers found the presence of histamine-releasing autoantibodies in approximately 40% of chronic urticaria patients: 50% of these had autoantibodies anti-IgE and 50% anti-FcεRI [90].

These observations are important for several reasons. Firstly, they demonstrate that approximately 50% of patients with chronic 'idiopathic' urticaria have an autoimmune disorder, characterized by the presence of at least two types of antibodies directed against different epitopes of the IgE-FcεRI network. Secondly, anti-FcεRI autoantibodies present in some patients with chronic urticaria represent the first example of an autoantibody against a receptor that activates cell function by receptor (FcεRI) cross-linking. This is also the first example of an allergic disorder in which an autoantibody against a receptor (FcεRI) can activate effector cells of allergic inflammation ($FcεRI^+$ cells).

The latter observation opens the possibility of the

occurrence of anti-IgE or anti-FcεRI antibodies in such severe allergic disorders as bronchial asthma. Preliminary evidence of anti-IgE autoantibodies has been presented in some patients with bronchial asthma [54]. Interestingly, anti-FcεRIα autoantibodies have been detected in approximately 50% of non-atopic asthmatics and in half they were able to cause histamine release from basophils [21].

Anti-FcεRI antibodies in autoimmune disorders

Anti-IgE antibodies were first described in such classical autoimmune disorders as rheumatoid arthritis [51], and subsequently found in several allergic disorders [52–59,62,63,77,78]. Anti-FcεRI antibodies were originally described in chronic 'idiopathic' urticaria, which in approximately 50% of patients can be considered an autoimmune disorder [90,106,107]. Therefore, it is not surprising that IgG anti-FcεRIα autoantibodies have been found in a significant percentage of patients with such classical autoimmune-mediated disorders as systemic lupus erythematosus (20%), dermatomyositis (36%), pemphigus vulgaris (39%) and bullous pemphigoid (13%) [109]. Interestingly, anti-FcεRIα autoantibodies found in these autoimmune disorders apparently did not induce histamine release from basophils [109], unlike those from patients with chronic urticaria [107]. Another difference between chronic urticaria patients and those with autoimmune-mediated disorders was the subclass-specificity. The anti-FcεRIα autoantibodies found in patients with chronic urticaria occurred mainly in the IgG1 and IgG3 subclasses, whereas those detected in other autoimmune disorders belonged mainly to subclasses IgG2 and IgG4 [109]. These important observations highlight the potential epitope heterogeneity recognized by anti-FcεRIα autoantibodies and suggest the involvement of such additional pathogenetic mechanisms as complement activation by these autoantibodies in some autoimmune disorders.

Concluding remarks

There is compelling evidence that anti-IgE autoantibodies are occasionally present even in normal donors and more frequently in a variety of atopic and inflammatory disorders. The prevalence of biologically active anti-IgE autoantibodies in these conditions is starting to be documented. Naturally occurring anti-IgE autoantibodies belong to the IgM, IgA or IgG classes of immunoglobulins. The IgM and IgA anti-IgE immunoglobulins seem to be of limited interest because of their low affinity, restricted specificity and common prevalence. In general, IgG anti-IgE appear to be functionally more active than IgM anti-IgE [77,78,89]. Therefore, anti-IgE autoantibodies are heterogeneous with respect to their class. They also appear to be functionally heterogeneous within the same isotype. We and others have demonstrated that only IgG anti-IgE from a small percentage of patients with atopic dermatitis and urticarial syndromes induce the release of mediators from basophils and mast cells.

Recent studies suggest that some of the anti-IgE autoantibodies present in allergic patients might be non-anaphylactogenic, thus representing a possible protective mechanism preventing the association of IgE with its receptor on $Fc\epsilon RI^+$ cells. This fascinating hypothesis is supported by experimental observations [84] and by the findings that humanized anti-IgE antibodies can be beneficial in some allergic disorders by reducing IgE and the expression of FcεRI [86–88].

Anti-IgE autoantibodies are also present in the serum of patients affected by a variety of autoimmune diseases (rheumatoid arthritis, SLE and systemic sclerosis). The latter finding is of great interest because it is now becoming evident that mast cells, basophils and their chemical mediators play a pathogenetic role in these inflammatory disorders [42,91–94].

Anti-FcεRIα autoantibodies also occur in a significant percentage of patients with chronic urticaria [89,90,106–109], non-atopic asthma [21] and some autoimmune diseases, i.e. systemic lupus erythematosus, pemphigus vulgaris, etc. [109]. The prevalence of this new class of autoantibodies in other allergic disorders and in other autoimmune diseases remains to be determined.

In conclusion, a body of evidence suggests that anti-IgE and anti-FcεRI autoantibodies, present in a significant percentage of patients with allergic disorders, are relevant to the pathogenesis of these conditions. Much remains to be learned about the immunochemistry of these autoantibodies (affinity, epitope specificity, IgG subclass, etc.), the prevalence of biologically active anti-IgE and anti-FcεRIα autoantibodies and, finally, their precise role in the pathogenesis of human inflammatory and autoimmune diseases. The information that will emerge from these studies may represent the basis for the development of novel therapeutic approaches in subsets of patients with autoimmune responses against the IgE-FcεRI network.

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