

Anti-IgE therapy

Paula Jardieu

Genentech Inc, San Francisco, USA

Controlling the IgE response at either the synthesis level or the effector phase should have a profound impact on the allergic cascade. For more than a decade, researchers have focused on ways of interfering with the binding of IgE to its high-affinity receptor on proinflammatory cells. Several approaches have also been taken to antagonize the complex interplay of cytokines and cell-associated molecules (CD40, CD23) that are implicated in IgE synthesis. Recently, anti-IgE antibodies have been developed that are potent IgE antagonists. These antibodies are currently under clinical investigation as potential therapeutics for allergic disease.

Current Opinion in Immunology 1995, 7:779–782

Introduction

Developing a means of controlling the IgE response has been an active area of research since the identification of IgE as the pivotal molecule in the allergic cascade [1,2]. Inhibition of IgE responses has been achieved by treating animals with modified allergens, such as pegylated [3] or urea-denatured antigens [4]. Recently, the majority of research on IgE regulation has focused on the T helper type 1 (Th1)/Th2 network. The Th2 cytokines (IL-4 and IL-13) have been shown to be mandatory for IgE synthesis [5,6], whereas the Th1 cytokines (IFN- γ) appear to inhibit IgE production [7]. For this reason, many researchers are convinced that understanding the regulation of IgE responses by T cells is the critical pathway for developing an effective therapeutic agent for atopic disease. Because of the pleiotropic nature of cytokines, it may be difficult to develop a specific immunoregulatory molecule that interferes with IgE responses via the cytokine network. A potentially more selective approach to IgE regulation comes from studies from a number of laboratories, including our own, which use anti-immunoglobulin reagents to directly alter IgE responses.

Anti-IgE effects in experimental models

As early as 1976, Manning *et al.* [8], reported complete suppression of the IgE response to *Nippostrongylus brasiliensis* in anti- μ treated mice. Serum IgE levels were specifically suppressed in these mice for greater than 100 days following a series of injections of E-specific polyclonal antibodies initiated within 24 hours of birth [9]. Similarly administration of polyclonal anti-IgE to

adult mice significantly decreased serum IgE levels and reduced the number of B cells producing IgE [10].

It was subsequently discovered by Chen and Katz [11] that injection of IgE into perinatal mice resulted in prolonged inhibition of IgE responses to antigen challenge. Following a similar experimental protocol, Haba and Nisonoff [12] extended these observations by demonstrating that the reduction in serum IgE levels was caused by the induction of anti-IgE antibodies. Support for these findings came from experiments in which passive transfer of polyclonal anti-IgE antibodies strongly inhibited IgE responses in adult mice [13]. These antibodies appear to act through specific binding to B cells bearing IgE as later studies demonstrated that a reduction in serum IgE levels correlated with a decrease in the number of B cells secreting IgE in the spleen and lymph nodes of anti-IgE treated mice. Adoptive transfer experiments further supported the notion that the anti-IgE antibodies were solely responsible for the suppressive activity and that T cells did not play a role other than to provide help to the B cells for IgE secretion [14•]. In these studies, T cells became tolerant to IgE when the mouse began to produce IgE. B cells bearing surface (s)IgE appear to provide the major signal for induction of T-cell tolerance.

Recently, we have shown that serum IgE levels were undetectable for greater than two months in mice treated with a single injection of a monoclonal anti-IgE antibody even with weekly exposure to antigen. This response appeared to be antigen specific as dinitrophenyl ovalbumin (DNP-OVA) suppressed mice were able to respond to keyhole limpet hemocyanin (KLH) [15•]. Moreover, splenocytes taken from the mice treated with anti-IgE failed to synthesize IgE *in vitro*. Subsequent analysis by reverse transcription PCR demonstrated a

Abbreviations

IL—interleukin; m—membrane; s—surface; Th—T helper.

complete inhibition of IgE mRNA levels in these B cells (P Jardieu, unpublished data). Flow cytometric analyses of B cells taken from anti-IgE treated mice revealed a dose-dependent decrease in the expression of the low-affinity receptor for IgE, FcεRII (CD23), following antibody treatment. In other studies, anti-IgE treatment of mice infected with *Schistosoma mansoni*, which induces supra high levels of IgE, resulted in decreased serum IL-4 levels in the treated mice compared to controls [16••]. This decrease may result from the reduced IgE levels after antibody treatment, which in turn led to decreased mast cells degranulation and release of IL-4 from the intracellular granules [17]. As IL-4 is the major cytokine for IgE class switching, the reduction in IL-4 could contribute further to the reduction in IgE production following anti-IgE treatment. Furthermore, the decrease in IL-4 levels could also account for the observed decrease in CD23 expression in the anti-IgE treated mice as IL-4 is known to upregulate the expression of CD23 on B cells.

The CD23 molecule is widely distributed on many cell types and has been implicated as a key molecule in the regulation of IgE synthesis [18,19••]. Indeed, allergen presentation to specific T cells can be facilitated when IgE-allergen complexes, after binding to CD23, are endocytosed by antigen-presenting cells [20]. Studies of antibodies to CD23 have also implicated this molecule in regulation of *in vivo* IgE synthesis [21]. CD23 provides a costimulus for IgE synthesis driven by IL-4 [22•], presumably by binding to the CD21 ligand on B cells. Thus, antibodies to CD23 may represent viable candidates for IgE regulation.

Human anti-IgE antibodies

Human anti-IgE autoantibodies have been identified and have been proposed to be intrinsic regulators of IgE synthesis. In support of this notion, high anti-IgE levels at birth are associated with a reduced allergy prevalence in infants at risk of developing atopy [23]. Anti-IgE autoantibodies have been isolated that either enhance or suppress IgE synthesis *in vitro* [24]. Using F(ab') and F(ab')₂ fragments of an inhibitory anti-IgE antibody, it was further shown that divalent recognition was required to effect IgE synthesis [25]. These autoantibodies appear to exert these effects at the level of transcription. Depending on the ε domain specificity, anti-IgE autoantibodies have been shown to both inhibit and enhance binding of IgE [26•]. Given the putative regulatory role of CD23 in IgE regulation, it is tempting to speculate that the mechanism of action of anti-IgE antibodies on IgE responses is via CD23 pathway. This hypothesis remains to be proven.

Anti-IgE autoantibodies have also been described that appear to block the binding of IgE to the high-affinity receptor for IgE (FcεRI) [27]. Similar to the dual

activities of autoantibodies on IgE synthesis, studies have found that IgG anti-IgE antibodies in asthma patients consist of two functionally distinct subpopulations: those that upregulate, and those that downregulate, the release of mediators from mast cells and basophils [28•]. Taken together, these studies suggest that anti-IgE antibodies have the potential to interfere with IgE responses both at the level of IgE production and the level of IgE-dependent release of histamine and other vasoactive mediators.

Potential therapeutics

The reported activity of autoantibodies against IgE provide support for development of such molecules as therapeutics for allergic disease. To date, one approach has been to engineer an antibody that binds to membrane (m)IgE on B cells and inhibits IgE synthesis by these cells [29]. The antibodies are selected by the ability to bind to unique epitopes expressed on mIgE, but not surface (s)IgE. This property of the antibody would eliminate the harmful side effect of mast-cell degranulation, as it would not be able to bind to sIgE on mast-cell receptors [30].

An alternative approach has been to identify antibodies that block the binding of IgE to FcεRI by virtue of binding IgE at the same site as the high-affinity receptor [31••]. This antibody should also lack the harmful side effect of inducing FcεRI receptor cross-linking because the antibody would be unable to bind to receptor-bound IgE on mast cells as the epitope would already be occupied by receptor. Using the technique of homology mutagenesis, an antibody has been identified that appears to recognize identical residues in the Cε3 domain of IgE as the FcεRI [32••]. As these residues in the Cε3 domain are also present on mIgE, this antibody also binds to mIgE B cells and affects IgE synthesis [31••]. Clinical trials are ongoing to determine if elimination of IgE by anti-IgE antibodies during the course of allergen exposure will have significant impact on allergic symptoms.

Another potential therapeutic approach has been to develop a soluble form of the FcεRI [33]. By definition, this molecule can block the binding of IgE to mast cells and basophils, and has no capacity to stimulate degranulation. As the residues recognized by FcεRI are also expressed on mIgE, the FcεRI also inhibits IgE synthesis [34]. An important issue associated with this molecule is the potential for development of an antibody response to the receptor that might trigger mast-cell degranulation. Indeed anti-FcεRI autoantibodies have been proposed to be the etiological agent in the pathogenesis of chronic urticaria [35].

Monoclonal antibodies directed against lymphokines involved in IgE regulation have also been considered as possible therapeutics for allergic disease. The pivotal role

of IL-4 in development of IgE-secreting B cells make it the most likely target for an immunotherapeutic. In a murine model for asthma, where aeroallergen sensitized mice are repeatedly challenged with antigen, IL-4-deficient mice exhibited reduced airway eosinophilia and peribronchial inflammation compared to normal controls [36]. Although the use of a neutralizing anti-IL4 antibody in an asthma model has yet to be reported, these results suggest that IL-4 is a crucial mediator of airway inflammation. Although IL-4 is clearly a critical participant in allergic inflammation, it also drives T-cell differentiation including CD4(+) T-cell subsets. Thus, a neutralizing anti-IL4 antibody could have undesirable effects on general immunity.

Conclusions

Regardless of the approach, modulation of IgE activity represents an exciting new potential for intervention in allergic disease. At the very least, the introduction of molecules which inhibit IgE responses in the clinic will provide important confirmation of the role of IgE in atopic diseases.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Ishizaka K, Ishizaka T: **Biological function of IgE antibodies and mechanisms of reaginic hypersensitivity.** *Clin Exp Immunol* 1970, **6**:25-42.
2. Ishizaka K, Tomioka H: **Mechanisms of passive sensitization. I. Presence of IgE and IgG molecules on human leukocytes.** *J Immunol* 1970, **105**:1459-1467.
3. Bach MD, Brashler JR: **IgE antibody specific abrogation of an established immune response in mice modified antigens.** *J Immunol* 1975, **114**:1799-1807.
4. Sehon AH: **Suppression of IgE antibody responses with tolerogenic conjugated of allergens and haptens.** *Proc Allergy* 1982, **32**:161-202.
5. Stavnezer J, Radcliffe G, Lin Y, Nietupski J, Berggren L, Sitia R, Severson E: **Immunoglobulin heavy chain switching may be directed by prior induction of transcripts from constant region genes.** *Proc Natl Acad Sci USA* 1988, **85**:7704-7708.
6. Zurawski G, De Vries JE: **Interleukin 13, an interleukin 4-like cytokine, that acts on monocytes and B cells, but not on T cells.** *Immunol Today* 1994, **15**:19-26.
7. Coffman R, Carty J: **A T cell activity that enhances polyclonal IgE production and its inhibition by interferon- γ .** *J Immunol* 1986, **136**:949-954.
8. Manning DD, Nanning JK, Reed NR: **Suppression of reaginic antibody (IgE) formation in mice by treatment with anti- μ antiserum.** *J Exp Med* 1976, **144**:288-292.
9. Bozelka BE, McCants ML, Salvaggio JE, Lehrer SB: **IgE isotype suppression in anti- μ treated mice.** *Immunology* 1982, **46**:527-532.
10. Bozelka BE, McCants ML, Salvaggio JE, Lehrer SB: **Effects of anti-E on total and specific IgE levels in adult mice.** *Int Archs Allergy Appl Immunol* 1985, **78**:51-56.
11. Chen SS, Katz DH: **IgE class-restricted tolerance induced by neonatal administration of soluble or cell-bound IgE.** *J Exp Med* 1983, **157**:772-788.
12. Haba S, Nisonoff A: **Inhibition of IgE synthesis by anti-IgE: role in long-term inhibition of IgE synthesis by neonatally administered soluble IgE.** *Proc Natl Acad Sci USA* 1990, **87**:3363-3367.
13. Haba S, Nisonoff A: **Mechanisms of induction of tolerance to syngeneic IgE.** *Int Immunol* 1992, **4**:101-105.
14. Haba S, Nisonoff A: **Role of antibody and T cells in the long-term inhibition of IgE synthesis.** *Proc Natl Acad Sci USA* 1994, **91**:604-608.
- Passive transfer experiments led to identification of anti-IgE autoantibodies as the suppressive agents following inoculation with syngeneic IgE.
15. Haak-Frendscho M, Robbins K, Lyon R, Shields R, Hooley J, Schoenhoff M, Jardieu P: **Administration of an anti-IgE antibody inhibits CD23 expression and IgE production in vivo.** *Immunology* 1994, **82**:306-313.
- Potential mechanisms of action of anti-IgE antibodies on membrane Ig bearing B cells is via CD23.
16. Amiri P, Haak-Frendscho M, Robbins K, McKerrow JH, Stewart T, Jardieu PM: **Anti-immunoglobulin E treatment decreases worm burden and egg production in *Schistosoma mansoni*-infected normal and interferon γ knockout mice.** *J Exp Med* 1994, **180**:43-51.
- Anti-IgE may affect IgE synthesis by indirectly blocking degranulation of mast cells and the subsequent release of IL-4 from granular stores.
17. Williams ME, Kullberg MC, Barbieri S, Gaspar P, Berzofsky JA, Seder RA, Sher A: **Fc ϵ receptor positive cells are a major source of antigen induced interleukin-4 in spleens of mice infected with *S. mansoni*.** *Eur J Immunol* 1993, **23**:1910-1916.
18. Yukawa K, Kikutani H, Howaki H, Yamasaki K, Yokota A, Nakamura H, Barsumian EL, Hardy RR, Suemura M, Kishimoto T: **A B-cell specific differentiation antigen, CD23, is a receptor for IgE (Fc epsilon R) on lymphocytes.** *J Immunol* 1987, **138**:2576-2580.
19. Campbell AM, Vignola AM, Chenz P, Godard Ph, Bousquet J: **Low-affinity receptor for IgE on human bronchial epithelial cells in asthma.** *Immunology* 1994, **82**:506-508.
- IgE may play a direct role in airway hyper-responsiveness via binding to bronchial epithelium.
20. Van der Heijden FL, Van Neerven RJJ, Kapsenberg ML: **Relationship between facilitated allergen presentation and the presence of allergen-specific IgE in serum of atopic patients.** *Clin Exp Immunol* 1995, **99**:289-293.
21. Flores-Romo L, Shields J, Humbert Y, Graber P, Aubry J-P, Gauchat J-F, Ayala G, Allet B, Chavaz M, Bazin H et al.: **Inhibition of an in vivo antigen-specific IgE response by antibodies to CD23.** *Science* 1993, **261**:1038-1041.
22. Henchoz S, Gauchat J-F, Aubry J-P, Graber P, Pochon S, Bonney J-Y: **Stimulation of human IgE production by a subset of anti-CD21 monoclonal antibodies: requirement of a co-signal to modulate e transcripts.** *Immunology* 1994, **81**:285-290.
- Further support for the hypothesis that CD21-CD23 ligation affects IgE synthesis.
23. Vassella CC, Odelram H, Kjellman NIM, Borres MP, Vanto R, Björkstén B: **High anti-IgE levels at birth are associated with a reduced allergy prevalence in infants at risk: a prospective study.** *Clin Exp Allergy* 1994, **24**:771-777.
24. Stadler BM, Stampfli MR, Miescher S, Furukawa K, Vogel M: **Biological activities of anti-IgE antibodies.** *Int Arch Allergy Immunol* 1993, **102**:121-126.
25. Stampfli MR, Miescher S, Aebischer I, Zürycher AW, Stadler BM: **Inhibition of human IgE synthesis by anti-IgE antibodies requires divalent recognition.** *Eur J Immunol* 1994, **24**:2161-2167.

26. Miescher S, Vogel M, Stämpfli MR, Wasserbauer E, Kricek F, Vorburger S, Stadler BM: **Domain-specific anti-IgE antibodies interfere with IgE binding to FcεRII.** *Int Arch Allergy Immunol* 1994, **105**:75–82.

Epitope mapping of anti-IgE autoantibodies that either enhance or suppress IgE binding to CD23, depending on domain specificity.

27. Stadler BM, Furukawa K: **Immunoglobulin E regulation beyond the cytokine network.** *Res Trends* 1993, **5**:160–161.
28. Shakib F, Smith SJ: **In vitro basophil histamine-releasing activity of circulating IgG1 and IgG4 autoanti-IgE antibodies from asthma patients and the demonstration that anti-IgE modulates allergen-induced basophil activation.** *Clin Exp Allergy* 1994, **24**:270–275.

Clinical correlations between anti-IgE autoantibody and disease severity.

29. Davis FM, Gossett LA, Chang TW: **An epitope of membrane-bound but not secreted IgE: implications in isotype-specific regulation.** *Biotechnology* 1991, **9**:53–56.
30. Chang TW, Davis FM, Sun CRY, MacGlashan DW Jr, Hamilton RG: **Monoclonal antibodies specific for human IgE-producing B cells: a potential therapeutic for IgE-mediated allergic diseases.** *Biotechnology* 1990, **8**:122–126.
31. Shields RL, Whether WR, Zioncheck K, O'Connell L, Fendly B, Presta LG, Thomas D, Saban R, Jardieu PM: **Inhibition of allergic reactions with antibodies to IgE.** *Int Arch Allergy Immunol* 1995, **107**:308–312.

Identification of an anti-IgE antibody that blocks binding of IgE to FcεRI via binding to residues on IgE identical to those on FcεRI.

32. Presta L, Shields R, O'Connell L, Lahr S, Porter S, Gorman C, Jardieu P: **The binding site on human immunoglobulin E for its high affinity receptor.** *Am Soc Biochem Mol Biol* 1994, **269**:26368–26373.

Homology scanning mutagenesis was used to identify the six residues in the ε3 domain of IgE which are required for FcεRI binding.

33. Haak-Frendscho M, Ridgway J, Shields R, Robbins K, Gorman C, Jardieu P: **Human IgE receptor α-chain IgG chimera blocks passive cutaneous anaphylaxis reaction in vivo.** *J Immunol* 1993, **151**:351–358.
34. Yanagihara Y, Kajiura K, Ikizawa K, Toshio T, Okumura K, Ra C: **Recombinant soluble form of the human high-affinity immunoglobulin E (IgE) receptor inhibits IgE production through its specific binding to IgE-bearing B cells.** *Am Soc Clin Inv* 1994, **94**:2162–2165.
35. Hide M, Francis DM, Grattan CEH, Barr RM, Winkelmann RK, Greaves MW: **The pathogenesis of chronic idiopathic urticaria: new evidence suggests an auto-immune basis and implications for treatment.** *Clin Exp Allergy* 1994, **24**:624–627.
36. Brusselle G, Kips J, Joos G, Bluethmann H, Pauwels R: **Allergen-induced airway inflammation and bronchial responsiveness in wild-type and interleukin-4-deficient mice.** *Am J Respir Cell Mol Biol* 1995, **12**:254–259.

P Jardieu, Department of Immunology, Genentech Inc, 460 Point San Bruno Boulevard, San Francisco, CA 94080, USA.