

EDITORIAL

Controlling allergy with anti-idiotypic antibodies

The antigenic determinants expressed by the variable regions of antibody molecules are collectively termed the idiotype (Id). There is evidence in some immune responses for the production of antibodies against Id and that such anti-Id could bear the internal image of antigen. According to the network theory [1], anti-Id antibodies serve to regulate the Id response and this property has been used experimentally to manipulate the immune responses associated with autoimmunity, cancer and allergy.

In addition to its regulatory effect on the synthesis of IgE (Id) [2], in allergic conditions the binding of anti-Id to mast cell and basophil bound IgE may prevent interaction of IgE with allergen. However, such Id-anti-Id interaction on the mast cell and basophil surface will, as shown in an article [3] published in this issue of the journal, lead to cross-linking of IgE molecules and degranulation of these cells. Such an undesirable effect would clearly preclude therapeutic exploitation of anti-Id antibodies. However, those authors argue that mast cell and basophil degranulation by anti-Id will depend on the availability of sufficient numbers of adjacently bound IgE molecules displaying the appropriate idiotype. They consider that this is unlikely to occur frequently, and that as such anti-Ids are weak degranulators compared with allergens, which exhibit several epitopes that can be recognized by IgE.

A therapeutically useful anti-Id should therefore be one that targets IgE secreting B cells and blocks binding of allergen to mast cell bound IgE molecules, but without cross-linking them. To achieve this goal, we propose that we should, in the first place, look for naturally occurring IgG4 anti-Id antibodies.

We hypothesize that IgG4 anti-Id, despite being structurally bivalent, is unlikely to cause degranulation of mast cells and basophils, because the short and inflexible hinge of IgG4 renders it effectively functionally monovalent [4–6]. Fortunately, IgG antibody responses in allergic individuals are often of the IgG4 subclass, as its synthesis, like that of IgE, is up-regulated by IL-4 [7]. Thus, the functional monovalency of IgG4 and bivalency of other IgG subclasses (e.g. IgG1) provide a direct system for studying the effects of monovalent and bivalent anti-Id on basophil degranulation *in vitro*. However, recent observations [8] that some individuals possess a polymorphism in Fc γ R111 which can be activated to mediate ADCC by K cells through IgG4 binding, raise the possibility of indirect cross-linking through Fc γ receptors.

The therapeutic applicability of a naturally occurring IgG4 anti-Id may depend to a large degree on its effect at the B cell level. B cell clones expressing surface immunoglobulin with the same Id and binding specificity for allergenic peptides as expressed in their secreted IgE antibodies may be affected in varying ways by the IgG4 anti-Id. In experimental animals, it appears that nanogram doses of anti-Id enhance and microgram doses suppress the appearance of the appropriate Id-bearing antibodies [9,10].

For instance, if IgG4 anti-Id is shown to down-regulate *in vitro* human IgE synthesis, its production could be boosted by immunization with an Id derived peptide identified by screening a peptide library expressed on filamentous phage surface [11] with an isolated IgG4 anti-Id. The great attraction of this strategy is that therapy is aimed at stimulating the production of a naturally occurring, rather than a novel, antibody. The possibility remains, however, that such immunization will also elicit anti-Id responses in other less beneficial isotypes.

To get round this problem, we are currently constructing chimaeric mouse-human IgG4 anti-Id (i.e. consisting of mouse variable region domains and human IgG4 constant region domains) against the Id of *Der p* 1-specific IgE. Once this antibody has been produced it will then be fully humanized, by recombinant DNA techniques, to facilitate future clinical applications, recognizing the likely benefits of *in vivo* use of humanized antibody as opposed to mouse reagents [12–14]. The added advantage of opting for an engineered IgG4 anti-Id is that, for instance, if indirect cross-linking through Fc γ receptors proves to be a problem (see above), the Fc region of IgG4 will be mutated (e.g. by removal of the N-linked glycosylation site) to prevent these interactions [15].

Allergic individuals also have naturally occurring anti-globulins directed against the Fc region of IgE, which are collectively termed autoanti-IgE antibodies [16]. These differ from anti-idiotypic antibodies in that they are not directed against allergen-specific IgE, and as such they may have a more general immunoregulatory effect on IgE. Some of the potential therapeutic problems associated with the use of anti-Id antibodies to suppress allergic reactions and the suggested solutions (see above) are also applicable to anti-IgE autoantibodies.

There is, however, a major difference between anti-Id and anti-Fc autoantibodies in terms of their interactions with high- and low-affinity receptor bound IgE.

Resonance energy transfer studies have demonstrated that IgE, in contrast to IgG, has a bent shape and that the IgE molecule binds to its receptor with its convex surface facing the membrane [17]. The high-affinity receptor (Fc ϵ RI) binding site, located in the N-terminal segment of C ϵ 3, is thus accessible only on the same convex face; the second site on the opposite chain will be occluded on the concave surface. Therefore, the success of strategies based on using naturally occurring autoanti-IgE antibodies that block binding of IgE to Fc ϵ RI, without causing mast cell degranulation, will depend on the bent structure of IgE, as the Fc ϵ RI binding site would otherwise have an accessible counterpart on the other side of the molecule. It is therefore of great interest and therapeutic relevance that circulating autoanti-IgE antibodies are mainly directed against a region of IgE (aa301-339) [18] encompassing the high-affinity receptor binding site (aa330-335).

Based on these observations, we predict that anti-Fc autoantibodies are unlikely to bind to receptor-bound IgE and as such may prove to be therapeutically safer than anti-Id antibodies. However, as such intervention strategies become available in the near future, the allergist will have to decide between the selective or general control of IgE.

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References

- 1 Jerne NK. Towards a network of the immune system. *Ann Immunol* 1974; 125:373-89.
- 2 Zhou EM, Kisil FT. Regulation of levels of serum antibodies to ryegrass pollen allergen Lolp IV by an internal image anti-idiotypic monoclonal antibody. *Immunology* 1995; 84:343-349.
- 3 Weyer A, Le Mao J, Etieban M et al. Human auto-anti-idiotypic antibodies to mite-specific IgE can degranulate human basophils in vitro. *Clin Exp Allergy* 1995; 25: 935-41.
- 4 Aalberse RC, van der Gaag R, van Leeuwen J. Serologic aspects of IgG4 antibodies. I. prolonged immunisation results in an IgG4-restricted responses. *J Immunol* 1983; 130:722-6.
- 5 van der Zee JS, van Swieten P, Aalberse RC. Serologic aspects of IgG4 antibodies. II. IgG4 antibodies form small, nonprecipitating immune complexes due to functional monovalency. *J Immunol* 1986; 137:3566-71.
- 6 Snow ME, Amzel LM. A molecular-mechanics study of the conformation of the interchain disulphide of human immunoglobulin G4 (IgG4). *Mol Immunol* 1988; 25:1919-24.
- 7 Ricci M. IL-4: a key cytokine in atopy. *Clin Exp Immunol* 1994; 24:801-12.
- 8 Greenwood J, Clark MR, Waldmann H. Structural motifs involved in human IgG antibody effector functions. *Eur J Immunol* 1993; 23:1098-104.
- 9 Rajewsky K, Takemori T. Genetics, expression and function of idiotypes. *Annu Rev Immunol* 1983; 1:569-607.
- 10 Muller CE, Rajewsky K. Idiotope regulation by isotype switch variants of two monoclonal antibodies. *J Exp Med* 1984; 159:758-72.
- 11 Scott JK, Smith GP. Searching for peptide ligands with an epitope library. *Science* 1990; 249:386-90.
- 12 Riechmann L, Clark MR, Waldmann H, Winter G. Reshaping human antibodies for therapy. *Nature* 1988; 332:323-7.
- 13 Gorman SD, Clark MR, Routledge EG, Cobbold SP, Waldmann H. Reshaping a therapeutic CD4 antibody. *Proc Natl Acad Sci USA* 1991; 88:4181-5.
- 14 Routledge EG, Lloyd I, Gorman SD, Clark MR, Waldmann H. A humanised monovalent CD3 antibody which can activate homologous complement. *Eur J Immunol* 1991; 21:2717-25.
- 15 Bolt S, Routledge E, Lloyd I et al. The generation of a humanised, non-mitogenic CD3 monoclonal antibody which retains *in vitro* immunosuppressive properties. *Eur J Immunol* 1993; 23:403-11.
- 16 Shakib F, Smith SJ, Pritchard DI. Do autoantibodies to IgE play a role in IgE-mediated events? *Immunol Cell Biol* 1995; 73:109-12.
- 17 Sutton BJ, Gould HJ. The human IgE network. *Nature* 1993; 366:421-8.
- 18 Shakib F, Powell-Richards A. Elucidation of the epitope locations of human autoanti-IgE: recognition of two epitopes located within the C ϵ 2 and the C ϵ 4 domains. *Int Arch Allergy Appl Immunol* 1991; 95:102-8.

F. SHAKIB

*Division of Molecular & Clinical Immunology,
University of Nottingham Medical School,
Queen's Medical Centre,
Nottingham NG7 2UH,
UK*

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