

EDITORIAL

Clinical & Experimental Allergy

Altered immunoglobulin E diversity and regulation of allergic inflammation in asthma

This editorial discusses the findings of the paper in this issue by S. Kerzel et al. [4] pp. 591–601.

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The clinical efficacy of anti-immunoglobulin E (IgE) therapy indicates a central role for IgE in perpetuation of allergic inflammatory diseases. Omalizumab is now utilized in treatment of a wide variety of allergic conditions including severe asthma, allergic rhinitis, atopic dermatitis, food allergy and urticaria either alone or adjunct with other therapies such as steroid administration or allergen-specific immunotherapy [1, 2]. Current research activity is focused on the cellular and molecular mechanisms by which IgE influences the immunopathogenesis of allergic disease [3]. Increased knowledge of how IgE exerts its effects will underpin effective clinical use of anti-IgE treatment. In this issue Kerzel et al. [4] investigate the effects of altered antibody repertoire on the outcomes of an experimental model of allergic asthma.

Immunoglobulin E triggers allergic reactions and contributes to perpetuation of allergic inflammation

IgE is the specific effector molecule responsible for triggering allergic reactions. Binding of IgE to its high affinity receptor (FcεRI) induces a conformational change in IgE locking it onto its receptor [5, 6]. From this vantage point, cell bound IgE can transduce intracellular signals causing immediate release of preformed mediators from blood basophils and tissue resident mast cells as well as cytokines and chemokines that amplify the allergic cascade [7]. B cells are not only the precursors of IgE-secreting plasma cells but secrete cytokines and are themselves efficient at presentation of antigen captured by IgE bound to the low affinity IgE receptor (FcεRII/CD23) to activated T cells, a process known as IgE-

facilitated antigen presentation [8, 9]. Local activation, differentiation and proliferation of IgE-producing B cells in inflamed lung and nasal mucosa have now been clearly demonstrated placing the IgE-producing B cell within site of action with capacity to perpetuate an inflammatory allergic cascade (reviewed in [8]).

Immunoglobulin E diversity is encoded by the heavy chain complementarity-determining region three

An important issue regarding the role of IgE in allergic disease is the molecular diversity of IgE generated in patients with atopic diseases. The variable domains of the Ig heavy and light chain are juxtaposed with three hypervariable loops from each chain forming complementarity determining regions (CDR) that together contribute to the antigen-binding interface. Ig genes of antigen-driven B cells accumulate somatic hypermutations in their CDR during adaptive immune responses. The third CDR of the heavy chain (CDR-H3) has a highly variable composition and structure conferred by the greatest nucleotide sequence diversity occurring in this region of the Ig gene [9]. Consequently the CDR-H3 of the antigen-binding interface often determines the antigen specificity of the antibody [10]. A transgenic mouse strain generated with diverse variable region in the heavy chain and restricted lambda light chains demonstrated experimentally that most of the antibody specificity was generated by the molecular diversity specified by the heavy chain [11].

A number of studies of IgE heavy chain transcripts isolated from patients with allergic asthma or atopic dermatitis, encoded by the variable domain gene segment from family five showed unusually high levels of somatic hypermutation outside the CDR of the Ig genes [9]. The observations suggested that these IgE antibodies were binding antigen, either of allergen or infectious origin, in a superantigen manner where the framework regions of the antibody rather than the CDR contributed to antigen contact. Foreseeably an infectious agent present in skin of

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patients with atopic dermatitis or airway mucosa of patients with recurrent respiratory infections associated with asthma could interact with IgE antibodies encoded by the heavy chain variable domain five gene segments. A small number of superantigens have been described for B cells [12]. The question why an infectious agent would interact particularly with the IgE class of antibody encoded by the heavy chain variable domain five, which is a minor representative of the heavy chain variable gene segments, has not yet been answered. Notably, many other molecular analyses of IgE repertoires in patients with allergic disease do not support the superantigen hypothesis for activation of IgE-producing B cells but instead indicate that IgE responses in allergic disease are characteristic of a typical antigen driven, oligoclonally expanded, affinity matured B cell response (reviewed in [9]).

An experimental model tests the role of complementarity determining region three in allergic sensitization and regulation of allergic asthma

To assess the contribution of the CDR3-H3 to allergic sensitization with an experimental allergen ovalbumin (OVA), Kerzel et al. used transgenic mice engineered with reduced diversity in the CDR-H3 of the Ig gene (Δ D-iD mice). These mice showed marked differences in their allergic phenotype from wild-type mice [4]. OVA immunized Δ D-iD mice raised lower allergen-specific IgE antibody than wild-type mice whereas their ability to produce OVA-specific IgG1 was unaffected. That the reduction in the diversity of the CDR-H3 of IgE limited the allergic sensitization to OVA confirms the importance of this hypervariable loop of the Ig in antigen binding. As expected, the results did not support a role for framework region interaction with this allergen, OVA.

Further to the investigation of the contribution to antigen binding of the CDR-H3, this study produced experimental data to support a role for IgE-producing B cells in the perpetuation of allergic inflammation [4]. The OVA-sensitized and -challenged Δ D-iD mice contained fewer eosinophils in the bronchiolar lavage fluid and had attenuated IL-4, IL-5 and IL-13 synthesis compared with wild-type mice. These results indicate that the IgE repertoire not only affects the sensitization to an allergen but contributes to the regulation of ongoing allergic inflammation. Despite diminished T-helper type 2 (Th2) cytokine production the OVA-sensitized and -challenged Δ D-iD mice did not differ from their wild-type counterparts in airway mucus production or allergen-induced bronchoconstriction. This observation is not completely consistent with the reduction of IL-13, a cytokine considered to be involved in mucus production. However, because asthma in humans is polygenic and the immunopathology complex, it is not surprising that a reduction in IgE diversity did not abrogate all aspects of allergic inflammation in the

Δ D-iD mice. It was proposed that the observed reduction in the Th2 cytokine production was a consequence of quantitative and qualitative changes in IgE. There was a reduced level of ova-specific IgE out of the total IgE as well as reduced IgE diversity causing low affinity binding of OVA. Both of these would diminish IgE-facilitated allergen presentation thereby down regulating allergic inflammation by failure to perpetuate the allergic activation of T cells.

Understanding changes in serum immunoglobulin E during clinical treatment of allergy

During effective subcutaneous allergen-specific immunotherapy, changes in serum IgE are slow to manifest despite demonstrable reductions in IL-5 relative to IFN- γ , and increases in IL-10 [13]. To date there has been no research conducted to observe any changes in the diversity of variable genes encoding IgE that might occur during immunotherapy. Lim et al. [14] recently reported an observation of decreased IgE diversity relative to IgG judged by CDR-H3 spectratyping in two out of three patients treated with Omalizumab but a controlled study has not been undertaken. Notably, increases in serum IgG4 over IgE have been associated with successful allergen-specific immunotherapy [15, 16]. This observation seems paradoxical because Ig class switching to both these antibodies is driven by Th2-type cytokines (IL-4 and IL-13) and CD40 ligand stimulation of B cells. Also, both these Igs are associated with allergic disease [17, 18]. The paradox could be reconciled by the presence of the type I and II receptors for IL-4 and IL-13 on different cell types, actions of additional cytokines including IL-7, IL-9, IL-10 and IL-21, divergent intracellular signalling leading to altered STAT6 phosphorylation, or interactions with different types of T regulatory cells leading to differential regulation of B cell switching [19, 20]. The mechanisms for altered class switching to IgG4 in subcutaneous-specific immunotherapy, or to IgA2 in sublingual immunotherapy are yet to be fully understood. Nonetheless, an abundance of IgG4 over IgE may ameliorate allergic disease by swamping out IgE due to the 10 000-fold higher serum concentration of IgG4 over IgE. Alternatively, IgG4 blocking antibodies may compete for the same allergen binding sites [21]. Moreover, the capacity of IgG4 antibodies to swap their heavy chain-light chain pairs giving rise to bi-specific IgG4 renders them incapable of allergen-antibody-mediated receptor cross-linking on inflammatory cells thus attenuating allergic inflammatory signals [22].

The experimental observations of Kerzel et al., indicating a role for IgE and IgE-producing B cells in the perpetuation of allergic inflammation are significant as they help validate the clinical use of anti-IgE therapy and demonstrate that IgE is not simply the output of B cells

orchestrated by effector T cells and allergen-activated dendritic cells. By shifting the focus of attention back onto IgE and the IgE-producing B cell new opportunities in addition to anti-IgE treatment may become apparent including the possibility of blocking the IgE-FcεR1 interaction [8]. Research studies of the immunogenetic characteristics of IgE responses in patients receiving Omalizumab treatment and of IgE and IgG4 responses pre- and post-immunotherapy are required to elucidate how antibody responses change during treatment of patients with atopic diseases. This field of research is important given the involvement of IgE-facilitated antigen presentation in the regulation of allergic inflammation and the potential for IgG blocking antibodies to attenuate the amplification of the atopic disease process.

References

- Holgate ST, Djukanovic R, Casale T, Bousquet J. Anti-immunoglobulin E treatment with omalizumab in allergic diseases: an update on anti-inflammatory activity and clinical efficacy. *Clin Exp Allergy* 2005; 35:408–16.
- Klunker S, Saggar LR, Seyfert-Margolis V *et al.* Combination treatment with omalizumab and rush immunotherapy for ragweed-induced allergic rhinitis: inhibition of IgE-facilitated allergen binding. *J Allergy Clin Immunol* 2007; 120:688–95.
- Owen CE. Immunoglobulin E: role in asthma and allergic disease: lessons from the clinic. *Pharmacol Ther* 2007; 113:121–33.
- Kerzel S, Wagner J, Rogosch T *et al.* Composition of the immunoglobulin classic antigen-binding site regulates allergic airway inflammation in a murine model of experimental asthma. *Clin Exp Allergy* 2009; 39:591–601.
- Garman SC, Wurzburg BA, Tarchevskaya SS, Kinet JP, Jardetzky TS. Structure of the Fc fragment of human IgE bound to its high-affinity receptor Fc epsilonRI alpha. *Nature* 2000; 406:259–66.
- Wan T, Beavil RL, Fabiane SM *et al.* The crystal structure of IgE Fc reveals an asymmetrically bent conformation. *Nat Immunol* 2002; 3:681–6.
- Perona-Wright G, Mohrs K, Taylor J *et al.* Cutting edge: Helminth infection induces IgE in the absence of mu- or delta-chain expression. *J Immunol* 2008; 181:6697–701.
- Gould HJ, Sutton BJ. IgE in allergy and asthma today. *Nat Rev Immunol* 2008; 8:205–17.
- Davies JM, O'Hehir RE. Immunogenetic characteristics of immunoglobulin E in allergic disease. *Clin Exp Allergy* 2008; 38:566–78.
- Ippolito GC, Schelonka RL, Zemlin M *et al.* Forced usage of positively charged amino acids in immunoglobulin CDR-H3 impairs B cell development and antibody production. *J Exp Med* 2006; 203:1567–78.
- Xu JL, Davis MM. Diversity in the CDR3 region of V(H) is sufficient for most antibody specificities. *Immunity* 2000; 13:37–45.
- Roben PW, Salem AN, Silverman GJ. VH3 family antibodies bind domain D of staphylococcal protein A. *J Immunol* 1995; 154:6437–45.
- Rolland JM, Drew AC, O'Hehir RE. Advances in development of hypoallergenic latex immunotherapy. *Curr Opin Allergy Clin Immunol* 2005; 5:544–51.
- Lim A, Luderschmidt S, Weidinger A *et al.* The IgE repertoire in PBMCs of atopic patients is characterized by individual rearrangements without variable region of the heavy immunoglobulin chain bias. *J Allergy Clin Immunol* 2007; 120:696–706.
- van Neerven RJ, Wikborg T, Lund G *et al.* Blocking antibodies induced by specific allergy vaccination prevent the activation of CD4+ T cells by inhibiting serum-IgE-facilitated allergen presentation. *J Immunol* 1999; 163:2944–52.
- Nouri-Aria KT, Wachholz PA, Francis JN *et al.* Grass pollen immunotherapy induces mucosal and peripheral IL-10 responses and blocking IgG activity. *J Immunol* 2004; 172:3252–9.
- Snow RE, Chapman CJ, Holgate ST, Stevenson FK. Clonally related IgE and IgG4 transcripts in blood lymphocytes of patients with asthma reveal differing patterns of somatic mutation. *Eur J Immunol* 1998; 28:3354–61.
- Aalberse RC, Van Milligen F, Tan KY, Stapel SO. Allergen-specific IgG4 in atopic disease. *Allergy* 1993; 48:559–69.
- Meiler F, Klunker S, Zimmermann M, Akdis CA, Akdis M. Distinct regulation of IgE, IgG4 and IgA by T regulatory cells and toll-like receptors. *Allergy* 2008; 63:1455–63.
- Jeannin P, Lecoanet S, Delneste Y, Gauchat JF, Bonnefoy JY. IgE versus IgG4 production can be differentially regulated by IL-10. *J Immunol* 1998; 160:3555–61.
- Strait RT, Morris SC, Finkelman FD. IgG-blocking antibodies inhibit IgE-mediated anaphylaxis in vivo through both antigen interception and Fc gamma RIIB cross-linking. *J Clin Invest* 2006; 116:833–41.
- Aalberse RC, Schuurman J. IgG4 breaking the rules. *Immunology* 2002; 105:9–19.