

NEWS AND COMMENTARIES

Allergen capture by IgE and IgG

Enhanced cell-binding by allergen multimers: how complex is it?

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Allergic diseases are the most common chronic disease of the western world, costing \$7.8 billion per year in lost productivity and medical care in Australia alone.¹ IgE is central to the immunopathogenesis of allergic diseases and important advances are now being made on multiple fronts of IgE research. In particular, two groups independently invested in the generation of IgE reporter mice to address the vexing question of the route of development of the elusive IgE+ B cell.^{2,3} Two new anti-IgE mAb targeting membrane IgE and cell-bound IgE have the potential to deplete the cellular source of IgE.^{4,5} These could be candidates for alternative anti-IgE treatment options with advantages over current anti-IgE therapy (OmalizumAb), which depletes free serum IgE. Researchers are still intrigued by the modes of interaction of IgE with allergen, and with both its receptors; the high affinity FcεR1 on mast cells and basophils, and the low affinity, C-type lectin, IgE receptor, CD23,⁶ on B cells and monocytes (Figure 1a and b). A new approach to the study of the complexity of these interactions was recently reported by Reginald *et al.*⁷ on page 167 of this issue.

For patients with moderate to severe allergic disease whose symptoms cannot be resolved with antihistamines or other pharmacotherapy, specific immunotherapy

with increasing doses of allergen is often an effective treatment option. This approach was first adopted for hay fever 100 years ago.⁸ During allergen-specific immunotherapy, a number of immunological changes accompany the desensitisation process. Mechanisms for which there is good evidence include the induction of allergen-specific T-regulatory cells producing TGFβ and/or IL-10 capable of suppressing Th2 allergic responses to allergen.⁹ An additional observation from clinically successful allergen-specific immunotherapy is the generation of allergen-specific IgG (in particular IgG4 but also IgG1). One mode of action of IgG4 antibodies can be attributed to the unique capacity of IgG4 for Fab arm exchange.¹⁰ Dissociation and re-pairing of IgG4 Fab arms creates bivalent antibodies capable of interfering with IgE-allergen complex formation. Evidence is building that IgG4 induced during allergen-specific immunotherapy can block allergen cross-linking of IgE bound to FcεR1, by basophils and mast cells.¹¹ Allergen-specific IgG may also inhibit the capture of IgE-allergen complexes by CD23 on monocytes and B cells. CD23-captured IgE-allergen complexes can be internalized, processed and presented to activated or memory antigen-specific T cells.

It is reasonably well accepted that allergen-specific IgG induced during allergen immunotherapy are likely to be beneficial to the resolution of allergic disease (Figure 1c). However, allergen-specific IgG levels do not necessarily correlate with protective effects of immunotherapy.¹² It appears, we don't have all the pieces of the puzzle with

respect to the complex interactions of IgE with its receptors or with allergen during immunotherapy.

Reginald *et al.*⁷ propose a model in which allergen-specific IgG can enhance the capture of IgE-allergen complexes by CD23 (Figure 1d). This paper suggests that while the above blocking mechanism for allergen-specific IgG might be protective against allergies, other effects of allergen-specific IgG, such as the formation of immune complexes containing both IgG and IgE, could enhance the CD23-mediated uptake and presentation of allergen. Reginald *et al.*⁷ controlled the valency of IgE-allergen interaction by using monoclonal IgE in conjunction with monomeric and trimeric Bet v 1, the major birch pollen allergen. With trimeric allergen, the authors showed an increase in IgE-allergen capture by CD23 compared with monomeric allergen (Figure 1b). When rabbit antiserum to the monomeric Bet v 1 allergen was added, larger CD23-binding complexes containing monoclonal IgE and IgG formed. This new data shows that, under certain circumstances, allergen-specific IgG is capable of increasing the amount of IgE-allergen complex bound to CD23-expressing cells.

These data should be considered alongside recent findings from a series of chimeric monoclonal IgE with different affinities for multiple epitopes on the major house dust mite allergen, Der p 2.¹³ For IgE-allergen binding to FcεR1 on basophils, the number of epitope interactions between IgE and allergen was found to be important for complex formation. The data of Reginald *et al.*⁷ extend on this by showing that IgG

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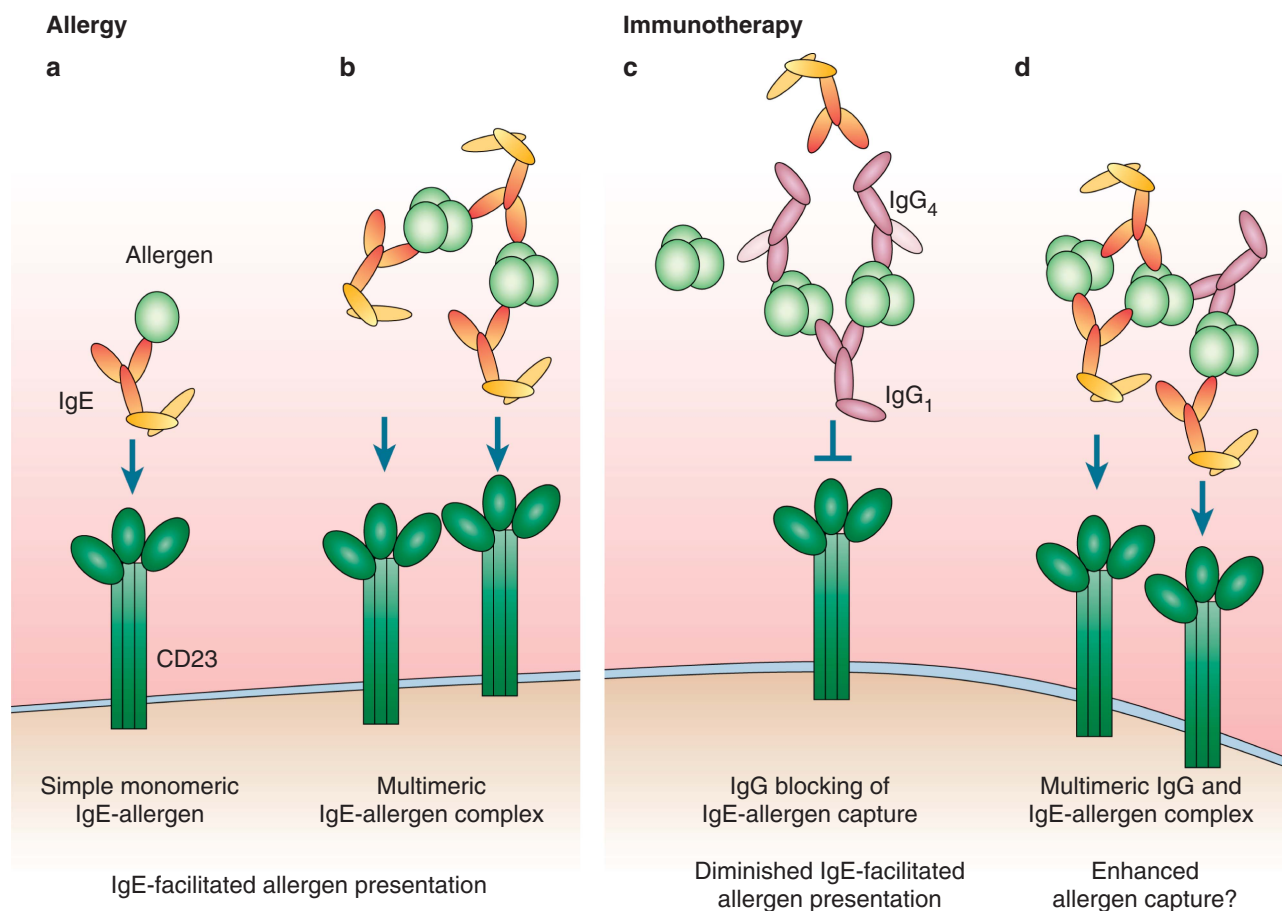


Figure 1 Capture of immune complexes by CD23. In the situation of allergy, one IgE molecule specifically binds to an epitope on an allergen depicted in its simplest form (a). This complex can be captured by CD23, internalized and allergen presented. However, most protein allergens have multiple epitopes forming an immune complex with multiple IgE molecules (b). IgE binding to allergen is enhanced by the avidity of multiple IgE-allergen interactions and occurs prior to the capture of the complex by CD23. During immunotherapy, the induced allergen-specific IgG competes with IgE for the allergen, thus blocking subsequent CD23 capture of IgE-allergen complexes,¹¹ (c). Both IgG1 and IgG4 may participate in this process. If IgG4 has switched Fab arms,¹⁰ then the variable domain may be of a different specificity (depicted by different variable domain colors) reducing immune complex formation. Additionally, it is possible that both IgE and IgG participate in immune complex formation (d) potentially enhancing CD23 capture of allergen immune complexes.⁷

can enhance large Ig-allergen complex formation when the IgG does not interfere with the binding of IgE to allergen. These recent reports highlight the potential of allergen-specific Ig to increase allergic inflammation, a timely cautionary note for the immunotherapy field.

This model now needs to be fitted into the big picture of IgE interactions with receptors and with allergen within the context of patients with allergic diseases. A potential limitation of this model is that it does not explore the interplay between IgG subclasses and the unique properties of IgG4. The humanized monoclonal IgE antibody to Bet v 1 may not represent the affinity, titer and repertoire of natural allergen-specific IgE of patients with allergic disease, and most protein allergens contain multiple IgE and IgG

binding sites. The contribution of IgG to large Ig-allergen complexes (Figure 1d) will ultimately depend on the affinity of Ig for allergen and the repertoire of epitopes for IgE and IgG.

Further research on human serum IgE and IgG epitope recognition of allergens would address these significant knowledge gaps pertaining to IgE-allergen interactions. We are yet to understand the range and diversity of epitopes on the major clinically important allergens that are recognized by IgE from the serum of patients with debilitating and life-threatening allergic diseases. In addition, research on the clonality of IgE + B cells responding to these epitopes and their affinity of interaction is critical for understanding the contribution of specificity, affinity and avidity of IgE-allergen binding.

Ultimately, we need to understand better how relatively low concentrations of allergen-specific IgE and IgG4, despite their different properties, are the main factors in IgE-allergen interaction, whereas IgG1 with its higher concentration, does not appear to be as involved. These driving forces underlying IgE-allergen interaction are highly likely to directly impact upon allergen crosslinking of IgE-FcεR1 on inflammatory cells and the capture of IgE-allergen by CD23, with the consequences of allergic reactions and the perpetuation of allergic inflammation.

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Cell cycle control of T cell memory

Non-T cells KIP T cell memory under control

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The retention of memory T cells after infection is critical in allowing the immune system to protect the host from reinfection. The differentiation process from effector to memory T cell involves dynamic changes in proliferative capacity, and for this reason cell cycle regulation has long been thought to control various aspects of memory development. In particular, the cell cycle regulator p27^{Kip1} is thought to have an important role in the development and maintenance of effector and memory CD8⁺ T cells. In this issue, Jatzek *et al.*¹ find that p27^{Kip1} ablation within T cells has surprisingly little effect on the CD8⁺ T cell response to infection; instead p27^{Kip1} expression by non-T cells appears to have an unanticipated role in restraining CD8⁺ T cell memory.

Cell cycle regulation is necessary at multiple points during the differentiation of a naïve CD8⁺ T cell to a memory cell. The initial response to antigen obviously requires proliferation, however, as effector cells

become more terminally differentiated, they lose their proliferative ability.² This loss in proliferative ability is paralleled by a loss in their ability to persist as memory cells. In contrast, less differentiated effector cells are more proliferative, and have greater memory potential. Thus, proliferative ability appears linked to memory potential. Although controversial, memory T cells may also be intrinsically augmented in their proliferative response to antigen relative to naïve T cells.^{3,4} In addition, memory cells possess the ability to maintain their numbers through homeostatic turnover in response to the cytokine interleukin (IL)-15. Overall, these findings reinforce the view that memory T cells are in a fundamentally different proliferative state to naïve and effector T cells.

How are these proliferative differences enforced? The cell cycle inhibitor p27^{Kip1} is an attractive candidate. p27^{Kip1} is expressed at high levels in nonproliferative naïve and anergic T cells, and restrains the proliferative capacity of these cell types.^{5,6} Although p27^{Kip1} must be downregulated for naïve T cells to proliferate, it is reexpressed in senescent effectors. Strikingly, however, effector cells with elevated memory

potential retain lower p27^{Kip1} levels.⁷ Thus, senescent effector cells may fail to persist into memory partly due to p27^{Kip1}-dependent restriction of proliferative responsiveness to homeostatic cytokines. Low p27^{Kip1} expression is retained through to memory, as resting memory T cells have greatly diminished p27^{Kip1} expression relative to naïve cells. This low p27^{Kip1} expression was suggested to have a role in the cell cycle reprogramming thought to underlie the augmented proliferative capacity of memory cells.⁸ Collectively, these results would predict that p27^{Kip1} loss within CD8⁺ T cells would have a dramatic effect on the immune response characterized by an elevated primary response, diminished contraction, and augmented memory cell numbers due to enhanced IL-15-mediated proliferation.

An initial study by Suresh and colleagues examining the CD8⁺ T cell response in p27^{Kip1} ^{−/−} mice appeared to support this idea. Although the knockout mice displayed normal effector cell expansion and differentiation, these mice displayed diminished effector cell contraction, and an elevated number of memory cells that were more functional (as assessed by their ability to produce multiple cytokines) and proliferated

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