

Atopic allergy and other hypersensitivities

Editorial overview

Jean-Pierre Kinet

Addresses

Harvard Medical School and Laboratory of Allergy and Immunology,
Beth Israel Deaconess Medical Center, Research North Building,
99 Brookline Avenue, Boston, MA 02215, USA;
e-mail: jkinet@caregroup.harvard.edu

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On the origin of allergy

In many developing countries where parasite infestations are endemic, humans learn to co-habit with a large number of parasites and microbes soon after birth. This constant exposure is likely to stimulate the Th2 arm of the T cell response maximally and result in high IgE levels. Is this beneficial to the host? An increasing number of studies, including epidemiological studies, do indeed support a protective role for IgE against the pathology resulting from parasitic infestations. In addition, recent experimental studies with genetically engineered mice deficient for the high affinity IgE receptor (FcεRI) show that the absence of FcεRI results in a substantial increase in the severity of schistosome-induced liver pathology [1]. While the mechanism of IgE-derived protection remains unclear, these studies clearly establish a protective role for the IgE–FcεRI network.

It seems possible that high parasite burdens and allergic responses within the same individual are somehow mutually exclusive. This may reflect the fact that priming our immune system early in life, as a result of repetitive contacts with parasites, induces maximal Th2 responses. These maximal responses may leave little room for environmental allergens to stimulate an already burdened immune system. In addition, at high IgE levels, the IgE–FcεRI network is already saturated and specific IgE responses are in competition. In this situation, the impact of potential allergenic IgEs will therefore be diluted.

The competition between IgEs of different specificities to activate effector cells may have been a critical factor in the emergence of a number of amplification mechanisms that have been uncovered as characteristics of the IgE–FcεRI network. One of these mechanisms is the increase of FcεRI expression on effector cells in response to an increase in IgE levels [2–7]. This may be a necessary positive feed back loop to allow a particular IgE to access effector cells. Another mechanism is the capacity of the effector cells to give a maximal response with only 10% of the corresponding receptor being engaged. That is the case for mast cells and basophils that express the β chain of FcεRI (FcεRIβ), a molecule with a huge amplification function [8,9]. The

FcεRIβ chain is not only an intrinsic amplifier of FcεRI signaling but also amplifies FcεRI surface expression; the latter being accomplished through β assisting in the maturation of the receptor after synthesis (E Donnadieu, J-P Kinet, unpublished data). When the amplification functions of FcεRIβ are considered factorially, the net effect of the presence of FcεRIβ in an FcεRI complex may be a 20–30-fold increase in the intensity of effector responses. The IgE–FcεRI network seems to have evolved to permit maximal response and protection from a small fraction of specific IgEs. This would allow maximal diversification of our defense system and permits a robust but measured response to a large number of microbes and parasites.

These various amplification functions may have evolved to give a selective advantage to the host when the system worked at maximal capacity, during continued challenge. They may have the opposite effect at much lower capacity, that is at low IgE levels, when competition between IgEs is minimized and amplification of what should otherwise have been measured responses is maximized. These low IgE levels are seen in our ‘clean’ societies in which parasitic infestations and microbial exposures are infrequent or absent and they unfortunately allow allergenic IgEs to have their effects maximized. Thus the same genetic variations that might have conferred a selective advantage against parasitic infestations, with greater Th2 and enhanced IgE responses, are instead translated into genetic predisposition for allergic diseases.

Much effort has been devoted to identify genes that underlie predisposition to allergic diseases and asthma. Moffatt and Cookson (pp 606–609) summarize the latest findings in this regard. Of interest is the finding that various polymorphisms of the gene for FcεRIβ have been shown to be strongly associated with infantile atopic dermatitis. Another interesting association is between polymorphisms in the *CD14* gene (that encodes the lipopolysaccharide [LPS] receptor) and low IgE levels. This suggests that there may be a relationship between exposure to bacterial antigens such as LPS and low IgE levels, with the implication that this type of exposure may protect against the development of allergy. Another interesting finding is that many of the loci linked to allergy coincide with loci linked to other inflammatory diseases, in particular inflammatory bowel diseases (IBD). It seems possible that a selective advantage was provided by some of these genes towards (for example) intestinal helminth infections, with which we used to coexist constantly. This advantage may now translate to an over-reactive inflammatory response towards nonpathogenic factors that were, in the past, made irrelevant by the constant presence of microbes and parasites.

The above contentions are supported by genetic studies and by interesting epidemiological studies that are also discussed by Moffatt and Cookson. Furthermore, the proposed close relationship between allergic diseases and parasitic infestations is supported by molecular studies. The review by Corry (pp 610–614) emphasizes the similarities between allergic and parasitic pathologies. Both show analogous Th2 responses — characterized by the production of IL-4, IL-13 and IL-5 — with a resulting increase in IgE synthesis and eosinophilia.

Distinguishing the respective roles of IL-4 and IL-13

The critical role of IL-4 and IL-13 in allergic and parasitic diseases is now well established. However the exact role of the two cytokines has been a subject of much discussion. It is obvious that the cytokines IL-4 and IL-13 have overlapping roles. There is a structural basis for this overlap; their respective receptors share a common component in the IL-4R α chain. The IL-4 receptor is made of the IL-4R α and a common γ chain shared by a number of other cytokine receptors. The IL-13 receptor is composed of the same IL-4R α , associating with IL-13R α 1 and IL-13R α 2. The respective roles of the two cytokines with respect to allergic and parasitic diseases has been analyzed in a number of recent studies. The article by Corry emphasizes the differences as well as the overlapping features of these two critical cytokines.

Pan and Rothman (pp 615–620) focus their attention on a number of recent reports analyzing the role of mutations in the IL-4R α chain, in particular naturally occurring variants that have been associated with allergic diseases. Furthermore they discuss the results of the molecular dissection of various motifs found in the IL-4R α chain, including tyrosine-containing motifs implicated in tyrosine kinase activation and in the transmission of proliferative signals and immunoreceptor tyrosine-based inhibitory motifs (ITIMs) that appear to negatively regulate proliferative signals. Thus, the IL-4R α chain possesses both activating and inhibitory signaling motifs.

The emerging fields of negative signaling and chemokine involvement in allergy

The inhibitory motif found in the IL-4R α chain is a hallmark of a growing number of receptors whose function is to counterbalance the action of classical activating receptors, such as antigen receptors on T cells and B cells or of Fc ϵ RI on mast cells. The field of negative signaling has seen an explosion of new information in the past few years. The list of new members of this family is still growing and encompasses receptors with a clear function and others for which the biology is still unclear. The review by Scharenberg (pp 621–625) summarizes the recent advances in this field and emphasizes the aspects that are the most relevant to the allergic response. In particular, he underlines the importance of the Fc γ RIIb inhibitory receptor in the negative regulation of IgE-producing B

cells and Fc ϵ RI-mediated degranulation of mast cells and basophils.

Chemokines and their respective receptors regulate the trafficking of leukocytes and play an essential role in controlling their migration to the sites of inflammatory reactions. There are now 39 human chemokines and 17 chemokine receptors that have been described. Many of the chemokines bind to several receptors and vice versa, an aspect of the biology of chemokines that complicates their study and the assignment of a specific role for each member. Homey and Zlotnik (pp 626–634) review the chemokines and their receptors and focus on those chemokines known today to be involved in the pathogenesis of allergic asthma and atopic dermatitis. It is becoming clear that the role of chemokines is not restricted to controlling the traffic of leukocytes; some chemokines also participate in promoting cellular differentiation towards the Th1 and Th2 phenotypes.

Several of our articles reflect the fact that complexity in the signaling pathways that control the IgE-based immune response is still emerging. Scharenberg clearly illustrates that fine tuning between positive and negative regulatory responses has been evolved to precisely control the degree of effector responses. It remains to be seen if we have yet gained enough understanding of our intrinsic negative regulatory molecules to translate into a therapeutic approach. The increasing complexity of the chemokine field, and its apparently high degree of relevance to allergy, leaves us with many fascinating questions as well as optimism that targets for therapy may lie within.

Current perspectives in the field: anti-IgE therapy definitively reconnects the early and late phases

Increasing genetic and molecular evidence is emerging for the close ties between allergic and parasitic pathologies. I hope that the reviews in this section provide insight as to how the critical checks and balances of the immune system are, to some extent, used against us in the development of allergy; I also hope that the reviews move us closer to a real understanding of how allergy develops. Perhaps food for thought will also be provided upon the recognition that the cleaning of our society has left a vestigial arm of the immune response with nothing to strike at but harmless allergens.

Finally, it is appropriate to consider how our current insights into IgE networks and Fc ϵ RI signaling have helped in the design of a very promising therapy and are now helping us interpret the results from its clinical trials. There is a humanized anti-IgE monoclonal antibody, rhuMab-E25, which is directed against the Fc ϵ RI-binding domain of human IgE. This agent is currently the basis of a clinical trial for the treatment of allergic rhinitis and asthma. Three results of this clinical trial are worth discussing here because they demonstrate *in vivo* the

existence of some of the critical mechanisms leading to an allergic phenotype.

First, rhuMab-E25 downregulates IgE production. As Scharenberg's article points out, rhuMab-E25 binds not only to free IgE but also to the surface IgE on IgE-producing B cells. In addition, the Fc fragment of rhuMab-E25 then crosslinks inhibitory Fc γ RIIb receptors on these IgE-producing B cells — leading to their decreased proliferation.

Second, rhuMab-E25 downregulates Fc ϵ RI expression on basophils [10] and presumably on other Fc ϵ RI-expressing cells. The downregulation of IgE levels reverses one of the amplification mechanism discussed above: more IgE, more Fc ϵ RI; less IgE, less Fc ϵ RI. Thus the therapeutic effect of decreasing IgE levels is amplified at the receptor level. In turn, this decrease in Fc ϵ RI levels allows a more efficient blocking of IgE binding to effector cells.

Third, rhuMab-E25 reduces both early and late phase responses [11]. I would like to emphasize this result not only because of its importance for the therapy of asthma but also because it demonstrates that one of the most prevalent concepts about the pathogenesis of asthmatic disease should be reassessed. In the field of allergy and asthma, there is a somewhat artificial distinction between the early and late phase responses to allergens. The 'early' phase is due to IgE and Fc ϵ RI on mast cells and basophils and is also called type I allergic reaction or immediate hypersensitivity reaction. It is characterized by the release of histamine and other mediators and in extreme cases may lead to anaphylaxis. The later phase is characterized by influx of many inflammatory cells including eosinophils into an inflammatory site. In my view, there is a necessary linkage between early and late phases and there is no way to dissociate the late phase from the early phase, even when the early phase is undetectable. Analysis of the bronchi of asthmatics — particularly in advanced cases — shows mostly cells involved in the inflammatory processes of the late phase reaction, leading many pulmonary physicians to believe that asthma is an inflammatory disease detached from its early component.

The fact that rhuMab-E25 reduces both the early and late phase response to inhaled allergen, including eosinophil counts in the sputum, suggests that there is an obligatory connection between the IgE–Fc ϵ RI network and the late phase reaction. Most importantly, it indicates that an intervention at the 'early' phase level is

capable of modulating the later inflammatory response. This illustrates that defining the late phase as IgE independent is unsupportable by the data from this human clinical trial. In fact the IgE network is fundamental to the later phase of an allergic response and is a viable target for therapy of the entire disease progression. Now that we have evidence that intervention at the 'early' phase can modulate the disease development as a whole, the recent crystallization of Fc ϵ RI α may prove to be helpful [12]. The crystal structure may help us in the design of new therapeutic agents directed at the IgE–Fc ϵ RI interaction in a manner analogous to the action of rhuMab-E25.

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