

Allergy and hypersensitivity

Editorial overview

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Jean-Pierre Kinet's research focuses on the molecular understanding of the role and function of Fc receptors and antigen receptors in the immune system and in particular in allergy. His recent work has investigated the function of various ion channels and the mechanisms of calcium entry in response to antigen receptor activation.

This section of *Current Opinion in Immunology* is entirely devoted to reviews discussing recent advances in the field of allergy and hypersensitivity. The Editorial overview below will summarize these reviews, point to remaining questions and controversies, and discuss other recent and relevant work. It will also discuss the potential of new therapeutic strategies in allergic diseases.

Adapters: a complex circuitry

IgE-dependent activation of mast cells through the high-affinity IgE receptor (FcεRI) is of central importance in allergy. In the first review, Juan Rivera (pp 688–693) focuses on the essential roles of adapter molecules in the signaling cascades initiated after FcεRI engagement with IgE and antigen. Among these essential adapters are LAT, SLP-76 and Gab2. The purpose of these adapters is to coordinate protein–protein interactions and orchestrate the functions and activities of enzymes within the FcεRI pathway. All of these adapters are capable of interacting with numerous enzymes as well as with other adapters, creating a multitude of interactions that not only enhances the specificity of signaling but also gives more flexibility to generate a diversity of responses. This provides investigators with a unique challenge in understanding the dynamics of signaling complexes that underlie activation. Of particular importance is recent work by the Rivera's laboratory [1] that has uncovered an essential role for Fyn kinase in the Gab2 pathway leading to mast cell degranulation upon FcεRI engagement. Antigen receptors on mast cells, similar to those on T cells, activate at least two Src family kinases (Lyn and Fyn in the case of FcεRI) to initiate downstream signaling cascades. It is becoming apparent that two major signaling complexes are formed, which are localized in different areas of the membrane. The first complex consists of Fyn–Gab2–PI3K and is localized outside the lipid rafts. It is inhibited by Lyn kinase via a phosphatase and, for that reason, becomes constitutively activated in Lyn-deficient mast cells. The second complex is centered around the adapter protein LAT, and is associated with lipid rafts and requires Lyn and Syk activation. It contains SLP76, vav1, Btk, PLCγ1 and 2, and also PI3K (probably from a pool different to the Gab2-associated PI3K pool). The first complex is essential for degranulation and the second one for calcium mobilization. In Syk-deficient mast cells, however, no degranulation or calcium mobilization is observed. Therefore, these two complexes do not function completely independently indicating an additional level of complexity that is not yet understood.

The LAT adapter was initially discovered in T cells by Larry Samelson's group [2]. LAT is as essential to the function of the T cell antigen receptor in T cells as it is to the function of FcεRI in mast cells. In an effort to dissect the importance of specific tyrosine residues to the function of LAT, two independent groups reported that knock-in mice, in which Tyr136 of LAT was replaced with phenylalanine showed a severe inhibition of T cell development followed later by a lymphoproliferative disorder with a Th2 bias that resulted in extremely high levels of circulating IgEs [3,4]. Therefore, the removal of a single tyrosine can sufficiently affect the interactions of LAT with other signaling molecules to induce a dramatic phenotype. Note that the phenotype of mast

cells was not investigated. Nevertheless, these studies emphasized the fact that impairment or modulation in the LAT pathway could contribute to allergic phenotypes.

A new role for IgE

Multivalent allergens aggregate allergen-specific IgEs that are already bound to FcεRI on mast cells and basophils. This process of aggregation of IgEs on the cell surface initiates a signaling cascade that leads to cell degranulation, and the release and synthesis of numerous mediators and cytokines, which together induce the symptoms of the allergic response. Until recently, monomeric (i.e. non-aggregated) IgE binding was thought to be silent in terms of signal transduction and cell activation. Sarbjit Saini and Donald MacGlashan (pp 694–697) review recent data that demonstrate that monomeric IgE can upregulate the level of surface-expressed FcεRI. Furthermore, preventing the binding of IgE to its receptor induces a downregulation of FcεRI levels. In recent clinical trials it was shown that anti-IgE therapy did not only decrease the levels of circulating IgE but also decreased the levels of FcεRI expression; it is therefore likely that part of the therapeutic efficacy of anti-IgE therapy is due to the downregulation of FcεRI. Studies on the molecular mechanism of this ligand-induced receptor modulation have shown that the majority of upregulation can be explained simply by the capacity of IgE to stabilize receptor expression at the cell surface, thereby inhibiting receptor degradation. The steady state levels of cell surface expressed receptors is the result of the balance between new receptor incorporation in the membrane and receptor degradation. As a consequence, decreasing receptor degradation results in receptor accumulation. This is strictly dependent on receptor synthesis and therefore any factors, such as cytokines, that are capable of enhancing or inhibiting receptor synthesis will naturally indirectly modulate receptor accumulation. Another role for monomeric IgE has also been suggested; mast cell survival. This is more controversial because the survival effect seems to require a certain type of IgE and is inhibited by monovalent haptens. Thus, it is not clear whether cell survival can be induced by strictly monomeric IgE or by self-aggregating IgE that could induce weak signaling. Nevertheless, the fact that weak signaling in mast cells may have an anti-apoptotic effect *in vitro* is a novel finding. Follow-up studies are needed to determine whether this *in vitro* observation is relevant to *in vivo* situations.

Inhibitory receptors: a new gold mine

The review by Howard Katz (pp 698–704) summarizes the present state of our knowledge on the role of inhibitory receptors in allergy. The first of these receptors to be identified is FcγRIIB, the inhibitory IgG receptor that is expressed on many cells of the immune system. This receptor was identified long ago and has been studied extensively. Recently, an unexpectedly large variety of other inhibitory receptors has been uncovered that are probably relevant to allergy because they are expressed on mast cells, basophils and eosinophils, that is, cells that are directly implicated in allergic inflammation. A number of investigators have initiated classical gene

targeting experiments as a first step in understanding the function of these receptors. For example, the author's laboratory has used this strategy to demonstrate conclusively that gp49B1 constitutively inhibits mast cell activation [5]. Although this work is paving the way for an understanding of how these inhibitory receptors function in mast cell activation, many questions still remain. What is the relative contribution of each of these inhibitory receptors in regulating the effector response? How are the negative signals generated by these receptors integrated and balanced with the positive signals? Could polymorphisms in these inhibitory receptors contribute to the allergic phenotype? Even with just a glimpse into the role of these receptors, one can predict that the rich diversity of these receptors will lead to the identification of novel targets for therapeutic interventions.

The contribution of anaphylatoxins to allergy, inflammatory diseases and asthma

Norma and Craig Gerard (pp 705–708) summarize the many recent studies involving the complement proteins C3a, C5a and their respective receptors. As in many other fields, genetic deletion and natural mutations have been used to dissect the contributions and mechanisms of action of these anaphylatoxins in various models of inflammation and, in particular, in animal models of lung inflammation and asthma. The authors emphasize that the apparent contradictions seen in some of these animal studies may be explained by the different roles of complement activation in both the immunization and the effector phases of the models. There is also evidence that a correlation exists between the concentration of the anaphylatoxins and the severity of the cellular infiltrates seen in human asthmatic lungs. There is significant interest in the pharmaceutical industry in developing inhibitors to target these pathways. Small molecule antagonists targeting C3a and C5a receptors have been developed and clinical trials are underway to test their therapeutic potential in a number of inflammatory diseases.

Asthma genetics

Genomewide screens for asthma genes in 11 different populations have provided evidence that at least 18 genes contribute to the asthma phenotype; however, the individual contribution of each of these genes to the phenotype is likely small. The review by Sabine Hoffjan and Carole Ober (pp 709–717) summarizes the state of knowledge in this regard and focuses on the IL-4 and IL-13 pathways, which have been implicated in many studies. The review discusses the importance of variations detected in the IL-4 and IL-13 genes in the coding and regulatory regions, in the intergenic region, and in the common receptor α chain and STAT6—the main signal transducing molecule for these two cytokines. Of particular interest are the gene–gene interactions that have been detected between ligand and receptor in this pathway. A polymorphism in the IL-13 promoter was shown to be associated with bronchial hyperresponsiveness, whereas another polymorphism in the receptor α chain was shown to be associated with

serum IgE levels. In the same population sample, however, individuals homozygous for the two alleles had almost a five-times greater risk of developing asthma than those with other genotypes. Obviously our understanding of the genetic influence on the susceptibility to develop asthma is fragmentary at best. The identification of these culprit genes is only the first step. More gene–gene interactions and gene–environment interaction studies are needed. Then the mechanism by which particular gene variants may influence the asthma phenotype will also have to be uncovered before one can understand the pathogenesis of asthma. The hope is that in the process, one will be able to identify pathways that have not been recognized so far that could be attractive targets for therapeutic intervention.

Allergen-specific immunotherapies: en route to the ultimate cure?

The ultimate treatment of all allergic diseases would be the abrogation of the reactivities towards the allergen offenders, or in other words, complete desensitization. When achieved, this desensitization would be curative and would remove any need for other treatments. That desensitization can be induced is not in question; it has been reported using poorly defined allergens. However, desensitization using current methods is unpredictable and can induce serious side effects. In their review, Rudolf Valenta and Dietrich Kraft (pp 718–727) retrace the history of the last decade in this field, from the isolation of a cDNA encoding an allergen to the crystal structure and the engineering of recombinant allergens. An ideal strategy is envisioned and proposed, in which recombinant allergens are mutated to reduce allergenic activity to a minimum, yet in which the T cell epitopes that are necessary to induce a protective antibody response are maintained. Clinical trials are underway to test this approach. This strategy is very promising but its efficacy will require further investigation. For example, the ideal route of administration is not yet clear and treatment may need to be modified according to patient genotype and phenotype. However, there is no reason to think that this strategy will fail and it is only a question of time before some kind of desensitization becomes the routine therapy of allergic disorders. One can even hope that, in the process of learning how desensitization is best elicited, one might also learn how to design regimens for desensitization against the self-antigens of a number of autoimmune diseases.

Mast cells as novel therapeutic targets of autoimmune diseases.

Michaela Robbie-Ryan and Melissa Brown (pp 728–733) discuss the evidence that mast cells are not only involved in allergy and asthma but may also play an important role in autoimmune diseases. The authors remind us that the brain is an organ rich in mast cells and that in multiple sclerosis (MS) patients and in rodent models of MS (experimental autoimmune encephalomyelitis, EAE), mast cells are associated with sites of demyelination. Data generated in their own laboratory show that mast cell-deficient mice have a decrease in the severity of the induced EAE disease

[6]. The magnitude of the disease in these mice is restored after injection of cultured mast cells. These data implicate mast cells as crucial players in the inflammatory processes observed in this autoimmune setting. Interestingly, an independent study has just been published that reports a very similar experiment with analogous results in the context of an autoimmune murine model of rheumatoid arthritis [7]. Together these studies provide a strong argument for an important role for mast cells in at least some autoimmune diseases and point to mast cells as a novel and very attractive therapeutic target in these diseases.

The role of histamine and its receptors in modulating the immune response

Histamine is an important mediator in gastrointestinal and circulatory functions, in neurotransmission and other brain functions, and in inflammatory reactions. It has four different G-coupled receptors to mediate its various biological effects: H1R, H2R, H3R and H4R. Both H1R and H2R are expressed on many cells of the immune system including dendritic cells, T and B cells, monocytes and eosinophils. H4R is expressed on mast cells, basophils and eosinophils. The opinion article by Marek Jutel *et al.* (pp 735–740) focuses on the role of histamine in immune regulation. In particular, the authors summarize the important work done in their own laboratory. Data generated using H1R- and H2R-deficient mice show that histamine enhances Th1-type responses by triggering H1R, the predominant receptor on Th1 cells. In addition, both Th1 and Th2 responses are negatively regulated by H2R. Mice lacking H1R have enhanced expression of Th2 cytokines (IL-4 and IL-13) and increased OVA-specific antibody responses with high levels of IgE and IgG1. In view of the widespread use of various anti-histamines it will be important to test the effect of these drugs on the different receptor pathways and their effects on the immune response.

References

1. Parravicini V, Gadina M, Kovarova M, Odom S, Gonzalez-Espinosa C, Furumoto Y, Saitoh S, Samelson LE, O'Shea JJ, Rivera J: **Fyn kinase initiates complementary signals required for IgE-dependent mast cell degranulation.** *Nature Immunol* 2002, 3:744-748.
2. Zhang W, Sloan-Lancaster J, Kitchen J, Triple RP, Samelson LE: **LAT: the ZAP-70 tyrosine kinase substrate that links T cell receptor to cellular activation.** *Cell* 1998, 92:83-92.
3. Aguado E, Richelme S, Nunez-Cruz S, Miazek A, Mura AM, Richelme M, Guo XJ, Sainy D, He HT, Malissen B, Malissen M: **Induction of T helper type 2 immunity by a point mutation in the LAT adaptor.** *Science* 2002, 296:2036-2040.
4. Sommers CL, Park CS, Lee J, Feng C, Fuller CL, Grinberg A, Hildebrand JA, Lacana E, Menon RK, Shores EW, Samelson LE, Love PE: **A LAT mutation that inhibits T cell development yet induces lymphoproliferation.** *Science* 2002, 296:2040-2043.
5. Daheshia M, Friend DS, Grusby MJ, Austen KF, Katz HR: **Increased severity of local and systemic anaphylactic reactions in gp49B1-deficient mice.** *J Exp Med* 2001, 194:227-233.
6. Secor VH, Secor WE, Gutekunst CA, Brown MA: **Mast cells are essential for early onset and severe disease in a murine model of multiple sclerosis.** *J Exp Med* 2000, 191:813-822.
7. Lee DM, Friend DS, Gurish MF, Benoist C, Mathis D, Brenner MB: **Mast cells: a cellular link between autoantibodies and inflammatory arthritis.** *Science* 2002, 297:1689-1692.