

Atopic allergy and other hypersensitivities

Interactions between genetic susceptibility, innocuous and/or microbial antigens and the immune system

Editorial Overview

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Abbreviations

IFN	Interferon
IL	Interleukin
STAT	Signal transducer and activator of transcription
TCR	T cell receptor
Th	T helper
Th1	Type 1 Th
Th2	Type 2 Th
TNF	Tumor necrosis factor

In the past few years, convincing evidence has accumulated to suggest the existence of functionally polarized responses by the CD4⁺ T helper (Th)-cell subsets that depend on the cytokines they produce (reviewed in [1] and [2]). Type 1 Th (Th1) cells produce tumor necrosis factor (TNF)- β and the macrophage-activating interferon (IFN)- γ , thus providing a phagocyte-dependent protective response. By contrast, type 2 Th (Th2) cells produce interleukin (IL)-4, IL-5, IL-10 and IL-13, which trigger vigorous antibody responses, including IgE production, and inhibit several macrophage functions, thus providing a phagocyte-independent protective response [1,2]. Obviously, the CD4⁺ Th cell-mediated effector response is much more complex and sophisticated than a simple Th1 or Th2 split and there are clearly Th cells secreting combinations of cytokines that defy the paradigm [1,2]; however, the Th1/Th2 terminology has proved extremely useful for better understanding and synthesizing a complex reality, as well as for stimulating many studies in different fields of biology and medicine. Th1- or Th2-dominated responses are not only responsible for distinct types of protection against infectious agents, but also appear to be involved in the pathogenesis of several immunopathological conditions, including some hypersensitivity states. For example, Th1 responses play a pathogenic role in organ-specific autoimmune disorders, whereas Th2-dominated responses against innocuous antigens (allergens) are responsible for atopic allergy (reviewed in [3]).

The molecular mechanisms responsible for Th1 or Th2 polarization are now being clarified. The early presence

of IL-4 at the time of antigen presentation is the most potent stimulus for the Th2 differentiation, whereas IL-12 and IFNs favor Th1 development [1–3]. The binding of these cytokines to their receptors typically results in rapid tyrosine-phosphorylation of signal transducers and activators of transcription (STATs). Of these, STAT4 appears selectively activated by IL-12 and targeted disruption of *Stat4* gene results in the inhibition of Th1 responses. On the other hand, signaling by IL-4 occurs through activation of STAT6, and knockout of the *Stat6* gene results in deficient Th2 responses [1]. *Stat4* and *Stat6*, however, are not the only genes that regulate the expression of IFN- γ and IL-4, respectively, in Th cells. As discussed in this issue by Szabo et al. (pp776–781), several key transcription factors are involved in the development of Th2 cells. While the interaction of IL-4 with its receptor on naive T cells results in STAT6 activation, antigen interaction with the T-cell receptor (TCR) results in the activation and translocation of NF-AT proteins to the nucleus where they can interact with NIP45, giving rise to the *de novo* synthesis of AP-1 proteins. Then, two events which appear to be critical for IL-4 expression in the Th cell and subsequent commitment to the Th2 pathway occur: (a) maintenance of GATA-3 expression, and (b) induction of the proto-oncogene c-maf. c-maf's transcriptional activity appears to be specific to the IL-4 promoter, since it is unable to transactivate the promoters of other Th2 cytokine genes, such as IL-5 and IL-10, while GATA-3 may function as a more general regulator of Th2 cytokine expression. In contrast, in the case of naive Th precursors activated under Th1-inducing conditions (in the presence of IL-12 and the absence of IL-4), c-maf expression is not up-regulated and GATA-3 expression is extinguished. It is still unclear, however, whether a factor analogous to c-maf or GATA-3, which is specific for Th1 cells, exists.

The early production of IL-4 or IL-12/IFN- γ at the time of antigen presentation, which triggers the cascade of transcription factors responsible for Th cell polarization, is under the influence of both environmental and genetic factors. Among environmental factors, a role has been demonstrated for the route of antigen entry, the physical form of immunogen, the type of adjuvant, and the dose of antigen [3]. Thus, it is obvious that pathogens themselves can influence the type of Th response that develops in the infected host. For example, some intracellular bacteria and viruses stimulate IL-12/IFN- α /IFN- γ production by cells of the innate immune system, thus favoring the

development of Th1 responses. In Th2 development, the initial stimulus, as well as the source, for IL-4 production has not been clearly defined. Likewise, the genetic mechanisms that concur in controlling the differentiation of Th cells into the prevalent Th1 or Th2 profile still remain elusive.

The preferential development of specific Th2 responses against innocuous antigens (aeroallergens and food allergens) in a minority of the population (the so-called atopic individuals) reflects, at least in part, alterations in mechanisms of neonatal tolerance, which are discussed in this issue by Holt and Macaubas (pp782–787). These authors point the fact that the failure of newborn animals to develop adult-equivalent T-cell memory following parenteral immunization is due to an intrinsic skewing within the T-cell compartment towards the Th2 cytokine phenotype, leading to a failure to prime for Th1 immunity, which is maintained by dendritic cells. Accordingly, several reports suggest that initial T-cell priming against major environmental allergens occurs as a result of their transplacental transfer, particularly during the last trimester. There is some indication that this Th2-priming process may be strongest in infants with positive atopic family history, which suggests an important role for genetic alterations of mechanisms that control IL-4 production in the pathogenesis of atopic allergy.

Genetic alterations, however, are not sufficient to explain all cases of atopic allergy, as suggested by the observation that prevalence of allergy is increasing over recent decades in developed countries. This suggests an additive role of environmental factors in regulating the development of Th2 cells and/or of their function. Three years ago, in contrast with the current view that the rising prevalence of atopy in developed countries was due to pollution, I suggested that this increase could be at least partly related to the strong reduction in childhood infections (just when aeroallergen sensitization is occurring), particularly tubercular infection, which induces the production of cytokines antagonistic to Th2 development [4]. This hypothesis was mainly based on *in vitro* data obtained in my laboratory showing that cytokines produced by cells of the 'innate immune system' (macrophages, NK cells) in response to *M. tuberculosis* and/or its components, as well as to synthetic double-stranded RNA polyinosinic acid; polycytidylic acid, are able to shift the development of allergen-specific T cells from the Th2/Th0 to the Th1 profile [3]. Two recent epidemiological studies, which are discussed in this issue by Hopkin (pp788–792), strongly support the possibility that the decline of tubercular infection and perhaps of other infections in childhood is an important factor underlying the rising severity and prevalence of atopic disorders over the last decades in westernized societies. A highly significant inverse association between delayed hypersensitivity to *M. tuberculosis* and atopy was indeed found among Japanese schoolchildren. Positive tuberculin responses were associ-

ated with a lower incidence of asthma, lower serum IgE levels, and cytokine profiles biased toward Th1 responses; this suggests that exposure and response to *Mycobacterium tuberculosis* (*M. tuberculosis*) during childhood may, by modification of immune profiles, inhibit the development of atopic disorders. Likewise, African children who had been vaccinated with measles virus showed significant increased risk of a positive prick test to house dust mite than unvaccinated children who had had natural measles infection. The cytokines produced in response to *M. tuberculosis* and double-stranded RNA viruses, that are able to down-regulate the development and/or function of allergen-specific Th2 cells, are IL-12, IFN- γ and IFN- α . Thus, changes in the infectious environment may have really been of great importance in influencing the increased prevalence of atopic allergy in westernized societies and in higher social classes within communities. It should be recalled that microbes involved in changes of immune system programming do not necessarily have to be pathogens since saprophytes, particularly those that constitute the microflora of the gut, may also play a role in planning the development of effector functions in the immune system. As suggested by Hopkin in his article (pp788–792), the density and character of these microflora can be significantly affected by life style or oral antibiotics with the potential to disturb immune programming through gut-associated lymphoid tissue.

Interactions between genetic susceptibility, microflora of the gut and the immune system certainly play an even more important role in the genesis of Crohn's disease, another hypersensitivity status which has been discussed in this issue by Romagnani et al. (pp793–799). Their article summarizes evidence which suggests a critical role for activated CD4⁺ T cells showing a Th1-like profile of cytokine production in the pathogenesis of Crohn's disease. The cytokines produced by Th1 cells activate local macrophages to release pro-inflammatory cytokines, toxic oxygen metabolites and NO, which are responsible for the transmural intestinal inflammation. Moreover, recent data indicate that the Th1 response at intestinal level is initiated and maintained by enhanced IL-12 production, probably in the presence of defective IL-4 and/or IL-10 production, which results in the breakdown of tolerance against the intestinal microflora. Thus, Crohn's disease appears to represent a hypersensitivity condition with an opposite cytokine profile to atopic allergy, which provides additional support to the validity of the Th1/Th2 paradigm.

The great progress in the knowledge of interactions between innocuous or microbial antigens and the immune system allows us to hope for the development of new therapeutic approaches for hypersensitivity states. Successful results have been reported in the treatment of patients with Crohn's disease by administration of anti-TNF- α antibody, which neutralizes one of the most dangerous inflammatory cytokines, and are expected by

the administration of IL-10, which inhibits the production of IFN- γ by T cells and the pro-inflammatory activities of macrophages.

New therapies for atopic allergy are also being developed. As discussed in this issue by Huang *et al.* (pp800–804), DNA-based immunization with Der p 5, one of the allergens of the mite *Dermatophagoides pteronyssinus*, induces the production of IgG, but not IgE, and results in 90% reduction in the level of specific IgE antibody induced by classic sensitization with Der p 5 plus alum as adjuvant, as well as of allergen-induced airway hyperresponsiveness. The suppression of both specific IgE antibody production and airway hyper-responsiveness is due to a biased Th1 immune response, which could be transferred with CD8⁺ T cells from DNA-immunized animals. The inhibitory effect of DNA-based immunization on the synthesis of specific IgE antibody has also been demonstrated in a model based on the injection of a gene construct encoding β -galactosidase (β -gal). Interestingly, the Th1 response induced by DNA-based immunization was found to be able to suppress an ongoing β -gal protein-induced Th2 response in an antigen-specific manner. Thus, the DNA-based immunization approach seems to represent a possible new therapeutic strategy for allergic disorders.

Another novel therapeutic strategy for atopic disorders is the use of humanized monoclonal anti-IgE antibody.

This strategy has already been discussed by Jardieu [5]. At that time, only the concept and attractiveness of non-anaphylactogenic anti-IgE antibodies as therapeutic tools were discussed. In this issue, Heusser and Jardieu (pp805–814) provide more complete information on the effects of these antibodies, their functional activities in animal models, such as inhibition of skin reactions, inhibition of lung eosinophilic infiltration and lung T cell cytokine production, their effects on bronchoconstriction and bronchial hyperreactivity, and their safety. More importantly, the results with humanized anti-human IgE antibodies on rhinitis symptoms and asthmatic response are reported. Clinical trials in patients with allergic rhinitis and allergic asthma reveal that these antibodies are well tolerated and represent excellent candidates for the inhibition of allergic inflammatory reactions and, therefore, for successful treatment of allergic diseases.

References and recommended reading

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