A question of nature: some antigens are bound to be allergens

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Keywords: allergy, helminth, evolution, Th2, allergen, cross-reactivity, allergenicity

Many allergens are proteins that have homologs in metazoan parasites, such as helminths [reviewed in Ref. (1)]. Indeed, it was proposed that this is a feature of most or even all environmental allergens (1). It has also been hypothesized that allergenicity itself would depend on the homology between allergen and helminth (2): a molecule would be an allergen because it would share antigenic determinants with a parasite — a question of nature. This notion was based on (i) the fact that the immunity against helminths is associated with a Th2, IgE-producing immune response (3–8); (ii) the fact that many allergic diseases are caused by this same type of immune response (9); (iii) the premise that there would be a propensity to mount Th2 immune responses against helminths and, of course, against antigens sharing antigenic determinants with them.

The sharing of antigenic determinants with parasites would not be the only feature of a molecule that would lead to the elicitation of a Th2 immune response. For instance, the honey bee venom phospholipase A2 elicits a Th2 immune response by disrupting the epithelial cell membrane and releasing IL-33, a cytokine that promotes the Th2 immune response (10). In addition, four (out of more than 20) aeroallergens from the dust mite Dermatophagoides pteronyssinus are proteases (11–13). They might elicit a Th2 immune response by directly inducing the release of another Th2 immune response-promoting cytokine, the IL-4, from mast cells, as suggested by an in vitro study (14) or by acting as described above for the bee venom phospholipase A2.

The allergenicity of a molecule, therefore, could depend on factors (13) other than the sharing of antigenic determinants with helminths. The hypothesis that allergenicity could depend on this sharing of antigenic determinants could, anyway, still hold for most allergens, which are not proteases. It does not entail, however, that someone would have first to be infected by a helminth for cross-reactive memory Th2 cells to be formed and later on become activated by an allergen. This would be contradicted by the increased prevalence of allergic reactions in populations in which helminth infections are reduced, such as those from industrialized countries (15,16).

In order to account for the elicitation of cross-reactive Th2 immune responses by allergens sharing antigenic determinants with helminths in individuals who have not been in contact with those parasites, an expanded helminth-reactive Th2 cell population should constitutively exist in these individuals. The evolution of this expanded helminth-reactive lymphocyte population would have to had been accounted for, of course, by the effects of random mutation and natural selection. In addition, the selective pressure could not had varied to a great extent along relatively short periods of time, and in this case, immune responses against ubiquitous and more conserved antigenic molecules should have been the best candidates to be the targets of the selection.

However, natural selection cannot significantly modify the repertoire of the immune system as a whole, due to the enormous variability of the antigen-recognizing receptor that occurs during the somatic differentiation of the lymphocytes: one cannot select for a character that will appear after the selection. Therefore, the selection should be exerted on a subpopulation of lymphocytes with a relatively limited repertoire of antigen recognition. This subpopulation does indeed exist.

Non-template (N)-nucleotide additions in the DNA encoding the antigen-recognition moieties (complementarity-determining regions) of T-cell receptors/antibodies are the major determinants of immunological diversity (17,18). These N-nucleotide additions do not occur (in the case of the mouse) or occur in a reduced degree (in the case of human beings) early in ontogeny (19). Cells with receptors containing proteins encoded by these genes without N-nucleotide additions (N−) persist in adult life with an antigen-recognition repertoire rather less variant than that of the cells whose genes coding the antigen receptors had the N-nucleotide additions (N+) (19). Newborn N− T cells have been shown to be Th2 cells, and they, and their N− B cell counterparts, are found in high frequencies in the mucosa-associated lymphoid tissues (20–23).

Because these cells are Th2 cells, are preferentially present in the mucosa, and have a reduced antigen-recognizing repertoire, and despite the fact that they, as a whole, have been shown to be multireactive (19), we propose that, due to natural selection, their N− repertoire is biased to the recognition of ubiquitous parasite antigens. This hypothesis is amenable to experimental testing.
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ACKNOWLEDGMENTS

Lain Pontes-de-Cardalvo and José Mengel are recipients of productivity scholarships from the Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPq.
Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.