The Role of IgG4 as Blocking Antibodies in Asthmatics and in Bee Keepers

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Abstract

Sera from 40 asthmatic patients and from 77 bee keepers were evaluated by solid-phase radioimmunoassay for their allergen-specific IgG4 antibody levels. The results indicated that allergen-specific IgG4 antibodies become prominent upon repeated parenteral stimulation with antigen, i.e. immunotherapy and bee stings, and suggested the possible association of IgG4 with blocking antibodies in these allergic conditions.

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It has been well established that degranulation of basophils and tissue mast cells, upon the interactions between cell-bound IgE antibodies and specific allergens, plays an important role in inducing symptoms of immediate hypersensitivity. It has been also known that human basophils and mast cells bind IgG antibodies besides IgE [1, 2]. Recently, antibodies of the IgG4 subclass have been claimed to represent in man the 'second type of homocytotropic antibodies'. The role of IgG4 in immediate hypersensitivity reactions has been quite controversial in this respect; some investigators proposed the association with so-called IgG short-term sensitizing anaphylactic antibodies [3], while some authors suggested that allergen-specific IgG4 might react as allergen-neutralizing or blocking antibodies in a certain type of allergic disorders [4, 5]. We have previously quantified human basophil de-granulation induced by antibodies specific for IgE and IgG4 with flow-cytometry and showed that (1) not only IgE but also IgG4 molecules are present on basophil surface, (2) basophils from allergic donors possess higher amounts of IgE and IgG4 as compared to those from nonallergic donors, and (3) sensitization of basophils with excess amounts of IgG4 antibodies may inhibit IgE-mediated basophil degranulation [6,7]. Since these data indicated that IgG4 subclass is also a functional component of immediate hypersensitivity with the possible role as blocking antibodies, we subsequently determined allergen-specific IgG4

antibody contents in sera collected from 40 asthmatics sensitive to house dust mite *Dermatophagoides faunae* and from 77 bee keepers, in order to demonstrate this point further. Allergen-specific IgE, IgG and IgG4 antibodies were determined by solid-phase radioimmunoassay employing anti-IgE, anti-IgG (Pharmacia, Sweden) and anti-IgG4 (gift from Dr. F. Skvaril, University of Berne, Switzerland), respectively.

In assessment with sera collected from asthmatic patients, it was shown that asthmatics undergoing specific immunotherapy possess a significantly higher mean value of house dust mite specific IgG4 antibodies than normal controls and asthmatics without immunotherapy ($p < 0.01$ and $p < 0.05$). Moreover, evaluation of 11 patients before and after immunotherapy revealed that

IgG4 antibodies tend to increase during immunotherapy. It appears that the asthmatic patients who responded fairly well to immunotherapy tended to show increased IgG4 antibody levels. In addition, there was a significant correlation between the levels of IgG and IgG4 antibodies ($r = 0.51$), but not between those of IgE and IgG4 antibodies, in asthmatic patients [8].

Then we evaluated the relationship between the presence of allergen-specific IgE and IgG4 antibodies and their effect on the response to bronchial provocation tests in 10 asthmatic patients sensitive either to house dust mite or to *Candida albicans*. It was found that the presence of IgE antibodies is associated with the appearance of immediate and dual responses, but

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the presence of IgG4 antibodies is not necessarily associated with the appearance of late asthmatic response upon bronchial antigen challenge, in contrast to the previous report by Gwynn et al. [9] who showed that IgG4 antibodies may produce late asthmatic reactions. It was also found that the levels of IgG4 antibodies were not affected at all during bronchial provocation tests [10].

In assessment with sera collected from bee keepers, we employed phospholipase A (PLA), a major aller-genic substance from bee venom, as a coupling antigen to solid phase. It was found that the levels of PLA-specific IgG and IgG4, but not IgE, antibodies are significantly higher in bee keepers than those in nonallergic individuals ($p < 0.01$ and $p < 0.001$). It was also found that PLA-specific IgG4 antibodies tend to increase as the frequency of bee stings per year goes up. In addition, there was a significant correlation between the levels of IgG and IgG4 antibodies ($r = 0.75$), while no relationship was observed between IgE and IgG4 antibody levels in bee keepers, as was the case for asthmatics. However, it was not clear whether IgG4 antibodies act as blocking antibodies in our study, and further experiments remain to be done, including bee venom sensitive individuals with specific immunotherapy, to elucidate the exact role of IgG4 in bee sting allergy [11].

In conclusion, the experimental results obtained so far indicated that allergen-specific IgG4 antibodies become prominent upon repeated parenteral stimulation with antigen in asthmatics and in bee keepers, and suggested the possible association of IgG4 with allergen-neutralizing or blocking antibodies which produce protective effect during clinical course in these allergic conditions.

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