Component-Specific Immunoglobulin E in the Diagnosis of Allergic Disease in Childhood: More of the Same or Something More?

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Although the alarming rate of increase in the prevalence of allergic disease and asthma in the last decades of the 20th century seems to have abated [1,2], allergic rhinitis, atopic dermatitis and asthma are by far the most common chronic diseases affecting children worldwide.

Allergic disease in childhood is an end result of complex interactions between genetic factors and environmental exposures [3], leading to a phenotypical progression of symptoms, from food hypersensitivity and allergic eczema in the first year of life to respiratory disease (allergic asthma and rhinitis) in later years – a sequence of events aptly named "the allergic march" [4]. Each of these allergic manifestations may have its own clinical presentation and course as well as temporal progression, with some – for example cow's milk hypersensitivity [5] and atopic dermatitis [6] – most likely to resolve in the preschool years, while others are more likely to persist.

The hallmark of allergic disease is an immune system skewed towards a Th2 predominant phenotype, with increased production of immunoglobulin E and sensitization to environmental allergens (allergen-specific IgE). Increased levels of total serum IgE at birth and in early life have been associated with an increased risk for the development of persistent asthma [7,8] and atopic dermatitis [9]. Early sensitization and levels of sIgE to perennial respiratory allergens have been associated with increased risk of childhood asthma [10,11]. In the field of food allergy, quantitative measurements of sIgE in the serum of sensitized children correlate well with the risk of challenge-associated reactions [12,13], and decreases in this level over time seem to correlate with the resolution of the clinical reactivity [14].

Several factors have led to the availability and use of detailed maps of component- and even epitope-specific sensitization data for both research and clinical applications [15]. These include: advances in the identification, isolation and characterization of the specific component proteins eliciting hypersensitivity responses from various allergen sources [16-18]; molecular tools for rapid expression and mass production of recombinant replica of these protein components [16]; and the development of tools enabling the simultaneous measurement of quantitative sIgE to a large number of antigens in a relatively small serum sample using micro-arrays and recombinant technologies [19].

The aim of this review is to familiarize the reader with the state of the art in component- and epitope-specific diagnosis in allergic disease in childhood, as well as future prospects for novel therapeutic approaches incorporating these data.

Peptide-specific diagnosis of food hypersensitivity

Cow's milk allergy

Although it is held that cows' milk allergy presenting in infancy almost invariably resolves by 6 years of age, IgE-mediated cows' milk allergy can persist throughout childhood and into adult life [20]. Age-dependent levels of cow's milk-specific IgE can predict with 90% or 95% accuracy challenge-associated clinical responses [12,13], but not the severity of the reaction or the probability of persistence. It has become clear that the persistence of clinical reactivity is in part driven by the development of specific IgE recognizing linear (non-degradable as opposed to conformational, or three dimensional) epitopes of allergenic proteins (as1-casein, as2-casein, and k-casein) in milk [21,22]. Milk epitope-specific IgE was significantly higher in patients with persistent cows' milk allergy reaching the second decade with a significantly improved discriminant capability when compared to patients who developed early (by age 3 years) or even delayed (by age 8) tolerance [23].

Peanut allergy

Studies on the natural history of peanut hypersensitivity have shown that in about 20% of children the clinical allergy resolves even when evidence of sensitization (skin-prick test or serum) persists [24]. Both the pattern (recognition of specific major immunodominant peptide epitopes on Ara h1 and Ara h2) and the intensity of peptide-specific IgE in patients with severe reactions differ significantly as compared to patients with mild reactions or those who have acquired tolerance [25]. Moreover, in a recent study of skin-prick test using recombinants of the three major peanut allergens, Ara h1, h2 and h3, Astier et al. [26] showed that patients monosensitized to Ara h2 had significantly lower severity scores compared to patients with multiple component sensitization.

Oral allergy syndrome, natural rubber latex allergy, and IgE to cross-reactive carbohydrate derivatives and profilins

Component-resolved diagnosis of allergenic proteins has led to the recognition of cross-reactive IgE-binding epitopes without clinical

Ig = immunoglobulin
sIgE = allergen-specific IgE

associated-disease, mainly from plant and food sources. These structures (mainly carbohydrates and ubiquitous proteins, like profiling) are capable of binding IgE *in vitro* but generally do not show positive skin-prick test responses or cause significant allergic disease and are a cause of false positive sensitization [27].

Recombinant allergen–IgE cross-inhibition studies have shown that the sensitizing agents in a significant proportion of food-allergic patients with oral allergy syndrome are pollen-derived allergens ultimately responsible for many forms of plant food allergy [28].

Component-resolved diagnosis of dust mite allergy

The most prevalent and well-studied indoor perennial allergen sources are the domestic mites. More than 10 species have been found in house dust, 3 of which are very common in homes worldwide and are the major source of mite allergens [29]. The most common of these species are the D*ermatophagoides farinae* and D*ermatophagoides pteronyssinus* (family Pyroglyphidae). In tropical climates, the storage mite B*lomia tropicalis* (family Echymyopodidae) can be a prevalent mite in dwellings, mostly in cohabitation with the P*yrogliphid* mites, leading to dual or multiple sensitizations in susceptible individuals. In addition, other astigmatid mites (storage mites) can be found in homes and are a potent source of allergens. Most notable are species in the families Glycyphagidae (G*lycyphagus domesticus* and L*epidoglyphus destructor*) and the Acaridae (T*yrophagus putrescentiae* and A*carus siro*).

In the last few years significant advances have been made in the identification and characterization of specific mite allergenic proteins, their function and localization as well as the relative importance for species-specific sensitization and cross-reactivity with other mite-associated as well as non-mite allergens [30].

Patients sensitized to house dust mites can be subdivided on the basis of their component-resolved responses into two groups: those sensitized only to the house dust mite major allergens (group 1 and group 2 in the P*yroglyphid* mites) and those with a broader pattern of sensitization, including highly cross-reactive epitopes (e.g., the group 10 tropomyosins). In geographic areas with dual or multiple mite species exposure, Manolio and colleagues [31] found that the presence of specific IgE to both Blo t5 (the major allergen of B*lomia tropicalis*) and Der p1 (the major allergen of D*ermatophagoides pteronyssinus*) is associated with an increased risk of asthma. Studies of component-resolved dust mite sensitization in children with respiratory allergy have shown that the most common epitopes involved (after group 1 and 2 allergens contributing approximately 50% of all mite-specific IgE in these patients) are allergenic groups 4, 5 and 7 – each contributing approximately 10% of the total mite-specific IgE measured [32]. The data are important for the future formulation of an immunomodulatory vaccine that is component-based as well as for tailoring immunotherapy for individual patients.

Component-resolved diagnosis of pollen allergy

The availability of protein- and epitope-specific diagnostic tools has been shown to differentiate patients with both sensitization and clinical disease on exposure to allergenic pollen from birch and grass from those with sensitization but without evidence of clinical disease [33].

Sensitization to unique allergenic epitopes from specific grasses has increased the diagnostic accuracy and enabled the use of more effective single component immunotherapy vaccines in patients with allergy to G*raminea* (grass) and multiple positive skin-prick test to these closely related allergenic sources [34].

Epitope-specific sensitization to fungi and molds

Studies of sensitization to fungi and molds in patients with respiratory allergy almost universally demonstrate a significant number of patients simultaneously sensitized to two or more fungal species [35,36]. Epitope-specific diagnostic tools have the capability of resolving the question of whether this finding is due to multiple concomitant sensitization events secondary to multiple exposures or to sensitization to one or more common allergenic proteins abundant in more than one fungal species. Moreover, skin testing with recombinant epitopes from A*spergillus fumigatus* can facilitate the differentiation of asthmatic patients with allergic bronchopulmonary aspergillosis from those with fungal IgE sensitization [37].

Future "components" in the diagnosis and treatment of allergic disease

Identification of T cell-specific epitopes in major allergenic protein components, i.e., amino acid sequences that are capable of inducing T cell-mediated recognition but not IgE-mediated reactions, may enable future immunomodulatory vaccines "lacking" the currently ubiquitous immediate side effects of immunotherapy.

Individually tailored component-based immunotherapy vaccines should prove more effective since they address specifically the pattern of sensitization in each individual patient, and they are safer because they avoid inadvertent reactions induced by the new sensitizing epitopes present in the currently available extracts [38,39].

Finally, recombinant therapy could enable the production of stable "one protein fits all" constructs, which could include all major unique sensitizing epitopes of, for example, perennial respiratory allergens. These, together with the appropriate adjuvants, may allow for universal immunization strategies against "the allergy epidemic."

Conclusions

Component-resolved diagnosis in allergic disease in children enables better definition of clinical reactivity, challenge-associated severity and prognostic accuracy than the commonly available quantitative, allergen-specific tests. As such, it is likely that these tests will become available for both diagnostic and therapeutic use.

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