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EDITORIAL

Component-resolved allergen testing: The new frontier

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Abstract

The discovery that allergen specific IgE (sIgE) identified individuals who were allergic to specific allergens, revolutionized allergy and immunology. Recently, component-resolved allergen testing (CRD) has shown promise in improving the field yet again. Prior to development of CRD immunoassays, whole allergen extracts were used to detect IgE mediated allergic disease either by oral, cutaneous, or conjunctival provocation. The most widely used immunoassays detect sIgE to either whole allergen sources or individual allergic components. The use of CRD micro-assay technology (not Food and Drug Administration approved in the United States) has been used to evaluate multiple allergens in parallel. This technique allows for determination of primary *vs* secondary sensitizations from either close sequence homology or cross-reactive carbohydrate determinants. Published studies have shown beneficial uses in hymenoptera venom immunotherapy, anaphylaxis, and food allergy. The use of component testing for aeroallergen immunotherapy has been studied, however clinical use is hampered by lack of allergen components approved for injection. Therefore, although promising in many respects, the frontier of CRD testing requires more data before it can be widely used in clinical practice.

Key words: Component resolved diagnosis; Molecular allergy; IgE; Polysensitization; Immunotherapy; Venom allergy; Food allergy

Core tip: Component-resolved allergen diagnostic testing is testing for specific allergenic proteins in a given allergen. This testing modality may revolutionize diagnostics and treatment of immediate hypersensitivity reactions. Several promising studies and allergen components have been described for patients with food allergy, venom allergy, and idiopathic anaphylaxis. Some appear to have clinical utility, such as ω-5 gliadin in evaluating wheat dependent, exercise induced anaphylaxis. Components for many of the relevant aeroallergens have been characterized; however, readily available allergen components for injection are lacking, and further research is needed before these practices can be recommended for

widespread clinical use.

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INTRODUCTION

The discovery of IgE in 1966 by the Ishizaka group provided a molecular explanation for the underlying cause of Type 1 hypersensitivity[1]. Soon after its discovery, *in vitro* methods to detect allergen specific IgE (sIgE) were developed. Prior to this discovery, detection of Type 1 hypersensitivity reactions were based on clinical history and provocation *via* oral, cutaneous, or conjunctival routes, all of which carried a significant risk of allergic reactions including anaphylaxis.

We now know that Type 1 hypersensitivity reactions are secondary to cross-linking of IgE bound to the high affinity FcεRI on mast cells and basophils resulting in the release of inflammatory mediators (*e.g.*, histamine and leukotrienes). Bound IgE in this case is specific to a particular allergen; in fact, it is this IgE that makes an environmentally innocuous substance capable of eliciting an allergic reaction. Through the widespread use of DNA and molecular sequencing we have found that allergen sources such as timothy grass pollen contain many different proteins-some of which drive allergic responses and others that have no pathogenic potential[2-4]. Current *in vivo* and *in vitro* testing for IgE mediated allergies uses extracts from allergen sources. False negative results can occur because the individual extracts may not contain relevant allergens for a specific patient. These tests are also limited because they do not allow discrimination between true allergy and sensitization from cross-reactive allergens[5,6].

There are many reviews discussing the more than 130 available allergy components from more than 50 allergy sources[2,3,7-10]. Components consist of several different protein families including storage proteins, profilins, cross-reactive carbohydrate determinants (CCD), and serum albumin, to name a few. Many of these components have been shown to cross react with plants that are taxonomically unrelated. An example is the Bet v 1 homologue, a pathogenesis-related protein family 10 (PR-10) protein from birch (*Betula verrucosa)*, associated with oral allergy syndrome. There is known pollen cross reactivity with *Rosaceae* fruits (apple, cherry, apricot, peach, and pear) and *Apiceae* vegetables (celery and carrot)[7]. This cross-reactivity, and the subsequent clinical disease of oral allergy syndrome, highlights the importance that component testing may play-especially in polysensitized patients. Components were already being identified in 1999 when Valenta *et al*[11] proposed the term component resolved diagnostics to refer to the science of determining specific allergenic protein(s) to which a patient is sensitized. Another term applied to this field is "molecular-based allergy diagnostics".

In this editorial review we aim to describe currently available technology and uses for component resolved diagnostic testing. Promise has been shown in the diagnosis and treatment of anaphylaxis, food allergy, and allergen and hymenoptera venom immunotherapy. For the sake of this editorial we will limit our discussion to several representative allergen components. For a more thorough discussion, we recommend one of the comprehensive reviews on this subject[2,3,5,7,8,10].

SINGLE COMPONENT *VS* MICROARRAY TESTING

At the present time the FDA has only approved testing for single components (or allergens). Two frequently used enzyme linked-immunoassays are ImmunoCAP ™ (Phadia/Thermo Fischer Scientific, Uppsala, Sweden) and Immulite (Siemens Healthcare Diagnostics, Los Angeles, CA, United States)[12]. Both of these assays are quantitative for serum IgE to a particular allergen source or component, however values cannot be compared between the two due to differences in assay technology. ImmunoCAP uses a 3-dimensional cellulose sponge matrix with either complete allergen sources or allergen components that are covalently bound. In contrast, Immulite uses an allergen source or component coated bead.

In an effort to determine sensitivities to more than one component, the use of microarray technology has been explored. ISAC (Immuno Solid phase Allergen Chip) 112 (Phadia/Thermo Fischer Scientific, Uppsala, Sweden) uses ImmunoCAP technology to detect 112 allergy components[10]. It has been increasingly used in Europe, although it is not FDA approved. Allergen components are fixed to the microarray slide surface and component sIgE from the serum is then determined, much like single component testing. However, unlike single component testing, microarray technology can evaluate multiple allergen components in parallel. In polysensitized individuals this allows for a more comprehensive view of the sensitization profile, as well as identifying possible cross-reactive pollen or food proteins. Each assay has advantages and disadvantages as shown in Table 1.

Whether using microarray or single component testing, results must be interpreted with care. Positive values denote sensitization, but may be clinically irrelevant. This is especially important with regards to food allergy. To the untrained clinician a positive result despite tolerance in the diet may prompt removal of important protein sources (*e.g.*, milk and soy) needed for proper growth and development. For this reason these tests should be ordered only by those trained to properly interpret the results.

Table 1 Comparison of single component and microarray tests

Single component	Microarray
Serum	Serum or plasma
40 μL per component	30 μL total
One allergen at a time	Up to 112 allergens in parallel
Recombinant, natural, or crude protein	Natural or recombinant protein
Quantitative	Semi-Quantitative
Automated	Manual
Can be affected by high total IgE	Interference between IgE and IgG
Highly sensitive	Less sensitive

POTENTIAL USES OF CRD TESTING

There are several proposed uses for CRD testing in allergy including allergen and hymenoptera venom immunotherapy (allergy shots), risk stratification for food allergy, latex allergy diagnosis, and evaluation of anaphylaxis[10,11,13]. There have been promising results using CRD in many of these areas, as discussed below.

Anaphylaxis

Allergists define anaphylaxis as a life threatening, systemic, immediate hypersensitivity reaction involving more than one organ system. The most commonly implicated triggers are medications, food, and hymenoptera venom[14]. Fortunately in the vast majority of cases, with the exception of hymenoptera, the correct agent is identified. However, in those patients who have repeated or even delayed episodes of anaphylaxis without any trigger (*i.e.*, idiopathic anaphylaxis) there is a need for a better way to identify causative antigens. In fact, a recent article discussed the use of the ISAC array to identify likely causes of idiopathic anaphylaxis in 20% of patients studied[15].

In adult patients it has been shown that co-factors are relevant in 39% of food allergy anaphylaxis[14]. Exercise, the most commonly implicated co-factor, has been associated with reactions to ω-5 gliadin in wheat. In 1999, Palosuo *et al*[16], described 18 adult patients with this clinical phenomenon. All 18 patients had sIgE against ω-5 gliadin (Tri a 19) in their sera, and in 15 of them this reactivity was verified by skin prick testing. Wheat avoidance prior to exercise prevented recurrence in 15 of the patients. Interestingly, the three patients who continued to have recurrent symptoms were shown to have unintentionally ingested wheat products prior to the exercise. Using a cutoff of 0.89 kU_A/l for ω-5 gliadin achieved a sensitivity of 78% and specificity of 96% for the detection of wheat dependent exercise induced anaphylaxis (WDEIA)[17]. In 100 patients tested, 40 met this cutoff, and 39 of them were diagnosed with WDEIA. Thus, detection of ω-5 gliadin could be used to diagnose this condition without performing a provocation challenge, and the authors recommend testing for this allergen component in patients with suggestive symptoms[17].

Prior to the demonstration of galactose-α-1,3-galactose (α-gal, a sugar moiety) as the cause of delayed anaphylaxis from ingestion of "red meat", it was commonly believed that only proteins were the source of IgE mediated anaphylactic reactions. α-gal was first described in 2009 in patients who had immediate hypersensitivity reactions while receiving Cetuximab for treatment of colorectal and squamous cell head and neck cancers[18]. Cetuximab, a chimeric mouse-human monoclonal antibody against the epidermal growth factor receptor, contains α-gal in the Fab fragment. Of 76 patients who received treatment, 25 patients had immediate hypersensitivity reactions. In 17 of these patients sIgE to α-gal was found to be present in their sera before they began treatment. Further supporting the idea that these antibodies were not raised against Cetuximab, 15 control patients also were found to have sIgE against α-gal in their serum.

α-gal is a carbohydrate moiety present in non-primate mammals such as cows, pigs, lambs, and cats. Based on this knowledge, Commins *et al*[19] evaluated patients with delayed anaphylaxis, angioedema, or urticaria following ingestion of "red meat" such as beef, pork, or lamb. Patients in this study had similar clinical presentations with symptoms presenting 3-6 h after ingestion of red meat. It was noted also that a large percentage of patients were from Virginia, Tennessee, North Carolina, Arkansas, and Missouri. Further, over 80% of patients had a history of a tick bite from the Lone Star tick, *Amblyomma americanum*. In a follow-up report it was noted that similar cases have been found in Australia and Europe associated with bites from *Ixodes holocyclus* and *Ixodes ricinus*, respectively[20]. It is now well accepted that sensitization to galactose-α-1,3-galactose may result from a tick bite, and that having IgE against galactose-α-1,3-galactose causes delayed anaphylaxis to red meat in susceptible individuals. Another similar disease, cat-pork allergy, has also been well described in the literature. In this condition, primary exposure to cat albumin leads to development of cross-reactive IgE antibodies against pork albumin. Upon ingestion of pork, patients may develop symptoms ranging from oral pruritus to anaphylaxis, although, not every ingestion is associated with a reaction. Patients do not have reactions to beef or other meats and, unlike α-gal, there is no association with tick bites[20].

Food allergy

Milk and egg are the two most common foods causing allergic reactions. In the United States, peanut is third most common, with self-reported peanut allergy rapidly increasing[21,22]. A complete discussion of all described food component allergens is outside the scope of this editorial, but can be found in many review articles[2,3,5,7,8,10]. The gold standard diagnosis for food allergy requires a double blind placebo controlled food challenge (DBPCFC). This procedure involves exposing the patient to a known food allergen (or placebo)

while evaluating for reaction. In addition to the risk of a potential life threatening reaction, this procedure is expensive and time consuming[23]. A patient is said to have passed the food challenge if no reaction is noted for up to 24 h after ingestion. Skin prick and or sIgE testing are routinely used as a means to evaluate when a patient is deemed "low risk" for reacting to a challenge[21]. Patients with a low risk can undergo an open food challenge rather than a DBPCFC. Open challenges are much less expensive and don't require the use of a placebo. However, because they lack the blinded approach, subjective symptoms can cloud the results of these tests. Further, using the "low risk" stratification the success rate for food challenges is still not 100%[24]. Dilemmas arise in those patients who never consumed a food to which they were later found to be sensitized to by allergy testing. Why certain patients pass a challenge with a given food and others do not even though their skin test reactivity or sIgE levels are similar has perplexed the field, as well. It has been hypothesized that this difference is due to sensitivity to different components of the various allergens. Thus, the use of CRD testing might provide additional information on risk stratification and could help guide clinical decision making on who will pass (or even be challenged) a food challenge.

Milk is an important food source in the first 6 mo of a child's life, whether it is breast milk or a cow's milk based formula. In cow's milk, casein (Bos d 8) and whey (β-lactoglobulin/Bos d 5 and α-lactalbumin/Bos d 4) are the most relevant allergen components associated with IgE mediated reactions[2]. Casein is a heat and enzyme stable protein that is associated with a more severe phenotype and persistent food allergy. Alternatively, whey proteins are heat and enzyme labile and are associated with a less severe phenotype. It has been shown that patients who tolerate baked milk have earlier resolution of their allergy than those that do not[25]. Not surprisingly, sIgE against whey proteins are more prevalent in those that outgrow milk allergies, and those with sIgE against casein are much less likely to pass a baked milk challenge or outgrow their food allergy[2,26-28]. A recent paper demonstrated that casein sIgE testing, thus, could be useful prior to an open food challenge to predict reactivity to baked milk[26]. While further studies are needed, these data suggest that CRD testing may provide appropriate stratification of risk, making milk food challenges much safer (and maybe someday obsolete).

Egg is the second most common food allergy and is found in a large number of fresh and pre-packaged food sources. Like milk, egg allergy is typically outgrown prior to adulthood[29,30]. Historically patients have been tested with whole egg, egg white, and/or egg yolk extracts. Molecular diagnostics have allowed further characterization of allergens in these sources. The two most clinically relevant allergens are ovomucoid (Gal d 1) and ovalbumin (Gal d 2)[29,31]. Ovomucoid is a heat and enzyme stable protein comprising approximately 10% of egg white and is associated with a more severe phenotype with delayed allergy resolution. Ovalbumin is the most abundant egg white protein, is heat and enzyme labile, and is associated with less severe clinical reactions[29]. SIgE testing to ovomucoid predicts tolerability to heated/baked egg[32]. Using microarray technology it was shown that 44 of 47 patients who lacked sIgE to ovomucoid were able to tolerate a boiled egg challenge. Additionally they showed that 20 of 21 patients sensitized to ovomucoid reacted to raw egg[33]. This supports the notion that the presence of sIgE to ovomucoid is associated with a higher frequency of clinical allergy to egg, whereas its absence predicts patients who could tolerate boiled egg.

Self-reported peanut allergy has been increasing world-wide in modernized societies. In the United States it is the third most common food allergy and increased in prevalence from 0.4% in 1997 to 1.4% in 2008[23]. A diagnosis of peanut allergy carries significant burden on a patient's quality of life. Many schools require children to sit at special tables at lunch, there is increased scrutiny of birthday treats, and certain restaurants must be avoided. This also imposes an economic and healthcare burden on the patients. Therefore, it is important to distinguish patients with true IgE mediated peanut allergy versus those who are just sensitized but unlikely to clinically react to the food. The peanut storage proteins Ara h 1, 2, and 3 are commonly associated with severe allergic reactions. In contrast Ara h 8 a PR-10 protein (Bet v 1 homologue) that is associated with the oral allergy syndrome and is most likely indicative of birch tree sensitization[23,34,35].

Ara h 2 has been consistently reported to be the most specific component in diagnosing true peanut allergy[2,3,7,8,21,23]. In 2013, research teams from the United States and Sweden performed peanut component testing (Ara h 1,2,3,8) on serum from 167 patients with suspected peanut allergy[36]. All patients underwent oral food challenges with 106 of them having clinical reactions. sIgE to Ara h 2 alone was shown to demonstrate specificity between 85% to 95% for a true peanut allergy, which improved diagnostic accuracy over sIgE to whole peanut. Importantly in this study it was noted that 3 subjects with peanut sIgE $\geqslant$ 15 kU_A/L who lacked any sIgE to Ara h 2 tolerated peanut on challenge. Further, 82% of patients with whole peanut sIgE $\leqslant$ 15 kU_A/L but a positive IgE to Ara h 2 had clinical reactions on peanut challenge. Clearly the implications of these data are tremendous and have the potential to significantly change the clinical practice of peanut food challenges (*i.e.*, having sIgE to Ara h 2 would need to avoid peanut, otherwise can be challenged regardless of sIgE to whole peanut).

Aeroallergen immunotherapy

The vast majority of patients receiving allergen immunotherapy (AIT) are polysensitized, with multiple positive skin or *in vitro* testing to indoor and outdoor

aeroallergens. With the characterization of various protein families has come the realization that many proteins from taxonomically unrelated species cross-react. In 2013, the World Allergy Organization published a consensus document describing the use of recombinant/purified allergens to help in discriminating between genuine sensitization and reactions due to cross reactive allergens[10]. In theory, this knowledge may decrease the number of allergens in a patient's AIT prescription, if only the clinician knew the relevant cross-reacting allergens. This is where the ISAC 112 microarray could be of benefit, as there are a large number of components tested at once (without an a priori knowledge of the subject's sensitivities/reactions). Nonetheless, any version of CRD should allow the clinician to get a better picture to what it is that the patient is actually allergic.

Two of the most well studied and relevant outdoor aeroallergens are grass and tree pollens. Of the grasses, timothy has been most studied with regards to allergy component testing. Eight components (Phl p 1, 2, 4-7, 11, and 12) are commercially available. The two most relevant components, Phl p 1 and Phl p 5, are highly cross-reactive with other grass species[2]. A recent study comparing CRD, sIgE, skin prick testing, conjunctival provocation, and basophil activation testing showed that the use of rPhl p 1, a recombinant Phl p 1, alone was sufficient to diagnose timothy grass pollen allergy in a central European population[37]. Additionally, a study of patients with grass allergy in southern Spain demonstrated that the use of CRD changed immunotherapy prescriptions for 55% of patients in the study[38]. To date similar studies have not been published in the United States.

Because of the association between birch tree allergy and the oral allergy syndrome, birch tree components have been studied quite extensively[2,3,7-9]. There are 4 commercially available birch components: Bet v 1, 2, 4, and 6. The PR-10 protein, Bet v 1, is present in 95% of patients with clinical birch allergy and is a marker of primary sensitization[2]. PR-10 proteins in other tree pollens such as *Rosaceae* fruits (apple, cherry, apricot, peach, and pear) share sequence homology with Bet v 1 and are known as Bet v 1 homologues. Patients with birch allergy may develop itching of the lips, tongue, and mouth following ingestion of raw fruits; however, symptoms are not present when the fruits are cooked. Both Bet v 2 and Bet v 4 are markers of cross reactivity. Bet v 2, a member of the profilin family has shown cross reactivity with pollens (trees, grasses, weeds) and foods (fruits, peanut, legumes, and vegetables). Bet v 4, a member of the calcium-binding protein family, cross-reacts only with pollens such as trees, grass, and weeds[2,7].

Hymenoptera venom immunotherapy

CRD testing has shown great progress in the field of hymenoptera venom immunotherapy. Approximately 50% of patients with venom allergy have positive sIgE testing to both honeybee and yellow jacket[39]. CCD and homologous protein allergens (*e.g.*, hyaluronidase) are believed to be the causes of this phenomenon[40]. As a result, a patient's true sensitization profile to venom may be inaccurate, leading to unnecessary allergens being added to their immunotherapy prescription. A recent study evaluated sIgE levels to recombinant honey bee (rApi m 1) and yellow jacket (rVes v 1 and rVes v 5) allergens, all of which lack CCDs[41]. Of patients with positive sIgE testing to both species, only 47% were found to be sensitized to both honey bee and yellow jacket venom components. Therefore, in over half of these patients, initial skin testing or serum sIgE testing was clouded by cross-reactivity, which could be sorted out using CRD. However, it is important to note that the detection of incidental sIgE to hymenoptera venom may increase with tests such as ISAC. It is recommended in clinical practice that patients without a history of allergic reactions to stings should not have skin prick or sIgE testing performed. The clinical relevance of a positive test without a history of a reaction is similar to the problem with food allergy testing, where positive tests must be correlated with the clinical history. Therefore, a positive anti-venom IgE test in the absence of clinical disease is of unclear significance[42].

CONCLUSION

CRD testing is a new frontier in evaluating IgE mediated hypersensitivity reactions. Research has shown potential benefits in idiopathic anaphylaxis, food allergy, and venom allergy, while there is some possible utility in aeroallergen allergies. The ISAC 112 has been used to detect pollen cross reactivity in polysensitized patients, which may help focus patients' immunotherapy prescriptions. However, at the present time commercial allergen components are not easily available and many more studies need to be published before CRD becomes a main stay of clinical practice. We believe this is only a matter of time, and expect with increased research in the future, our patients will benefit from the more targeted guidance CRD appears to provide.

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