

Food allergen cross-reactivity and clinical significance

Cross-reactivities are found among allergens within the same food group as well as between foods and non-food allergens. Some cross-reacting food allergens are phylogenetically closely related (legumes, fishes, crustaceans, fruits, and tree nuts) whereas other cross-reactivities have been described between foods and unrelated or only distantly related allergens especially pollens.¹⁻⁶

The clinical relevance of food allergen cross-reactivity depends on the food in question. For example, the in vitro cross-reactivities among crustaceans are thought to be clinically relevant, eg, shrimp-allergic subjects can have clinical symptoms after ingesting lobster and crab.⁶⁻⁸ In contrast, cross-reactivities among legumes seem to be of less clinical importance, eg, peanut-allergic subjects may show in vitro IgE antibody reactivity to beans or peas but usually do not have clinical symptoms to beans or peas.⁹⁻¹¹ In this regard, in vitro diagnostic procedures using RAST, CAP, or ELISA for the detection of allergen-specific IgE are not always sufficient to diagnose accurately food allergy and should be combined with an oral food challenge. An oral food challenge, however, may not be necessary if a convincing history identifies the offending food allergen. Because of this, the case study presented in this issue (Ann Allergy Asthma Immunol 2000;85:461-466) is a good example for the use of both in vitro methods and food challenge to

establish the clinical relevance of cross-reactivity between shrimp, a crustacean, and scallop, a mollusk.

Among food allergens of animal origin, shellfish is a frequent cause food allergies.^{12,13} Most allergenic shellfish belong to the class crustacea and include shrimp, crab, crawfish, and lobster. To understand the molecular basis of allergen cross-reactivity, the structures of the allergen and its epitopes must be determined. A first step is the amino acid sequence determination of the allergen. Based on its amino acid sequence, the major crustacean allergen has been identified as the muscle protein tropomyosin in several crustacea species such as *Penaeus indicus* (Indian shrimp, Pen a 1),¹⁴ *P. aztecus* (brown shrimp, Pen a 1),¹⁵ *Metapenaeus ensis* (greasyback shrimp),¹⁶ *Charybdis feriatus* (common crab, Cha f 1),¹⁷ *Panulirus stimpsoni* (spiny lobster, Pan s 1),¹⁸ and *Homarus americanus* (American lobster, Hom a 1).¹⁹ In mollusks, Cra g 1 and Tur c 1 are the major allergens in the oyster *Crassostrea gigas*²⁰ and in the gastropod *Turbo cornutus*,²¹ respectively. Both allergens were identified as tropomyosins based on the sequences of peptides that were obtained by proteinase digestion. Similarly, a 38-kD IgE-binding protein designated as Tod p 1 from Pacific squid, *Todarodes pacificus*, was identified p 1 as another allergenic tropomyosin.²²

So far, evidence for a clinical relevance of cross-reactivities between shrimp and mollusks is mostly indirect. Based on clinical histories, some shrimp-sensitive subjects showed evidence of mollusk sensitivity and significant RAST reactivity and positive skin prick test (SPT) to oyster extract

was found in 50% crustacean-sensitive-allergic subjects.²³ Furthermore, significant RAST inhibition of the IgE antibody reactivity to oyster with shrimp, lobster, crab, or crayfish was demonstrated; however, this cross-reactivity did not correlate well with clinical sensitivity. Leung et al²⁴ reported IgE reactivity to a 38-kD protein present in different mollusks such as Gastropoda (abalone, whelk), Bivalvia (mussel, pen shell, scallop, oyster and clam), and Cephalopoda (cuttlefish, squid, octopus) in sera from shrimp-allergic subjects that could be inhibited with recombinant shrimp tropomyosin. In another study, the cross-reactivity between the Pacific squid *Todarodes pacificus* and shrimp allergens was examined by using human sera and shrimp tropomyosin-specific monoclonal antibodies. In addition to allergenic shellfish, tropomyosins of other invertebrates were identified as allergens; house dust mite allergens Der f 10 and Der p 10 and Per a 7 from the American cockroach (*Periplaneta americana*)²⁵⁻²⁹ were cloned, sequenced, and identified as allergens. The data suggest that tropomyosins, present in both foods and inhalants, are important invertebrate pan-allergens.

Are the structural and immunological similarities among invertebrate tropomyosins clinically significant? In the case of shrimp allergy, it is easy to understand why in vitro cross-reactivity translates into clinically relevant cross-reactivity; tropomyosin is the only major allergen in shrimp and at least 85% of shrimp-specific IgE is directed towards this allergen. Furthermore, sequence identities among crustacea tropomyosins range between 93% and 99%,³⁰ their tropomyosins

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only differ in a few amino acid positions. Mites are another important source of invertebrate allergens; a study³¹ showed that house dust mite immunotherapy may induce IgE antibodies against snail and shrimp. Since subjects demonstrated a positive skin prick test to shrimp and clinical symptoms (oral allergy syndrome) after eating shrimp, this suggests that increased exposure to mite antigen (through mite immunotherapy) results in sensitization to cross-reacting seafood tropomyosins. Other factors, however, may influence sensitization and reactivity since allergy to shrimp is not well correlated with allergy to house dust mites. The fact that crustacea contain significant amounts of muscle tissue including tropomyosin in contrast to house dust mites may explain why tropomyosin is not a significant allergen in mites as in shrimp. Mite immunotherapy may expose subjects to sufficient mite tropomyosin to stimulate the production of enough mite-specific IgE antibodies which induce clinical symptoms. In this regard, mollusks and crustacea are more similar; the part to which humans is exposed is mostly muscle tissue and may explain why clinically relevant sensitizations may occur just by normal exposure.

In conclusion, in vitro cross-reactivity among arthropoda allergens, particularly those from crustaceans, insects and arachnids, and other invertebrates such as mollusks is mostly due to the structural similarity of the various tropomyosins. The clinical relevance of these cross-reactivities may depend on the species of origin. Since crustacea tropomyosins are almost identical there is a good chance of multiple reactivities; however, a small percentage of shrimp-allergic subjects do not have tropomyosin-specific IgE antibodies and may not react with other crustacea. On the other side, cross-reactivity of mite and cockroach tropomyosin with that of crustacea does not necessarily mean that mite-allergic subjects will react to shrimp and other crustacea, although this may not always be true for other forms of exposure, such as mite immunotherapy.

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