Review article

Cross-reactive epitopes and their role in food allergy

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Allergenic cross-reactivity among food allergens complicates the diagnosis and management of food allergy. This can result in many patients being sensitized (having allergen-specific IgE) to foods without exhibiting clinical reactivity. Some food groups such as shellfish, fish, tree nuts, and peanuts have very high rates of cross-reactivity. In contrast, relatively low rates are noted for grains and milk, whereas many other food families have variable rates of cross-reactivity or are not well studied. Although classical cross-reactive carbohydrate determinants are clinically not relevant, α-Gal in red meat through tick bites can lead to severe reactions. Multiple sensitizations to tree nuts complicate the diagnosis and management of patients allergic to peanut and tree nut. This review discusses cross-reactive allergens and cross-reactive carbohydrate determinants in the major food groups, and where available, describes their B-cell and T-cell epitopes. The clinical relevance of these cross-reactive B-cell and T-cell epitopes is highlighted and their possible impact on allergen-specific immunotherapy for food allergy is discussed. (J Allergy Clin Immunol 2023;151:1178-90.)

Key words: *Allergens, allergenic cross-reactivity, B-cell, clinical cross-reactivity, cross-reactive epitope, cross-reactive IgE, food allergy, IgE antibody, T-cell, tropomyosin*

Abbreviations used
α-Gal: Galactose-α-1,3-galactose
CCD: Cross-reactive carbohydrate determinant
CMA: Cow's milk allergy
CM: Cow's milk
CN: Casein
HDM: House dust mite
HMW: High molecular weight
WDEIA: Wheat-dependent exercise-induced anaphylaxis

Allergenic cross-reactivity can be clinically manifest or irrelevant. *In vitro* diagnosis of food allergy and its management is often hampered by cross-reacting food proteins.[1,2] IgE binding to cross-reactive clinically irrelevant allergens results in false-positive results on *in vitro* diagnostic tests. However, unidentified sources of cross-reactive allergens of clinical relevance may lead to unintentional exposure and allergic reactions, posing a health risk for the affected individuals. The concept of cross-reactivity between related or unrelated allergen sources is extensively addressed in the literature. However, this information is often not accompanied with data on identifying specific allergens or epitopes. The most common view in the current literature is that cross-reactive allergenic proteins present with a high primary amino acid sequence identity of above 70%.[3] However, relevant IgE-binding epitopes are often below 20 amino acids in length and allow for a much better assessment of allergenic cross-reactivity.[4] In addition, shared cross-reactive T-cell epitopes could explain some of the clinical desensitization to food allergens observed after successful pollen immunotherapy[5]; however, the cross-reactive T-cell epitopes have been studied for very few allergens. Well-characterized cross-reactive B-cell and T-cell epitopes between food allergens will not only assist in developing more specific and accurate molecular diagnosis but also contribute to the development of lead candidates for targeted immunotherapy. In this review, we summarize the basic concepts of allergenic cross-reactivity, discuss about protein and carbohydrate epitopes, and provide an overview of the cross-reactive allergens belonging to the major food allergen groups.

CONCEPT OF ALLERGENIC CROSS-REACTIVITY AND THE ROLE OF IgE (B-CELL) AND T-CELL EPITOPES

Cross-reactivity in allergy is a broad term used to define the ability of (secondary) allergen(s) to recognize IgE antibodies and/

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S.K. is funded by Austrian Science Fund (FWF; grant no. M 3295 Meitner-Programm).
Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication October 18, 2022; revised December 14, 2022; accepted for publication December 19, 2022.
Available online March 15, 2023.

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0091-6749

https://doi.org/10.1016/j.jaci.2022.12.827

or invoke a cellular (T-cell, mast cell, or basophil) response in the body upon exposure, which has been already sensitized to a primary (initiator) allergen that shares 1 or more epitope with the secondary allergen. These shared regions are defined as cross-reactive epitopes. IgE cross-reactivity is often recognized when allergic symptoms arise to an allergen source without prior exposure. However, IgE cross-reactivity might be clinically manifest or irrelevant.

IgE cross-reactivity can be defined as the relationship between 1 antibody and 2 or more allergens.[6] Sensitization occurs to a primary allergen via a T_H2 response, leading to the generation of allergen-specific IgE antibodies.[7] These IgE antibodies may be directed to several conformational and/or to linear epitopes on the allergen.[8] When the individual is later exposed to a food source containing homologous proteins/allergens via ingestion, inhalation, or contact, the preformed primary allergen-specific IgE antibodies are able to recognize these secondary allergens via cross-reactive epitopes, and may lead to cross-linking on basophils and mast cells, resulting in mediator release and subsequent clinical symptoms (Fig 1). The secondary allergen may be a complete or incomplete allergen in that it may or may not be capable of inducing primary allergic sensitization by itself (co-sensitization).[6,9] In some cases, the route of exposure may differ between the primary and secondary allergen. For example, primary sensitization to shrimp tropomyosin may occur via ingestion, but secondary exposure and cross-reactive IgE binding to dust mite tropomyosin occurs via inhalation.[10] In addition, the IgE antibody's binding affinity to the secondary allergen may be weaker as compared with that to the primary allergen, depending on the number of cross-reactive epitopes and binding affinity. All these factors, in addition to the physicochemical stability and amino acid sequence homology or structural homology of the secondary allergen, play a role in the clinical relevance of IgE cross-reactivity.

T-cell cross-reactivity can be defined as the reaction of T cells to more than 1 peptide-MHC ligand.[11] T-cell cross-reactivity is possible for several reasons including MHC binding promiscuity and degeneracy in peptide-TCR recognition as a mechanism that has evolved to recognize a wide range of external antigenic peptides.[12] However, in terms of allergenic T-cell cross-reactivity, the most likely cause and mechanism is sequence homology of the T-cell cross-reactive peptide residues among closely related allergen sources.[13] A cross-reactive T-cell epitope is able to stimulate memory T cells and induce subsequent IgE production (Fig 2). A well-known example is the Bet v 1 immunodominant T-cell epitope Bet v $1_{142\text{-}156}$, and its cross-reactivity to homologous peptides from PR-10–like food allergens from apple, peach, pear cherry, hazelnut, celery, and carrot.[14,15] The presence of this dominant peptide was also detected after *ex vivo* antigen processing and MHC class II presentation.[16] Cross-reactive T-cell epitope peptides have also been shown to play a role in $CD4^+$ memory T-cell survival, in absence of the primary priming allergen.[17] In the context of predicting T-cell cross-reactive epitopes among closely related allergens, the peptide sequence homology is known to play an important role; higher the homology, stronger the cross-reactivity.[13] However, the structural stability of closely related allergens may also play a role, which may not be associated with sequence homology, in the generation of homologous T-cell peptides, and subsequent T-cell cross-reactivity.[18]

CROSS-REACTIVE EPITOPES IN THE MAJOR FOOD ALLERGEN GROUPS

The clinically relevant cross-reactive allergens belonging to the major food groups are summarized below, and a brief overview on the current knowledge on cross-reactive IgE- or T-cell epitopes provided (Fig 3).

Legumes

Peanut and soybean are the most significant allergen sources of the *Fabaceae* family and consequently the best characterized concerning cross-reactivity of their allergens.

Peanut allergy. Sensitization to peanut can be associated with sensitization to other members of the *Fabaceae* family such as soy and lupine, with tree nuts, or with pollen. Among peanut-allergic children, up to 67% were sensitized to other legumes and up to 28% had confirmed allergy to at least 1 other legume.[19,20] Similarly, allergy to tree nuts is common among children with peanut allergy, with up to 86% having sensitization to tree nuts and up to 40% clinically confirmed tree nut allergy.[21]

All known peanut allergens were determined to comprise 85% of the total protein content of peanut, whereas seed storage proteins of the 2S albumin (Ara h 2, 6, and 7), the vicilin (Ara h 1), and the legumin (Ara h 3) protein families together accounted for 75%.[22] In addition, the allergens of these 3 families have been identified as major allergens in other legumes and tree nuts. Consequently, frequent cosensitization of peanut-allergic individuals to other legumes and tree nuts has been interpreted by cross-reactive epitopes present in homologous allergens from the 3 protein families. Although, for the majority, the sequential IgE epitopes have been identified, their cross-reactivity was only rarely investigated. Apart from a conserved pattern of 8 cysteine residues, the sequence of Ara h 2 shows very low sequence identities (<36%) to 2S albumins from other legumes and tree nuts. However, their structural similarity has been proposed as the immunologic basis for the observed coallergies.[23]

Ara h 1 shows 39% to 53% sequence identities with vicilins from tree nuts and botanically related legumes. Using homology modeling, 5 surface-exposed epitopes of Ara h 1 have been predicted on the basis of the conformational similarity to be cross-reactive with Gly m 5, Jug r 1, Ana o 1, and Cor a 11.[24] However, in inhibition assays with IgE-binding peptides from Ara h 1, 2, and 3 and corresponding peptides from walnut allergens (Jug r 1, 2, and 4), no relevant cross-reacting IgE antibodies could be detected in sera from peanut- and walnut-allergic patients.[25] Similarly to IgE cross-reactive epitopes, T-cell cross-reactive epitopes between peanut and other seeds are poorly defined. In 4 of 5 patients with peanut and hazelnut coallergy, cross-reactive T-cell response was driven by cross-reactivity to Ara h 1 and 2, but the specificity of cross-reactive T-cell epitopes was not defined.[26] Peanut oleosins (Ara h 10, 11, 14, and 15) might be a cause of IgE cross-reactivity to oil-contained seeds. The linear IgE epitope DKARDVKDRAKDYAG, localized in the C-terminal domain of Ara h 15 with high sequence identity to other seed-derived oleosins, was recognized by IgE from soybean- and rapeseed-allergic patient.[27] Peanut allergens belonging to the Bet v 1 (Ara h 8), the profilin (Ara h 5), the defensin (Ara h 12 and 13), and the cyclophilin (Ara h 18) protein families are mostly involved in pollen-associated food allergy. Furthermore, the nonspecific lipid transfer proteins (Ara h 9, 16, and 17) are involved in the so-called nonspecific lipid transfer protein

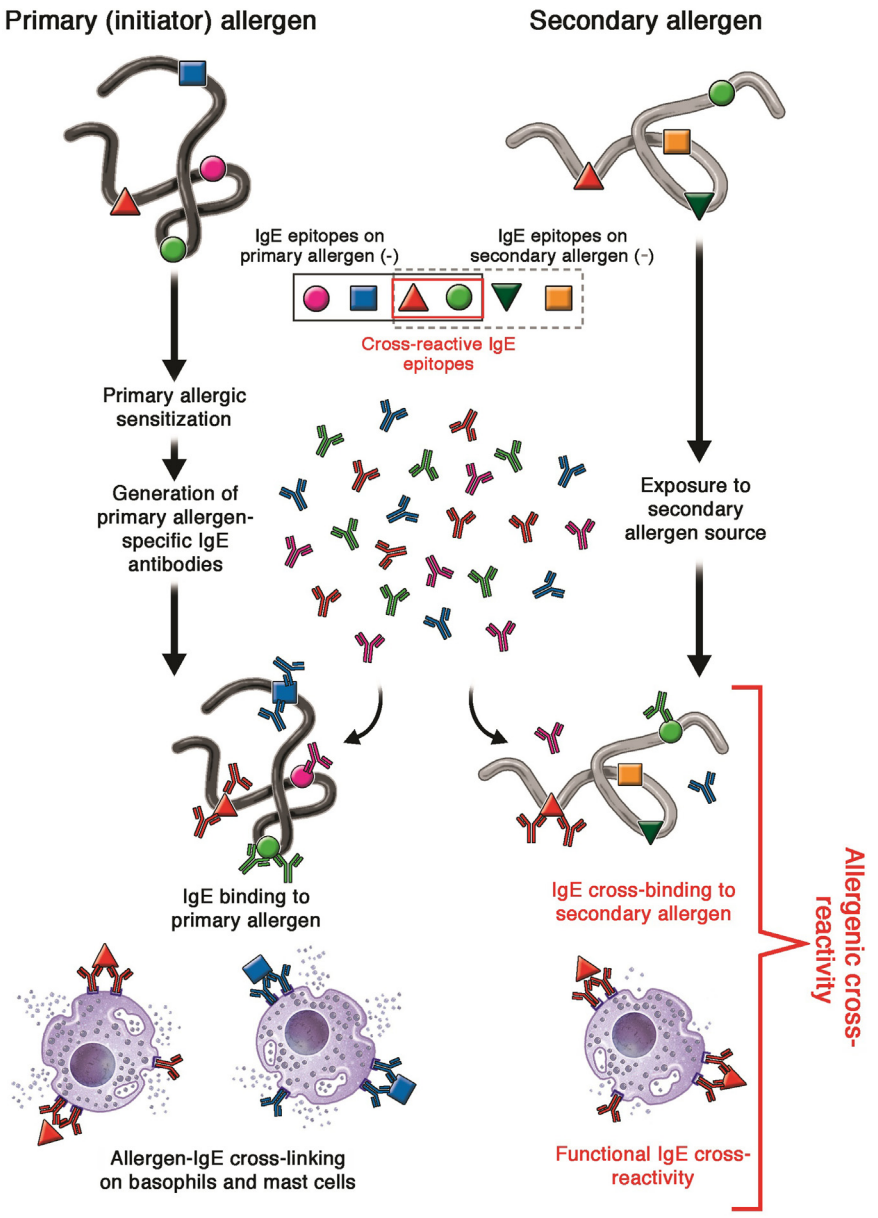

FIG 1. Simplified schematic representation of the mechanism of IgE-mediated allergenic cross-reactivity. The process of primary allergic sensitization ultimately leads to the generation of IgE antibodies targeted against antigenic epitopes on the initiator allergen. These primary allergen-specific IgE antibodies can recognize secondary allergen(s), containing 1 or more homologous epitopes, and lead to IgE cross-linking and mediator release from basophils and mast cells.

syndrome.[28] One IgE-binding surface area on Bet v 1 and Ara h 8, identified by using phage-displayed epitope mimics, was shown to be involved in IgE cross-reactivity to Gly m 4.[29]

Although cross-reactivity has been commonly recognized between members of the same protein family, several lines of evidence demonstrated IgE cross-reactivity between members of different protein families of seed storage proteins. It was demonstrated that IgE cross-reactive to Ara h 1, 2, and 3 comprised the major fraction of IgE specific to these allergens in sera from peanut-allergic patients.[30] The cross-reactive IgE antibodies manifested identical gene rearrangements in unrelated individuals as well as high affinity and cross-reactivity to the peanut allergens.[31] The 3 Ara h 2 epitopes implicated in this cross-reactivity (1: WLQGDRRCQSQLER, 2: SYGRDPYSPSQDPYS, and 3: PDRRDPYSPSPYDRR)[30] have also been identified as immunodominant epitopes in different studies.[32-34] The molecules named covalent heterobivalent inhibitors containing only 1 immunodominant epitope of Ara h 2 (DPYSPOHSDRRGAGSS) and 1 of Ara h 6 (QDRQ) yielded an almost complete inhibition of basophil degranulation to peanut extract in *in vitro* cellular assays with patients' sera.[35] IgE- and T-cell cross-reactivities between Ara 1, 2, and 3 were also observed in mice.[36]

Soybean allergy. Primary soybean allergy is associated with sensitization to soybean vicilin Gly m 5 (7S globilin, β-conglycinin), legumin Gly m 6 (11S globulin, glycinin), 2S

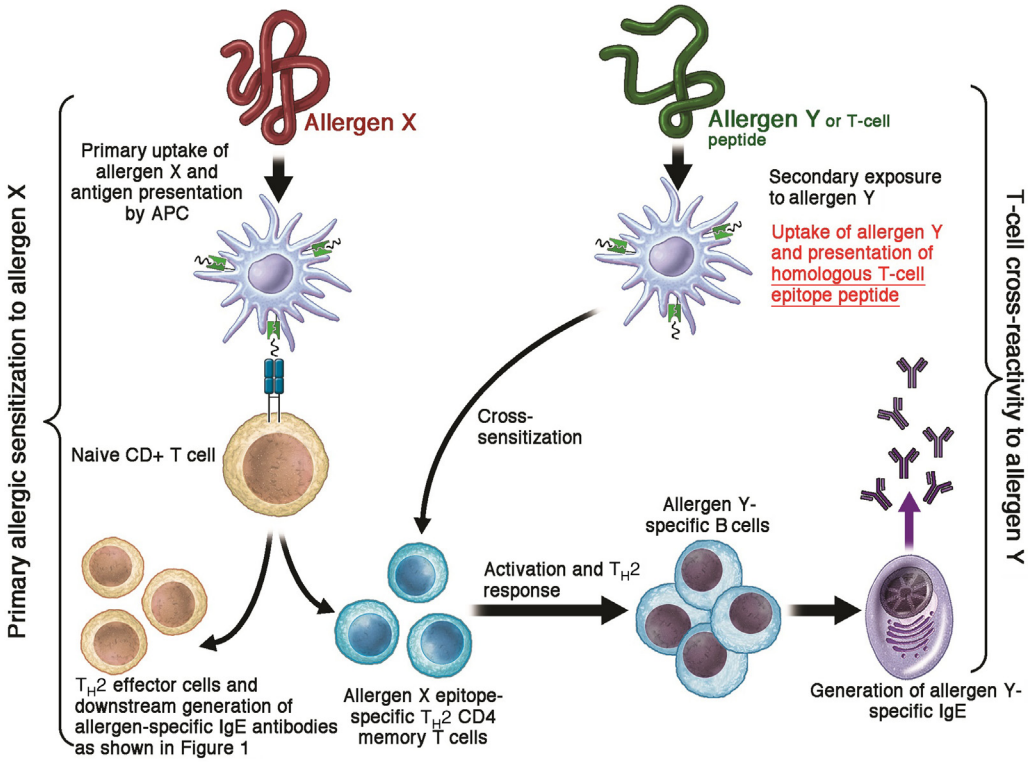

FIG 2. A simplified representation of T-cell epitope-mediated allergenic cross-reactivity. Primary allergen (allergen X) exposure and subsequent antigen presentation by dendritic cells to naive T cells in the presence of IL-4 lead to the differentiation and expansion of allergen-specific T_H2 cells. Later exposure to secondary allergen (allergen Y) containing homologous T-cell epitopes leads to cross-sensitization by activating primary allergen-specific memory T cells, and subsequent generation of secondary allergen-specific IgE antibodies.

albumin Gly m 8, and the oil body–associated Gly m Bd 30K and Gly m Bd 28K. The seed storage proteins, Gly m 8, Gly m 5, and Gly m 6, are major contributors (80%) to the protein content of this seed and are recognized as potential diagnostic markers for severe allergic reactions to soybean.[37,38] Linear epitopes of Gly m 6.0201 (GSNILSGFAPEF) and Gly m 6.0501 (GSVLSGFSKHFL) overlapped with a previously identified epitope hot spot (HS#2) of legumins from peanut and tree nuts.[39] However, further studies are necessary to confirm the cross-reactivity including inhibition assays and histamine release assays to confirm the ability of these epitopes to inhibit IgE and activate effector cells.

In birch-endemic regions, soybean allergy is based on cross-reactivity between birch pollen allergen Bet v 1 and its related allergen Gly m 4 in soybean.[40] Investigation of the conformational IgE epitope profile of soybean allergen Gly m 4 using Gly m 4–type model proteins harboring individual and multiple putative epitopes found 4 putative IgE-binding areas suitable to discriminate allergic and tolerant subjects.[41] However, the study did not investigate how those epitopes are involved in cross-reactivity with Bet v 1. By a combination of different bioinformatics tools, predicted Gly m 4 T-cell epitopes AKADALFKAIEAYLL and ADALFKAIEAYLLAH[42] share high sequence identity (80%) to the immunodominant Bet v 1 T-cell epitope TLLRAVESYLLAHSD" (aa 142-156), and thus could be responsible for cross-reactivity at the T-cell level.[14]

In addition, Gly m 5 and Gly m Bd 30K cross-reactive epitopes have been described to be involved in reactions to a soybean protein formula in patients allergic to cow's milk (CM) (summarized by Bublin and Breiteneder[3]). Three peptides on Gly m 5 and 4 peptides on Bos d 9 (α-casein [CN]) with a common core motif were identified using a Bos d 9 (α-CN)-specific mAb.[43] Recently, application of cross-reactive soybean allergen Gly m Bd 30K peptide NKIQDKVTIDGY comprising an immunodominant cross-reactive T-cell and IgG epitope was shown to prevent IgE-mediated milk sensitization in mice through the induction of blocking IgG.[44]

Tree nut allergy

The tree nut allergy prevalence varies from less than 1% to approximately 3%.[21] Walnut, hazelnut, cashew, pistachio, almond, Brazil nut, and macadamia are the typically reported tree nut allergen sources. Most of the patients with allergy to tree nut are sensitized to multiple nuts, but strong clinically relevant cosensitization was found only between highly botanically related cashew and pistachio as well as between walnut and pecan (summarized by Cox et al[1]). Their concurrent allergies and extensive *in vitro* IgE cross-reactivity have been interpreted by the high sequence identities (≥70%) of their homologous allergens from the vicilin, legumin, or 2S albumin protein families. 2S albumins Ana o 1 from cashew and Pis v 3 from pistachio share 81% sequence identity. Using molecular modeling, a surface patch

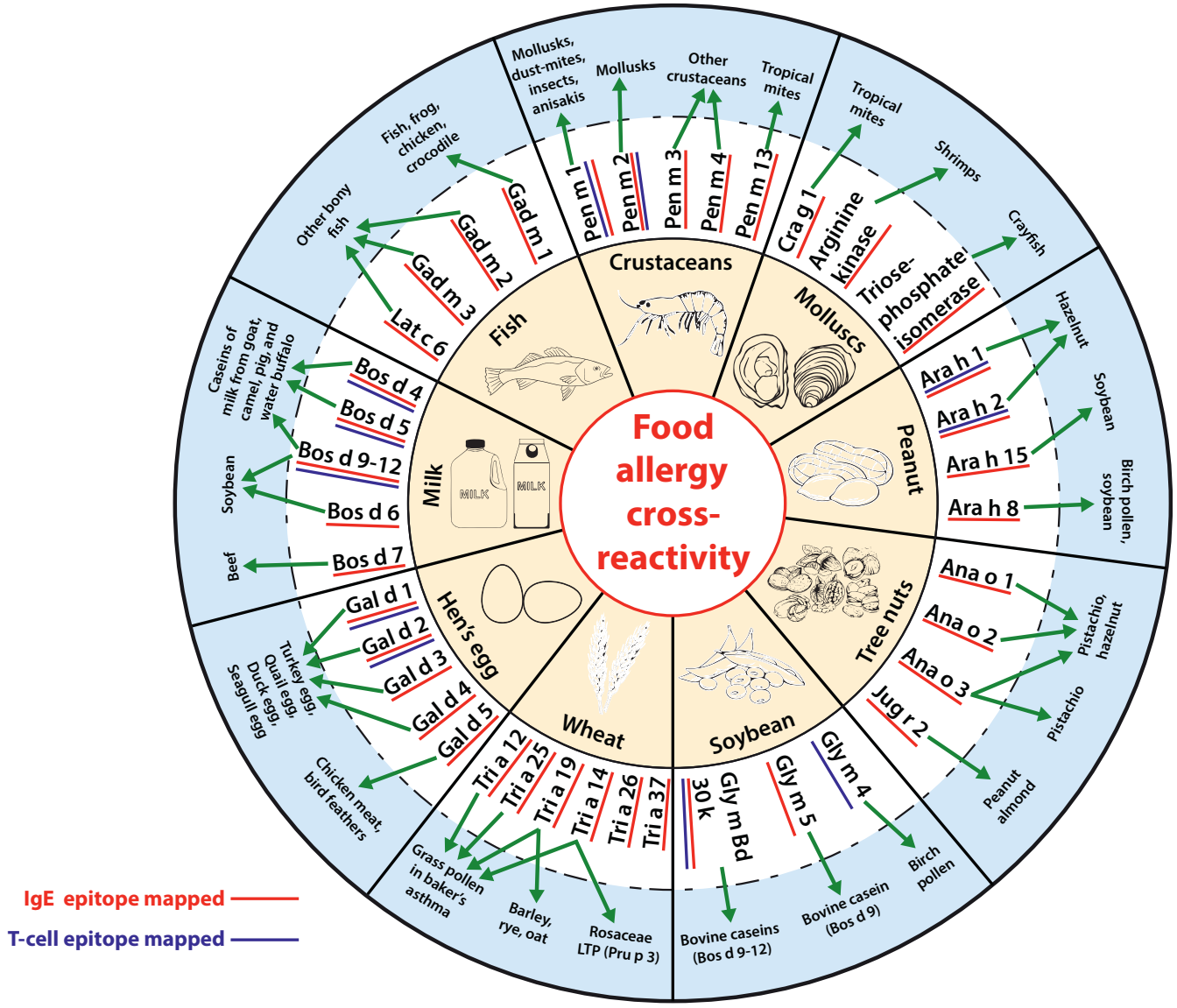

FIG 3. An overview of the clinically relevant cross-reactive allergens belonging to the major food groups, and the secondary allergen sources against which cross-reactivity is documented.

comprising 2 of the previously identified Ana o 3 linear IgE epitopes was predicted to be part of a conformational epitope responsible for cross-reactivity to Pis v 1.[23] At the T-cell level, it has been demonstrated that cashew allergens Ana o 1 (vicilin) and Ana o 2 (legumin) share cross-reactive T-cell epitopes to pistachio and/or hazelnut but not to walnut.[45] In Central-Northern Europe, hazelnut, walnut, and almond are often involved in the so-called pollen-food allergy syndrome due to the cross-reactivity of Bet v 1–specific IgE to hazelnut Cor a 1.04, walnut Jug r 5, and almond Pru du 1.[46,47] A possible cross-reactive epitope might be located in the highly conserved glycine-rich region.[47]

Similar to peanuts, cross-reactive epitopes between unrelated allergens from cashew and hazelnut have been identified. In a recent study using individual cashew and hazelnut allergens, it was shown that the intraspecies cross-reactivity between unrelated allergens belonging to the 2S albumins, vicilins, and legumins families was higher than the intraprotein family cross-reactivity between the 2 nut species.[48] Moreover, IgE with high affinity to Ana o 3 cross-reacted not only with the unrelated cashew nut allergens Ana o 1 and 2 but also with the hazelnut allergen Cor a 9. These cross-reactive IgE might be responsible for cross-reactivity between unrelated tree nuts. Peptide QRQCQQRCE from the N-terminal polypeptide (alpha-hairpinin) of walnut vicilin Jug r 2 was identified to share similar physicochemical properties to the immunodominant epitope of 2S albumin Ara h 2 (DRRCQSQLE). A rabbit antibody raised against the peptide was cross-reactive not only to Ara h 2 but also to almond legumin Pru du 6 and walnut vicilin Jug r 2.[49] Nevertheless, the clinical relevance of IgE cross-reactivity of these allergens is unknown and requires more research.

Shellfish allergy

Shellfish (crustacean and mollusk) allergy affects approximately 3% of the general population.[50,51] Because of the increasing number of allergic cases to shellfish, diagnostics and

food-labeling practices define crustacean and mollusk allergy separately.

Crustacean allergy. Edible crustaceans are decapods, containing several members of species such as shrimps, crabs, lobsters, and crayfish.[52] Many diverse species with homologous allergens are consumed in different regions of the world, posing a challenge to designing diagnostic tools and immunotherapeutic solutions. In individuals with crustacean allergy, clinical or immunologic cross-reactivity has been observed to mollusks, inhaled insects, edible insects, mites, and anisakis. Several cross-reactive crustacean allergens have been identified and characterized including tropomyosin, arginine kinase, myosin light chain, sarcoplasmic calcium-binding protein, fatty acid–binding protein, triose phosphate isomerase, filamin, troponin C, and hemocyanin. Several novel allergens were recently discovered in shrimps using a transcriptomic approach.[53]

Tropomyosin or Pen m 1 is the major crustacean allergen and a cross-reactive invertebrate pan allergen.[54] Extensive epitope mapping analysis identified 8 IgE-binding epitopes in Pen a 1[55] and Lit v 1.[56] Most of the IgE-binding epitopes are identical among crustaceans, and exhibit more than 70% amino acid sequence identity to tropomyosin in other sources as shown by multiple sequence alignment analysis.[54,57] Several IgE epitopes that have been experimentally elucidated in other crustacean species, such as Siberian prawn[58] and Mud crab,[59] show a high homology with IgE epitopes of Pen a 1 as well as to dust mite, Der p 10, and cockroach, Bla g 7. Recent studies have shown that only 30% to 40% of crustacean-allergic individuals may be primarily sensitized to tropomyosin.[10,60,61] This implies that there are other crustacean allergens that might play a role in allergic sensitization, and responsible for cross-reactivity between shellfish and other invertebrates.

Arginine kinase (Pen m 2) is a cross-reactive allergen against other invertebrates, particularly to molluscs[62] and mites.[63] Recently, IgE epitopes have been elucidated in Mud crab using phage display library, and cross-reactive epitopes have been elucidated using informatics analysis.[57,64,65] Similarly, 3 conformational IgE epitopes from myosin light chain were elucidated from crayfish and cross-reactivity demonstrated to other crustacean species.[66] Recently, a new shrimp allergen, fatty acid–binding protein, or Lit v 13, was identified and characterized, with a cross-reactive IgE epitope located in regions amino acid 40-85 and 107-136, with reactivity to Blo t 13 of tropical mites.[67]

In crustacean species, T-cell epitopes have been identified to a lesser extent. Shrimp tropomyosin T-cell epitopes were identified in Pen a 1 using cytokine release and CD4 T-cell proliferation assays in shellfish-allergic subjects.[68] The immunodominant T-cell epitopes were also identified in Met e 1 and Pen m 1,[18,69] as well as for Pen m 2.[70] T-cell epitope-specific cross-reactivity among crustacean allergens in allergic patients has not been experimentally demonstrated. However, higher IL-4$^+$/IFN-γ^+ ratios in dividing CD4$^+$ and CD56$^+$ lymphocytes were shown in crustacean-allergic patients as compared with nonatopics on exposure to shrimp extract.[71] Generation of T-cell peptides and cross-reactivity of shrimp tropomyosin to dust mite, cockroach, and anisakis tropomyosin was shown to be dependent on structural stability, more than on amino acid sequence identity.[18] The role of allergen stability on T-cell peptide generation has implications on how cross-sensitization and cross-allergenicity may occur between ingested shellfish allergens and other inhalant/ingested invertebrate allergens.

Mollusk allergy. Edible mollusks are mainly classified into *bivalves* (oyster, clams, mussels), *gastropods* (abalone, snails), and *cephalopods* (octopus, squid). Worldwide, more than 300 different mollusk species are consumed. Oyster, abalone, squid, and octopus among other edible species are frequently implicated mollusks in food allergy, with most of the cases exhibiting gastrointestinal symptoms. Similar to crustaceans, tropomyosin is the major mollusk allergen.[72] Arginine kinase from oyster has been shown to have similar IgE epitopes as Pen m 2.[62] Recently, triose phosphate isomerase was characterized as a novel octopus allergen with 8 linear and 1 conformational IgE-binding epitopes and cross-reactivity demonstrated to crayfish.[73,74] Recent developments in proteomics and transcriptomics analysis have helped with the rapid identification of novel allergens and their cross-reactive epitopes in Pacific oyster, which is one of the most widely consumed mollusk.[72,75,76]

Allergy to mollusks is widely considered to be as a result of primary allergic sensitization to shrimps or other crustaceans, and clinical symptoms on ingestion of mollusks as a result of cross-reactive anticrustacean IgE antibodies. Oyster tropomyosin elicits IgE cross-reactivity to shrimp tropomyosin even though they share very low amino acid sequence identity.[54] However, our recent study demonstrated that a mollusk tropomyosin (Hal l 1) from abalone is capable of generating IgE antibodies in a mouse model, independent of previous exposure to crustacean tropomyosin. These abalone tropomyosin-specific IgE antibodies could bind to shrimp tropomyosin, Pen m 1.[77] This study opens up the possibility that individuals may be susceptible to primary sensitization to mollusk allergens that may contain cross-reactive IgE epitopes, which could lead to cross-allergenicity to crustaceans or other invertebrates. Currently, no experimental data are available on T-cell epitopes, cross-reactive or otherwise, among mollusk allergens and presents an avenue for future research.

Fish allergy

Fish are divided into the super classes of bony fish (*Osteichthyes*), comprising most edible fish worldwide, and cartilaginous fish (*Chondrichthyes*), which include rays, skates, and sharks.[54,78] The prevalence of fish allergy is approximately 1% of the world population, with higher frequency among children (up to 5%) and regions with high fish consumption and among fish-processing workers (up to 36%).[54,79] Sensitization occurs usually via ingestion, but also through skin contact and inhalation, resulting in different symptoms, including anaphylaxis, asthma, and dermatitis.

Fish allergens have been identified in most parts of the fish, including fish muscle, skin, bones, roe, and blood. Most well-studied allergens are heat stable; however, increasingly less-stable allergens are identified, due to reduced food processing and more regional studies. Registered allergens include parvalbumin, aldolase A, β-enolase, tropomyosin, creatine kinase, collagen, triosephosphate isomerase, pyruvate kinase, L-lactate dehydrogenase, glucose 6-phosphate isomerase, glyceraldehyede-3-phosphate, and vitellogenin.

The best-studied allergen is the calcium-binding protein parvalbumin, ranging in molecular weight from 10 kDa to 13 kDa and sensitization ranges from 70% to 95%, depending on the study population. Most fish express different molecular isoforms of parvalbumin (up to 5), most likely being responsible for

differential clinical reactivity, resulting in monosensitivity (eg, salmon and cod) but mostly multiple sensitivity.[80] Parvalbumins cluster into 2 distinct phylogenetic lineages of parvalbumin, with β-parvalbumins being predominantly expressed in bony fish, causing most of the reported IgE-mediated allergic reactions. Cartilaginous fish contain predominantly α-parvalbumins, with much lower IgE reactivity.[81,82] β-Parvalbumins also contain a greater proportion of acidic amino acid residues and have an isoelectric point (pI) below 4.8. Other established allergens include enolases and aldolases from cod, salmon, tuna, carp, and catfish, with IgE reactivities ranging from 13% to 56%. In addition, collagen and tropomyosins have been identified in several fish species.[83] Although *in vitro* cross-reactivity has been demonstrated for most allergens in different fish species, the clinical relevance is yet to be confirmed.

IgE cross-reactivity seems to be limited between α- and β-parvalbumins. In contrast, frequent cross-reactivity is seen between beta-homologues, due to the very high structural homology, particularly in the 2 calcium-binding regions.[84] More than 16 different parvalbumins are registered with the International Union of Immunological Societies (IUIS) database, and large amino acid sequence diversity between species such as cod, carp, and salmon has been demonstrated.[85] Notably, parvalbumin isoforms from the same species often share less than 68% amino acid sequence identity as shown for barramundi and rainbow trout, adding complexity to correct diagnosis.[86] Parvalbumins of the α-lineage share only 43% to 60% amino acid sequence identity with β-parvalbumins, explaining the lower allergenicity of cartilaginous fish.[82]

IgE-binding epitopes of β-parvalbumin are identified in about 4 different patches[87]; however, none share identical epitopes. Although the most conserved amino acid region is in the first calcium-binding site, the most common IgE-binding sites are between position 25 and 45.[87] A second frequent IgE epitope is in the second calcium-binding site, explaining reduced antibody reactivity after depletion of calcium ions from parvalbumin. One epitope in the first 20 amino acids of the N-terminal region has only been demonstrated for salmon, and probably explains the monosensitivity seen to this fish species.[88] The number of linear epitopes and IgE reactivity to the C-terminal epitope seem to correlate with severity of allergic reactions.[89] Clinically relevant cross-reactivity to nonfish parvalbumins has also been demonstrated, for frog (Ran e 2), chicken (Gal d 8), and recently for crocodile (Cro p 1, Cro p 2).[90,91]

Because parvalbumin is the most frequent IgE-binding fish allergen, a strategy for immunotherapy using hypoallergenic parvalbumins has been developed. Mutations in the 2 calcium-binding sites resulted in significantly reduced IgE binding. The immune response observed in sensitized mice and rabbits, supported by peptide-specific antibody responses, clearly demonstrated IgG-driven protection against allergic reactions.[92] These finding are supported by a recent study using 7 overlapping peptides to identify IgE- and IgG4-binding epitopes on Asian seabass parvalbumin.[87] Patients demonstrated patient-specific antibody-binding profiles; however, peptide recognition differed between antibody isotypes.

Hen's egg allergy

Egg allergy is one of the most frequent food allergies in children worldwide and can affect up to 10%.[93,94] Sensitization and exposure occur usually via ingestion, but skin contact and inhalation of aerosolized particles has also been reported. Although up to 75% of allergic children seem to outgrow egg allergy during later childhood, severe symptoms are common in the early years, including vomiting, abdominal pain, and urticaria. Importantly, the remaining allergic children experience allergy into adulthood.[95] The early identification of children with persistent egg allergy is critical to management and component-resolved diagnosis seems to identify several egg white allergens as good predictors.

Egg white contains 4 major allergens, ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin (Gal d 3), and egg lysozyme (Gal d 4), whereas alpha-livetin (Gal d 5) is present in egg yolk. Other less well-characterized allergens include phosvitin, apovitellenins-I and -VI as well as ovomucin. Clinical cross-reactivity occurs between various bird egg proteins (eg, hen, turkey, duck, seagull, and quail[96]), probably due to 1 or several of these allergens. Reduced allergenicity is shown for baked eggs (180°C, >30 minutes), indicating the presence of conformational IgE epitopes. IgE binding to specific allergens can assist in determining the degree of clinical reactivity, persistence of sensitization, and cross-reactivity to other bird egg proteins. Elevated IgE level to the heat-stable Gal d 1 might indicate sustained egg allergy to all forms of egg. The less-stable allergens Gal d 2, Gal d 3, and Gal d 4 indicate a higher risk of clinical reactions to raw and slightly heated egg. Less studied are the allergens in egg yolk, which seem to predominantly affect adults. Clinical cross-reactivity to Gal d 5 can cause the bird-egg syndrome, and sensitization to airborne avian allergens.[97] In addition, it was observed in children that Gal d 5 specific IgE was strongly correlated with persistent egg allergy.[95]

Several studies analyzed the linear epitopes of Gal d 2 and identified up to 5 epitopes, of which some had β-turns and β-sheets exposed on the protein surface structure.[98] Epitope studies of Gal d 1 identified 3 intradomain disulfide bonds in each of the 3 domains, leading to its high stability. Up to 9 IgE epitopes were identified in these 3 domains. Subsequently, hypoallergenic variants of Gal d 1 have been produced in several studies, through disruption of stabilizing disulphide bonds in domain III, resulting in much reduced IgE binding.[99] Gal d 4 has 4 disulfide bonds, and 3 IgE epitopes have been identified so far. T-cell epitope studies have only been conducted for Gal d 1[100] and Gal d 2[101] in a BALB/c mouse model.

Cow's milk allergy

Cow's milk allergy (CMA) is one of the most common food allergies worldwide (0.5%-7.5% in westernized countries).[91] CN and whey constitute approximately 80% and 20% of CM protein, respectively. CNs (αs1-, αs2-, β-, and κ-CN, Bos d 8), beta-lactoglobulin (Bos d 5), and α-lactalbumin (Bos d 4) are considered major allergens, whereas BSA (BSA, Bos d 6), lactoferrin, and immunoglobulin (Bos d 7) are considered minor allergens.

CN is a phosphoprotein that interacts with calcium phosphate and presents in the micelle structure in CM. The labile structure impedes heat denaturation and aggregation, and specific IgE antibodies preferentially recognize sequential epitopes. However, CN is easily degraded by digestive enzymes such as pepsin and trypsin, so major IgE-binding epitopes exist at amino acid sequence sites that are not cleaved by these enzymes.[91,102] IgE epitope mapping has been investigated using an overlapping

peptide array technique.[103] Although the suggested IgE and IgG4 epitopes were varied among the reports, the identified epitopes were related to the diagnosis of CMA,[104] acquisition of natural tolerance,[105] and the outcome of oral immunotherapy.[106] Tetramer-guided T-cell epitope mapping identified 23 T-cell epitopes, and suggested a possibility of epitope spreading in subjects with persistent CMA.[107]

When considering the cross-reactivity between mammalian milk, the composition of each protein fraction and sequential homologies are important. The total protein content in milk from the order *Artiodactyla* (cow, sheep, goat, camel, and pig) is higher than that from the order *Perissodactyla* (horse and donkey). The ratio of CN to whey protein is very similar among the family *Bovidae* (cow, sheep, goat), whereas the milk from the family *Equidae* (horse, donkey) has a lower ratio, which is even lower in human milk. The highest sequential homologies are observed between CM and other *Bovidae* (84%-91% in CNs, 71%-97% in whey proteins). Lower homologies are associated with the milk from *Camelidae* (camel), *Suidae* (pig), *Equidae*, and humans. Consistent with these compositional and sequential properties, immunologic cross-antigenicity has been demonstrated by inhibition assays between CM and *Bovidae* (60%-89%), but much less between CM and *Equidae*. Clinically, high concordance of skin prick test positivity (63%-100%) and reactivity of oral food challenge test (92%) is confirmed between CM and *Bovidae*, whereas these are lower between CM and *Camelidae*, *Suidae*, and *Equidae* (1%-31%). Although it is difficult to prove true clinical cross-reactivity, the remission of most goat and sheep milk allergies after CM oral immunotherapy provides indirect evidence of the clinical cross-reactivity between them.[108,109]

Patients with CMA sometimes react to raw or weakly heated bovine meat, due to the presence of common allergenic proteins, including serum albumins (Bos d 6) and immunoglobulins (Bos d 7).[1] In contrast, 73% to 93%[1,110,111] of beef-allergic patients, especially sensitized to Bos d 6, were shown to react to CM. Although there is no evidence of direct clinical cross-reactivity, approximately 10% of patients with CMA are reported to be allergic to soybean.[112] Moreover, several studies have shown immunologic cross-antigenicity between CM and the Gly m 5,[113] Gly m Bd 28k,[3] and Gly m Bd 30k.[44,114]

Although amino acid sequence homology between αs1-CNs and β-CN is quite low (4%), specific IgE levels between them were strongly correlated, and simultaneously decreased during CM oral immunotherapy.[115,116] Moreover, complete IgE inhibition was observed by β-CN against αs1-CN in ELISA. The partial amino acid sequences of αs1-CN (E61-E70) and β-CN (I12-E21) showed a low propensity distance value (5.30) under *in silico* analysis,[117] which suggests high sequential homology. These conserved sequences have been known as CN phosphopeptide, which has the core motif of "SSSEE," consisting of phosphorylated serine residues. Patients with severe CMA exhibit allergic reactions to CN phosphopeptide–containing products such as oral care products, chewing gums, topical creams, and toothpaste.[118] These findings suggest that partial cross-reactive epitopes, but not the entire sequential homology, play a vital role in the cross-antigenicity between CN fractions.

Wheat allergy

Wheat is among the 5 most common food allergens in children; the prevalence varies from 0.4% to 4% depending on age and region.[91,119] Wheat proteins are classified as water/salt-soluble fraction (albumin/globulin) and water/salt-insoluble fraction (gluten). Gluten is a large disulfide-bonded polymer composed of gliadin and glutenin. Gliadins are characterized as glutamine-rich, alcohol-soluble grain storage prolamins and are classified as α/β-, γ-, and ω-gliadins. Glutenins are alcohol-insoluble, acid/base-soluble proteins classified into high molecular weight (HMW) and low molecular weight.

Twenty-eight wheat allergens are listed in the WHO-IUIS nomenclature database.[91] Proteins constituting gluten are the major allergens in immediate-type wheat allergy in children and wheat-dependent exercise-induced anaphylaxis (WDEIA), with ω-5 gliadin (Tri a 19) and HMW-glutenin (Tri a 26) reported as major components.[4,91,116] Many proteins in water/salt-soluble fraction, including α-amylase inhibitor (Tri a 15, 28-30), nonspecific lipid transfer protein (Tri a 14), wheat profilin (Tri a 12), thioredoxin (Tri a 25), thiol reductase homolog (Tri a 27), serpin (Tri a 33), serine protease inhibitor (Tri a 39), and peroxidase were found to be significant allergens in patients with baker's asthma and immediate-type wheat allergy.[4,91,120-122] α-Purothionin (Tri a 37) is associated with severe wheat allergy,[123] and IgG and IgE reactivity to α-purothionin has been reported to be useful in distinguishing between wheat allergy and sensitization.[124]

Epitope studies have identified a consensus sequence consisting of QQX_1PX_2QQ (X_1 = L, F, S, I; X_2 = Q, E, G) in ω-5-gliadin as the IgE-binding epitope in Japanese and European patients with WDEIA.[4,125] IgE from patients with WDEIA also reacts strongly with HMW-glutenin, and QQPGQ, QQPGQGQQ, and QQSGQGQ have been identified as IgE-binding epitopes.[126] These sequences are present repeatedly in the primary structure of ω-5 gliadin and HMW-glutenin, respectively. However, a consensus sequence QPQQPFPQ in γ-gliadin and ω-2 gliadin was identified in patients with WDEIA after transdermal sensitization to hydrolyzed wheat protein. It was identical to the epitope sequence identified in European patients orally sensitized with hydrolyzed wheat protein.[127,128] In these cases, deamidation of glutamine (Q) residue, converted to glutamate residue (E), strengthens the IgE-binding affinity, and the substitution of 3 glutamines, QPEEPFPE, increases its recognition. Thus, the deamidation of gluten generates neo-epitopes responsible for hydrolyzed wheat protein allergy.[129] T-cell epitopes have been studied in celiac disease, and it is known that the deamidation of specific motifs in gluten generates effective T-cell epitopes. Although an association between the HLA-DPB1*02:01:02 allele and WDEIA has been reported,[130] T-cell epitopes in wheat allergy are not yet elucidated.

Wheat has a wide range of *in vitro* cross-reactivity among other grains of the grass *Poaceae* family. Prolamine is considered responsible for the cross-reactivity between gliadin in wheat, hordein in barley, secalin in rye, and avenin in oat.[91,121,131] Among wheat-allergic patients, cross-reactive grain allergies confirmed by oral food challenge are observed in 8% to 56% for barley, 12% for rye, and 7% to 20% for oat.[119,132-135] Early studies of patients with WDEIA showed that γ-3 hordein in barley and γ-70 and γ-35 secalin in rye cross-react with ω-5 gliadin.[131] Inhibition ELISA confirmed that ω-5 gliadin inhibited the binding of IgE to solid-phase γ-3 hordein and γ-secalins. These proteins are major storage proteins of the endosperm, containing unusually rich proline and glutamate residues in their primary structure, and are highly homologous to each other.[136,137]

For immediate-type allergy in children, inhibition ELISA studies using serum from patients with comorbid wheat and barley allergy showed that wheat completely inhibited the binding of IgE to barley solid phase, even at lower concentrations than barley.[135,138] Immunoblotting[138] and ELISA[135] inhibition showed that multiple barley fractions were inhibited with wheat, indicating that multiple fractions, not only gliadin, might be involved in cross-reactivity between wheat and barley. In addition, in patients with oral food challenge–confirmed wheat and barley allergy, successful wheat oral immunotherapy simultaneously ameliorated the barley allergy.[138] This indicated that in the clinical cross-reactivity between wheat and barley, mostly wheat is the primary allergen and barley is the cross-sensitized allergen. Other types of wheat allergy involving cross-reactivity have been reported, suggesting that IgE produced by sensitization to grass pollen–derived proteins cross-reacts with peroxidase-I and beta-glucosidase in wheat foods, resulting in immediate wheat allergy or WDEIA.[139] There are no reports on wheat allergy immunotherapy with IgE epitopes. Although reductions in all gliadin and glutenin component-specific IgE have been reported in oral immunotherapy for patients with immediate wheat allergy, no specific component was found to correlate with the efficacy of oral immunotherapy.[140]

CROSS-REACTIVE CARBOHYDRATE DETERMINANTS AND THEIR ROLE IN FOOD ALLERGY

Glycosylation is one of the common post-translational modification of proteins in most organisms. Carbohydrate moieties can vary in structure and complexity, and may play a role in protein functionality, structural stability, solubility, and protein transport. Carbohydrate determinants found on glycoproteins from plants, nonprimate mammals, and invertebrates do not occur in humans. Therefore, these glycans are highly immunogenic and capable of inducing a strong antibody response. These carbohydrate moieties are termed as cross-reactive carbohydrate determinants (CCDs). The presence of α 1,3-linked core fucose (plant and insect) and β1,2-linked xylose (plant and helminth) motifs on N-glycans is high among plant and invertebrate allergens and exhibit antibody cross-reactivity.[141] Anti-CCD IgE antibodies are found primarily in individuals with multiple sensitizations to plant glycoprotein allergens. In a study by Holzweber et al,[142] it was shown that 22% of allergic patient sera contained anti-CCD IgE antibodies. Similarly, 10% to 50% of patients with zucchini, celery, carrot, or tomato allergy had anti-CCD IgE.[143] The presence of anti-CCD IgE antibodies does not correlate with clinically relevant allergic symptoms in most, if not all, cases. This may be due to the presence of anti-CCD IgG antibodies that act as blocking antibodies.[144] Inhibition of these anti-CCD IgEs can increase the diagnostic efficiency.[145] In an interesting study, CCDs have also been shown to play a role in cross-reactive antibodies between peanut allergen Ara h 1 and *Schistosoma mansoni* egg antigens and cross-binding abolished on removal of glycan groups.[146]

In contrast to the low clinical effects of classical CCDs, the IgE-mediated clinical response to galactose-α-1,3-galactose (α-Gal) is well established. Anti–α-Gal IgE antibodies are produced in individuals on exposure to glycoproteins in tick saliva after a tick bite, and can bind to α-Gal found in red meat that is bound to either proteins or lipids, and lead to cross-linking on the surface of basophils and mast cells. Interestingly, α-Gal–induced red meat allergy elicits a delayed-onset allergic response usually after 3 to 6 hours of ingestion.[147,148] In contrast, immediate allergic reaction and anaphylaxis was observed to intravenous administration of cetuximab, a therapeutic drug known to contain α-Gal.[149] Recently, it was shown that α-Gal from glycolipids, and not glycoproteins, is able to cross the intestinal monolayer and trigger an allergic reaction. This may explain the delay in allergic reaction to red meat allergy due to the slow digestion and absorption process of lipids.[150] It is interesting to note that in case of both classical CCDs and α-Gal–based CCDs, the primary sensitization can occur through percutaneous exposure via an arthropod (insect sting or tick bite). However, current literature do not show any evidence of CCDs playing a role in arthropod-related food allergy (crustacean, mollusk, or edible insects) and may be a potential topic of future research in understanding the role of glycoproteins in allergic sensitization and cross-reactivity.

Allergy to galacto-oligosaccharides, an ingredient that is present in milk formulations and dairy products, may be associated with primary sensitization to dust mites.[151] Glycoproteins present in tropical mites may induce cross-reactive IgE antibodies, which may in turn bind to dietary galacto-oligosaccharides. Such cross-reactivity may also explain allergy to galacto-oligosaccharide–supplemented beverages shown among a group of oyster shuckers having sea squirt allergy.[152] Because of the growing knowledge and clinical significance of the role of carbohydrate epitopes in allergic diseases, CCDs are included as potential allergenic epitopes in the WHO/IUIS Allergen Nomenclature.[153]

ROLE OF CROSS-REACTIVE EPITOPES IN ALLERGEN-SPECIFIC IMMUNOTHERAPY FOR FOOD ALLERGY

The presence of cross-reactive epitopes in allergen preparations used for allergen immunotherapy plays an important role in the safety and efficacy of the treatment and in its objective of achieving desensitization and clinical tolerance.

One example of immunotherapy and concurrent sensitization/desensitization is that of house dust mite (HDM) immunotherapy and sensitization or allergy to shellfish. IgE sensitization and clinical symptoms were seen in a patient after receiving HDM immunotherapy, and IgE binding to snail in another patient.[154] In a separate study, 1 patient showed a decrease in specific IgE to both Der p 10 and Pen a 1 after receiving HDM immunotherapy as well as loss of reactivity toward seafood.[155] A study by Asero[156] showed in a 3-year follow-up study that none of the 70 patients receiving HDM immunotherapy developed sensitization or clinical symptom to shrimps and reported regular consumption of crustaceans and mollusks. Most studies focus on tropomyosin as the major cross-reacting allergen. However, several other HDM and shrimp allergens belong to the same allergen families, including arginine kinase, myosin light chain, sarcoplasmic calcium-binding protein, hemocyanin, fatty acid–binding protein, and filamin C, which play a role in HDM/shrimp cross-reactivity.[10,157]

This phenomenon has also been observed in pollen-related food allergy syndrome. A recent study showed that patients on a 5-grass pollen sublingual tablet immunotherapy declared good tolerance to offending plant-based foods.[5] Patients on subcutaneous immunotherapy with birch pollen extract showed tolerance to

soy milk, although some patients elicited systemic reactions in the rapid escalation phase of the treatment.[158] In a clinical study, allergen-specific immunotherapy with fresh apples showed an increased tolerance to consumption and decreased skin reactivity, as well as decreased conjunctivitis reactivity to birch extract.[159]

Based on the extensive cross-reactivity between tree nuts as well as on the unexpected cross-reactivity between unrelated allergens described above, there is great potential for single nut therapy or single allergen to have therapeutic effects for multiple nut allergies. Current research into walnut allergy reaffirms what animal models demonstrated, that cross-desensitization between tree nuts might occur.[160,161] Elizur et al[162] showed that walnut oral immunotherapy can be an effective way to induce desensitization to walnut as well as cross-desensitization to pecan and hazelnut in patients who were allergic to the 3 tree nuts.[162] Furthermore, a recent study in an anaphylactic mouse model showed that vaccination against either Ara h 1 or Ara h 2 was sufficient to induce protection against the whole peanut extract consisting of multiple allergens.[163]

The presence or modification of cross-reactive epitopes can be controlled in protein- or peptide-based immunotherapy for food allergy. Well-characterized cross-reactive T-cell epitopes may help in desensitization to multiple food sources as elucidated for cashew allergens.[45] Factoring in the presence or absence of cross-reactive T- or B-cell epitopes is important while developing immunotherapeutic lead candidates for major food-group allergies such as fish or shellfish. Because of the vast number of consumed species, presence of multiple sensitizing allergens, and the structural and immunologic differences among the allergens they contain, it is a challenge to design a single peptide- or protein-based candidate. Current advances in immunoinformatic tools may help in deciding specific shared cross-reactive peptide sequences covering a range of different allergen sources. However, it should be noted that structural differences among allergens from the same protein family might result in differential cross-reactivity.[18,164]

CONCLUSIONS AND FUTURE DIRECTIONS

It is clear that allergenic cross-reactivity plays a central role in the initiation and progress of allergic reactions to food. Identification and characterization of B-cell and T-cell cross-reactive epitopes in clinically relevant food allergens is important for improving our understanding of mechanisms of clinical cross-sensitization and cross-reactivity, as well as to design improved diagnostic assays to be able to predict cross-reactivity to the initiator allergen source, with high sensitivity and specificity. More importantly, it is important to take into account the presence of cross-reactive epitopes in the development of protein- or peptide-based molecules for allergen-specific immunotherapy. Cross-reactive food allergen epitopes could potentially be harnessed to induce desensitization and tolerance to a wider range of related food sources.

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