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Carbohydrates as food allergens

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The literature supports the notion that carbohydrate epitopes, on their own, do not contribute significantly to the induction of allergic reactions. They bind weakly to IgE antibodies and have been termed as cross reactive carbohydrate determinants. These epitopes cause confusion in *in vitro* IgE testing through nonspecific cross-reactivity. Coincident with the rising trends in food allergy prevalence, there has recently been reports of anaphylaxis induced by carbohydrate epitopes. There are two distinct groups, each with unique characteristics and geographical distribution. Anaphylaxis and acute allergic reactions related to the carbohydrate galactose-α-1,3-galactose (α-Gal) epitope that are present in the monoclonal antibody, cetuximab and red meat have been described in the United States and Europe populations where tick bites have been found to be the primary sensitizer. Another carbohydrate inducing anaphylaxis is galacto-oligosaccharides in commercial milk formula which has been described in the several Asian populations including Singapore. The latter is unique in that the allergen is a pure carbohydrate. We summarize the current literature on carbohydrate-induced food allergy, and evaluate the two new groups of carbohydrate allergy that have defied previous findings on carbohydrates and their role.

Keywords: Carbohydrates; Cross reactions; Oligosaccharides; Food hypersensitivity; Anaphylaxis

INTRODUCTION

IgE-mediated food allergy is an immediate immune reaction triggered by exposure, typically through ingestion, to allergens of the offending food. The part of the allergen responsible for IgE binding or the allergenic epitope is usually conformational. Thus, the folded protein in its 3-dimensional shape contributes to IgE binding and amino acid sequences that are some distance apart in the linear sense, couples with the antibody to form the antigen-antibody complex responsible for the allergic reaction. Rarely, epitopes are purely sequential, meaning that a short linear sequence of amino acids consecutive to each other is wholly responsible for forming the antigen-antibody complex.

In contrast, carbohydrates on their own are poorly immunogenic. Carbohydrates covalently attach to proteins

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to form glycoproteins. The glycan portion of mammalian glycoproteins is generally not immunogenic. They are common to most mammals and therefore the mammal's own immune system develops tolerance to these carbohydrate moieties. Conversely, nonmammalian glycoproteins that are dissimilar to the mammal's own glycoproteins, can induce the formation of IgG and sometimes IgE antibodies. The prime example of a nonallergenic glycan is the α1-6 linked fucose residue which is common to both mammalian and nonmammalian glycans. In contrast, α1-3 linked fucose and β1-2 linked xylose residues of plant glycoproteins are immunogenic as they are not found in mammals [1].

Much has been written about carbohydrate epitopes over the last four decades, and it was traditionally thought that they could not induce allergic reactions. However, reports in recent years have overturned this assumption. Here, we provide a perspective on the history of research into carbohydrate epitopes in food allergy, and the current evidence in this field.

METHODS

We undertook a search in PubMed using the terms "carbohydrate AND food allergy", "cross reactive carbohydrate determinants" and "galacto-oligosaccharide". There were no language or time period restrictions. The reference lists of retrieved articles were also searched for literature of relevance to the topic. Only articles pertinent to the subject topic of this review were included. There were 1,607 articles identified using these criteria. After screening abstracts, 38 relevant articles were retrieved and the reference lists reviewed to obtain another 24 articles.

CROSS-REACTIVE CARBOHYDRATE DETERMINANTS

Aalberse et al. [2] pioneered the term cross-reactive carbohydrate determinants (CCD). In that paper, the authors systematically demonstrated that the allergen causing nonspecific IgE binding in the serum of their donors was likely a carbohydrate which was heat-resistant and unlikely to be of clinical significance—observations that have generally held true over the decades. Many studies since [3-6] support the prevailing view that CCD was often responsible for induction of specific IgE in asymptomatic patients. The absence of symptoms is due to lack of biological activity of the sugar chain [4, 7-9].

CCDs are present in many plants, including food allergens peanut, kiwi, potato, rice. Removing the carbohydrate compound from allergenic glycoprotein is shown to reduce IgE binding in the *in vitro* assay [1]. Most anti-CCDs IgE is are induced by grass pollen exposure and hymenoptera stings [2, 9, 10]. An association has also been reported with significant alcohol intake [11-15]. Various studies put the prevalence of anti-CCD IgE at approximately 20–37% of patients with allergy to grass pollen and insect venom [9, 16-18]. There also appears to be variation in prevalence based on age; Holzweber et al. [19] examined the sera of 6,220 patients with suspected sensitization to pollen, food or insect venoms, and found that the peak of occurrence of anti-CCD antibodies was in teenagers, at 36% of the cohort.

However, the true prevalence of anti-CCD IgE in the general population is unknown. The largest cross-sectional study of an unselected cohort to date involving food allergy and CCD was by Amoah et al. [20] of schoolchildren in Ghana, aimed at evaluating peanut allergy in a population where the prevalence of peanut allergy is low. The authors found 17.5% (233/1,328) of their tested cohort had peanut-specific IgE; as with the earlier studies that found CCD responsible for false-positive IgE results, most had negative skin prick tests and only 21 children reported symptoms on ingestion of peanut. They also demonstrated a strong correlation between children who did have peanut-specific IgE, with anti-CCD IgE; and previous *Schistosoma haematobium* infection being a possible trigger for inducing cross-reactivity, again likely through CCD.

For the purposes of discussing the molecular structures of various CCDs' and the corroboration with their biochemical and (lack of) clinical symptoms, we recommend an excellent review paper which also provides an in-depth explanation of the evolution of knowledge regarding CCD over the decades [21]. To summarize, plants have N-glycans common to each other and not found in humans may be immunogenic. Some of these N-glycans are also found in insects, parasitic worms and snails. Despite the abundant literature on CCD, studies supported the concept that they were insignificant clinically. The reasons for the inability of CCD to cause clinical reactions include their inability to crosslink IgE receptors on effector cells, especially given that many CCD are monovalent; and incidental immunotherapy to CCD in patients over the course of their life, resulting in induction

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of blocking antibodies of the IgG_4 type.

The main difficulty posed by CCD is in *in vitro* IgE testing, as the aim of such testing is usually to determine the substances the patient has a true allergy to. Patients with anti-CCD antibodies may show positive IgE results to multiple cross-reactive food and pollen allergens in the absence of any symptoms, essentially resulting in many false positives with all of the attendant complications thereof for both patient and physician. A good clinical history coupled with awareness of this confounding issue will obviate the urge to test for IgE to multiple substances of questionable relevance—a scenario that allergy specialists face commonly, where the patient walks in through the door of the clinic and asks to "test for everything because they are not sure what they are allergic to". Another example is in the setting of venom immunotherapy, as distinguishing between double sensitivity and double reactivity to bee and wasp venom for the purposes of immunotherapy is possible, but entails additional work—traditionally, inhibition testing.

Some earlier studies imply that skin prick tests appear to be more specific than and thus, superior to *in vitro* IgE testing [3, 4] in a scenario where CCD is involved, provided there are no contraindications to performing the skin prick test in the patient. Component-resolved diagnostics are another means of overcoming this problem [22-26], though three caveats exist. First, the recombinant proteins used must be devoid of CCD. Second, interpretation of the specific components must take into account the fact that allergens to which patients react will vary geographically, as has been described in peanut allergy [27]. Lastly, component-resolved diagnostics require specific technical expertise and thus are not as widely available in many parts of the world.

Eliminating the involvement of CCD in *in vitro* testing is ideal. Periodate, which is a powerful oxidizing agent, continues to be used to remove CCD for research purposes, but has the undesirable effect of possibly reducing the antigenic effect of the coupled protein [28, 29]. More recent studies using CCD blockers [19], CCD-reduced plants [30] and surface Plasmon resonance imaging microarrays using peptide and carbohydrate epitopes [31] show promise in improving the diagnostic accuracy of in-vitro IgE tests.

ASIAN FOOD ALLERGENS: BIRD'S NEST AND RICE

On a more regional note, we describe two food allergens more commonly consumed in the Asian region. Their allergenic epitopes appear to involve carbohydrates. Chinese swiftlets are birds found in the Southeast Asian region as well as on islands of the Pacific and Indian oceans. Their nests are considered food delicacies especially in Asia, and are usually double-boiled with various ingredients such as rock sugar, to make soup. The nest-cementing substance, which comes from the male swiftlet, is a glycoprotein that is composed of 9% sialic acid, 7.2% galactosamine, 5.3% glucosamine, 16.9% galactose, 0.7% fucose, and the rest being protein and inorganic ash [32]. Cases of anaphylaxis to bird's nest were, at one time, the most common cause of anaphylaxis in the National University Hospital in Singapore [33] and new cases are still seen by the authors every year.

Subsequent study [34, 35] has elucidated a 66-kDa protein that lost its IgE-binding ability on treatment with periodate, but not with heating, suggesting that the carbohydrate moiety was necessary to induce an allergic reaction. Data on amino acid sequencing of the peptide component of the protein suggested homology to the ovoinhibitor precursor in chicken, but this was unlikely to be significant as chicken is a commonly ingested food in the country, yet none of the patients had chicken allergy. The structure of this glycoprotein has not yet been elucidated.

Another food allergen typical of the Asian region is rice. Rice is the seed of *Oryza sativa*, and is a staple food in many parts of the world. Despite this, there have been very few reports of rice allergy upon ingestion [36-39]. Recently, Trcka et al. [40] characterized the allergens in rice responsible for inducing anaphylaxis in a German patient, as well as 8 other German patients who had hypersensitivity symptoms after ingestion of rice. The authors found that CCD significantly contributed to IgE binding of all of the putative allergens, including that of the most likely allergen, a 56-kDa glycoprotein. The structure of the glycoprotein has not yet been elucidated.

TICK BITES, RED MEAT ALLERGY AND CETUXIMAB

The truism that sugar chains on glycoproteins are of no clinical

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Table 1. Possible linkage configurations of 3-sugar-unit component of galacto-oligosaccharide

No.	Structures
1	b-D-Gal-(1⟶4)-b-D-Gal-(1⟶6)-D-Glc
2	b-D-Gal-(1⟶4)-b-D-Gal-(1⟶4)-D-Glc
3	b-D-Gal-(1⟶4)-b-D-Gal-(1⟶3)-D-Glc
4	b-D-Gal-(1⟶4)-b-D-Gal-(1⟶2)-D-Glc
5	b-D-Gal-(1⟶6)-b-D-Gal-(1⟶4)-D-Glc
6	b-D-Gal-(1⟶6)-b-D-Gal-(1⟶6)-D-Glc
7	b-D-Gal-(1⟶2)-a-D-Glc-(1«1)-b-D-Gal
8	b-D-Gal-(1⟶4)-a-D-Glc-(1«1)-b-D-Gal
9	b-D-Gal-(1⟶4)-b-D-Gal-(1⟶4)-D-Fru
10	b-D-Gal 1 ↓ 6 b-D-Gal-(1⟶2)-D-Glc
11	b-D-Gal 1 ↓ 6 b-D-Gal-(1⟶3)-D-Glc
12	b-D-Gal 1 ↓ 6 b-D-Gal-(1⟶4)-D-Glc
13	b-D-Gal 1 ↓ 4 b-D-Gal-(1⟶2)-D-Glc

Adapted from Yanahira S, et al. Biosci Biotechnol Biochem 1995;59:1021-6 [62].

significance has been increasingly challenged in recent years.

The bulk of the literature has focused on red meat allergy, where consumption of this meat results in anaphylactic reactions, unique for their tendency to have a delayed presentation several hours after ingestion. The reactions occur as a result of IgE binding to the oligosaccharide galactose-α-1,3-galactose (α-Gal), which is a sugar chain commonly found as part of glycoproteins and glycolipids in mammals.

Recognition of the role that α-Gal played in allergy first surfaced in 2008, when Chung et al. [41] investigated the sera of patients who had experienced hypersensitivity reactions after receiving cetuximab. The authors demonstrated a near-perfect correlation (r=0.92) between the IgE antibodies against α-Gal with antibodies that bound to cetuximab. Coincidentally, they also observed the coexistence of antibodies to cat, dog and beef proteins, and went on to show that the binding of IgE antibodies against cat, dog, beef, and pork proteins and cetuximab could be inhibited by soluble α-Gal and could be absorbed out of the serum with porcine thyroglobulin, which is also glycosylated with α-Gal.

The following year, researchers based at the University of Virginia [42] published a series of 24 patients who had allergic reactions 3 to 6 hours after ingestion of beef, pork or lamb, with absorption experiments pointing to IgE specific to α-Gal as the likely culprit. The skin prick test results were disproportionately small, relative to what would usually be expected for a protein allergen. An association of red meat allergy with tick bites in the history of the patients was noted to match an earlier report by van Nunen et al. [43] back in 2007 prior to formal publication [44]. The inference that the sensitizing agent to α-Gal could be the previous tick bite in these patients was borne out by subsequent work showing that *Amblyomma americanum* [45], *Ixodes ricinus* [46], and *Ixodes holocyclus* [44] could be the primary sensitizer. Hamsten et al. [46] went on to find a strong association between tick bite sensitization and the B-negative blood groups in their patients.

Since then, multiple case reports and small series have been published [47-51] describing the association between antibodies to α-Gal and red meat allergy. Commins et al. [52] has recently demonstrated the reproducibility of delayed anaphylaxis to red meat in patients with IgE to α-Gal through open food challenges. Of note is that serum tryptase was elevated in only a minority of the positive challenges.

GALACTO-OLIGOSACCHARIDE ALLERGY

Allergy to the body fluid of the sea squirt, *Styela plicata,* is a form of occupational asthma found in workers on oyster farms in Hiroshima Prefecture, Japan. Inhalation of particles from the sea squirt causes airway disease, manifesting as rhinitis and asthma. The allergenically active epitopes are oligosaccharitols from the H-antigen of the sea squirt [53, 54].

Although it was otherwise thought that carbohydrate epitopes had no clinical significance in allergy, we now know that galacto-oligosaccharide (GOS) allergy defies this assumption; the first report of allergy to GOS was in these same oyster shuckers

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in Hiroshima, Japan [55] who drank a lactic acid beverage in November 1991. GOSs are nondigestible, heat-stable carbohydrates comprising 2–6 sugar units in length, produced by β-galactosidase that transfers the galactose to the lactose moiety [56]. Unlike the α-Gal epitope which is bound to protein, GOS is a unique allergen as it is a pure carbohydrate. GOS encourage the growth of *Lactobacilli and Bifidobacterium* in the gut, which is associated with desirable effects such as improving constipation [57] and decreasing cancer risk in a rat model [58].

Though the lactic acid beverage was a commonly available drink consumed in large quantities all over Japan at that time, symptoms were reported only in patients who had a history of exposure to the sea squirt on an oyster culture farm. All eight of the patients [55] had immediate-type hypersensitivity reactions on ingestion of the beverage, four of whom also had active sea squirt allergy at that time. 30% of the GOS contained in the beverages ingested by the patients had 1–3 or 1–6 binding of two galactose molecules with glucose, while the remaining 70% was those of 1–3 or 1–6 binding of 3 to 6 galactose molecules. The authors demonstrated the GOS that yielded positive results on scratch tests and histamine release tests had more than four saccharide molecules linked by 1–3 or 1–6 binding. Cross-reactivity was observed between the GOS antibody and crude sea squirt antigen, suggesting that the sea squirt antigens were the primary sensitizer in these patients with GOS allergy.

Thereafter, there were no further reports of GOS allergy until the introduction of a new milk formula product supplemented with GOS. Within a month of its introduction in 2009, paediatricians in Ho Chi Minh City, Vietnam, noticed that there were allergic reactions in children who took this formula [59]. At around the same time, people in Singapore known to be cow's-milk tolerant began developing anaphylaxis after taking GOS-supplemented milk formula. Chiang et al. [60] evaluated 5 patients, all of whom were atopic, and demonstrated IgE sensitization through skin prick tests and basophil activation tests to GOS and fractions of GOS containing 3 sugar units or greater but not to the other potential culprits in the ingested formula: specifically cow's milk protein and long-chain fructo-oligosaccharide. GOS is a mixture of oligosaccharides with up to 7 units of sugar in length. The number of possible configurations for GOS increases exponentially with each additional sugar moiety. An example of the possible structures of GOS with only 3 sugar units is illustrated in Table 1.

At the same time as these reports emerged, GOS-supplemented lactic acid beverages had continued to be consumed not only in Japan, but also in many parts of the world on a daily basis. Kaneko et al. [61] reported patients who developed allergic reactions after ingesting GOS produced by β-galactosidase originating from a combination of *Aspergillus oryzea* and *Streptococcus thermophilus*, or by *Bacillus circulans*. The authors demonstrated that the tetrasaccharide Galβ1-4(Galβ1-4Galβ1-6)Glc was most likely to be the fraction inducing allergic reactions. Given that GOS differs on the basis of the origin of the β-galactosidase used, the authors went a step further to produce a different, hypoallergenic GOS formulation named Oligomate 55N to be incorporated into a commercially available milk drink. This was derived from *Sporobolomyces singularis* and *Kluyveromyces lactis*.

In contrast to red meat allergy, the primary sensitizer for GOS allergy remains unknown. This may be a substance geographically restricted to Asia, as the series of patients with reactions to GOS are confined only to specific regions.

GOS allergy is also unusual in that it does not fit into any defined category of an allergen, though it induces specific IgE and is biologically active. Kaneko et al. [61] found that GOS was not antigenic in isolation, but were immunogenic when coupled with carrier proteins. Chiang et al. [60] found that the baso phil activation test with GOS remained positive even after the serum protein was removed. If so, this may suggest that the protein component that binds to GOS may be a protein on the surface of the cells. This would fulfil one-half of the traditional definition of a hapten, which are molecules that bind to antibodies, but cannot induce an immune response on their own.

CONCLUSION

Though most carbohydrate epitopes are likely to be insignificant clinically, specific carbohydrate epitopes such as α-Gal and GOSs can cause severe allergic reactions on ingestion. This is a relatively recent phenomenon and parallels the general increase in allergic disease worldwide. The specific geographical restriction of all of these cases implies a primary sensitizer confined to their respective regions. Further work on the exact mechanisms in carbohydrate allergy is urgently needed to increase our understanding of this emerging disorder.

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