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Allergenicity of Carbohydrates and Their Role in Anaphylactic Events

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Abstract The IgE response to pollen allergens often includes IgE antibodies specific for glycosylation motifs on the pollen proteins. These oligosaccharides are present on many different species and are known as *cross-reactive carbohydrate determinants*. However, IgE antibodies to plant-derived cross-reactive carbohydrate determinants seem to have only minor clinical significance and have not been related to anaphylaxis. Recently, two novel forms of anaphylaxis have become apparent in the southeastern United States: 1) reactions during the first infusion of the monoclonal antibody cetuximab and 2) adult-onset delayed anaphylaxis to red meat. Detailed investigation of serum antibodies established that in both cases, the patients had IgE antibodies specific for the mammalian oligosaccharide galactose alpha-1, 3-galactose. Identification of these cases is helpful in avoiding infusion reactions to cetuximab or recommending specific avoidance of meat derived from mammals. However, the current evidence does not fully resolve why these IgE antibodies are so common in the Southeast or why the anaphylactic or urticarial reactions to red meat are delayed.

Keywords Anaphylaxis · Oligosaccharides · Cross-reactive Carbohydrate Determinants · Red Meat · IgE to Alpha-Gal

Introduction

Many or most of the allergens we inhale or ingest are glycosylated with oligosaccharides that are at least potentially immunogenic. Despite this, the normal teaching and the bulk of the current evidence show that the IgE antibodies associated with allergic disease are specific for protein epitopes whose structure is defined by the amino acid sequence and/or tertiary structure of a section of the protein. There are at least three reasons why carbohydrate epitopes are not considered important.

1. In those cases in which IgE antibodies against carbohydrate epitopes have been identified, they seem to have limited clinical relevance (eg, the plant epitope MUXF3) [1, 2].
2. Most research has focused on protein epitopes. This includes studies using recombinant molecules in which the oligosaccharides may not be the same as those on the natural molecules [3•, 4].
3. In general, the oral or inhaled route does not induce IgE antibodies against nonprotein epitopes.

Recently, we have become aware of an oligosaccharide that is common to all mammals, except the higher apes, and that can be the target for IgE antibodies [5••, 6]. These IgE antibodies are common in a large area of the Southeast, including Virginia, North Carolina, Arkansas, Tennessee, and southern Missouri [7••, 8••, 9]. The presence of these IgE antibodies became clear because one of the monoclonal antibodies used in the treatment of colon cancer was found to produce rapid hypersensitivity reactions, including frank anaphylaxis, in these states but not in other regions of the United States [8••, 9]. The identification of the specific oligosaccharide came from two studies. First, ImClone Systems (New York, NY) published an elegant study on the glycosylation of cetuximab (the monoclonal involved). That study identified several oligosaccharides on the Fab region of the heavy chain that can be antigenic in humans, one of which is galactose alpha-1, 3-galactose (alpha-gal), which is well recognized as a transplantation barrier between the lower mammals and humans [10, 11]. Second, detailed studies of the pretreatment sera of patients who had had reactions to cetuximab proved that the sera contained IgE antibodies specific for alpha-gal [5••]. At that time, it was also clear that

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these IgE antibodies were common in a control group from Tennessee but were present in less than 1% of the 340 adult women from Boston who were tested [5••].

During the studies of reactions to cetuximab, many different sera were screened for IgE antibodies to alpha-gal using cetuximab in an ImmunoCAP assay (Phadia AB, Uppsala, Sweden) [5••, 12]. Those studies identified IgE antibodies to alpha-gal in the sera of several patients who presented to the clinic with repeated episodes of anaphylaxis, angioedema, or generalized urticaria. In turn, those results led to the identification of a very strong correlation between this specificity of IgE antibodies and a characteristic history of anaphylaxis or severe urticaria that started 3 to 5 h after the patients consumed red meat [7••].

Previous Data on Carbohydrate Antigens

The presence of IgE antibodies to carbohydrate antigens was first identified from in vitro experiments looking at cross-reactivity between different plant-derived antigens [1, 2, 13]. In part because of this approach, the carbohydrate epitopes identified were generally, or exclusively, cross-reactive, which led to the designation *cross-reactive carbohydrate determinants* (CCDs). The best recognized of the CCDs is MUXF3, which is present on many different plant proteins but was first defined on a protein (bromelain) derived from pineapple stem [14]. This protein is not a significant allergen in its own right, so IgE antibodies binding to bromelain are almost always specific for MUXF3. This is an important principle because these oligosaccharide epitopes may be better presented on a parent molecule than on an artificial carrier. However, it is important to remember that the relationship to the parent molecule may alter the antigenicity of the sugars, just as the presence of an oligosaccharide may alter the antigenicity of the associated peptide [15, 16].

In the studies on plant-derived carbohydrate epitopes, it has been consistently reported that skin test responses are poor relative to serum IgE antibodies. Thus, it is not unusual to find class II or III IgE antibody response to a plant allergen in which the skin tests are negative. In keeping with the skin test results but not the serum assays, these patients often do not have significant symptoms.

More relevant, there are no reports of anaphylaxis or urticaria occurring when patients with serum IgE antibodies to MUXF3 consume plant foods carrying this epitope. Also, none of the other plant-derived CCDs have been associated with anaphylaxis.

Previous Evidence for IgE Antibodies Cross-reacting Between Different Mammalian Antigens

Several different syndromes involving mammalian cross-reactivity have been described. The pork-cat syndrome can cause anaphylactic responses when an individual consumes pork [17]. However, the cross-reactive IgE antibodies in these cases are specific for protein epitopes on albumin [18••]. On the other hand, Mamikoglu [19] reported on a series of patients in Arkansas who had IgE antibodies to beef, pork, and lamb that could have been cases with IgE antibodies to a mammalian CCD such as alpha-gal [19].

The Clinical Syndrome of Delayed Anaphylaxis After Consumption of Red Meat in Patients With IgE to Alpha-Gal

Once the concept of delayed anaphylaxis became known, physicians in a large area of the Southeast began to recognize cases. Cases have now been reported from Georgia, South Carolina, Mississippi, Kentucky, Oklahoma, Texas, and West Virginia, as well as the original five states in which hypersensitivity reactions to cetuximab were common. In most cases, the histories are characteristic in that reactions start 3 to 5 h after an individual consumes beef, pork, or lamb. In addition, most of the patients make it clear that chicken, turkey, and fish do not cause reactions. With venison, the experience has been mixed. Perhaps the most striking feature is that almost all these individuals report no immediate symptoms at the time of consuming beef (or other red meat).

Almost all the individuals involved are adults who can easily identify a time as an adult when they could consume meat without a problem. Thus, the syndrome is adult-onset delayed anaphylaxis to red meat [7••, 18••]. It is important to remember that allergy to meat is rare in adults and that the general teaching is that reactions to food are not delayed beyond 1 h. There is another reason why this syndrome had not been recognized until recently. Skin testing with commercial extracts using the prick technique generally yields poor or negative results (ie 2- or 3-mm wheals). The reactions are better with freshly prepared meat extracts or intradermal skin tests, but they are still unimpressive given the titers of IgE antibodies to beef, pork, and lamb. For many allergists, it was difficult to take seriously a patient who reported reactions starting 4 h after eating red meat and who had negative prick tests.

Possible Causes of a Carbohydrate-Specific IgE Response

It is not difficult to argue that oligosaccharides are immunogenic. The A and B antigens of red blood cells are excellent examples, but there are many others [20, 21]. In addition, it has been recognized that all immunocompetent humans have serum IgG antibodies specific for alpha-

gal [6]. Thus, the question is why do some individuals produce IgE responses against oligosaccharides? IgE antibody responses to plant-derived carbohydrate epitopes such as MUXF3 seem to be a common feature of IgE antibody responses to many pollens. For these, there do not seem to be obvious regional or other features that selectively enhance the responses to this CCD [2]. However, extensive evidence indicates that the stings of bees and other venomous insects can induce IgE antibody responses to CCDs that cross-react with plant glycoproteins [22]. Some patients who have IgE antibodies to plant CCDs also have IgE specific for protein epitopes on allergens derived from the same pollen, whereas other sera have IgE antibodies to the CCDs but not to plant-derived proteins. The important thing from our point of view is that there is already an example of a percutaneous arthropod antigen exposure that can induce an IgE antibody response to a carbohydrate.

When it became clear that reactions to cetuximab and delayed reactions to red meat were restricted to a geographic region of the country, many different explanations for a regional IgE antibody response were considered. In particular, regional plants or fungi and helminth parasites were considered; however, none of these were supported by objective evidence or a comparable regional distribution. On the other hand, from 2006 to 2008, anecdotal evidence was obtained about the possible role of tick bites. In this region, bites from dog ticks, seed ticks, and "chiggers" (the larval form of harvest mites) are very common. However, it is not possible to distinguish larval mites from larval ticks without a hand lens. Upon questioning patients, the association between tick bites and the presence of IgE antibodies to alpha-gal seems to be very strong. Thus, tick bites are now the primary hypothesis in the attempt to explain the causes of IgE antibody responses to this oligosaccharide. Strikingly, Van Nunen and colleagues [23] in Sydney have maintained for years that individuals who experienced extensive or severe response to tick bites could become allergic to beef. This is almost certainly the same phenomenon that we have observed in the United States, but the ticks in Sydney are a different species, *Ixodes holocyclus* [23].

At present, it is not possible to explain how tick bites could induce an IgE antibody response to a mammalian carbohydrate antigen. We assume that these ticks also induce IgE antibodies to oligosaccharides in the animals that are their primary hosts, but that response would have to be against a different carbohydrate. The possibility that tick saliva in the skin provides an adjuvant that strongly helps IgE responses to oligosaccharides in general would be a novel immunologic model. The importance of the skin as a site for IgE antibody responses or perhaps a route for induction of IgE responses is strongly suggested by results in patients with atopic dermatitis [24, 25]. Similarly, both the major pathogenic schistosomes and duck schistosomes entering the skin can give rise to IgE antibody responses [26, 27]. It now seems likely that tick bites should be included as an important cause of IgE antibody responses in humans, including the response to alpha-gal.

Relevance of Carbohydrate Antigens to Urticaria, Angioedema, and Anaphylaxis

The literature on plant-based CCDs does not include references to urticaria or anaphylaxis. In particular, in the large surveys by Mari [2] and others, neither of these appears as a relevant diagnosis. In addition, Aalberse (personal communication) has screened sera from patients with chronic urticaria for IgE antibodies to plant-based CCDs without finding significant positive results. Therefore, the finding of multiple cases of delayed anaphylaxis or generalized urticaria associated with IgE antibodies to alpha-gal raises questions about why this should happen with this CCD but not with others. The patients do not have any rapidly developing symptoms, although the reactions that develop after 3 to 5 h can be severe. The implication is that there is a real delay before the oligosaccharide appears in the circulation in a form that can trigger histamine release from mast cells and/or basophils. Digestion and absorption of carbohydrates is generally rapid, and most of the glycosylation on proteins or lipids is thought to be cleaved off the parent molecules [28]. Sugars or oligosaccharides entering the circulation as monomers would not be expected to cross-link IgE receptors. Similarly, protein absorption is largely complete within 1 h, and it is unlikely that sections of protein-bearing repeated glycosylation epitopes would be absorbed. By contrast, lipid absorption is slower, and a significant portion of the lipid is formed into chylomicrons that take time to pass up the lymphatic duct and into the superior vena cava [29]. How much of the surface of chylomicrons is in the form of glycolipids is not clear. However, even if only 5% of the glycolipid ingested was incorporated into chylomicrons, that might represent an important allergen load. Furthermore, after entering the circulation, chylomicrons go through a series of changes before becoming very low density lipoprotein, and those modified forms could be more effective at triggering histamine release [30]. Theoretically, a lipid- or glycolipid-based model could explain the absence of any symptoms for several hours and the severity of the attacks when they begin. We have anecdotal evidence that the quantity of fat in the "red meat" meals is an important determinant of the occurrence and severity of reactions in patients with IgE to alpha-gal. A secondary question is why reactions of this kind do not occur or have not been reported in patients who consume plant-based

foods bearing CCDs to which they have IgE antibodies. However, answering that question would require knowing extensive details about the digestion and absorption of plant-based carbohydrates and lipids.

Conclusions

Anaphylaxis that occurs without an immediate cause is a significant medical problem. Recurrent cases cause severe anxiety to the patients and their families and carry a real risk of morbidity and mortality. With the many cases that present at night or many hours after eating, in which no obvious venom or pharmacologic explanation exists, identifying causes has always been challenging [31–33]. The recent evidence regarding IgE antibodies to alpha-gal provides a challenge in terms of explaining the sequence of events but also a clear implication that there could be other forms of delayed anaphylaxis [34]. In adults, it is not difficult to avoid beef, pork, and lamb. In most (but not all) cases, severe reactions require a considerable dose such that minor exposures are not a problem. Thus, identifying cases in which IgE to alpha-gal is a likely explanation for their reactions to red meat can be very helpful in educating them about how to avoid attacks and in reassuring them about the nature of the underlying process. Avoidance is so successful in this condition that it is difficult to consider desensitization as an option for the "red meat" cases. By contrast, there are cases in which cetuximab is indicated, and a successful desensitization regime has been published [35].

The ongoing story of adult-onset delayed anaphylaxis to red meat has many lessons. That the monoclonal antibody cetuximab caused severe reactions in a limited area of the country was completely unexpected given the extensive track record of other monoclonals. The demonstration that all the IgE antibodies reacting with cetuximab are specific for an oligosaccharide present on the Fab section of the antibody at amino acid 88 was the outcome of close collaboration among Bristol-Myers Squibb (New York, NY; Dr. Mirakhur), ImClone Systems (Drs Hicklin and Zhou), several oncologists (Dr. Chung and others), as well as our team at the University of Virginia [5••, 10]. Without this collaboration, it would have been extremely difficult to unravel the unexpected role of a common mammalian oligosaccharide. Of course, this finding has major implications for the recombinant protein industry. There is always a potential risk for allergenicity when a recombinant molecule is expressed in a heterologous cell line because the cell line is capable of using sugars in glycosylation that are not present in humans [3•, 4].

The subsequent realization that individuals with these same IgE antibodies were also at risk for anaphylaxis after consuming red meat came from anecdotal cases and extensive screening of sera from our clinics [7••]. That in turn led to the recognition of the characteristic history—that is, delayed reactions occurring 3 to 5 h after exposure with no symptoms before that time. We are also aware of patients who presented with chronic urticaria who were found to be positive for IgE to alpha-gal, but it is not a common cause of that condition. The correlation with tick bites came through some luck, in which sera were available before and after a severe episode of tick bites. However, in addition, extensive literature searches (courtesy of Google) suggested that this area was most closely associated with a tick-borne disease, Rocky Mountain spotted fever.

Several features of the syndrome are unclear. In particular, it is not clear how tick bites induce an IgE antibody response to a carbohydrate epitope, and in particular to this epitope. In addition, the mechanism of the delay that follows the consumption of meat containing alpha-gal is unclear. What is certain is that IgE antibodies to a major mammalian carbohydrate epitope are common in a large area of the United States and that they are associated with two different forms of anaphylaxis. When the full mechanisms of this syndrome are established, we expect the information to open models of allergic disease that may have very wide relevance.

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