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Invited review article

Delayed anaphylaxis to alpha-gal, an oligosaccharide in mammalian meat

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Ab, antibody; Alpha-gal, galactose-alpha-1,

3-galactose; CCD, cross-reactive

carbohydrate determinant; EGFR, epidermal

growth factor receptor;

IgE, immunoglobulin E; mAb, monoclonal

antibody; NO, nitric oxide;

N-PMM, non-primate mammalian meat;

sIgE, specific IgE

ABSTRACT

IgE-mediated hypersensitivity refers to immune reactions that can be rapidly progressing and, in the case of anaphylaxis, are occasionally fatal. To that end, identification of the associated allergen is important for facilitating both education and allergen avoidance that are essential to long-term risk reduction. As the number of known exposures associated with anaphylaxis is limited, discovery of novel causative agents is crucial to evaluation and management of patients with idiopathic anaphylaxis. Within the last 10 years several apparently separate observations were recognized to be related, all of which resulted from the development of antibodies to a carbohydrate moiety on proteins. Interestingly, the exposure differed from airborne allergens but was nevertheless capable of producing anaphylactic and hypersensitivity reactions. Our recent work has identified these responses as being due to a novel IgE antibody directed against a mammalian oligosaccharide epitope, galactose-alpha-1,3-galactose ("alpha-gal"). This review will present the historical summary of the identification of cetuximab hypersensitivity due to alpha-gal IgE and discuss the non-primate mammalian meat food allergy as well as current goals and directions of our research programs.

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Introduction

IgE antibodies to carbohydrate epitopes on allergens are thought to be less common than IgE antibodies to protein epitopes and also of much less clinical significance (see www.allergen.org).^{1–3} Thus, when anaphylactic reactions to the monoclonal antibody cetuximab were recognized as a major regional complication of this cancer treatment the initial investigation focused on finding IgE antibodies to a protein epitope.^{4,5} It was unexpected when it became clear that these reactions

were causally related to pre-existing IgE antibodies (Ab) specific for the glycosylation product galactose-alpha-1,3-galactose ("alpha-gal") moieties present on cetuximab.⁴ This carbohydrate is a well-recognized immunologic barrier in xenotransplantation. In fact, xenoreactive antibodies directed against the alpha-gal moieties decorating non-primate mammalian tissue are often implicated in acute organ rejection. For the field of food allergy and anaphylaxis, this discovery led to the finding that IgE Ab to alpha-gal was implicated in the delayed food allergy to mammalian meat (e.g., beef, pork, lamb). Not only have those studies opened up investigations of how the IgE response to alpha-gal is different from typical IgE responses directed towards protein allergens but also raised global awareness and recognition of delayed reactions to red meat in numerous geographical locales throughout the world.^{6–17}

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Cetuximab-induced hypersensitivity reactions

In clinical trials for the monoclonal antibody (mAb) cetuximab, which is specific for the epidermal growth factor receptor (EGFR), it became clear that the antibody was causing hypersensitivity reactions in a group of southern US states that were not evident elsewhere.⁵ Importantly, there were two anaphylactic reactions to cetuximab in Bentonville, Arkansas in 2006. These reactions to cetuximab developed rapidly during the first infusion of the antibody and occasionally proved fatal, including one in Bentonville.^{4,5,18} In part because our group had developed the IgE fluorometric enzyme immunoassay or CAP assay to cetuximab using the streptavidin technique, we were subsequently asked to investigate the reactions to cetuximab.¹⁹ Through a series of collaborations, we demonstrated that the patients who had reactions to cetuximab also had IgE antibodies specific for this molecule before they started treatment.⁴ Characterization of cetuximab glycosylation revealed 21 distinct oligosaccharide structures, of which approximately 30% have one or more alpha-1,3 linked galactosyl residues.²⁰ Analysis of the IgE antibodies to cetuximab demonstrated that these antibodies were, in fact, specific for the galactose-alpha-1,3-galactose (alpha-gal) residues on the heavy chain portion of the mAb.²⁰ In keeping with what is known about IgE Ab and responses, a desensitization protocol for cetuximab has been established and continues to be successfully used for patients requiring the medication despite the presence of IgE to alpha-gal.²¹

The red meat connection

Also in the 2006–2008 time period, we evaluated a number of patients who had presented with episodes of generalized urticaria, angioedema or recurrent anaphylaxis. Despite there being no clear immediate cause for their symptoms, several of the patients reported that they felt the reactions might be due to eating meat 3–5 h earlier. Prick tests were performed with commercial extracts of beef, pork or lamb and produced small wheals that often would be reported as negative. However, given the compelling history described by the patients, we extended our analysis to intradermal skin testing with commercial meat extracts or prick skin tests with fresh meat extracts both of which demonstrated strong positive results.⁷ The skin findings were confirmed with blood tests for specific IgE Ab to alpha-gal and mammalian antigens.⁷

It is important to note that we were not alone in finding a connection between eating red meat and allergic reactions in adults. In fact, anaphylactic or urticarial reactions to red meat were recognized in Australia due to the original observations of Dr. Sheryl Van Nunen.¹⁷ In 2006, she had reported to the New South Wales Allergy Society that individuals who had experienced tick bites were at risk of reactions following ingestion of red meat perhaps due to an antigen transmitted from ticks feeding on the small mammal bandicoot. Her results were published in 2009 and related to the published evidence about IgE to alpha-gal.^{4,7,17} Subsequently, with Dr. Mullins we confirmed that the patients with delayed reactions to red meat in Australia had IgE antibodies specific for alpha-gal.¹⁶ Cases of reactions to red meat have now been extended to include children²² and identified in France, Sweden, Germany, Japan, and Australia as well as in the United States (Table 1, Fig. 1).^{6–17}

In our most recent survey, we have seen over 1500 cases of delayed urticaria or anaphylaxis to red meat in Virginia and North Carolina. We have evaluated a subset of these patients for symptoms, lung function, exhaled NO, and serum IgE. The resulting evidence demonstrated that IgE to alpha-gal had no association with asthma.²³ Thus even patients with high titer IgE to alpha-gal living in a house with a cat had no increase in their risk of asthma. This

was surprising since cats, like all non-primate mammals, have alpha-gal on many of their proteins and lipids. On the other hand, using an assay for alpha-gal, we were not able to detect this antigen airborne in homes with a cat even where Fel d 1 was present at high levels.²³

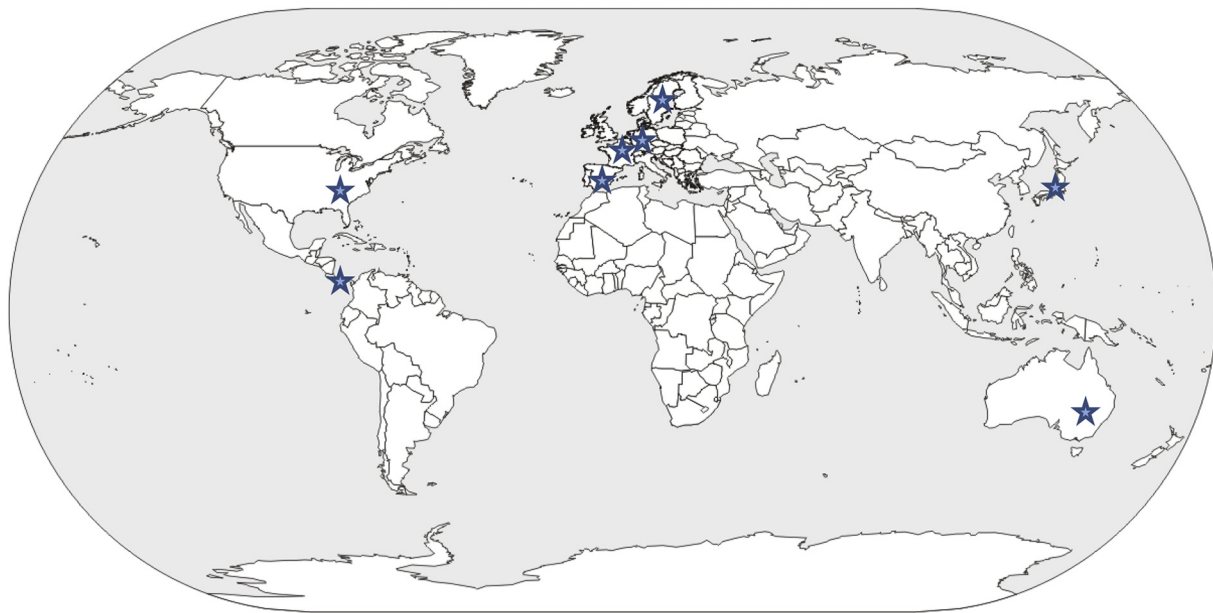
The characteristics of reactions due to alpha-gal IgE are different from typical food allergic reactions. While common complaints include both gastrointestinal symptoms and hives, patients do not develop any symptoms until several hours after eating red meat. In fact, many reactions are delayed for 4–6 h or even longer. Although the most common reported and observed symptom that heralded a reaction was pruritus, symptoms can progress to be severe or even life threatening. Many patients do not report any symptoms prior to the onset of a reaction and, equally, symptoms do not occur with every exposure to red meat. In each known instance, the onset of allergic reactions due to alpha-gal represented a break in oral tolerance where the patient had tolerated mammalian meat in the past, often for over 25 years.

More recently we have begun to recognize clinical nuances reported by patients with the alpha-gal food allergy. It appears as though some patients have a relatively straightforward clinical course once the diagnosis of IgE to alpha-gal is made. In these patients, clinical guidance related to an appropriate avoidance diet of eliminating beef, pork, lamb (and other sources of non-primate mammalian meat) is sufficient to effectively cease the allergic reactions. It bears noting that such patients largely reported reactions confined to episodes of consuming fatty portions of red meat. On the contrary, an apparent subset of patients diagnosed with IgE to alpha-gal develops a more sensitive response to alpha-gal containing foods and products. In these instances, we have noted that elimination of mammalian meat alone does not result in complete amelioration of reactions. Our clinical approach has been to follow meat avoidance with dietary elimination of dairy and related foods. If this step does not lead to cessation of reactions, complete avoidance of alpha-gal containing products – to include gelatin and other by-products, may be necessary. Reconciling the various, nuanced clinical presentations of this unique food allergy with a scientific understanding of the explanation are the subject of ongoing studies. One potential hint might be found in the ongoing mass cytometry studies which allow for a detailed analysis of B cell populations. We are testing the hypothesis that the levels at which patients show loss of tolerance to select foods vs. all alpha-gal products are reflected in the emergence of B cell subsets that correlate with auto-immunity signatures, such as seen in lupus or arthritis. Alternatively, the number, amount and chronicity of tick bites could be important in creating an IgE Ab response that has

Table 1
Details from summarized worldwide reports of alpha-gal allergy.

Country	Suspected tick species	Timing of reactions	Implicated foods	Reference
Australia	<i>Ixodes holocyclus</i>	1–6 h	N-PMM, kangaroo, horse, gelatin	16,17
France		0.5–5 h	N-PMM, pork kidney, horse	8,9
Germany	<i>Ixodes ricinus</i>	0.25–5 h	N-PMM, pork kidney, gelatin	12,13
Japan		>2 h	N-PMM	11
Panama	<i>Amblyomma cajennense</i>	1.5–6 h	N-PMM	15
Spain	<i>Ixodes ricinus</i>	2–6 h	N-PMM	10
Sweden	<i>Ixodes ricinus</i>	1.5–6 h	N-PMM, moose	14,26
United States	<i>Amblyomma americanum</i>	2–6 h	N-PMM, squirrel, gelatin	6,7,22,24

N-PMM, non-primate mammalian meat = e.g., beef, pork, lamb, goat, venison, rabbit.



★ = Location of published reports of mammalian meat allergy due to sIgE to galactose-alpha-1,3-galactose detailed in Table I

Fig. 1. Outline map of the world showing relative location of geographical distribution of reported cases of patients with delayed allergic reactions to non-primate mammalian meat due to IgE to alpha-gal.

undergone somatic hypermutation and, therefore, would potentially have binding characteristics for the alpha-gal epitope that result in a more profound loss of clinical tolerance to non-primate mammalian foods and products.

Ticks and delayed anaphylaxis

Currently, it is our hypothesis that bites from ecto-parasitic ticks are the sensitizing event that leads to the development of sIgE to the oligosaccharide alpha-gal, which results in a loss of tolerance to non-primate mammalian meat and related food products in some individuals.²⁴ The evidence for tick bites as a major cause of IgE to alpha-gal comes from several observations (Box 1). First we have documented increases in IgE antibodies after

Box 1

Evidence supporting a role for tick bites in the development of sIgE response to alpha-gal.

- Four cases reported in detail where there is epidemiologic evidence that sIgE to alpha-gal increased following documented tick bites
- The IgE antibodies to alpha-gal are found in areas where tick bites are common
- IgE antibodies to alpha-gal correlate with the presence of IgE antibodies to tick proteins
- The known global distribution of delayed anaphylactic reactions to red meat is similar to the known distribution of various tick species
- Staining of the gastrointestinal tract of *Ixodes ricinus* showed the presence of galactose-alpha-1,3-galactose (see Ref. 26)

tick bites in four subjects. Second, there is a significant correlation between reports of prolonged itching after tick bites and the presence of IgE antibodies to alpha-gal in the serum. Bites of larval lone star ticks, like adult ticks, can be intensely pruritic. Interestingly, bites from the deer tick *Ixodes scapularis*, which transmits Lyme disease, do not generally induce a pruritic skin response. In fact, itching after tick bites has been associated with a decrease in the risk of developing positive Lyme serology.²⁵ Third, there is an excellent correlation between IgE to alpha-gal and IgE to extract of the lone star tick ($r = 0.75$; $p < 0.001$).²⁴ In addition, recent evidence from Professor van Hage's group in Stockholm demonstrating the presence of alpha-gal in the gut of the tick and a similar correlation with tick bites in southern Sweden has strengthened this correlation.²⁶ Finally, subjects living in areas void of ticks do not have IgE to alpha-gal.^{4,14,23} The lone star tick is the primary tick in the USA whose larvae bite humans, and in several cases we have found high titer IgE antibodies to alpha-gal following bites from larval ticks, often known as "seed ticks". One of our current research questions is to understand why tick bites can give rise to such a dramatic IgE response and why those IgE Abs are specifically directed against the alpha-gal oligosaccharide. In the process, we will investigate whether this response has more in common with other responses to oligosaccharides (e.g., of the IgM class) or with IgE responses to proteins (e.g., undergone sequential class-switching). There is increasing evidence that the skin can be an important route for IgE Ab responses to proteins such as peanut and wheat.^{27,28} However, with those antigens neither the process through which the antigen enters the skin nor the time frame from exposure to antibody response is known. We do not believe that every person bitten by a tick ends up with an IgE response and another of our goals is to determine whether there are inherent factors that create a risk for the IgE response. In many ways, the alpha-gal IgE response is similar to the sensitization that occurs to inhaled plant oligosaccharides such as MUXF3 – a hapten on the glycoproteins of many plant species.^{1,29,30} Unlike alpha-gal, IgE

antibodies to these plant-derived cross-reactive carbohydrate determinants (CCDs) have not been shown to contribute to symptoms related to pollen exposure.^{1–3,31}

Patients with IgE to alpha-gal typically report symptoms beginning 3–6 h after eating meat.⁷ In formal challenge studies using pork or beef, hives and other symptoms were delayed at least two hours after meat ingestion.³² More recent work has shown that the time frame to reaction can be decreased with co-factors such as exercise or alcohol.¹² Delayed reactions after eating meat are distinct from the reactions to cetuximab, which develop rapidly and symptoms often peak within 20 min of initial administration of the drug.^{4,5,18} In keeping with the more rapid time frame, *in vitro* responses of basophils isolated from subjects with delayed meat reactions show activation with glycoproteins within 20–30 min.³² Skin test responses, whether prick or intradermal, to cetuximab are also rapid.⁸ Thus, the delay in response after eating meat does not reflect an inability of basophils or mast cells to be activated by these glycoproteins. On the contrary, we believe that the results to date suggest the allergenic form of the oligosaccharide enters the circulation several hours after eating. Lipids would make a likely form of the allergen given the absorption and processing that must occur before these particles enter the bloodstream.³³ In fact, alpha-gal is present on both glycoproteins and glycolipids (including chylomicrons).³⁴ Our current concept is that the most likely explanation for the delay in symptoms is that the allergenic form of alpha-gal exists as a glycolipid.

Our studies have shown that during a challenge, circulating basophils assessed *ex vivo* upregulate the expression of CD63 in a similar time frame as the patients develop symptoms.³² Surprisingly, a proportion of non-allergic controls also demonstrated upregulation of CD63, although they do not experience any symptoms. Evidence that basophils and mast cells have receptors for LDL was reported many years ago.^{35,36} One potential explanation for this enigmatic finding is that the existing IgG or IgM response specific for alpha-gal (known as “anti-Gal”³⁷) present in all immunocompetent individuals is binding alpha-gal glycolipids and activating basophils to upregulate CD63. The implication is that lipid particles with alpha-gal on the surface can cause pro-inflammatory mediator release not only in individuals with IgE Ab to alpha-gal but also in those who are non-allergic. The long-term, potential ramification of pro-inflammatory mediator release due to eating mammalian meat could begin to look like a society with high rates of atherosclerotic cardiovascular disease that may not be amenable to existing pharmacologic therapy because it is driven by antibody-mediated lipid uptake. These possibilities are areas of ongoing and future investigations for our group.

Conclusion

The finding that IgE to alpha-gal explains two novel forms of anaphylaxis has not only changed several established rules about allergic disease, but has opened up at least two new areas of research. The results provide evidence that: IgE responses to an oligosaccharide can induce significant or severe allergic symptoms, ticks can induce high titer food specific IgE responses in adult life breaking long-held periods of oral tolerance, and also that eating mammalian products carrying this epitope does not give rise to any symptoms during the few hours or more. Like so many new findings, this area of research provides both challenges and opportunities. The delay in onset of symptoms following eating red meat is best explained by delayed arrival of the relevant form of antigen in the circulation, but the question remains as to what form of glycoprotein or more likely glycolipid takes 3 h or more to appear in the circulation. Finally, the often-rapid production of IgE antibodies to alpha-gal after tick bites provides a striking model of an ecto-

parasite-induced IgE response. This parasite only enters through the skin and the tick saliva contains a wide variety of agents that could act as antigens and/or as adjuvants. However, it remains a striking challenge to identify why the response is so robust and why it is directed so consistently against the alpha-gal carbohydrate residue.

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Conflict of interest

TPM holds a patent on the use of streptavidin solid phase to evaluate IgE antibodies to recombinant molecules. The rest of the authors have no conflict of interest.

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