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# Meat allergy and allergens

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ABSTRACT

IgE-mediated hypersensitivity to ingested animal products, including both mammalian and avian sources, is increasingly appreciated as an important form of food allergy. Traditionally described largely in children, it is now clear that allergy to meat (and animal viscera) impacts both children and adults and represents a heterogeneous group of allergic disorders with multiple distinct syndromes. The recognition of entities such as pork-cat syndrome and delayed anaphylaxis to red meat, i.e- the α-Gal syndrome, have shed light on fundamental, and in some cases newly appreciated, features of allergic disease. These include insights into routes of exposure and mechanisms of sensitization, as well as the realization that IgE-mediated reactions can be delayed by several hours. Here we review mammalian and avian meat allergy with an emphasis on the molecular allergens and pathways that contribute to disease, as well as the role of *in vitro* IgE testing in diagnosis and management.

## 1. Introduction

Despite the fact that some animal products are well established food allergens, such as milk and eggs, allergy to meat itself has historically been considered to be quite rare. Case reports of allergy to mammalian and avian meat became more commonplace starting about 20 years ago, which in part also coincides with an increasing appreciation of food allergy in general (Platts-Mills, 2015). IgE-mediated reactions to many different types of meat have now been reported. The list includes beef, pork, lamb, and poultry, but also a host of others including kangaroo (Boyle et al., 2007), whale (Moore et al., 2007), seal (Moore et al., 2007) and crocodile (Ballardini et al., 2017). A number of relevant allergens have been identified and characterized, and we have an increasing appreciation of the natural history of meat allergy and relevant cross-sensitizations. About 10 years ago a new form of meat allergy was recognized, which involves delayed anaphylaxis to mammalian meat, that relates to the oligosaccharide Gal-α1,3Gal-β1,4GlcNAcR (α-Gal) (Commins et al., 2009). This allergy, which is often known as the α-Gal syndrome, has challenged many traditional paradigms of how we think about food allergy (Wilson et al., 2017). The present review considers various forms of meat allergy with a special emphasis on mammalian meat, aiming to highlight several advances over the last decade.

## 2. Immunology and epidemiology

Good estimates of the prevalence of meat allergy do not exist. Reactions to mammalian meat are more common than for avian meat, at least anecdotally, but neither is common. Mammalian meat allergy was once largely thought to be restricted to children, most commonly those with atopic dermatitis or cow's milk allergy (Werfel et al., 1997), but now is equally appreciated in adults. Part of the explanation relates to the fact that several different forms of meat allergy have now been recognized. There is significant regional variation in meat allergy, which is likely a function of differences in local dietary habits, but other environmental factors are also important. This is dramatically highlighted by the realization that IgE sensitization to α-Gal is mediated by bites from certain hard ticks. Thus, for example, there is a markedly higher rate of allergic reactions to mammalian meat in the southeastern United States, an area endemic with *Amblyomma americanum* (lone star ticks), as compared to other parts of the country (Commins et al., 2011).

The mechanisms and routes of exposure that lead to anaphylactic sensitization have been an active area of inquiry for over a century dating back to the pioneering work of Richet and Portier (Cohen and Zelaya-Quesada, 2002). For some food allergens, such as peanut, there has been convincing evidence that allergy results from epicutaneous sensitization (Du Toit et al., 2008; Tordesillas et al., 2014), but for many food allergens the route of sensitization is incompletely understood. For 'primary' mammalian and avian meat allergy the suggestion is that the inciting exposure is *via* the GI tract. However, many allergens can also be present in airborne particles or skin products (Kligman and Papa, 1965) leading to the possibility of respiratory or cutaneous sensitization. Indeed, examples of syndromes where sensitization is established to have occurred outside the GI tract include: pork-cat

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**Table 1**
Meat allergy syndromes.

| Source | Allergy syndrome | Major Allergen(s) | Route/Mode |
|---|---|---|---|
| Mammalian Meat | **Pork-cat** | Serum albumins | Respiratory exposure to cat serum albumin in dander |
| | **α-Gal** | Galα1-3 Galβ1-4GlcNAcR | Skin *via* tick bites |
| Avian meat | **Bird-egg** | Serum albumin | Respiratory exposure to bird serum albumin in feathers |
| | **Fish-chicken** | Parvalbumin, Aldolase, Enolase | Oral |

(Posthumus et al., 2013), bird-egg (Hemmer et al., 2016) and α-Gal syndromes (Commins et al., 2011) (see Table 1). Generally these forms of allergy disproportionately impact adults and older children compared to primary meat allergy, however young children can also be affected. Fish-chicken syndrome is a more recently described entity that likely involves cross-sensitization from GI exposure (Kuehn et al., 2016).

## 3. Biology and biochemistry

Serum albumin constitutes one of the most important contributors to both mammalian and avian meat allergy. In contrast, the oligosaccharide α-Gal is selectively present only on mammalian tissue and IgE antibody to an equivalent oligosaccharide has not been described in avian allergy. Other less commonly identified allergens include immunoglobulin, myosin light chain kinase, parvalbumin, enolase and aldolase (see Table 2) although this list is certainly not complete (Restani et al., 2009).

### *3.1. Albumins*

Serum albumins are ~70 kD α-helical proteins that are highly conserved in sequence and conformation across many animals, including mammals and birds (Chruszcz et al., 2013) (see Table 3). Serum albumins have multiple biologic functions but importantly they can cross capillary endothelia and are present in epithelia. Thus, in addition to being present in mammalian foods such as meat, milk and eggs, animal pelts and bird feathers also contain serum albumins, with the implication that inhalant and cutaneous exposure can occur (Liccardi et al., 2011). There are several consequences that can result from the multitude of different sources of animal albumin. One is that it is common for subjects with beef allergy to have a co-existing milk allergy. Indeed, this was reflected among 28 young Italian children with beef allergy where 26 were sensitized specifically to Bos d 6 and all of these had immediate reactions upon milk challenge (Martelli et al., 2002). Bird-egg syndrome represents a situation where primary sensitization to an avian serum albumin occurs *via* a respiratory route but subsequently subjects develop allergic symptoms upon ingestion of poultry (Szepfalusi et al., 1994; Quirce et al., 2001).

Cross-reactivity between albumins from different species is common, but most often involves phylogenetically similar sources.

**Table 2**
Important allergens from representative mammalian and avian meat sources.

| Source | Allergen name | Biochemical name |
|---|---|---|
| Bovine | Bos d 6 | Serum albumin |
| | Bos d 7 | Immunoglobulin |
| | α-Gal | Gal-α1,3 Gal-β1,4GlcNAcR* |
| Chicken | Gal d 5 | Serum albumin |
| | Gal d 7 | Myosin light chain kinase |
| | Gal d 8 | α-parvalbumin |
| | Gal d 9 | β-enolase |
| | Gal d 10 | Aldolase |

* α-Gal linkages have been described on a number of mammalian glycoproteins and glycolipids (Chruszcz et al., 2013; Liccardi et al., 2011; Martelli et al., 2002).

**Table 3**
Common serum albumin allergens in animals (from allergen.org, WHO/IUIS).

| Common name | Species | Allergen | Molecular Weight (kD) |
|---|---|---|---|
| Domestic cattle | *Bos domesticus** | Bos d 6 | 67 |
| Dog | *Canis familiaris* | Can f 3 | 69 |
| Guinea pig | *Cavia porcellus* | Cav p 4 | 66 |
| Domestic horse | *Equus caballus* | Equ c 3 | 67 |
| Cat | *Felis domesticus* | Fel d 2 | 69 |
| Chicken | *Gallus domesticus* | Gal d 5 | 69 |
| Domestic pig | *Sus scrofa* | Sus s 1 | 60 |

* traditionally referred to as *Bos Taurus*, but studies have not been done on native cow species.

Thus, cases of albumin-related allergy to both mammal and bird products are very rare (Restani et al., 1997; Cahen et al., 1998). Serum albumin cross-reactivity is a key feature in pork-cat syndrome, where primary sensitization to cat serum albumin, also known as Fel d 2, leads to allergic reactions upon ingestion of pork products containing pork serum albumin, *i.e.* – Sus s 1. Interestingly, some of these subjects also react to beef, which likely reflects further epitope spreading of the IgE response to include Bos d 6 (Posthumus et al., 2013). Although historically the syndrome has been called 'pork-cat', some have advocated that because cat sensitization precedes the allergic reaction to pork, that 'cat-pork' would be a more apt name (Hilger et al., 2017; Popescu, 2015). Other examples of clinically relevant albumin cross-reactivity have been described in case reports. One such recent example involved a woman with respiratory allergy to dog, who reported anaphylaxis to horse meat. Her ensuing work-up revealed elevated IgE responses to dog extract as well as the serum albumins to dog (Can f 3) and horse (Equ c 3). Supporting a diagnosis that would be consistent with 'dog-horse' is the fact that inhibition studies supported primary sensitization to Can f 3 (Morisset et al., 2016).

Serum albumins are generally considered heat labile, and as such the frequency and severity of reactions are likely reduced by consuming well-cooked animal products (Werfel et al., 1997; Fiocchi et al., 1998). Other approaches, such as freeze-drying, may be even more helpful for reducing allergenicity (Fiocchi et al., 1998; Restani et al., 2004).

### *3.2. α-Gal*

When considering α-Gal it is important to realize that it was first appreciated as a 'B like' blood group antigen by Landsteiner (Landsteiner and Miller, 1925). Indeed, it shares structural features with the blood group B antigen (Fig. 1), and is the target of abundant 'natural' IgM, IgG and IgA antibodies in immunocompetent humans (Hamadeh et al., 1995). The oligosaccharide is present in many mammalian foods, including meat, internal organs (such as kidney or tripe), milk and other dairy, and gelatin (Mullins et al., 2012), but also other products such as the monoclonal antibody cetuximab, anti-venom and the zoster vaccine (Chung et al., 2008; Fischer et al., 2017a; Stone et al., 2017). Among the features that distinguish α-Gal syndrome from other IgE-mediated meat allergies (see Table 4) is the fact that reactions are delayed, typically occurring 3–6 h after a relevant exposure (Commins et al., 2014). From a clinical perspective this is an important characteristic and helps distinguish reactions related to α-Gal from those caused by IgE to other allergens. Anecdotally, we have seen several