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Food Allergy

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Keywords

food, allergy, protein, epitope, processing

Abstract

Food allergy is receiving increased attention in recent years. Because there is currently no known cure for food allergy, avoiding the offending food is the best defense for sensitive individuals. Type I food allergy is mediated by food proteins, and thus, theoretically, any food protein is a potential allergen. Variability of an individual's immune system further complicates attempts to understand allergen-antibody interaction. In this article, we briefly review food allergy occurrence, prevalence, mechanisms, and detection. Efforts aimed at reducing/eliminating allergens through food processing are discussed. Future research needs are addressed.

IgE: immunoglobulin isotype E

INTRODUCTION

Food allergy, type I hypersensitivity, is caused by food proteins (the antigens) through cross-linking of immunoglobulin isotype E (IgE) on the mast and/or basophil cell surface (Sutton & Gould 1993, Gould et al. 2003) and is different than food sensitivity that may be caused by a food component (e.g., lactose intolerance). It is recognized that non-IgE-mediated food allergies are known (Nowak-Węgrzyn et al. 2015) and are important in understanding and treating adverse reactions to food. Globally, food allergies appear to be on the rise (Sackesen et al. 2011, Sicherer 2011, Burks et al. 2012, Lopata & Kamath 2012, Sharp & Lopata 2014). In recent years, food allergies in western countries seem to be increasing and reportedly affect ~5% of adults and ~8% of children (Sicherer & Sampson 2014).

Theoretically, any food protein may be considered a potential allergen. However, food groups most commonly known to cause food allergies include cow's milk, hen's eggs, wheat, soy, peanuts, tree nuts, fish, and seafood (Longo et al. 2013, de Silva et al. 2014, Ho et al. 2014, Sicherer & Sampson 2014). Bovine cow's milk allergy is the most commonly experienced food allergy, notably by infants and children. Cereal-induced allergies, particularly wheat-induced allergies, are also widely experienced. It should be mentioned here that celiac disease attributed to wheat proteins is different than wheat allergy. Wheat allergy may be caused by any protein present in the wheat kernel and is due to an IgE-dependent mechanism. Unlike IgE-dependent wheat allergy, celiac disease is an autoimmune disorder that causes both innate and adaptive immune responses in genetically predisposed individuals who are exposed to gluten and other environmental factors. In celiac disease, partially hydrolyzed gliadins are deamidated by tissue transglutaminase in the mucosa of the small intestine. This specific and ordered deamidation enhances the recognition of the gliadins by the CD4⁺ T cells in the lamina propria of the small intestine, leading to the immunological responses. Subsequent release of cytokines elicits histologic changes in the intestinal mucosa, which are exhibited by several clinical manifestations (Molberg et al. 1998, van de Wal et al. 1998, Green et al. 2015).

The clinical response to an allergenic protein depends on a variety of factors that include the sensitivity of the affected individual, nature of the food allergen, processing effect(s) on food containing allergen(s), and food components and their interaction(s) (e.g., the Maillard reaction and glycation with the allergenic protein). The adverse reaction(s) experienced by the sensitive individuals may be mild, moderate, or severe (e.g., anaphylaxis); in some instances, the reaction can be fatal. According to one report (Gupta et al. 2013), the annual economic impact of childhood food allergy in the United States alone was estimated to be \$24.8 billion. The global economic impact of food allergy is not fully documented (Boye 2012).

Currently, a cure for food allergy is unavailable, as a complete understanding of the molecular mechanism(s) involved is lacking. Avoidance of the offending food is therefore the best option for sensitive individuals; however, this avoidance can occur only if the presence of the offending allergen is known.

Food labeling is one of the important means to declare the presence of an allergen in food and food products. Ensuring consumer safety on a worldwide basis through food labeling is a complex and difficult task (Allen et al. 2014b). Increased international food trade may escalate the risk of food allergy due to different food allergen labeling regulations in different countries (Gendel 2012). Presence of undeclared allergens in food as a result of cross-contamination, accidental/inadvertent/unintentional addition, and incorrect labeling are some of the challenges that often lead to food recalls (**Table 1**), which can be expensive. FDA food recall data (2007–2012) indicate that bakery products, snacks, and candy are the most such recalled foods, accounting for 31%, 12.16%, and 10% of 732 recalls, respectively. Milk was the most frequently undeclared major food

Table 1 Food allergen prevalence, FDA recalls, and fatalities

Food allergens	Prevalence in the United States (Sicherer 2011)		FDA recalls		Fatalities (1986–2011)
	Overall	Children	2007–2012 (Gendel & Zhu 2013)	2013–2015 (FDA 2015)	
Peanut	1.3%	1.4%	69	46	90 (Bock et al. 2001, 2007; Foucard & Malmheden Yman 1999; Liew et al. 2009; Lin et al. 2008; Pumphrey 2000; Pumphrey & Gowland 2007; Sampson et al. 1992; Simon & Mulla 2008; Xu et al. 2014; Yunginger et al. 1988)
Crustacean	1.0%	0.5%	11	4	5 (Bock et al. 2007, Pumphrey & Gowland 2007, Simon & Mulla 2008, Yunginger et al. 1988)
Soy	0.7%	1.4%	153	46	5 (Bock et al. 2007, Foucard & Malmheden Yman 1999)
Tree nuts	0.6%	1.1%	119	43	54 (Bock et al. 2001, 2007; Foucard & Malmheden Yman 1999; Levy et al. 2012; Lin et al. 2008; Pumphrey 2000; Pumphrey & Gowland 2007; Sampson et al. 1992; Xu et al. 2014; Yunginger et al. 1988)
Wheat	0.5%	0.5%	171	23	NA
Bovine milk	0.4%	1.8%	296	98	20 (Bock et al. 2001, 2007; Colver et al. 2005; Levy et al. 2012; Lin et al. 2008; Pumphrey 2000; Pumphrey & Gowland 2007; Xu et al. 2014)
Fin fish	0.4%	0.2%	28	13	4 (Bock et al. 2001, Liew et al. 2009, Pumphrey & Gowland 2007, Yunginger et al. 1988)
Chicken egg	0.2%	1.8%	108	47	2 (Pumphrey & Gowland 2007, Sampson et al. 1992)
Others	NA	NA	8	3	55 (Colver et al. 2005, Liew et al. 2009, Lin et al. 2008, Pumphrey 2000, Pumphrey & Gowland 2007, Simon & Mulla 2008, Xu et al. 2014)

Abbreviations: FDA, Food and Drug Administration; NA, not available.

allergen (Gendel & Zhu 2013). The article noted that milk, wheat, and soy are the major food allergens often involved in food recalls. A recent detailed assessment of foods/food ingredients for labeling purposes (EFSA NDA Panel 2014) provides a comprehensive view of the European Food Safety Authority panel on Dietetic Products, Nutrition and Allergies of the European Union on food labeling issues, and the many points made may be globally applicable.

FOOD ALLERGEN CHARACTERISTICS

Sources of Food Allergens

Naturally occurring plant, animal, and fungal food allergens are known (Table 2). Approximately 400 proteins from more than 170 foods have been reported to cause IgE-mediated allergic reactions (Boyce et al. 2010). Attempts have been made to classify food allergens based on their sequence homology and domain architecture (Radauer et al. 2008) (Figure 1).

The most common animal food allergens include shellfish tropomyosins (Lopata & Lehrer 2009), fish β -parvalbumins (Ma et al. 2008), and milk caseins (Broekaert et al. 2008, Järvinen &

Table 2 Common food allergens^a

Food	Allergen (IUIS name; molecular weight) (http://www.allergen.org , http://www.allergome.com)	Types and numbers of epitopes mapped (IEDB 2015)
Bovine milk	α -Lactalbumin (Bos d 4; 14.2 kDa)	L (45), C (2), T (8)
	β -Lactoglobulin (Bos d 5; 18.3 kDa)	L (174), C (1), T (30)
	Bovine serum albumin (Bos d 6; 67 kDa)	L (10), T (7)
	Immunoglobulin G (Bos d 7; 160 kDa)	NA
	α S1-Casein (Bos d 9; 25 kDa)	L (203), T (39)
	α S2-Casein (Bos d 10; 26 kDa)	L (67)
	β -Casein (Bos d 11; 25 kDa)	L (125)
	κ -Casein (Bos d 12; 21.2 kDa)	L (124)
Chicken egg	Ovomucoid (Gal d 1; 28 kDa)	L (173), C (1), T (29)
	Ovalbumin (Gal d 2; 44 kDa)	L (13), T (14)
	Ovotransferrin (Gal d 3; 78 kDa)	NA
	Lysozyme C (Gal d 4; 14 kDa)	NA
	Serum albumin (Gal d 5; 69 kDa)	L (1)
	YGP42 (Gal d 6; 35 kDa)	NA
Crustaceans	Tropomyosin (Cha f 1, Cra c 1, Hom a 1, Lit v 1, Mac r 1, Mel l 1, Met e 1, Pan b 1, Pan s 1, Pen a 1, Pen i 1, Pen m 1, Por p 1; 34–39 kDa)	L (17) (Ayuso et al. 2010), T (4)
	Myosin light chain 1 (Art fr 5, Cra c 5; 17.5 kDa)	NA
	Myosin light chain 2 (Hom a 3, Lit v 3, Pen m 3; 20–23 kDa)	L (5) (Ayuso et al. 2010)
	Troponin C (Cra c 6, Hom a 6, Pen m 6; 20–21 kDa)	NA
	Sarcoplasmic calcium-binding protein (Cra c 4, Lit v 4, Pen m 4, Pon l 4; 20–25 kDa)	L (3) (Ayuso et al. 2010)
	Arginine kinase (Cra c 2, Lit v 2, Pen m 2; 40–45 kDa)	L (46)
	Triosephosphate isomerase (Arc s 8, Cra c 8; 28 kDa)	NA
	Troponin I (Pon l 7; 30 kDa)	NA
Mollusks	Tropomyosin (Hel as 1, Tod p 1; 36–38 kDa)	NA
Fin fishes	β -Parvalbumin (Clu h 1, Cyp c 1, Gad c 1, Gad m 1, Lat c 1, Lep w 1, Onc m 1, Sal s 1, Sar sa 1, Seb m 1, Thu a 1, Xip g 1; 11–12 kDa)	L (69)
	β -Enolase (Gad m 2, Sal s 2, Thu a 2; 47.3–50 kDa)	NA
	Aldolase A (Gad m 3, Sal s 3, Thu a 3; 40 kDa)	NA
	Vitellogenin (Onc k 5; 18 kDa)	NA
	Tropomyosin (Ore m 4; 33 kDa)	NA
Frog	α -Parvalbumin (Ran e 1; 11.9 kDa)	NA
	β -Parvalbumin (Ran e 2; 11.7 kDa)	NA
Insect	Arginine kinase (Bomb m 1; 42 kDa)	NA
Legumes	2S albumin (Ara h 2, 6, 7, Gly m 8; 15–17 kDa)	L (82), T (68)
	7S/8S vicilin (Ara h 1, Gly m 5, Len c 1, Lup an 1, Pis s 1, Vig r 2; 44–64 kDa)	L (197), T (89)
	11S legumin (Ara h 3, Gly m 6; 60 kDa)	L (143)
	Profilin (Ara h 5, Gly m 3; 14–15 kDa)	L (1)
	Bet v 1-related protein (Ara h 8, Gly m 4, Vig r 1, 6; 16–18 kDa)	T (1)
	nsLTP (Ara h 9, 16, 17, Len c 3, Pha v 3; 8.5–11 kDa)	NA
	Oleolin (Ara h 10, 11, 14, 15; 14–17.5 kDa)	L (1)

(Continued)

Table 2 (Continued)

Food	Allergen (IUIS name; molecular weight) (http://www.allergen.org , http://www.allergome.com)	Types and numbers of epitopes mapped (IEDB 2015)
	Defensin (Ara h 12, 13, Gly m 2; 8–12 kDa)	NA
	Hydrophobic seed protein (Gly m 1; 7 kDa)	L (2)
	Seed biotinylated protein (Gly m 7, Len c 2; 66–76.2 kDa)	NA
	Convicilin (Pis s 2; 63 kDa)	NA
	Seed albumin (Vig r 4; 30 kDa)	NA
Tree nuts	2S albumin (Ana o 3, Ber e 1, Car i 1, Cor a 14, Jug n 1, Jug r 1, Pis v 1; 7–16 kDa)	L (29)
	7S vicilin (Ana o 1, Cor a 11, Jug n 2, Jug r 2, Pis v 3; 44–55 kDa)	L (18)
	11S legumin (Ana o 2, Ber e 2, Car i 4, Cor a 9, Jug r 4, Pis v 2, 5, Pru du 6; 40–60 kDa)	L (106), C (2) (Xia et al. 2010, Zhang et al. 2011)
	Chitinase (Cas s 5; 32 kDa)	NA
	nsLTP (Cas s 8, Cor a 8, Jug r 3, Pru du 3; 9–13 kDa)	T (26)
	Bet v 1-related protein (Cor a 1; 17 kDa)	L (1), T (27)
	Profilin (Cor a 2, Pru du 4; 14 kDa)	NA
	Heat shock protein (Cas s 9; 17 kDa)	NA
	Oleosin (Cor a 12, 13; 14–17 kDa)	NA
	Manganese superoxide dismutase (Pis v 4; 25.7 kDa)	NA
	60S acidic ribosomal protein P2 (Pru du 5; 10 kDa)	NA
Cereals	Profilin (Hor v 12, Ory s 12, Tri a 12; 14 kDa)	NA
	nsLTP (Tri a 14, Zea m 14; 9 kDa)	L (10), C (1)
	2S albumin (Fag e 2, Fag t 2; 16 kDa)	L (1)
	7S vicilin (Fag e 3; 19 kDa fragment)	NA
	α -Amylase inhibitor (Hor v 15; 14.5 kDa)	NA
	α -Amylase (Hor v 16; 47.8 kDa)	NA
	β -Amylase (Hor v 17; 57.3 kDa)	NA
	Agglutinin (Tri a 18; 21.2 kDa)	NA
	Thioredoxin (Tri a 25, Zea m 25; 13–14 kDa)	NA
	ω -5 gliadin (Tri a 19; 65 kDa)	L (141)
	γ -Gliadin (Tri a 20; 35–38 kDa)	L (22)
	High-molecular-weight glutenin (Tri a 26; 88 kDa)	L (51)
	Low-molecular-weight glutenin (Tri a 36; 40 kDa)	L (8)
	α -Purothionin (Tri a 37; 12 kDa)	L (3)
	γ -Hordein (Hor v 20; 34 kDa)	NA
	γ -Secalin (Sec c 20; 70 kDa)	NA
Vegetables and fruits	Bet v 1-related protein (Act c 8, Act d 8, Api g 1, Dau c 1, Fra a 1, Mal d 1, Pru ar 1, Pru av 1, Pru p 1, Pyr c 1, Rub i 1, Sola l 4; 9–18 kDa)	C (6), T (40)
	Profilin (Act d 9, Ana c 1, Api g 4, Cap a 2, Cit s 2, Cuc m 2, Dau c 4, Fra a 4, Lit c 1, Mal d 4, Mus a 1, Pru av 4, Pru p 4, Pyr c 4, Sola l 1; 13–15 kDa)	NA
	nsLTP (Act c 10, Act d 10, 11, Api g 2, 6, Aspa o 1, Bra o 3, Cit l 3, Cit r 3, Cit s 3, Fra a 3, Lac s 1, Mal d 3, Mor n 3, Mus a 3, Pru ar 3, Pru av 3, Pru d 3, Pru p 3, Pun g 1, Pyr c 3, Rub i 3, Sola l 3, 6, Vit v 1; 7–11 kDa)	L (24), C (2), T (50)
	TLP (Act d 2, Cap a 1, Mal d 2, Mus a 4, Pru av 2, Pru p 2; 20–30 kDa)	NA

(Continued)

Table 2 (Continued)

Food	Allergen (IUIS name; molecular weight) (http://www.allergen.org , http://www.allergome.com)	Types and numbers of epitopes mapped (IEDB 2015)
Seeds	2S albumin (Bra j 1, Bran n 1, Ses i 1, 2, Sin a 1; 7–15 kDa)	L (12)
	7S vicilin (Ses i 3; 45 kDa)	NA
	11S globulin (Ses i 6, 7, Sin a 2; 51–57 kDa)	NA
	nsLTP (Hel a 3, Sin a 3; 9–12.3 kDa)	NA
	Profilin (Sin a 4; 13–14 kDa)	NA
	Oleosin (Ses i 4, 5; 15–17 kDa)	NA
Mushroom	Manganese superoxide dismutase (NA; 24 kDa) (Gabriel et al. 2015)	NA
	Mannitol dehydrogenase (NA; 27 kDa) (Gabriel et al. 2015)	NA

^aMolecular weights are determined by sodium dodecyl sulfate polyacrylamide gel electrophoresis under nonreducing conditions. Abbreviations: C, conformational epitope; IUIS, International Union of Immunological Studies; L, linear epitope; NA, not available; nsLTP, nonspecific lipid transfer protein; T, T-cell epitope; TLP, thaumatin-like protein.

PR:
pathogenesis-related

Chatchatee 2009). Based on bioinformatics analyses of 119 animal proteins, cataloged in InformAll and Food Allergy Research and Resource Program (FARRP) databases, proteins sharing <62% of their sequence identity with human homologs were reported to be allergenic (Jenkins et al. 2007). Most plant food allergens include storage and pathogenesis-related (PR) proteins (Breiteneder & Radauer 2004). The major allergenic proteins in cereals are glutenins and gliadins, and those in dicotyledonous seeds are 2S albumins, 7S vicilins, and 11S legumins. Nonspecific lipid transfer

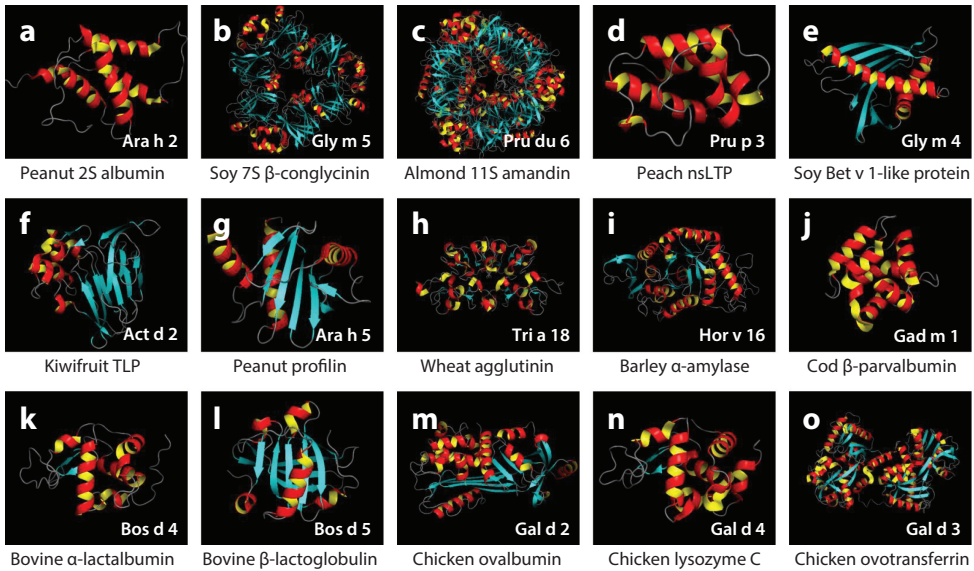


Figure 1
Select food allergen structures. (a–i) Plant food allergens (PDB numbers 1W2Q, 1IPK, 3FZ3, 2ALG, 2K7H, 4BCT, 4ESP, 4AML, and 1AMY). (j–o) Animal food allergens (PDB numbers 2MBX, 1HFZ, 4LZU, 1OVA, 4XJB, and 1OVT). Abbreviations: nsLTP, nonspecific lipid transfer protein; PDB, Protein Data Bank; TLP, thaumatin-like protein.

proteins, Bet v 1-related proteins, β -1,3-glucanases, chitinases, and thaumatin-like proteins (TLPs) are common PR allergens in a wide variety of plant foods (Jenkins et al. 2005).

The carbohydrates α -1,3-fucose and β -1,2-xylose are known pollen and insect venom glycans capable of inducing IgE-mediated cross-reactivity in plant and invertebrate foods, respectively (van Ree 2002). However, these oligosaccharides rarely induce clinical symptoms, except for galactose- α -1,3-galactose, a carbohydrate allergen in beef, pork, and lamb that can cause delayed anaphylaxis. Tick bites were reported to be the major route for immunosensitization to this allergen (Commings 2015). Anaphylaxis to mannitol in pomegranate and mushroom is also reported (Hegde & Venkatesh 2004).

TLP: thaumatin-like protein

GI: gastrointestinal

Nature of Food Allergens

Although food allergens have been thought to be 10–70 kDa water-soluble glycoproteins, supposedly stable to heat, acid, and proteolysis (Sicherer & Sampson 2010), considerable variability in these traits is observed (Sathe et al. 2002). The size, solubility, and stability ensure protein transport and survival, whereas glycation may affect stability and immunogenicity (Shreffler et al. 2006, Ilchmann et al. 2010, Song et al. 2015). For instance, the carbohydrate moiety of peanut vicilin is involved in dendritic cell activation and T_H2 cell maturation (Shreffler et al. 2006). Alternatively, almond's major allergen, amandin, is an $\sim$ 427 kDa hexameric protein free of carbohydrate (Sathe et al. 2002). Several food allergens are oligomeric (e.g., trimeric vicilins and hexameric legumins) or may contain repetitive peptide units (e.g., tropomyosins) that may enhance immunogenicity by increasing IgE epitope valence (Breiteneder & Mills 2005). Additional structural/functional similarities that may contribute to allergenicity are intramolecular disulfide bonds and ligand-binding ability. Lipid transfer proteins (LTPs), TLPs, 2S albumins, and α -amylase/trypsin inhibitors are examples of such food allergens rich in disulfide bonds. Disulfide bonds help epitope formation (Willison et al. 2013) and may stabilize allergenic proteins against heat denaturation and enzyme degradation (Hoffmann-Sommergruber & Mills 2009). Thus, the observed significant decrease in amandin immunoreactivity as a result of a single disulfide bond reduction was not unexpected (Willison et al. 2013). Binding of metals (e.g., parvalbumins, caseins), lipids (e.g., β -lactoglobulin, LTP), and steroids (e.g., Bet v 1-related food proteins) is known to stabilize food allergen structure (Breiteneder & Mills 2005). Antacid use by parvalbumin-allergic patients is of concern because acid neutralization reduces calcium removal. This increases parvalbumin resistance to pepsin hydrolysis, thereby increasing exposure of the sensitive individual to parvalbumin (Untersmayr et al. 2003).

The similar sequences (>70%) and structures shared between different allergens explain the observed cross-reactivity (Aalberse 2000). Noted clinical cross-reactivities (Sicherer 2001) include those among legumes (5%); tree nuts (37%); fish (50%); shellfish (75%); grains (20%); milk (4–92%); and pollen, fruits, and vegetables (55%). Cross-reactive allergens include profilins, LTPs, and Bet v 1-related proteins in pollen and plant foods; tropomyosins in invertebrate animals; parvalbumins in fish and amphibians; and milk caseins (Jenkins et al. 2005, 2007).

An important determinant of immunoreactivity is the epitope, which is the portion of a protein recognized by antibodies or T cells. Antibody-binding epitopes can be linear or conformational (**Figure 2**), whereas T cell-binding epitopes are exclusively linear (Scott et al. 1998). A linear epitope is typically a continuous short peptide segment (8–15 amino acids), whereas a conformational epitope is composed of a three-dimensional motif (Aalberse 2000). Owing to their susceptibility to heat denaturation and gastrointestinal (GI) digestion, conformational epitopes have been suggested to be less important in food allergies, with the exception of oral allergy syndrome (Lin & Sampson 2009). However, an IgE-binding conformational epitope of amandin has exhibited stability toward thermal processing and in vitro digestion when present in food matrices

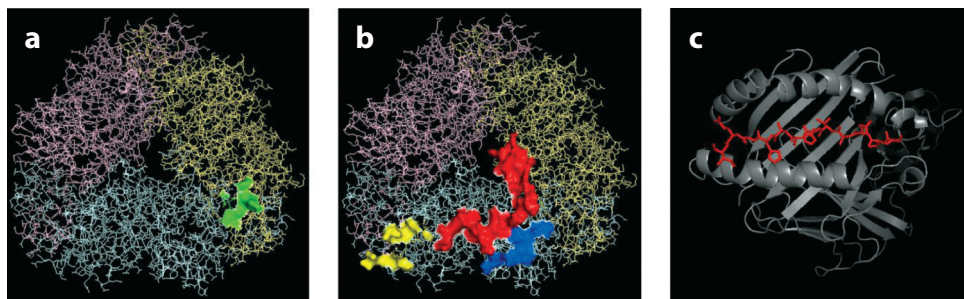


Figure 2

Conformational and linear amandin epitopes (PDB number 3FZ3) and ovalbumin T-cell epitope (PDB number 1IAO). (a) Amandin linear epitope amino acids 281–295 (*green*), mapped by Willison et al. (2011). (b) Amandin conformational epitope composed of three discontinuous strands: amino acids 21–45 (*red*), 320–328 (*yellow*), and 460–465 (*blue*), mapped by Willison et al. (2013). (c) Ovalbumin synthetic linear epitope amino acids 323–339 (*red*) complexed with major histocompatibility complex class II (*gray*), crystallized by Scott et al. (1998) (PDB number 1IAO).

(Venkatachalam et al. 2002, Willison et al. 2013, Mandalari et al. 2014). Because conformational epitopes are often potent (Albrecht et al. 2009, Padavattan et al. 2009), they need to be evaluated for their role in food allergies and for the effects of food processing on their immunoreactivity.

EXPOSURE TO FOOD ALLERGENS

Sensitization

Immune system exposure to an allergen that induces the allergen-specific IgE production without developing allergic symptom(s) is called sensitization. Food allergen sensitization in the GI tract leads to class 1 food allergy. Class 1 food allergy is more prevalent in young children owing to the immaturity of their gut barrier and immune system (Sampson 2004). The most frequent allergens that cause class 1 food allergy are cow's milk, hen's egg, and legumes (Breiteneder & Ebner 2000).

Class 2 food allergy is developed as a consequence of respiratory sensitization to inhalant allergens. Examples of class 2 food allergy include pollen-plant food allergies (Geroldinger-Simic et al. 2011), bird-egg allergies (Quirce et al. 2001), cat-pork allergies (Posthumus et al. 2013), and mite-seafood allergies (Boquete et al. 2011).

Cutaneous exposure is another non-oral sensitizing route, as demonstrated in a case of wheat allergy induced by sensitization to hydrolyzed wheat proteins in facial soap (Fukutomi et al. 2011). Likewise, skin exposure to peanut has been reported as a sensitization route, particularly in peanut-allergic patients with epithelial barrier dysfunction (Chan et al. 2012, Asai et al. 2013).

An interesting case of tick bite-induced red meat allergy illustrates an intracutaneous route of sensitization. The identified allergen in this case was galactose- α -1,3-galactose that registered delayed anaphylaxis (Commins et al. 2009).

Exposure to allergens can also occur transplacentally in utero. Intrauterine sensitization to milk, egg, and peanut has been reported (Sicherer et al. 2010, Kamemura et al. 2012). However, evidence is lacking to support that maternal diet during pregnancy/lactation can affect development of clinical food allergy in infants (Berin & Sampson 2013, Netting et al. 2014).

Reaction Sites

After sensitization, tissue mast cells and blood basophils are armed with allergen-specific IgE antibodies. Upon re-exposure, allergens cross-link IgE antibodies, triggering release of mediators that cause symptoms (Sicherer & Sampson 2010). Oral ingestion of the offensive food is the most common cause of food allergies. Adverse reactions can occur in the oral cavity (oral allergy syndrome) or throughout the GI tract, depending on the stability of the allergens (Sampson 2004). Inhalation of dust, steam, and vapor that contain airborne food allergens, notably cereals and seafood, can induce adverse reactions, including occupational asthma and anaphylactic shock (Cartier 2010). Skin exposure to food allergens (e.g., meats, vegetables, and fruits) can cause contact urticaria (Sampson 2004). In a case report, a female patient with a Brazil nut allergy, after being exposed to Brazil nut proteins in the semen of her boyfriend, developed widespread urticaria (Bansal et al. 2007).

Allergen Digestion and Uptake

The majority of food allergens are introduced through the GI tract, where proteins are degraded normally into nonimmunogenic peptides. However, up to 2% of dietary proteins can escape complete digestion and enter the draining enteric vasculature in immunologically intact forms (Sampson 2004). In addition, food allergens are often resistant to extreme pH, bile salts, and enzyme degradation. Subjecting almond, cashew, and pecan to simulated *in vitro* gastric and duodenal digestions decreased, but did not eliminate, immunoreactivity (Venkatachalam et al. 2006, Mandalari et al. 2014, Mattison et al. 2014).

Processing prior to consumption may alter digestibility and immunoreactivity of food allergens. It has been shown that high temperature can reduce allergenicity of egg ovalbumin and ovomucoid as a result of enhanced GI digestibility (Martos et al. 2011). In contrast, proteolysis-resistant aggregate formation upon heating increased peanut vicilin allergenicity (Beyer et al. 2001).

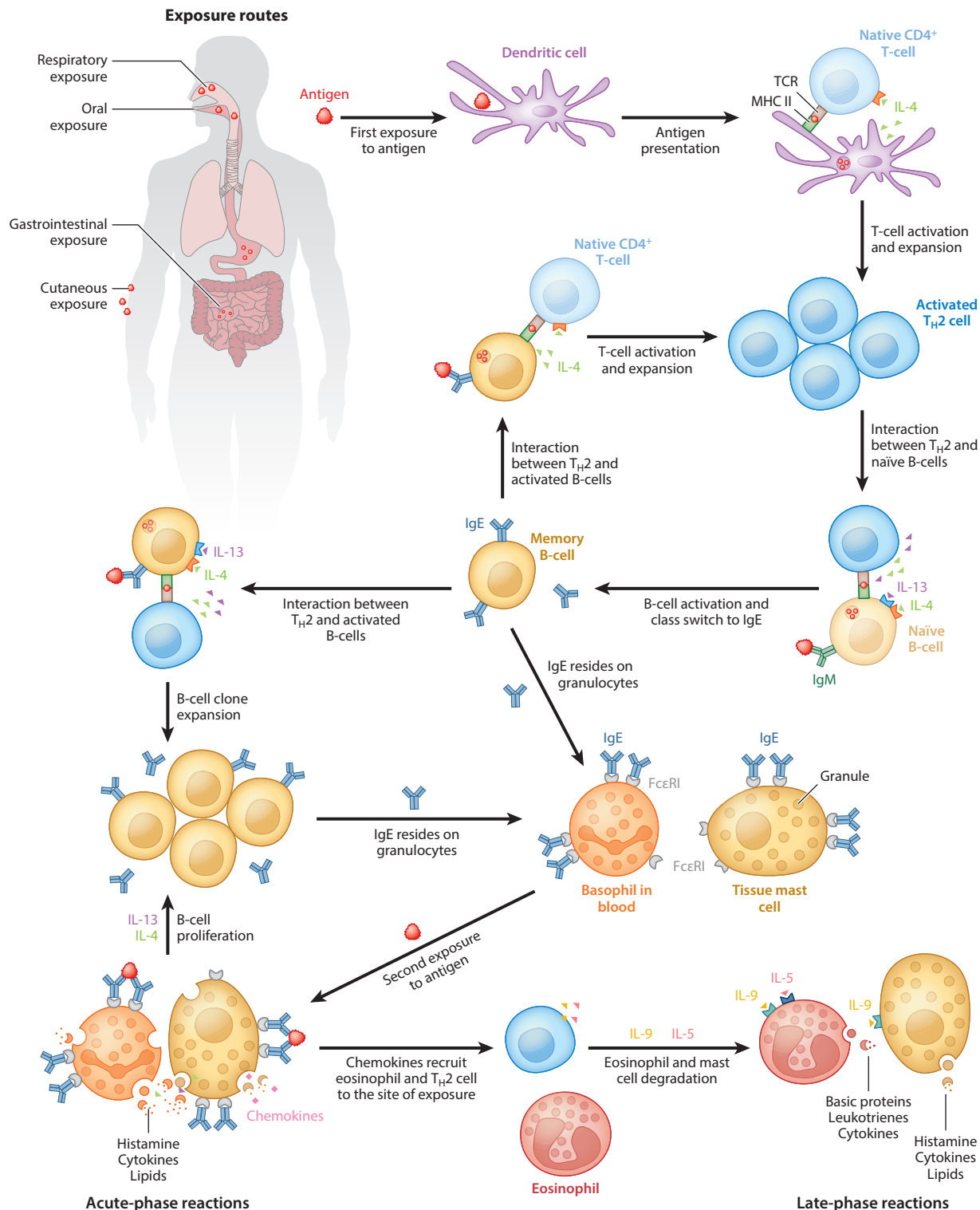
Proteins that survive GI digestion and come in contact with the mucosal barrier, a layer of mucus-covered epithelial cells joined by tight junctions, may cross the gut epithelium via different routes such as passage through transcytotic microfold cells and villous epithelial cells, or direct uptake by dendritic cells (Schulz & Pabst 2013). Immaturity of the mucosal barrier has been suggested to be a factor in the higher incidence of observed food allergies in infants and young children (Sicherer & Sampson 2010). Partial neutralization of gastric acid by antacid and increased gut permeability can lead to increased exposure to intact proteins and can thus enhance sensitization and allergic reactions (Untersmayr & Jensen-Jarolim 2008, Perrier & Corthesy 2011).

IMMUNE RESPONSE TO FOOD ALLERGEN

Mechanism

Food proteins that cross the mucosal barrier and access the immune system induce immunological tolerance by deletion or anergy of antigen-specific lymphocytes or generation of T regulatory cells (Berin & Mayer 2013). Development of oral tolerance depends on age, genetics, state of the mucosal barrier, physical properties of the antigen, dose and frequency of exposure, and gut microbiota (Sicherer & Sampson 2010).

In susceptible individuals, exposure to food proteins may induce allergic sensitization instead of oral tolerance. The pathogenesis of IgE-mediated food allergy is illustrated in **Figure 3**. After crossing the mucosal barrier, food proteins are taken up by dendritic cells and brought to local



lymph nodes. These internalized proteins are degraded into peptides and presented to native CD4⁺ T cells by major histocompatibility complex class II molecules on the dendritic cell surface. This process activates the native T cells into T_H2 cells, resulting in cytokine [i.e., interleukin (IL) IL-4, IL-5, IL-9, and IL-13] production. Subsequently, T_H2 cells activate naïve B cells and drive IgE class-switching with IL-4 and IL-13. The clone of activated B cells with high antigen affinity can be further expanded by T_H2 cells. Reciprocally, activated B cells can act as antigen-presenting cells to activate more T_H2 cells. IgE molecules produced by activated B cells are bound to high-affinity IgE receptors (FcεRI) on mast cells and basophils. Upon re-exposure, allergens cross-link the IgE molecules that reside on the granulocytes, which leads to degranulation. Subsequent release of mediators (histamines, chemokines, cytokines, and inflammatory lipids) causes acute-phase reactions. Following the acute-phase reactions, chemokines produced by mast cells recruit eosinophils and T_H2 cells at the reaction site. IL-5 and IL-9 produced by T_H2 cells activate mast cells and eosinophils, which release additional mediators and cause late-phase reactions (Hawrylowicz & O'Garra 2005, Larché et al. 2006).

IL: interleukin
FcεRI: high-affinity immunoglobulin ε Fc region receptor I
IgA: immunoglobulin isotype A
IgG: immunoglobulin isotype G
FcγRIIb: low-affinity immunoglobulin γ Fc region receptor IIb

Immune Variability

Immunoglobulin isotypes contribute to difficulty in understanding food allergy. Immunoglobulin isotype A (IgA) is the most abundant antibody that can bind and neutralize luminal antigens by preventing antigen attachment to the epithelium or by promoting antigen agglutination. Increased risk of food allergy in children has been associated with IgA deficiency (Janzi et al. 2009). Immunoglobulin isotype G (IgG), particularly IgG₄, is another protective antibody that competes with FcεRI-associated IgE for epitope binding. IgG also inhibits granulocyte activation by cross-linking FcεRI to low-affinity immunoglobulin γ Fc region receptor IIb (FcγRIIb) (Strait et al. 2006). Conversely, studies have demonstrated that IgG can enhance allergic reactions by activating mast cells, eosinophils, and complement, by inducing large allergen aggregates, or by changing the three-dimensional structure of the allergen (Denépoux et al. 2000, Sellge et al. 2005).

Diagnostic Methods

In 2010, an expert panel sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) developed guidelines for diagnosis and management of food allergy in the United States (Boyce et al. 2010). For diagnosing IgE-mediated food allergy, the panel recommended the use of medical history and physical examination, food-elimination diets, a skin-prick test, an allergen-specific IgE test, and oral food challenges. The panel did not recommend an intradermal test, a total serum IgE test, an atopy patch test, or the combination of a skin-prick test, specific IgE test, and atopy patch test. Although skin-prick and specific IgE tests are commonly used as rapid diagnostic methods, the results do not always correlate well with clinical symptoms. Therefore, a double-blind placebo-controlled food challenge remains the gold standard for food allergy

Figure 3

Schematic illustration of the mechanism of food allergy. In sensitive individuals, first exposure to an allergen activates T_H2 cells, which in turn activate B cells. Activated B cells produce allergen-specific IgEs that bind to basophils and mast cells. Re-exposure to the allergen activates the granulocytes by cross-linking the cell surface IgEs, which leads to release of mediators such as histamine and causes acute-phase and late-phase reactions. Abbreviations: CD4, cluster of differentiation 4; FcεRI, high-affinity immunoglobulin ε Fc region receptor I; Ig, immunoglobulin; IL, interleukin; MHC II, major histocompatibility complex class II; TCR, T-cell receptor; T_H2 cell, T helper 2 cell.

diagnosis, although it is not frequently performed owing to risk, cost, and time (Pongracic et al. 2012). Following the release of the NIAID recommended guidelines, a number of new methods, such as component-resolved diagnostics, epitope-binding patterns, T-cell proliferation, metabolomics, and basophil activation, have appeared to improve testing efficiency and to reduce costs and risks (Sicherer & Sampson 2014).

Symptoms and Treatments

Exposure to offending food may induce adverse reactions, including pruritus and angioedema for oral allergy syndromes; nausea, abdominal pain, vomiting, and diarrhea for GI disorders; urticaria and angioedema for cutaneous disorders; and nasal congestion, sneezing, cough, dyspnea, and wheezing for respiratory disorders. Food-induced anaphylaxis and death have also been documented (Sampson 2004). Prompt intramuscular injection of epinephrine is recommended as a first-line therapy for food-induced anaphylaxis, followed by transport to the nearest emergency facility (Boyce et al. 2010).

Oral, sublingual, subcutaneous, and intralymphatic immunotherapies have been attempted to treat food allergies prior to the appearance of symptoms. Use of protein/peptide vaccines, adjuvants, plasmid DNA–encoded vaccines, anti-IgE antibodies, Chinese herbal medicines, cytokines/anticytokines, prebiotics, probiotics, and bacterial lysates for immunotherapy have also been described (Sicherer & Sampson 2010, 2014). Careful studies are required to evaluate the safety and efficacy of these therapies, and therefore strict avoidance of the offensive food remains, so far, the best defense (Boyce et al. 2010).

FOOD ALLERGEN DETECTION METHODS

Food allergen detection methods (**Table 3**) are necessary for consumer protection (EFSA NDA Panel 2014). Depending on the desired end use, detection-method sensitivity may vary by an order of magnitude (Poms et al. 2004, van Hengel 2007, Kirsch et al. 2009). Detection methods may either target the allergen, which is ideal, or indirectly target a marker for the allergen presence, which is more common. Method selection is often dictated by the availability of antibodies and primers, the identified target allergen, the food-processing history, the food matrix (van Hengel 2007, Kirsch et al. 2009, Monaci & Visconti 2009, Tiwari et al. 2010, Cucu et al. 2013, Mandalari et al. 2014), and the degree of allergen characterization, particularly human allergy epitopes (Poms et al. 2004, Monaci & Visconti 2009). Chemical interactions between nontargeted proteins and the detection antibody pose additional problems when allergenic proteins from food matrices are analyzed (Cucu et al. 2013, Montserrat et al. 2015).

Immunoassays

Immunoassays are collisional interactions between a detection antibody and the targeted analyte that produce a detectable and quantifiable signal. Methods may employ IgG antibodies raised in animals, or IgE antibodies obtained directly from allergic patient sera. There are several important factors in immunoassays: (*a*) the relevance of detection by IgG with that of immunoreactivity of human allergic patients' IgE (Platteau et al. 2011), (*b*) the need to obtain representative patient IgE antibodies despite IgE isomorphism and the small quantity available (Poms et al. 2004, Kirsch et al. 2009), (*c*) target analyte consistency and stability (Cucu et al. 2013, Montserrat et al. 2015), and (*d*) access to the antigen reactive site(s) by the detection antibody (Kirsch et al. 2009, Montserrat et al. 2015).

Table 3 Detection methods

Method	Advantages	Limitations	Selected examples		
			Target	Format	LOD
Immunoassay [epitope(s)]					
ELISA	Sensitive, simple, inexpensive, rapid (Cucu et al. 2013, Jayasena et al. 2015, Kirsch et al. 2009, Poms et al. 2004, van Hengel 2007)	Cross-reactivity (Cucu et al. 2013, van Hengel 2007)	Amandin (Su et al. 2013)	Indirect sandwich	3 ng/mL
			Ara h 1 (Montserrat et al. 2015)	Direct sandwich	0.1 mg/kg
			Ara h 2 (Montserrat et al. 2015)		0.13 mg/kg
			Ara h 1 (Montserrat et al. 2015)	Direct competitive	0.19 mg/kg
			Ara h 2 (Montserrat et al. 2015)		0.06 mg/kg
			Amandin (Roux et al. 2001)	Indirect inhibition	5 ppm
Lateral flow	Portable, no special equipment, rapid (Poms et al. 2004, van Hengel 2007)	Mostly qualitative (Poms et al. 2004, van Hengel 2007)	Glycinin (Wang et al. 2015)	Direct sandwich	0.69 mg/kg
			Parvalbumin (Zheng et al. 2012)	Direct competitive	0.046 µg/mL
Immunoblot	Western blot: identifies allergen (Poms et al. 2004)	Time consuming (Poms et al. 2004)	Soybean SRP (Monaghan et al. 2008)	Western blot	200 ng
	Dot blot: simple, inexpensive (Poms et al. 2004)			Dot blot	5 ng
RAST/EAST	Clinically relevant (Poms et al. 2004)	Need human sera, mostly qualitative, costly (Poms et al. 2004)	Soybean (Pedersen et al. 2008)	EAST inhibition	0.8–12 ppm
RIE	Reproducible, quantitative (Poms et al. 2004)	Laborious and time consuming (Poms et al. 2004)	Peanut protein (Holzhauser et al. 1998)	NA	2 ppm
Cell-based (mediator)					
BHR	Sensitive, rapid, reproducible (Cucu et al. 2013)	Need human sera, mostly qualitative (Poms et al. 2004)	rMal d 4 (Ma et al. 2006)	NA	0.0001 µg/mL
			Gly m Bd 30K (Yamanishi et al. 1997)	NA	0.001 µg/mL
BAT	Sensitive, specific (Kirsch et al. 2009)	Need human sera, mostly qualitative (Kirsch et al. 2009)	Hazelnut (Worm et al. 2009)	NA	0.056 µg/mL

(Continued)

Table 3 (Continued)

Method	Advantages	Limitations	Selected examples		
			Target	Format	LOD
DNA-based (DNA)					
PCR	Conventional PCR: specific, sensitive, simple (Kirsch et al. 2009)	Targeted DNA fragment may not be allergen specific, time consuming, DNA contamination possible (Cucu et al. 2013, Kirsch et al. 2009, Poms et al. 2004, van Hengel 2007)	Hazelnut (Holzhauser et al. 2000)	Conventional	0.001%
			Buckwheat (Hirao et al. 2005)	Conventional	1 ppm
	Quantitative real-time PCR: accurate, specific, sensitive, quantitative, rapid (Kirsch et al. 2009, Poms et al. 2004)	Targeted DNA fragment may not be allergen specific, need special equipment, need appropriate calibrators, DNA contamination possible (Cucu et al. 2013, Kirsch et al. 2009, Poms et al. 2004, van Hengel 2007)	Cashew and macadamia (López-Calleja et al. 2015)	Quantitative real-time PCR	0.1 mg/kg
			Ara h 1 (Zhang et al. 2015)	Quantitative real-time PCR	0.005%
Direct methods (allergen)					
LC	Identifies allergen, high recovery, can detect multiple allergens simultaneously (Cucu et al. 2013)	Analyte properties influenced by environmental factors	Lysozyme (Kerkaert et al. 2010)	RP-HPLC	2.07 µg/g
			Soybean (García et al. 2006)	RP-HPLC	0.38%
LC-MS	Identifies allergen, sensitive, specific, reproducible, high recovery, can detect multiple allergens simultaneously (Fæste et al. 2011, Kirsch et al. 2009, van Hengel 2007)	Need costly and specialized equipment, need capable data processing software (Monaci & Visconti 2009, van Hengel 2007)	Casein (Gomaa & Boye 2015)	LC-Q-TOF-MS/MS	10 ppm
			Soy (Gomaa & Boye 2015)		10 ppm
			Gluten (Gomaa & Boye 2015)		100 ppm
			Lactalbumin, lactoglobulins A and B (Monaci & van Hengel 2008)	LC-QqQ-MS	1 µg/mL
			Sin a 1 (Posada-Ayala et al. 2015)	LC-QqQ-MS/MS	0.25 ppm

(Continued)

Table 3 (Continued)

			Selected examples		
Method	Advantages	Limitations	Target	Format	LOD
Multiplex assay					
PCR	Can detect multiple allergens simultaneously (Cucu et al. 2013, Gomaa & Boye 2015, Kirsch et al. 2009, van Hengel 2007)	Does not target allergen (Cucu et al. 2013, Kirsch et al. 2009, Poms et al. 2004, van Hengel 2007)	Black mustard (Palle-Reisch et al. 2015)	Quantitative real-time PCR	1 mg/kg
			Brown mustard (Palle-Reisch et al. 2015)		1 mg/kg
			White mustard (Palle-Reisch et al. 2015)		5–10 mg/kg
			Celery (Palle-Reisch et al. 2015)		10–50 mg/kg
Multi-analyte profiling	Can detect multiple allergens simultaneously (Cucu et al. 2013, Gomaa & Boye 2015, Kirsch et al. 2009, van Hengel 2007)	Need special equipment, cross-reactivity (Cho et al. 2015)	Crustacean, egg, milk, gluten, peanut, soy, almond, cashew, Brazil nut, hazelnut, coconut, pine nut, macadamia nut, walnut (Cho et al. 2015)	Sandwich	5 ng/mL
Miscellaneous methods					
PCR-ELISA	Specific, simple, cost-effective (Cucu et al. 2013, Poms et al. 2004)	Does not target allergen (Cucu et al. 2013, Kirsch et al. 2009, Poms et al. 2004, van Hengel 2007)	Hazelnut (Holzhauser et al. 2002)	Conventional PCR/direct ELISA	<10 ppm
ELISA-ICP-MS	Sensitive, quantitative, reproducible, can detect multiple allergens simultaneously (Careri et al. 2007)	Need special equipment (Careri et al. 2007)	Ara h 1 and Ara h 3/4 (Careri et al. 2007)	Indirect sandwich	2 mg/kg
Biosensor	Rapid, automated (Poms et al. 2004, van Hengel 2007)	Dependent on processing and matrix (Pilolli et al. 2013)	Ara h 1 (Alves et al. 2015)	Electrochemical	3.8 ng/mL
			β-Lactoglobulin (Eissa et al. 2012)	Electrochemical	0.85 pg/mL
			Ovalbumin (Pilolli et al. 2015)	Surface plasmon resonance	0.6–1 μg/mL
			Pen a 1 (Jiang et al. 2013)	Electrochemical	0.15 μg/mL

Abbreviations: BAT, basophil activation test; BHR, basophil histamine release; EAST, enzyme-allergosorbent test; ELISA, enzyme-linked immunosorbent assay; ICP, inductively coupled plasma; LC, liquid chromatography; LC-Q-TOF-MS, liquid chromatography quadrupole time-of-flight tandem mass spectrometry; LC-QqQ-MS, liquid chromatography triple quadrupole mass spectrometry; LOD, limit of detection; MS, mass spectrometry; NA, not applicable; PCR, polymerase chain reaction; RAST, radioallergosorbent test; RIE, rocket immunoelectrophoresis; RP-HPLC, reverse-phase high-performance liquid chromatography; SRP, sulfur-rich protein.

ELISA:

enzyme-linked
immunosorbent assay

RAST:

radio-
allergosorbent test

EAST:

enzyme-
allergosorbent test

RIE:

rocket immuno-
electrophoresis

BHR:

basophil
histamine release

BAT:

basophil
activation test

PCR:

polymerase
chain reaction

The more commonly used immunoassay formats are enzyme-linked immunosorbent assay (ELISA), Western blot (WB), and dot blot (DB). ELISA is currently the method of choice for routine screening and quantification of target analytes owing to its sensitivity, simplicity, and cost efficiency (Poms et al. 2004, van Hengel 2007, Kirsch et al. 2009, Cucu et al. 2013, Jayasena et al. 2015). Although several commercial IgG-based ELISA kits for a variety of analytes are available, these assays encounter several challenges, including (*a*) selection of target analyte(s), (*b*) analyte extraction protocols, (*c*) quantitative ranges, (*d*) selection/availability of reference standards, and (*e*) quantification units used for immunoreactivity. These factors make comparison of different kits targeting the same analyte(s) difficult (Cucu et al. 2013, Jayasena et al. 2015). This point is illustrated by a comparative study of six commercially available kits for peanut allergen detection that reported a wide variation in sample recovery and sensitivities (Jayasena et al. 2015). Food matrix, analyte source (van Hengel 2007, Tiwari et al. 2010, Cucu et al. 2013), and food processing (Montserrat et al. 2015) are also known to affect ELISA performance. It is therefore useful to determine immunoassay sensitivity, specificity, and robustness for optimal assay performance. Until recently, dipstick (lateral flow device) immunoassays have been used for qualitative applications (Poms et al. 2004, van Hengel 2007), and efforts have been reported to develop their quantitative counterparts (Zheng et al. 2012, Wang et al. 2015). Simple and rapid dipstick formats offer portability and operational ease. WB and DB use antibody detection of membrane-immobilized protein(s); WB includes a protein separation step, whereas DB does not.

Other forms of immunoassays include the radioallergosorbent test (RAST), the enzyme-allergosorbent test (EAST), and rocket immunoelectrophoresis (RIE). RAST and EAST use anti-human IgE antibodies to detect the presence of IgE antibodies in human sera (Poms et al. 2004, Kirsch et al. 2009). Although these assays are used mainly for clinical diagnosis, they have also been applied for qualitative and quantitative analyses (Poms et al. 2004). In RIE, an antibody-containing gel is used to form antigen-antibody precipitates as allergens migrate through the gel (Poms et al. 2004). This method is losing favorability owing to laborious gel-related processes and difficult staining protocols (Holzhauser et al. 1998, Poms et al. 2004).

Cell-Based Methods

Cell-based methods detect cell mediators released upon allergen exposure (Poms et al. 2004). The basophil histamine release (BHR) and hexosaminidase assays detect histamine released by basophils and β -hexosaminidase released by mast cells, respectively. The basophil activation test (BAT) detects the expression of mediators (e.g., histamine, leukotrienes, ILs) and basophil surface receptors (e.g., CD63 and CD203c). The BAT method is more sensitive and specific than the BHR assay, although all cell-based methods are limited by the need for human sera (Kirsch et al. 2009).

DNA-Based Methods

DNA-based methods, namely polymerase chain reaction (PCR), detect the presence of amplifiable gene segments coding for the targeted allergen. The primary limitation of DNA-targeting methods is the lack of correlation between the presence of a gene and the allergen expression (Poms et al. 2004, van Hengel 2007, Kirsch et al. 2009, Platteau et al. 2011, Cucu et al. 2013). As with immunoassays, DNA detection is susceptible to processing and matrix effects that may affect DNA integrity, extractability, or amplification (Platteau et al. 2011). Notably, DNA content is not influenced by geographical location or seasonal varieties (Poms et al. 2004, van Hengel 2007).

Conventional PCR, albeit economical, simple, and sensitive, is limited to qualitative analyses. The development of real-time quantitative PCR enabled DNA-based methods to be used for routine allergen screening (Poms et al. 2004, Kirsch et al. 2009).

Direct Methods

Liquid chromatography (LC) and LC–mass spectrometry (MS) can detect the targeted protein or peptide (García et al. 2006, Kerkaert et al. 2010, Platteau et al. 2011, Cucu et al. 2013). Target specificity, selectivity, sensitivity, quantification, and environmental factors that influence the target molecular properties are the major challenges in the selection of the appropriate LC detector. The LC-MS method has therefore received more favorable consideration (van Hengel 2007, Kirsch et al. 2009, Monaci & Visconti 2009, Fæste et al. 2011, Cucu et al. 2013, Posada-Ayala et al. 2015).

Combination Methods

To address the limitations of individual methods, combination detection methods are developed. For example, PCR-ELISA merges the specificity of the DNA-based assay with the simplicity and cost efficiency of ELISA to detect a probe (i.e., protein) hybridized to the targeted DNA segment (Poms et al. 2004, Cucu et al. 2013). ELISA inductively coupled plasma-MS detects a stable isotope-tagged secondary antibody in ELISAs (Careri et al. 2008, Cucu et al. 2013). In ELISAs, the MS-based detector is more sensitive and matrix independent than the detectors that are UV or fluorescence based (Careri et al. 2008).

Future Trends

Multiplex food allergen detection methods are gaining increased attention owing to their efficient and low-cost detection (van Hengel 2007, Kirsch et al. 2009, Mustorp et al. 2011, Köppel et al. 2012, Cucu et al. 2013, Gomaa & Boye 2015, Palle-Reisch et al. 2015). Biosensors have helped in the development of a variety of DNA or protein detection formats that include fast and automated analyses (Poms et al. 2004, van Hengel 2007, Pollet et al. 2011, Alves et al. 2015). To overcome the loss of target detectability, generating specific and sensitive antibodies against the native and processed allergens or their stable peptides (Cucu et al. 2012, 2013) is also of increased interest.

EFFECTS OF PROCESSING ON FOOD ALLERGENS

Raw versus Processed Food Allergens

Myriad foods and food ingredients containing allergen(s) are consumed raw or processed, either alone or in combination, and in various forms. Many allergic individuals may be sensitive to raw food but not its processed counterpart and vice versa. Consequently, understanding the role of food processing in food allergies is important (Mills & Mackie 2008, Venkatachalam et al. 2008, Sathe & Sharma 2009, EFSA NDA Panel 2014).

Food-Processing Methods

The choice of processing method depends on (a) purpose, (b) environment, (c) available equipment, (d) scale, (e) economics, and (f) desired outcome. Processing may be at home, in a restaurant/place of food service, by a commercial enterprise, or a combination thereof (Sathe & Sharma 2009).

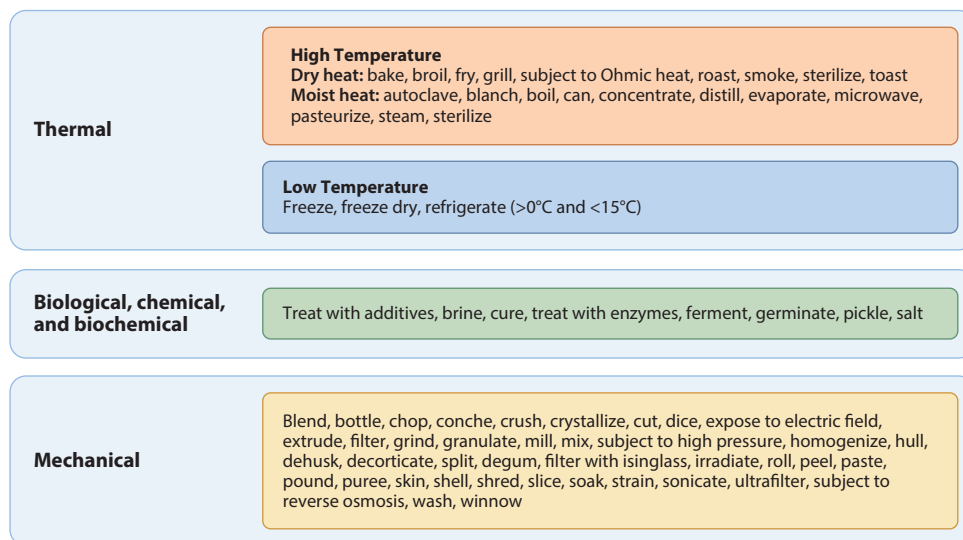


Figure 4

Food-processing methods. Exposure to the method(s) depends on the desired product characteristic(s).

Food-processing methods may be classified as thermal and nonthermal (**Figure 4**) and may be used singly or in combination.

Food-Processing Effects

Processing may result in structural changes, matrix interactions, and/or solubility changes, and may affect allergenicity of the final product (Sathe et al. 2005, Mills & Mackie 2008, Paschke 2009, Khuda et al. 2015). Proteins may undergo unfolding, fragmentation, aggregation, polymerization, or hydrolysis (Sathe & Sharma 2009, Khuda et al. 2015). Depending on the treatment and the allergen, allergenicity may increase, decrease, or remain unchanged (Paschke 2009, Sathe & Sharma 2009, Khuda et al. 2015). Allergen denaturation may destroy conformational epitopes, expose previously hidden epitopes, or form new epitopes, partially explaining the variable allergenicity of reported allergenic foods (Sathe et al. 2005, Mills & Mackie 2008, Paschke 2009, Khuda et al. 2015). Conformational epitopes are typically more inclined to undergo structural changes during processing (Sathe et al. 2005). If the Maillard browning reaction occurs between a reducing sugar and a protein amino group and results in protein glycation, it can introduce advanced glycation end products that may play a role in allergenicity (Davis et al. 2001, Khuda et al. 2015). Other covalent protein modifications may include oxidation, free radical damage, disulfide bond rearrangements, reactions with polyphenols, or deamination/deamidation reactions (Davis et al. 2001). Such chemical changes may affect the way proteins are released and digested in the GI tract, further influencing the immune response (Mills & Mackie 2008).

In recent years, the possible effects of different processing methods on food allergens have been investigated (**Table 4**). Despite such progress, much remains to be learned: (*a*) the extent of possible processing to reduce the immunoreactivity of the targeted allergen without compromising the acceptable sensory properties of the affected food, (*b*) the tolerance threshold in humans for

Table 4 Select examples of processing effects on immunoreactivity

Food	Allergen	Processing method	Outcome	Reference
Bovine milk	β -Lactoglobulin	High pressure	↓	Zeece et al. 2008
Bovine milk	β -Lactoglobulin	Sonication	—	Stanic-Vucinic et al. 2012
Bovine milk	β -Lactoglobulin	Thermal	↓	Taheri-Kafrani et al. 2009
		Glycation	↓	
Bovine milk	β -Lactoglobulin	Fermentation	↓	Yao et al. 2015
	α -Lactalbumin		↓	
	α -Casein		↓	
	β -Casein		↓	
Chicken egg	Ovomucoid	Thermal	↓	Jiménez-Saiz et al. 2011
		Glycation	↑	
	Ovalbumin	Thermal	↓	
		Glycation	↓	
Chicken egg	Ovalbumin	γ -Irradiation	↓	Lee et al. 2007
		Electron beam irradiation	↓	
Chicken egg	Conalbumin	Nine-step technological process	↓	Hildebrandt et al. 2008
	Lysozyme		↓	
	Ovomucoid		↓	
	Ovalbumin		↓	
Peanut	Ara h 1	Dry roast	↑	Maleki et al. 2000
	Ara h 2		↑	
Peanut	Ara h 1	Boil	↓	Blanc et al. 2011
		Dry roast	—	
Peanut	Ara h 1	Combined ultrasound + enzymatic treatment	↓	Yu et al. 2015
	Ara h 2		↓	
Almond	Almond major protein	γ -Irradiation	—	Su et al. 2004
		γ -Irradiation + thermal	—	
Cashew	Cashew major protein	γ -Irradiation	—	
		γ -Irradiation + thermal	—	
Walnut	Glutelin	γ -Irradiation	—	
		γ -Irradiation + thermal	—	
Cashew	Ana o 1	γ -Irradiation	—	Venkatachalam et al. 2008
		Thermal	—	
	Ana o 2	γ -Irradiation	—	
		Thermal	—	
	Ana o 3	γ -Irradiation	—	
		Thermal	—	
Almond milk	Amandin	High pressure	↓	Dhakal et al. 2014
		Thermal	—	
Codfish	Parvalbumin	Heat-induced glycosylation	↑	de Jongh et al. 2013
Shellfish	Tropomyosin	Thermal	↑	Kamath et al. 2013
Prawn	Tropomyosin	Thermal	↑	Kamath et al. 2014

(Continued)

Table 4 (Continued)

Food	Allergen	Processing method	Outcome	Reference
Crab	Tropomyosin	Boiling	—	Yu et al. 2011
		Ultrasound + boiling	↓	
		Autoclave	↓	
Soy	34-kDa protein	Galactomannan conjugation	↓	Babiker et al. 1998
		Transglutaminase treatment	—	
		Chymotrypsin digestion	—	
Soy	Unspecified	Fermentation	↓	Song et al. 2008
Soy	Soy protein isolate	High hydrostatic pressure	↓	Li et al. 2012
Buckwheat	Fag t 3	Polysaccharide conjugation	↓	Yang et al. 2013
Pasta	Durum wheat proteins	Drying temperature	—	De Zorzi et al. 2007
Apple	Mal d 1	Thermal	↓	Husband et al. 2011
		High pressure	↓	
	Mal d 3	Thermal	↓	
		High pressure	↓	
Celeriac	Api g 1	Thermal	↓	
		High pressure	↓	
Lentil	Unspecified	Enzymatic hydrolysis	↓	Cabanillas et al. 2010
Sesame	Unspecified	High pressure	↓	Achouri & Boye 2013
		Microwave	↓	
		Boil	↑	
		Roast	↑	

the targeted allergen, and (c) the acceptable risk level, which is to be established by the regulatory agencies with the authority to do so.

CONCLUSIONS

Conceptually, any protein in the human food supply can be a potential allergen, and thus allergen-free food for all is impractical. Because the immune system of different individuals sensitive to the same allergen may respond differentially, a universally applicable definition of food allergy is difficult. Using specific IgE to predict allergies is unreliable (García et al. 2009; Sanz et al. 2011; Peters et al. 2013; Treudler & Simon 2013; Sicherer & Sampson 2014; Klemans et al. 2015; Schoos et al. 2015; van Gasse et al. 2015a,b). Structure of the allergenic food protein may also influence its biopotency. Presence of food matrix components and their interaction(s) with the target allergenic protein further complicate the understanding of how an allergen elicits immune response in an affected individual. Further, the structure of the native allergen may experience change upon exposure to different food-processing methods, leading to changes in its immunoreactivity and immunogenicity. The minimum amount (threshold) needed to elicit an allergenic response from an individual also depends on the sensitivity of the individual. Threshold values for most allergenic foods are not yet established. Therefore, food labeling designed to protect sensitive consumers from the offending food(s) is challenging. Precautionary labeling potentially helps sensitive consumers reduce exposure to the known allergens (Allen et al. 2014a). Currently, the regulatory agencies and the food manufacturers/processors/handlers use two terms, contains or may

contain, to respectively declare or suggest the possible presence of the targeted food/food ingredient known or listed to be allergenic. Specific, sensitive, and robust methods for detection and accurate quantification of the targeted allergenic protein, in a practical and economic manner, are required for effective regulation enforcement and consumer protection. One of the challenges in achieving this goal is to establish an acceptable minimum risk for a targeted allergen; establishing this level then permits setting the desired detection level for the targeted protein. In the absence of a defined target and its detection level, setting and enforcement of standards remain elusive.

Because the major allergenic food groups are known, perhaps beginning with the major food(s) within the most prevalent group may be a reasonable starting point for establishing the threshold values (e.g., bovine cow's milk in the group milk). The next step for a specific food would be identification and subsequent characterization of the major allergens, including the human allergy-relevant epitopes on those major allergens. Determining the threshold value for such an identified and characterized allergen would then help establish the desired detection level. Preparation of the well-defined targets for the identified and characterized allergen is likely to facilitate detection and quantification method(s) that are of the desired accuracy, precision, and robustness. In such efforts, selecting the desired allergen for analysis may remain difficult because the amount of the target allergen may be small (ng/g) or abundant (mg/g). Determining the target quantity in the desired food in conjunction with the desirable detection threshold will help to define the acceptable analytical method. Collaborative efforts from manufacturers/processors/packers, regulatory agencies, researchers, and consumers are needed to provide a unified platform for attaining such goals.

SUMMARY POINTS

1. Increased incidence and awareness of food allergy are globally evident.
2. Any food protein, within the current definition of type I food allergy, may be allergenic.
3. Food recalls as a result of undeclared allergens, or cross-contamination with allergens, are on the rise and are of concern.
4. Progress in understanding the molecular mechanism of allergic reaction continues, although many details remain unresolved.
5. Defining the acceptable risk level for a food allergen remains challenging. As a consequence, identifying the target marker protein and an objective tolerance threshold for it remains elusive.
6. Development of allergen detection methods continues. Establishing threshold values would further assist these efforts.
7. Identification and characterization of a target allergen and its clinically relevant epitope(s) would be helpful in using food-processing methods to reduce/eliminate the target allergen and to improve consumer safety.

FUTURE ISSUES

1. Threshold values for major food allergens need to be established.
2. Development of specific, sensitive, robust, efficient, automated, and inexpensive immunoassays is suggested.

3. Allergy-relevant epitopes on major food allergens require identification and characterization.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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