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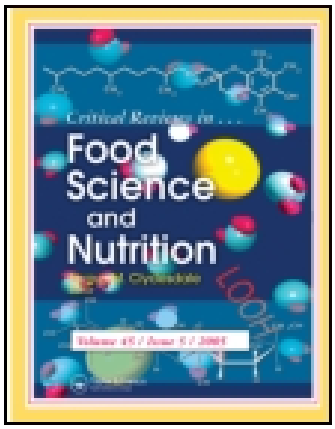

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Mouse Models of Food Allergy: How Well do They Simulate the Human Disorder?

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Mouse Models of Food Allergy: How Well do They Simulate the Human Disorder?

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Food allergy is a growing health problem with serious concerns due to high potential for fatality. Rapid advances in the knowledge on causes and mechanisms as well as in developing effective prevention/therapeutic strategies are needed. To meet these goals, mouse models that simulate the human disorder are highly desirable. During the past decade, several mouse models of food allergies have been reported. Here, we briefly reviewed the human disorder and then critically evaluated these models seeking answers to the following important questions: To what extent do they simulate the human disorder? What are the strengths and limitations of these models? What are the challenges facing this scientific area? Our analysis suggest that: (i) the mouse models, with inherent strengths and limitations, are available for many major food allergies; there is scope for additional model development and validation; (ii) models mostly simulate the severe forms of human disorder with similar immune and clinical features; (iii) the approaches used to develop some of the mouse models may be questionable; and (iv) the specific mechanisms of sensitization as wells as oral elicitation of fatal reactions in both humans and mice remains incompletely understood and therefore warrants further research.

Keywords Food allergy, mouse model, systemic anaphylaxis, allergen, hypersensitivity

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INTRODUCTION

Food allergy is a significant public health problem not only because it afflicts millions of people but also because of the life-threatening nature of allergic reactions (Sampson, 2003, 2004; Sicherer and Sampson, 2006, 2009, 2010; Wang and Sampson, 2007, 2011; Nowak-Wegrzyn and Sampson, 2011; Sicherer, 2011). A recent study (2011) reported that the prevalence of food allergies has significantly increased in the USA during the past decade especially among the children with nearly 8% under the age of 18 years afflicted (Gupta et al., 2011). Although children are more commonly afflicted than adults, the prevalence among adults is also significant (∼4% in USA) (Sicherer and Sampson, 2010; Sicherer, 2011). The prevalence of food allergy in the Europe, Canada, and Australia also appears to be of similar proportions (Hadley, 2006; Cochrane et al., 2009; Fox et al., 2009). Although food allergies afflict both sexes, among children younger than 18 years, it is relatively more common among males; and among adults (more than 18 years), an opposite trend was reported (DunnGalvin et al., 2006; Kelly and Gangur, 2009).

In view of this escalating and mysterious problem of food allergy, it is important that rapid progress is made not only in advancing the knowledge on causes and mechanisms but also, in developing effective prevention/therapeutic strategies to facilitate control and management of this escalating epidemic (Selgrade et al., 2009; Sicherer and Sampson, 2010; Nowak-Wegrzyn and Sampson, 2011; Sicherer, 2011). To accomplish this goal, food allergy mouse model that simulates the human disorder will be highly valuable as a research and development tool (Kimber and Dearman, 2002; Kimber et al., 2003a, 2003b; Bowman and Selgrade, 2009; Dearman and Kimber, 2009; Ladics and Selgrade, 2009; Selgrade et al., 2009). Here, we briefly reviewed the significance and complexity of the human disorder and then critically evaluated the currently available mouse models of food allergy seeking answers to the following important questions: To what extent do they simulate the human disorder? What are the strengths and limitations of these models? What are the challenges facing this scientific area?

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Significance of Food Allergies: Reactions Becoming More Common and More Severe

It is alarming that not only the prevalence but also the severity of food induced allergic reactions has increased during the past several years (Sicherer and Sampson, 2009, 2010; Gupta et al., 2011; Sicherer, 2011). A recent study from USA identified the prevalence of some of the common food allergies as follows: peanut (2%), milk (1.7%), shellfish (1.4%), tree nut (1%), egg (0.8%), fin fish (0.5%), wheat, soy, and strawberry at 0.4% each among US children (Gupta et al., 2011) (Table 1). Interestingly, this study found that nearly ∼40% of food allergic children suffered from a severe type of reaction characterized by shortness of breath and/or shock reactions which are potentially fatal (Gupta et al., 2011) (Table 1). In particular, such severe reactions are the leading cause of systemic anaphylactic events treated in hospital emergency departments (Sampson, 2004; Sicherer and Sampson, 2009; Wang and Sampson, 2011). Another study from the Mayo Clinic (Rochester, Minnesota) reported ∼10% rise in cases of anaphylactic reactions during 1990–2000 (Decker et al., 2008). These studies estimate that food allergies caused 50,000 emergency room visits per year (Decker et al., 2008). Another study estimated that food allergies among children rose by 18% during 1997–2007 (Branum and Lukacs, 2009). There are estimated 150–200 deaths due to food allergic reactions per year (Sampson, 2004; Wang and Sampson, 2007; Decker et al., 2008; Sicherer and Sampson, 2010; Gupta et al., 2011). Consistent with the increased prevalence and severity of food allergy, the economic burden from food allergies is also growing. Food allergies cost Americans at least half a billion dollars per year; these estimates include costs associated with hospital care, doctors visits and also indirect costs such as lost work days (Patel et al., 2011).

Since food allergies afflict children, schools, daycare centers, and parents are facing enormous challenges on a daily basis. Many schools have the pressure of training the kitchen staff, faculty and unaffected children and parents with food allergy awareness (Hourihane et al., 2002; Watura, 2002). Food allergy is also a significant challenge to the food and restaurant industries, as it is the leading cause for food recalls and food related lawsuits against restaurants (Dahl, 2006). Similarly, the agriculture and biotech industries face the challenge of potential allergenicity of novel foods developed by genetic engineering (Kimber et al., 1997; Kimber and Dearman, 2002; Kimber et al., 2003a, 2003b; Ladics et al., 2003; Selgrade et al., 2003; Ladics, 2008; Ladics and Selgrade, 2009; Selgrade et al., 2009; Ladics et al., 2010). For example, during 2001–2006, contamination of the human food chain by genetically engineered StarLink corn led to large scale food recall and cleanup at an estimated cost of several hundred million dollars (EPA, 2008).

Avoiding exposure to allergenic food is the only effective means of preventing a food allergic reaction. The need to avoid an allergenic food requires care when buying food, preparing, and consuming meals. Extreme precautions may be taken for fear of a potentially severe reaction caused by the accidental intake of an allergenic food. As a consequence, food allergy can significantly reduce the quality of life of sufferers and their families and can lead to nutritional deficits. Indeed, it is suggested that some food allergic individuals experience a lower quality of life than patients with other chronic conditions such as Type-1 diabetes mellitus (Cohen et al., 2004).

Table 1 Frequency and severity of childhood food allergies in the USA and the availability of mouse models

Common food allergy in USA[1] (most to least)	Prevalence (%)	Frequency of severe reactions (%)	Mouse model available
Peanut	2.0	52.4	Yes
Milk	1.7	31.2	Yes
Shellfish	1.4	46.8	Yes[2]
Tree nut	1.0	52.5	Yes [3]
Egg	0.8	29.5	Yes [4]
Fin Fish	0.5	40.6	No
Wheat	0.4	38.0	No
Soy	0.4	42.6	Yes
Strawberry	0.4	19.6	No

[1]Gupta et al. (2011); prevalence of peanut allergy in France, Germany, Israel, Sweden and UK : 0.06–5.9% (Boyce et al., 2011); prevalence of TN allergy in France, Germany, Israel, Sweden, and UK: 0.03–8.5%; *prevalence of milk allergy in Danish Cohort: 2.2%; [2]tropomyosin-based models available; [3]available for hazelnut and cashew nut; and [4]ovalbumin-based mouse model is available.

Why are Food Allergies on the Rise? Hypotheses

The current research convincingly demonstrates that there is a significant rise in the actual prevalence of food allergy over the past two-to-three decades (Sicherer and Sampson, 2010; Gupta et al., 2011; Sicherer, 2011). However, the underlying reasons for this phenomenon are largely unclear. Some of the major hypotheses suggested and debated are discussed below.

Although genetics might play an important role in disease susceptibility, the rising trend of food allergies over few decades implicates a critical role for environmental factors (Tan et al., 2012). One dominant theory, referred to as "Hygiene Hypothesis" attributes improved personal hygiene and elimination of major childhood infectious diseases to explaining the general rise of immune mediated disorders – both autoimmune and allergies (Rook, 2011). However, specific contribution of these factors (in particular quality of gut microbiome and elimination of childhood infections) to explain rapidly rising food allergies remains to be clearly examined (De Filippo et al., 2010; Rook, 2011). As opposed to food allergies, role of environmental pollution in exacerbating airways allergy and asthma has been studied extensively (Saxon and Diaz-Sanchez, 2005). Other critical environmental factors related to the food allergy epidemic might be changes in food production (e.g., food processing methods) and consumption (e.g., changes in food matrix, exposure doses, age at first exposure to solid food, etc. (Beyer et al., 2001; Sathe and Sharma, 2009)). One interesting hypothesis is that avoidance of early exposure to solid foods such as nuts and peanuts may prevent oral tolerance from

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getting established. Consequently, when such foods are introduced later in life, immune system may instead react with hypersensitivity responses (Sicherer, 2007; Du Toit et al., 2008; Greer et al., 2008). Furthermore, whether genetic modification or engineering to develop novel foods enhances food allergenicity is an ongoing challenge facing the biotech industry and the Government regulatory agencies around the globe (Metcalfe et al., 1996; Metcalfe, 2003; Dearman and Kimber, 2009; Selgrade et al., 2009; Ladics et al., 2010). It is noteworthy that well characterized and validated mouse models of food allergy could be used in principle to test these hypotheses.

The "Red-Flag" Allergenic Foods: Regulators Focus

Any food has the potential to be allergenic in sensitized subjects. A large number of foods (>160) have been reported to provoke allergenic reactions in sensitive individuals (Bush and Hefle, 1996). However, the number of allergenic foods of major clinical importance appears to be limited to 8–12 foods (Table 1) (Bousquet et al., 1998). According to the US FDA, the following foods are reported to cause allergy in 90% of the cases: Egg, milk, wheat, soy, peanuts, tree nuts, fish, and shellfish; these foods are often called "the red-flag foods" (Hefle et al., 1996; Lehrer et al., 2002; USFDA, 2011). According to the Canadian Food Safety Authority, the following foods are considered major allergenic foods: egg, milk, wheat, soy, peanuts, tree nuts, fish, shellfish, sesame seeds, and sulfites (CFIA, 2011). According to the European Union, the following foods are considered major allergenic foods for regulatory purpose: egg, cow's milk, fish, peanuts, tree nuts, soy, celery, cereals containing gluten, crustacean (crab, crayfish, lobster, and shrimps), sesame, mustard, and sulfites (EFSA, 2004).

Many Types of Human Food Allergies: Classification of the Complex Human Disorder

Currently, food allergies that are described in the literature can be classified into four groups based on specific clinical criteria and/or underlying mechanisms as follows: (i) *immediate vs. delayed hypersensitivity reactions (HSRs)*: this classification is based on kinetics of clinical reaction upon oral exposure to food; (ii) *transient vs. persistent food allergies*: this classification is based on whether they are outgrown (therefore, called transient) or not (therefore, called persistent); (iii) *Type-1 vs. Type-2 food allergies*: former type caused directly by the food itself and the latter due to cross-reactivity of antibodies against aeroallergens with other proteins from food; and (iv) *exercise induced food allergy*: this is based on whether physical exercise is required after food ingestion for clinical reactions to occur. These groups of disorders are briefly reviewed below.

Immediate vs. Delayed Food Hypersensitivity

Immediate reactions typically occur rapidly within minutes to few hours (usually less than one to three hours) upon exposure to food. Most food allergies including those that are life-threatening belong to this category. Delayed HSRs usually start 24–48 hours after food consumption. Typical examples are Celiac disease, subset of milk allergy, and sesame oil contact dermatitis. Other food hypersensitivities show a broader range of kinetics that starts within few hours but expands over one to two days. Such reactions are termed as mixed reactions (Table 2). Mechanistic basis of these reactions are further discussed in later section of this article.

Transient vs. Persistent Food Allergies

Based on clinical course and natural history, food allergies are broadly classified as transient or persistent (Kagan, 2003; Sicherer and Sampson, 2009, 2010; Sicherer, 2011). Food allergies that start in early childhood and usually resolve by adolescence include those caused by milk, egg, soy, and wheat (Sicherer and Sampson, 2009, 2010). Cow's milk allergy (CMA) is one of the most common food allergies in early childhood with an incidence of 2.5% among infants in United States. A majority of infants with CMA outgrow their allergy by three years of age, whereas a small percentage (15%) of this population has persistent allergy to cow's milk (Sicherer and Sampson, 1999). In the case of egg allergy, approximately 50% of egg allergic-children outgrow the allergy by the age of 3 years (Boyano-Martinez et al., 2002). The median age of resolution of wheat allergy is approximately 6.5 years (Keet et al., 2009).

Food allergies that may start in childhood but are rarely outgrown and, therefore, continue to pose threat to subjects during adult life are termed as persistent food allergies. Typical examples of food allergies that frequently persist include those caused by peanut, tree nuts, fish, and shell fish (Sicherer and Sampson, 2009, 2010; Sicherer, 2011). The expected natural

Table 2 Gell and Coombs classification: food-induced hypersensitivity reactions

	Gell and Coombs classification of hypersensitivity reaction (HSR)		
	Type-I (Immediate) HSR	Type-IV (Delayed) HSR	Type-I+ Type-IV (Mixed) HRS
Mechanism	IgE antibody and mast cell/basophil mediated	Cell (lymphocyte and monocyte)-mediated tissue damage	IgE, mast cell, basophil + eosinophil-mediated tissue damage
*Examples**	Most food allergies (peanut, tree nut, most milk, most wheat, soy, fish, shellfish, egg, and sesame allergy)	Celiac disease, contact dermatitis to sesame oil, food (milk, soy, rice, and oat), protein-induced enterocolitis syndrome	Eosinophilic gastro ententeritis; eosinophilic esophagitis (often associated with food allergy)

*Ref: Sampson (2003); Boyce et al. (2011).

course of peanut allergy is life-long persistence among the majority (80%) of patients, but some studies report about 20% of children with peanut allergy outgrow their allergy (Skolnick et al., 2001). It has been reported that only 9% of children with tree nut allergies such as cashew nut, walnut, and pecan are likely to outgrow their allergy (Fleischer et al., 2005).

Type-1 vs. Type-2 Food Allergies

Generally most food allergies are classified into Type-1 category because they are thought to be initiated by direct exposure to the food proteins (Sampson, 2003; Sicherer and Sampson, 2009; Sicherer, 2011). For example, exposure to peanut leading to peanut allergy is a Type-1 food allergy. In contrast, food allergies that result from immune (i.e., IgE antibody) cross-reactivity between aero-allergens (such as pollen) and food allergens where initial sensitization occurred due to exposure to the aero-allergens but not the food allergens are classified as Type-2 food allergies (This should not be confused with Gell and Coombs classification of Type-II HSRs; see Table 2). Typical examples include fruit allergies such as allergy to banana due to latex sensitization, allergy to hazelnut due to hazel pollen sensitization (Ortolani et al., 2000; Aalberse et al., 2001; Grob et al., 2002). To the best of our knowledge, there are no published studies examining whether sensitization to aeroallergens translates to clinical food allergy in mice. In principle, it is possible to use mouse models to evaluate this issue.

Exercise-Induced Food Allergies

In some unusual cases, ingestion of food by sensitized subjects may not result in an immediate clinical reaction such as hives or anaphylaxis; however, if the person engages in intense activity such as physical exercise clinical reactions would appear (Soyer and Sekerel, 2008). It is believed that enhanced activity such as exercise may enhance circulation thereby promoting rapid allergen absorption and distribution to systemic circulation and consequent mast cell activation (Morita et al., 2007). Some rare cases of peanut allergy belong to this unusual group (Shimamoto and Bock, 2002). This situation may be similar to what has been described for exercise-induced asthma in some individuals (Brannan and Turton, 2011).

Mechanisms of Food-Induced Hypersensitivity Reactions

Although food allergies are immune system-mediated adverse reactions, not all adverse reactions to foods are food allergies. There are several adverse reactions associated with foods that are immune system independent. These include, lactose intolerance due to metabolic disorders in the host (e.g., lactase deficiency), and toxic chemicals (e.g., histamine and tyramine) contained in the food itself (e.g., scombroid fish poisoning due to histamine) (Sampson, 2003).

Immune system mediated HSRs have been classified by Gell and Coombs into four types: Type-I, II, III, and IV (Rajan, 2003). Most food allergies are classified as immediate or Type-I HSR because they occur immediately, usually within minutes, after exposure to the food in sensitized subjects (Sampson, 2003). Type-I HSR is mediated by IgE antibody against the soluble antigen. Most food allergies are of this type (Table 3).

In contrast to Type-I HSR where IgE antibodies play a critical role, in Type-II HSRs, IgG, and IgM antibodies play a vital role. Here antibodies bind to insoluble antigens and activate the complement system, which in turn initiates the release of mediators that are responsible for the disease. Examples include some drug allergies, and autoimmune hemolytic anemia (Rajan, 2003; Murphy et al., 2008). In Type-III HSR, IgG, and IgM antibodies bind to circulating antigens and form large immune complexes. Failure to clear these complexes from the body leads to the disease conditions such as systemic lupus erythematosus (Rajan, 2003; Murphy et al., 2008). Significance of these reactions in food allergies is unknown at present.

The Type-IV HSR are delayed reactions mediated by $CD4^+$ T-cells and require intact antigen presenting cells like dendritic cells and macrophages (Rajan, 2003; Murphy et al., 2008). The Type-IV mechanism is considered to be a major cause of gluten enteropathy (or Celiac disease) (Sollid, 2002; Plenge, 2010). Notably, it is proposed that in addition to a Type-I mechanism, in some cases of milk allergies, a Type-IV mechanism may also be involved (Sampson, 2003) (Table 2).

Pathogenesis of IgE Antibody and Cell-Mediated Hypersensitivity Reactions to Food

Although the pathogenesis and the mechanisms of food allergy are not completely clear at present, most well studied food allergic reactions are thought to be mediated by IgE antibodies produced against the food proteins (Sampson, 2003; Murphy et al., 2008; Sicherer and Sampson, 2009). The immune reactions that occur in food allergy usually occur in two phases: (i) the sensitization phase when susceptible subject produces IgE antibodies against food proteins. There is usually no clinical reaction at this time; and (ii) the effector phase, when oral exposure to the same food protein triggers clinical reactions (Sampson and Burks, 1996; Sampson, 2003; Sampson, 2004; Sicherer and Sampson, 2006, 2009). Based on our current understanding, these two phases are thought to occur as discussed below.

During the sensitization phase, when the body encounters a particular allergen for the first time, the antigen presenting cells present it to B-lymphocytes; these cells undergo class-switching of the immunoglobulin with the help of signals from T helper (Th)-2 lymphocytes and produce allergen specific IgE antibodies. These IgE antibodies enter circulation and bind to Fc receptors on mast cells. Once this happens, subject is considered to be sensitized to the food. When the sensitized subject is exposed to the same allergen subsequently, the effector or elicitation phase sets in. Because, the IgE antibodies present on mast cells are cross-linked by the allergen, leading to cell activation and degranulation and release of mediators such as histamine that

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Table 3 Characteristics of major human food allergies

Feature	Human food allergy							
	Peanut	Cow's milk	Hazelnut	Cashew nut	Sesame	Egg	Shellfish	Soybean
Age	Both children and adults	Children > adults	Children and adults	Both children and adults	Children and adults	Children > adults	Children and adults	Children > adults
Outgrowing	Most do not (∼25% do)	Most do	Most do not	Most do not	Most do not	Most do	Most do not	Most do
Risk of systemic anaphylaxis	Yes, high	Yes	Yes, high	Yes, high	Yes, high	Yes	Yes, high	Yes
Mechanism	IgE	IgE and non-IgE (DTH)	IgE	Mostly IgE Some DTH to oil	Mostly IgE Some DTH to oil	Mostly IgE	Mostly IgE	Mostly IgE
Nature of allergen	Protein	Protein	Protein	Protein and oil	Protein and oil	Protein	Protein	Protein
*Threshold oral elicitation dose**	LOAEL: 0.25–10 mg protein	LOAEL: 0.36–3.6 mg protein	LOAEL 1 mg protein (Ref. 1) LOAEL: 32 mg protein (Ref. 2) 1–20 mg for adult (Ref. 3)	Unknown	1–2 mg for adults (Ref. 4) LOAEL: 30 mg sesame seed (Ref. 5)	0.13–1 mg protein	Unknown	88–522 mg protein

NOAEL: No observed adverse effect level; LOAEL: lowest observed adverse effect level; DTH: delayed type hypersensitivity reaction; *summary ranges of threshold doses for peanut, milk, egg, and soy are from USFDA (2006); Ref: 1. (Wensing et al., 2002); 2. (Hansen et al., 2003); 3. Selgrade et al., (2009); 4. (Teuber and Beyer, 2004); and 5. (Morisset et al., 2003).

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are responsible for the symptoms of the food allergy. Common symptoms of food allergy include skin reactions such as hives, gut reactions, respiratory distress, or cardiovascular reactions. Sometimes all these symptoms occur simultaneously resulting in a fatal situation known as systemic anaphylaxis (Sampson and Burks, 1996; Sampson, 2003; Sampson, 2004; Sicherer and Sampson, 2006, 2009).

It is noteworthy that there are food allergic reactions that are not IgE associated (Sampson and Burks, 1996; Sampson, 2003; Sampson, 2004; Sicherer and Sampson, 2006, 2009). For example, some milk allergies are non-IgE mediated; they are thought to be cell mediated reactions (Crittenden and Bennett, 2005). There are other HSRs to foods that are mediated by eosinophilis (Table 3) (Sampson and Burks, 1996; Sampson, 2003; Sampson, 2004; Sicherer and Sampson, 2006, 2009; Abonia and Rothenberg, 2011; Hommel et al., 2011). Celiac disease is not generally considered as a food allergy because it is a complex immune-mediated disorder which involves not only type-IV HSR mediated by CD4 T cells, but also an autoimmune reaction involving IgG antibodies directed against tissue transglutaminase enzyme produced by the intestine (Sollid, 2002; Plenge, 2010). For the sake of clarity, in this review of animal models, we have focused only on the IgE associated HSRs to food.

Food Allergy: Development of Animal Models

During the past decade, a number of animal models to study food allergies have been developed. It is interesting to see that foods can trigger allergic immune response and disease in many species (mice, rats, pigs, and dogs) as they do in humans (Metcalfe et al., 1996; Kimber et al., 1997; Knippels et al., 1998b; Buchanan and Frick, 2002; Helm et al., 2003; Kimber et al., 2003c; Knippels and Penninks, 2003; Frick et al., 2005; Selgrade et al., 2009; Hensel, 2011). Although food allergy is currently viewed primarily as a human disorder, there is growing concern that domestic pets such as cats and dogs may be naturally developing similar food induced disorders (Hensel, 2011).

While any animal model that simulates human disorder is desirable, each species and model offer specific advantages over others; each model also has disadvantages (Knippels et al., 1998a, 1998b; Li et al., 1999b; Li et al., 2000; Dearman et al., 2001; Li et al., 2001; Dearman et al., 2002, 2003a, 2003b; Helm et al., 2003; Kimber et al., 2003a, 2003b, 2003c; Knippels and Penninks, 2003; Kroghsbo et al., 2003; Birmingham et al., 2005; Dearman and Kimber, 2005; Bowman and Selgrade, 2008a, 2009; Selgrade et al., 2009). Here, we chose to review only mouse models largely because: (i) this species has been most widely used in immunology research; consequently, immunological reagents and genetically altered strains are readily available for detailed analysis; (ii) mice have short generation time, large litter sizes, and most strains breed well; (iii) in general mice have lower purchase and maintenance costs; (iv) large number of animals per experimental group can be studied leading to improved statistical power and high quality data generation; and (v) overall, it is the most economical model available to date to study allergic responses in general.

Based on the approach used and the readouts studied, food allergy mouse models may be divided into two general types: (i) *immune response plus disease models*: most models focus on both immune response (such as antibody responses) as well

as disease readouts (such as shock response) and (ii) *immune response models:* This is based on whether a mouse model focused on only an allergic (i.e., IgE antibody) immune response but not disease outcome. Based on whether adjuvant is used as part of the protocol, these models may be sub-divided into two categories: (a) *adjuvant based models* and (b) *adjuvant-free mouse models.* Both these approaches offer many advantages with some limitations as well (Tables 4, 5, 6). We have evaluated these approaches below.

Immune Response Plus Disease Models of Food Allergy

Adjuvant-Based Models

Immunologists have historically used immune enhancing agents called adjuvants to facilitate higher and rapid antibody responses to various microbial and nonmicrobial (e.g., food) antigens (Murphy et al., 2008). Typical examples of adjuvant include Freunds' complement adjuvant, incomplete adjuvant, aluminum hydroxide (commonly referred to as alum), bacterial toxins such as cholera toxin and enterotoxin (or superantigen) (Murphy et al., 2008).

There are specific reasons why adjuvant has been used in developing various food allergy mouse models (Table 4). In general, oral administration of food antigens to mice results in little or no immune response or disease; this phenomenon is referred to as "oral tolerance" (Chehade and Mayer, 2005); however, this innate default "oral tolerance" to food antigens can be breached if food antigens are coadministered with mucosal adjuvant such as cholera toxin or superantigen (Snider et al., 1994). Use of adjuvant also accelerates the HSR to foods via enhanced IgE antibody responses and more pronounced tissue damage including systemic anaphylaxis (Snider et al., 1994). Interestingly, some researchers have justified using adjuvant with the argument that pathogenesis of human food allergy may also involve natural co-exposure to food derived toxins such as bacterial enterotoxins (Ganeshan et al., 2009). Major advantage of this approach to develop food allergy models is that oral route is used not only to induce sensitization but also for elicitation of food allergic reactions. Some limitations of these models include the following: (i) it is challenging to evaluate natural response to food proteins alone in the absence of coexposure to adjuvant with these models; (ii) it is difficult to distinguish the effects of food allergen from those of adjuvant effects and from the synergistic effects of allergen plus adjuvant; and (iii) there is concern that these models may give false positive responses when used to evaluate allergenicity of novel proteins although such efforts have been published recently (Table 4, 6) (Kimber et al., 1997; Kimber and Dearman, 2002; Dearman et al., 2003a, 2003b; Kimber et al., 2003a, 2003b, 2003c; Dearman and Kimber, 2005, 2007, 2009; Bowman and Selgrade, 2008a, 2008b, 2009; Selgrade et al., 2009).

Adjuvant-Free Mouse Models

There are several mouse models of food allergy described in the literature that do not use an external adjuvant in model development (Table 4). Four of these models have used transdermal exposure to food antigens rather than oral exposure to bypass the innate "oral tolerance." In this approach, specific food antigen is repeatedly applied on the clipped skin of mice and then covered with a bandage (Navuluri et al., 2006; Birmingham et al., 2007; Gonipeta et al., 2009; Parvataneni et al., 2009b). After several weeks of such exposure mice develop robust systemic dose-dependent allergic immune responses as well as clinical disease (systemic anaphylaxis) upon oral exposure to the same food. Although it is largely thought that human food allergy results from oral sensitization to food antigen exposure, it has been argued that some human food allergies might actually result from sensitization due to transdermal exposure to food antigens during childhood (Lack et al., 2003; Strid et al., 2005; Hudson, 2006; Callard and Harper, 2007). Models for hazelnut, sesame, cow's milk, and cashew nut allergy have been described using this approach (Table 4) (Navuluri et al., 2006; Birmingham et al., 2007; Gonipeta et al., 2009; Parvataneni et al., 2009b).

Four oral sensitization mouse models that do not use adjuvant have been described for rice, shrimp tropomyosin, soybean, and peanut (Table 4) (Capobianco et al., 2008; Leung et al., 2008; Liu et al., 2008; Proust et al., 2008; Chen et al., 2011). These investigators report successful induction of IgE responses to oral administration of natural food proteins (rice, soybean, peanut, and shrimp tropomyosin) or recombinant protein (shrimp trophomyosin). In addition, they also demonstrate immunopathology in the intestine (rice and soy), anaphylactic symptoms (all cases) and vascular leakage (rice), and hypotension (soy) responses. An adjuvant free peanut allergy model using a single intragastric exposure to a large dose of peanut has been described (Proust et al., 2008). Although IgE responses to oral peanut exposure were observed in this model, they used intraperitoneal challenge to induce disease symptoms such as vascular leakage, hypothermia, decrease in breathing rate, and mast cell release of protease (Table 4).

Since these approaches are independent of an external adjuvant, they offer the inherent advantage that the readouts of food allergy including antibody/cytokine responses and the disease readouts are completely food allergen dependent. This makes the interpretation of data more straight forward. Using these models, it is also possible to elucidate the natural response to food proteins. In addition, compared to the adjuvant based approach, this method is arguably more humane and of less animal welfare concern. Limitations of some of these models are: (i) transdermal (not oral) exposure to food for inducing sensitization; (ii) use of systemic injection (not oral) to induce disease; and (iii) less robust readouts such as modest IgE responses and clinical scores of 1–2.

Immune Response Models

Similar to disease models, these models either use adjuvant or do not use an adjuvant in the sensitization protocol (Kimber et al., 1997; Dearman et al., 2001; Birmingham et al., 2002;

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Table 4 Characteristics of food allergy mouse models: a synopsis

Food allergy model	Sensitization (route, dose; age, gender; and adjuvant, allergens)	Elicitation of reactions (route, dose, and age)	Clinical and mechanistic features	References
Peanut	Intragastric gavage (two times exposure on day 0 and 7) 5 mg/mouse, 25 mg/mouse five weeks female C3H/Hej 10 μg Cholera toxin (CT) Allergen: (self-preparation) Crude peanut extract, Arh1, Arh2; using fresh raw whole peanut LPS content: not stated	Intragastric gavage 10 mg/mouse eight to ten weeks	Anaphylaxis symptoms Plasma histamine levels Histology mast cell degranulation (ear); RT IgE	Li et al. (2000)
Peanut	Single Intragastric gavage 80 mg/mouse six weeks female C3H/HeJ Without adjuvant Allergen: raw whole peanuts for sensitization and Crude peanut extract for challenge were provide by Allerbio (Varennes-es-Argonne, France) LPS content: not stated	Intraperitoneal injection 30 mg/mouse day 4, 7, 11, 14, 18, and 21 after sensitization	Ear test, intradermal skin test, scoring, RT, and IgE	Proust et al. (2008)
Peanut	Intranasal, 100 μg of PPE with 1 μg Cholera toxin/mouse; Oral, 1 mg of PPE with 15 μg Cholera toxin (2 times on day 0 and 7); 8–12 weeks female C57BL/6 mice allergen: Self-preparation of whole-peanut protein extracts (did not state raw or roasted); LPS content: not stated	Intranasal 200 μg/mouse day 15 and 16 after sensitization	Airway hyperreactivity Histology (lung, eosinophilia) flow cytometry (the frequency of MAC1+ cells in lung)	Fischer et al. (2005)
Peanut	Oral, 100 mg of whole peanut extract (WPE) with 10 mg SEB (eight times exposures over eight weeks); four to eight weeks female BALB/c or C57BL/6 Allergen: (self-preparation); did not state raw or processed; whole peanut extract(WPE) LPS content: not stated	Oral 5 mg/mouse Week 9	Blood eosinophil quantification, IgE, and symptom scoring	Ganeshan et al. (2009)
Cashew nut	Transdermal, 0.05, 0.5, and 1 mg/100 μl in saline (four times exposures for four weeks) six to eight weeks female BALB/c No adjuvant Allergen: cashew nut protein extract (Greer Labs) (did not state raw or processed) LPS content:<0.5 pg/mg	Oral 15 mg/mouse day 6 following the four weeks exposure	Systemic anaphylaxis symptom score, RT, and IgE	Parvataneni et al. (2009b)
Milk	Intragastric gavage (1+5 booster) 0.01, 0.1, and 1 mg protein/g bw; + 0.3 ug/g CT 3 wks female C3H/HeJ Allergen: homogenized milk (GAF Seelig Inc.) LPS content: not stated	Oral, six weeks after first exposure; 30 mg/mouse, twice, and 30 min apart	Anaphylaxis scores, vascular leakage, pathology (ear + intestine), lung function, histamine, and IgE	Li et al. (1999b)
Milk	Transdermal 1, 2.5 mg/100 μl in saline/mouse six times exposure six to eight weeks female BALB/c No adjuvant Allergen: milk whey protein extract (Greer Labs) (did not state raw or processed) LPS content: <0.5 pg/mg	Oral 15 mg/mouse day 13 following the 6 weeks exposure	Systemic anaphylaxis clinical scoring RT, and IgE	Gonipeta et al. (2009)
Hazelnut	Transdermal 0.005, 0.05, and 0.5 mg/100 μl in saline per mouse (six times exposures for 6 weeks) 6–8 weeks female BALB/c Without adjuvant Allergen: hazelnut/filbert protein (Greer Labs) (did not state raw or processed) LPS content: <0.5 pg/mg	Oral 13 mg/mouse day 10 following the 6 weeks exposure	Systemic anaphylaxis clinical scoring RT; histopathology of intestine IgE	Birmingham et al. (2007)
Sesame	Transdermal 0 and 0.5 mg/100 μl in saline per mouse 5 Exposure six to seven weeks BALB/c No adjuvant Allergen: sesame seed extract (Greer Labs) (did not state raw or processed) LPS content: not stated	Oral 13 mg/mouse	Systemic anaphylaxis clinical scoring RT, IgE	Navuluri, et al. (2006)

(Continued on next page)

Table 4 Characteristics of food allergy mouse models: a synopsis *(Continued)*

Food allergy model	Sensitization (route, dose; age, gender; and adjuvant, allergens)	Elicitation of reactions (route, dose, and age)	Clinical and mechanistic features	References
Egg (OVA)	Oral 100 mg Ovalbumin with 10 mg CT or various concentrations of *Staphylococcus aureus*-derived enterotoxin B (SEB) 8 exposures four to eight weeks female BALB/c, C57BL/6 Allergen: ovalbumin (OVA; Grade V) (Sigma-Aldrich) (did not state whether it is raw or processed) LPS content: not stated	Oral 5 mg/mouse Week 9	Eosinophilia, histology (ear) mast cell; blood pressure RT	Ganeshan et al. (2009)
Shrimp (tropomyosin)	Intragastric gavage, 0.1 mg recombinant His-tagged fusion protein of *M. ensis* tropomyosin (rMet e 1)+ CT, 4 exposures (0, 12, 19, and 26 days); female BALB/c, adults (more than four weeks); self-cloned allergen; LPS content: not stated	Oral, one week after last sensitization; 1 mg rMet e1,	Anaphylaxis scores, face swelling, IgE	Leung et al. (2008)
Shrimp (tropomyosin)	Intragastric gavage 30 or 100 μg of purified shrimp tropomyosin with 10 μg CT per mouse (four times exposure on days 0, 7, 21, and 35) eight weeks female C3H/HeJ Allergen: (self-preparation) tropomyosin purified from frozen shrimp *Metapenaeus ensis* LPS content: not stated	Intragastric gavage 600 μg/mouse, two weeks after sensitization	Systemic anaphylaxis symptom score, fecal histamine, and IgE	Capobianco, et al. (2008)
Soybean	Intragastric administration 1 mg of soybean glycinin or b-conglycinin 1 mL/mouse (daily for five weeks) Allergen: (provided protein) soybean glycinin and β-conglycinin female BALB/c LPS content: not stated	None	Plasma histamine, blood pressure, Mast cell (Toluidine blue) analysis; small intestine; IgE (after multiple sensitizations)	Liu et al. (2007)
Rice	Repeated oral exposure 30, 80 mg/mouse; raw rice protein; 6–8 wks Female BALB/c LPS content: not stated	Multiple sensitization/challenges; 30 mg oral	Symptom score, histopathology, vascular leakage; IgE (after multiple sensitization/challenge)	Chen et al. (2011)

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Dearman et al., 2002; Kimber and Dearman, 2002; Dearman et al., 2003a, 2003b; Kimber et al., 2003a, 2003b, 2003c; Dearman and Kimber, 2005, 2007, 2009; Fischer et al., 2005). As opposed to the disease models discussed above, there are few mouse models of food allergy described in the literature that use only immunological readouts (such as serum levels of IgE, IgG1 antibodies, or cytokine responses) (Birmingham et al., 2002; Fischer et al., 2005).

Immune response model using BALB/c mouse has been extensively examined for risk assessment of intrinsic allergenic potential of proteins (Kimber et al., 1997; Dearman et al., 2001, 2002; Kimber and Dearman, 2002; Dearman et al., 2003a, 2003b; Kimber et al., 2003a, 2003b, 2003c; Dearman and Kimber, 2005, 2007, 2009). It is claimed that this model may be useful in determining intrinsic allergenic potential of food proteins (Kimber et al., 1997; Kimber et al., 2003b).

Although these models may be useful to study immune responses to food antigens, it is difficult to use them to interpret disease outcome. This is particularly important because it is not uncommon to see humans with an antibody (IgE or IgG) response to food antigens without any clinical disease (Sampson, 2003; Selgrade et al., 2009; Wang and Sampson, 2009, 2011). Similarly, in BALB/c mice also induction of robust IgE response to peanut without clinical disease has been reported (Li et al., 1999a).

Mouse Models of Food Allergies vs. the Human Disorder: Similarities and Differences

Since many mouse models have been developed and well characterized, we have compared and contrasted the characteristics of disease induction in mouse models with that of humans. Major clinical characteristics of the human disorder vs. mouse models are summarized (Table 5).

Are Mechanisms of Sensitization to Foods Similar in Mice and Humans?

Route, Dose, and Timing of Sensitization

It is largely thought that human sensitization to foods occurs via the oral route of exposure to food proteins (Sampson, 2003; Sicherer and Sampson, 2006, 2009, 2010; Wang and Sampson,

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Table 5 Clinical presentation of food allergy in humans vs. mice

Type of allergenic reaction to food	Symptoms in humans[1]	Mouse models capture this symptom
Skin reactions	Hives	No
	Urticaria	Usually no; except one case[2]
	Angioedema	No
Eye reactions	Pruritis	No
	Conjunctival erythema	No
	Tearing	No
	Periorbital odema	Yes, in some cases[3,4,5,6,7,8,9]
Respiratory reactions	Nasal congestion	No
	Sneezing	No
	Pruritis	No
	Cough	No
	Dyspnea	Yes, in some cases[3,4,5,6,7,9]
	Wheezing	Yes, in some cases[3,4,5,6,7,9]
	Abdominal breathing	Yes, in some cases[3,4,5,6,7,9]
Gastrointestinal reactions	Angioedema of lips	No
	Swollen tongue	No
	Oral pruritis	No
	Nausea, vomiting	No vomiting, nausea in mice
	Colic	No
	Diarrhea	Yes, in some cases[3,5,6,9]
Cardiovascular reactions	Tachycardia	Yes, in some cases
	Bradycardia	Yes, in some cases[10,11]
	Hypotension	Yes, in some cases[10,11]
Systemic anaphylaxis	Shock	Yes, in most models[4,,7,8,9,10,11,12,13]
	Convulsions	Yes, in most models[3,4,5,6,7,8,12]
	Dizziness	Not applicable
	Fainting	No
	Loss of consciousness	No
	Sense of impending doom	Not applicable
	Tremors	Yes, in many models[3,4,5,6,7,8,12]
	Hypothermia	Yes, in most models[4,,7,8,9,10,12]
	Fatal or near fatal	In some models[3,4,5,6,7,8,9,10,11,12]

1. Sampson (2003); Sicherer and Sampson (2009); Boyce et al. (2011).
2. Li et al. (2001); 3. Capobianco et al. (2008); 4. Gonipeta et al. (2009); 5. Li et al. (1999b); 6. Li et al. (2000); 7. Navuluri, et al. (2006); 8. Parvataneni et al. (2009b); 9. Proust et al. (2008); 10. Ganeshan et al. (2009); 11. Liu et al. (2007); 12. Birmingham et al. (2007); and 13. Chen et al. (2011).

2011). It is suggested that normal human response to oral exposure to food is "oral clinical tolerance" mediated passively by lack of an immune response or actively by a tolerogenic immune response (Sampson, 2003; Sicherer and Sampson, 2009). When such a mechanism breaks down or fails to establish, food allergies might result due to an abnormal IgE response (Garside and Mowat, 2001; Chehade and Mayer, 2005). In mice oral administration of food proteins results in oral tolerance by an active immune mechanism involving T regulatory or Th3 immune responses (Chehade and Mayer, 2005; Finkelman, 2007). However, as reviewed before, there are studies demonstrating sensitization upon oral exposure to food proteins (rice, soybean, shrimp tropomyosin, and peanut) in mice (Leung et al., 2008; Liu et al., 2008; Proust et al., 2008).

As alluded earlier, transdermal exposure to allergenic food proteins from hazelnut, cashew nut, milk, and sesame seed in BALB/c mice (without any adjuvant) results in a clinical sensitization for systemic anaphylaxis (Table 4). There is some evidence and suggestion in the literature that transdermal exposure to food proteins in humans particularly during infancy or childhood might result in sensitization (Strid et al., 2005; Hudson, 2006; Callard and Harper, 2007).

Dose and frequency of food exposure and timing of food exposure required for sensitization in humans is largely unknown and whether early-life exposure to allergenic foods is protective or pathogenic is debated (Lack et al., 2003; Sampson, 2003; Sicherer and Sampson, 2006, 2009, 2010; Lack and Penagos, 2011). However, in mouse models, there is clear evidence for dose-response effects for sensitization (Table 4). Although many human food allergies start in early infancy and childhood, mouse models have generally used adult mice (more than four weeks age).

Use of Raw Food Extracts, Purified Proteins, or Recombinant Protein Allergen for Sensitization

Mouse models have used whole food extracts (from commercial sources such as Greer Laboratory Inc., NC, USA) or self (laboratory) made extracts or purified single proteins or recombinant allergen in inducing sensitization in mice (Table 4). In some cases raw foods and in other cases processed foods have been used. It is noteworthy that humans when exposed to foods are usually exposed to proteins in a complex food matrix; in many cases, not to raw foods, but to processed or cooked foods when food is consumed. However, exposure to raw food via skin or inhalation is possible in professional settings like bakeries (Droste et al., 2005). While use of raw food extracts make it easier to develop models, it becomes important to question whether mice might develop sensitization and food allergy disease if one used processed (such as autoclaved, baked, boiled, etc.) foods in these protocols (Table 6). Also use of recombinant allergens or purified single allergen in protocols in mouse models may likely to raise questions of relevance to human exposures (Table 6).

Use of Adjuvant in Mouse Models and Relevance to Human Food Allergies

It is largely unknown whether coexposure to bacterial toxins along with food proteins results in sensitization in humans.

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Table 6 Published mouse models of food allergy: strengths and limitations

Food	Reference	Strengths	Limitations/comments
Peanut	Li et al. (2000)	First demonstration that mice can get peanut allergy; clinical reactions similar to severe form of human disease; oral route for both sensitization and challenge; mice develop allergic skin reactions; peanut allergy is genetically controlled; C3H/HeJ model is TLR4 independent	Use of cholera toxin; threshold elicitation doses (LOAEL, NOAEL) unknown; adult mice used; gender effect not reported; Balb/c mice are resistant to PN allergy with this protocol; does processed peanut change the model characteristics?
	Proust et al. (2008)	Single intra-gastric route for sensitization; clinical reactions similar to severe form of human disease; C3H/HeJ model is TLR4 independent	Use of i.p., injections to challenge the mice to demonstrate clinical reactions; adult mice used; gender effect not reported; threshold elicitation dose (LOAEL, NOAEL) unknown; No skin reactions; does processed peanut change the model characteristics?
Hazelnut	Birmingham et al. (2007); Parvataneni et al. (2009a); Gonipeta et al. (2010)	No adjuvant; first demonstration that mice can get hazelnut allergy; oral route used for elicitation of reaction; clinical reactions similar to severe form of human disease; disease is long-lasting; hazelnut allergy phenotype is genetically controlled; gender effect studied; determined threshold for skin sensitization	Did not use oral route for sensitization; mice do not develop allergic skin reactions; adult mice used; threshold doses for elicitation (LOAEL, NOAEL) unknown; age effect not studied; role of LPS unknown; does processed hazelnut change the model characteristics?
Cashew nut	Parvataneni et al. (2009b)	No adjuvant; first demonstration that mice can get cashew nut allergy; oral route used for elicitation of reactions; clinical reactions similar to severe form of human disease; determined threshold for skin sensitization	Did not use oral route for sensitization; mice do not develop allergic skin reactions; adult mice used; threshold doses for elicitation (LOAEL, NOAEL) unknown; age/gender effect not studied; role of LPS unknown Does processed cashew nut change the model characteristics?
Milk	Li et al. (1999b)	First demonstration that mice can get milk allergy; clinical reactions similar to severe form of human disease; oral route for both sensitization and challenge	Use of cholera toxin; threshold elicitation doses (LOAEL, NOAEL) unknown; adult mice used; gender effect not reported; Balb/c mice are resistant with this protocol; does processing milk change the model characteristics?
	Gonipeta et al. (2009)	No adjuvant; oral route used for elicitation of reactions; clinical reactions similar to severe form of human disease	Did not use oral route for sensitization; mice do not develop allergic skin reactions; adult mice used; threshold doses for elicitation (LOAEL, NOAEL) unknown; age/gender effect not studied; role of LPS unknown; does processed milk change the model characteristics? Allergy to whey but not casein proteins
Tropomyosin	Capobianco et al. (2008); Leung et al. (2008)	First demonstration of shrimp allergy in mice; clinical reactions similar to severe form of human disease; C3H/Hej Model is TLR4 independent; Leung et al. (2008) used BALB/c mice;	Use of cholera toxin; threshold elicitation doses (LOAEL, NOAEL) unknown; adult female mice used; gender effect not reported; no skin reactions; does processed shrimp change the model characteristics? Leung et al. (2008): does natural protein trigger similar reactions? Role of LPS unknown
Soybean	Liu et al. (2007)	No adjuvant; first demonstration of soy allergy in mice; clinical reactions similar to severe form of human disease; use of oral route for sensitization and challenge	Used purified proteins (glycinin, beta-conglycinin); threshold elicitation doses (LOAEL, NOAEL) unknown; adult female mice used; gender effect not reported; no skin reactions; role of LPS unknown; does processed soy or whole soy extract change the model characteristics? Peak shock (BP) response is delayed (three h)
Rice	Chen et al. (2011)	No adjuvant; first demonstration of rice allergy in mice; clinical reactions similar to severe form of human disease; use of oral route for sensitization and challenge	Used raw rice flour; threshold elicitation doses (LOAEL, NOAEL) unknown; adult female mice used; gender effect not reported; no skin reactions; role of LPS unknown; does processed rice change the model characteristics? Clinical scores are mild (score of 1)

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However, as reviewed earlier, investigators have successfully used a protocol that involves coadministration of food proteins with mucosal adjuvants such as cholera toxin or bacterial enterotoxin (or superantigen) (Table 4). These approaches have resulted in highly attractive and useful mouse models of peanut, milk, and egg (ovalbumin) allergy (Li et al., 1999b; Li et al., 2000; Li et al., 2001; Ganeshan et al., 2009). It would be interesting to find out whether similar coexposure of bacterial toxins with food allergens accounts for human food allergies.

Are Mechanisms of Oral Elicitation of Reactions to Foods Similar in Mice and Humans?

While in some mouse models, an intraperitoneal route of food challenge has been used, in most cases, oral challenges have been developed (Table 4) (Dearman et al., 2003b; Birmingham et al., 2007; Gonipeta et al., 2009; Parvataneni et al., 2009b). Although other routes of exposures can elicit reactions, most human food allergies result upon ingestion of foods. Consequently, models that use this natural route are preferred. The oral challenge doses and the use of raw vs. processed food extracts for oral elicitation of reactions are also additional considerations (Table 4, 6). While humans tend to eat in most cases processed allergenic foods (such as peanuts, tree nuts, milk, egg, soy, wheat, fish, and shellfish), use of raw food extracts or single allergens or recombinant allergen in oral challenges in mouse models raise questions. In some cases, concern of endotoxin contamination of allergen preparations needs to be clarified (Table 4, 6). The oral threshold doses in humans remain incompletely determined although much progress in this area with LOAEL determined for many foods (Table 3) (USFDA, 2006). If mouse models were to be used in preclinical evaluation of novel therapeutics and vaccines for food allergy or for predicting allergenicity of novel proteins, it is critical that precise threshold doses are established in various models (Table 4, 6).

Are Immune and Clinical Characteristics Similar in Humans and Mice?

Induction of specific IgE antibody responses to foods as measured by an optimized ELISA or by passive cutaneous anaphylaxis assay has been used as a generally accepted standard in mouse models (Table 4) (Dearman et al., 2001; Birmingham et al., 2003). In humans specific IgE antibody measurement has been useful in diagnosis with specific levels predictive of disease severity in egg and peanut allergies (Sampson, 2001; Sicherer and Sampson, 2009). However, in some unusual cases, a clinical reactivity may be absent despite presence of demonstrable food specific IgE antibodies (Hourihane et al., 1997; Sampson and Ho, 1997). In mouse models also, there are reports that BALB/c mice can develop a robust IgE antibody response to peanuts without clinical reactivity (Morafo et al., 2003).

There are many similarities and differences in clinical presentation of food allergy in humans vs. mice (Table 5). In most models, clinical reactivity to foods is measured with a scoring scale for systemic anaphylaxis (zero to 5 scale: 0: no symptoms; 1: scratching, rubbing around the nose and head; 2: puffiness around the eyes, and mouth; pilar erecti, decreased activity with increased respiration; 3: wheezing, labored respiration, cyanosis around mouth and tail; 4: ataxia, circling, abdominal respiration; slight or no activity after prodding, tremor and convulsion; and 5: death) (Li et al., 1999b). A major drawback of this method is that it is highly subjective; precise scoring requires highly trained veterinarians or other skilled professionals. When the reactions are severe scoring becomes easier than when reactions are mild.

A significant drop in rectal temperature upon oral challenge has been used a gold standard for quantification of systemic anaphylaxis in mouse models. Use of repeated rectal measurement in mice having an acute food induced intestinal anaphylaxis raise questions on animal welfare. In some models use of drop in blood pressure has been examined. In human anaphylaxis, usually all vitals are monitored although skin temperature are measured.

In general in mouse models, hives or rashes are not reported. In one case, atopic dermatitis was reported (Li et al., 2001). Vomiting is absent in mice. As illustrated, there are several other differences in clinical responses between humans and mice (Table 5).

Are Mechanisms Underlying Oral Food-Induced Systemic Anaphylaxis Similar in Mice and Humans?

It is generally accepted that most oral food-induced systemic anaphylaxis in humans is mediated by IgE antibody, mast cell, and/or basophil pathway (Metcalfe, 2003; Sicherer and Sampson, 2009). In contrast, in mice systemic anaphylaxis may be mediated by IgE or IgG1 antibodies; involvement of mast cells and macrophages has been well demonstrated in basic studies (Finkelman, 2007; Khodoun et al., 2011). However, in a specific food allergy mouse model, relative contribution of these individual pathways to disease remains to be clarified on an individual case by case basis. There is some recent data that neutrophils might be involved in anaphylaxis in mice and humans (Jonsson et al., 2011; Khodoun et al., 2011; Lowell, 2011); however relevance of these findings to specific food induced systemic anaphylaxis upon oral exposure remains to be established.

Is Gender an Issue in Food Allergy in Mice and Humans?

Both sexes are afflicted with food allergies in humans, although there are relative differences based on age; among adults, most afflicted are females; among children, most afflicted are males (DunnGalvin et al., 2006; Kelly and Gangur, 2009). Most mouse models have used females. In mice, females tend to exhibit more robust IgE antibody responses in general (Venugopal

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et al., 1995; Melgert et al., 2005). A recent study using hazelnut allergy mouse model, reported that female mice exhibit higher IgE responses compared to males (Parvataneni et al., 2009a).

What is the Role of Host Genetics in Mouse vs. Human Food Allergies?

A number of studies implicate that genetics plays an important role in food allergy susceptibility (Bjorksten, 2005; Dreskin, 2006). Both HLA and non-HLA genes (such as STAT6) have been studied (Donovan et al., 1996; Amoli et al., 2002; Shreffler et al., 2006). In mice also role of genetics is critical for food allergy. For instance, clear role of non-MHC genetics was demonstrated in a transdermal sensitization model of hazelnut allergy (Parvataneni et al., 2009a). Role of genetics in cholera toxin based peanut and milk allergy was shown to operate at the TH1/TH2 responses with C3H/Hej being susceptible and BALB/c mice being resistant (Morafo et al., 2003). However, using different protocols, others report that BALB/c mice can develop peanut and milk allergy (Gonipeta et al., 2009; Mondoulet et al., 2011). Clearly, more research is needed to identify specific genetic polymorphisms that render the host resistant or susceptible to food allergies both in humans as well as in mice.

Is Natural History of Food Allergy in Humans and Mice Similar?

In humans, most milk, egg, soy, and wheat allergies start in childhood; however, they are outgrown in a majority cases (Sampson, 2003; Sicherer and Sampson, 2006, 2009, 2010). In contrast, peanut, tree nut, fish, and shellfish allergies tend to be persistent in most cases and are rarely outgrown (Sampson, 2003; Sicherer and Sampson, 2006, 2009, 2010). In mouse models natural history has not been well studied. Most models use a protocol that lasts from 4–12 weeks (Table 4). Notably, one recent long-term study reported that hazelnut allergy once established persists for at least 8 months despite allergen withdrawal (Gonipeta et al., 2010). In essence, the natural course of food allergies in individual mouse models remains to be elucidated.

CONCLUSIONS AND FUTURE DIRECTIONS

Human food allergies are a large group of complex HSRs mediated by the immune system. Mechanisms underlying these disorders are not completely understood. During the past decade, there has been significant progress in the development and characterization of several mouse models of food allergies. Reasonably well-characterized models are available for peanut, hazelnut, cashew nut, sesame, milk, shellfish, and soy allergies. There is scope for development of mouse models for other allergenic foods. Further research is needed to improve mechanistic understandings on disease development so that improved comparisons can be made to the human disorders. Most of the current models simulate the severe forms of human food allergic reactions such as systemic anaphylaxis. These models exhibit immune and clinical features similar to human disorder; however, with the exception one model, others do not exhibit eczema symptoms commonly seen in human food allergies. The approaches used to develop some of the mouse models (e.g., use of adjuvant, use of nonoral routes for sensitization/challenge, recombinant protein, etc.) may be questionable.

The knowledge on specific underlying mechanisms of sensitization as wells as oral elicitation of reactions in humans is still not completely understood (Sicherer and Sampson, 2009;

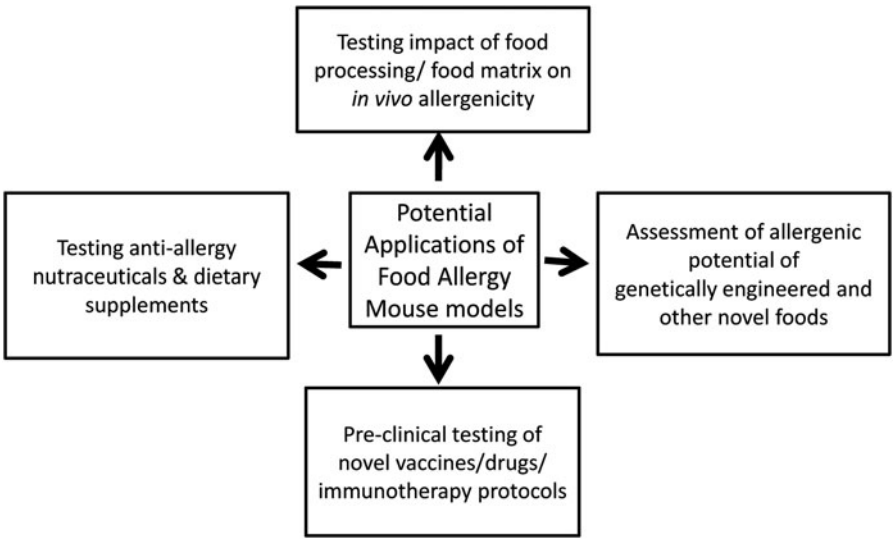

Figure 1 Potential application of well characterized food allergy mouse models in basic research and development including food and nutrition applications. Such models may also be used to test various hypotheses proposed to explain the ongoing food allergy epidemic in the developed countries. Although not reported as yet, it is possible to test the Type-2 food allergy concept (i.e., whether sensitization to aeroallergens actually translates to food allergy) in mice.

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Khodoun et al., 2011). Consequently studying mechanisms in mouse models is expected to assist in improving our understanding of the human disorder. Optimized and well-characterized mouse models are expected to be highly useful in a number of areas of research and development (Figure 1). Potential applications include, but not limited to: (i) developing novel antifood allergy strategies including vaccine/immunotherapy development, preclinical testing of hypo-allergenic foods and functional foods with antifood allergy benefits; (ii) evaluation of the impact of food matrix and food processing (e.g., thermal, radiation, and enzymatic processing) on *in vivo* allergenicity; (iii) assessment and prediction of allergenic potential of genetically engineered foods and other types of novel/exotic foods; readers are referred to excellent articles published recently on this topic; (Aldemir et al., 2009; Ladics and Selgrade, 2009; Selgrade et al., 2009; Ladics et al., 2010); and (iv) evaluating various hypotheses on why food allergies are on the rise in recent times. With further advances in basic and clinical aspects of human and mouse food allergy and immunology, there is tremendous hope and potential for effective prevention and management of food allergy epidemic in the future.

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