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Food allergy: Insights into etiology, prevention, and treatment provided by murine models

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Food allergy is a rapidly growing public health concern because of its increasing prevalence and life-threatening potential. Animal models of food allergy have emerged as a tool for identifying mechanisms involved in the development of sensitization to normally harmless food allergens, as well as delineating the critical immune components of the effector phase of allergic reactions to food. However, the role animal models might play in understanding human diseases remains contentious. This review summarizes how animal models have provided insights into the etiology of human food allergy, experimental corroboration for epidemiologic findings that might facilitate prevention strategies, and validation for the utility of new therapies for food allergy. Improved understanding of food allergy from the study of animal models together with human studies is likely to contribute to the development of novel strategies to prevent and treat food allergy. (J Allergy Clin Immunol 2014;133:309-17.)

Key words: *Food allergy, anaphylaxis, murine model, microbiota, regulatory T cells*

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Abbreviations used
AD: Atopic dermatitis
CM: Cow's milk
CT: Cholera toxin
DC: Dendritic cell
FAHF-2: Food Allergy Herbal Formula-2
Foxp3: Forkhead box protein 3
GF: Germ free
LP: Lamina propria
MLN: Mesenteric lymph node
OIT: Oral immunotherapy
PAF: Platelet-activating factor
SEB: Staphylococcal enterotoxin B
Treg: Regulatory T

The genetic revolution over the last decade has had few stronger influences than that on our ability to generate tools from the laboratory mouse. Work stemming from manipulating murine embryonic stem cells earned Drs Mario Capecchi, Martin Evans, and Oliver Smithies the Nobel Prize in Physiology and Medicine in 2007 and led to a new dawn of scientific inquiry that has revolutionized our understanding of most fields of biology, including immunology and allergy. These tools, such as gene deletions, gene insertions, gene reporters, and more, have allowed researchers to define biology in ways previously unobtainable. Despite this, concerns regarding what relevance murine models have in understanding human disease persist.

It goes without saying that mice and human subjects differ in many ways. This was spotlighted recently in an article reporting that the transcriptional responses observed in murine models of endotoxemia, burns, and trauma were not representative of those observed in patients' samples.[1] Although this study has been criticized by leaders in these areas,[2] it raised an important question of whether studies performed in mice (or any animal for that matter) have meaningful bearing on the diseases about which they are intended to inform.

Interestingly, allergy is one field in which this transcriptional analysis approach has shown remarkable consistency between murine and human samples. For example, a recent study using a murine model of atopic dermatitis (AD) included comparisons with data from affected human skin and showed a high degree of homology in the gene expression profile.[3] Using genetically modified mice, the authors definitively showed key roles for T cells and mast cells in disease pathogenesis. Similarly, in a murine model of severe asthma, Yu et al[4] performed transcriptional comparison analysis between the murine lung and patient lung biopsy specimens. Their data elegantly showed a highly significant association in gene expression patterns that was lost in mast cell–deficient mice but restored if mast cells were reconstituted by

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Terms in boldface and italics are defined in the glossary on page 310.

mean of adoptive transfer. There is no doubt that such validation approaches will be an important aspect of mechanistic studies moving forward, especially that researchers in the field of allergy possess a strong collection of tools to study the diseases.

This review aims to outline the role animal models might play in understanding food allergy, as well as to highlight how animal models might contribute to the development of future therapies. However, it is first worth discussing what precisely constitutes an animal model.

There are generally 3 main types of approaches to modeling human disease: homologous (in which the underlying cause, symptoms, and treatments are shared), isomorphic (in which the symptoms and treatments are shared), and predictive (in which symptoms might be different but treatments show efficacy). Within the allergy field, most models are isomorphic.

As we well know from asthma model research, sensitization with intraperitoneal ovalbumin and alum has been a mainstay approach of the airway inflammation community for many years. However, ovalbumin is not an allergen associated with asthma nor do human subjects encounter antigens through the intraperitoneal route or in the context of alum adjuvant. However, because the type 2 immune response and ensuing eosinophilic airway inflammation are highly associated with asthma, this isomorphic model has facilitated significant progress in our understanding of asthma mechanisms helped by the availability of tools such as ovalbumin-specific T-cell receptor transgenic mice, mAbs, and tetramers. In recent years, a shift toward using house dust mite has driven the desire for a more homologous disease model, although there are few data about the physiologic relevance of the levels of house dust mite extract delivered to the mice to elicit pathology. In the field of food allergy, there is insufficient information regarding the nature of food allergens and the mechanisms responsible for loss or lack of tolerance in patients for us to develop a true homologous model at this time because feeding of food allergens to mice elicits oral tolerance, as it does in most human subjects. Instead, mucosal adjuvants, such as ***cholera toxin*** (CT)[5] or ***staphylococcal enterotoxin B*** (SEB),[6,7] or genetically manipulated mouse strains susceptible to enteral sensitization[8] have been used. Interestingly, physiologic exposure to *Staphylococcus aureus*, SEB, or both has been closely connected with many allergic diseases in human subjects,[9] suggesting the potential for a homologous link, although connections between *S aureus* and food allergy remain to be determined. However, the use of these models has already provided significant advances in our understanding of the potential mechanisms of pathogenesis of food allergy and in the development of new therapies.

This review will address how such models can work in synergy with human studies to promote better understanding of the mechanisms, etiology, and potential therapy for food allergy. Key points of this review are listed in Table I.

DEFINING THE ETIOLOGY OF FOOD ALLERGY USING MURINE SYSTEMS

One of the critical advantages of using mouse models to study food allergy is that allergic sensitization or tolerance can be induced to specific allergens under controlled environmental conditions within defined genetic backgrounds, which is not possible in human subjects. This aspect of mouse models allows extensive and precise investigations into the mechanisms involved in disease etiology, such as identification of possible triggers, as well as pathways involved in food allergy. Normally, ingestion of food results in oral tolerance in mice, as in most human subjects. Although the immune mechanisms responsible for breakdown in oral tolerance are not fully understood, increasing evidence from mouse models indicates that alterations in ***regulatory T (Treg) cell*** function and environmental factors, such as microbiota, are likely important contributors to allergic sensitization and food allergy. Increased intestinal permeability has been suggested as a potential cause of food allergy,[10] possibly through increased exposure to intact protein. Loss of oral tolerance can also occur when food antigen is presented through alternative routes, such as the skin, and results in the development of food allergy.

Induction mechanisms of food allergy

To establish tolerance or initiate allergic responses against food antigens, ***dendritic cells*** (DCs) acting as professional antigen-presenting cells must encounter the antigens and bring them to local lymph nodes. Although the function of various intestinal antigen-presenting cell subpopulations to induce tolerance versus sensitization is currently unclear and requires further investigation (for further information, see Pabst and Mowat[11] and Ruiter and Shreffler[12]), under normal conditions, $CD103^+$ DCs have been thought to capture antigen in the lamina propria (LP) and Peyer patches and migrate to the mesenteric lymph nodes

GLOSSARY

CHOLERA TOXIN (CT): A highly toxic protein secreted by the bacterium *Vibrio cholerae*, which causes severe gastric inflammation in animals and is often used to induce an immune response in biological experiments.

DENDRITIC CELLS (DCS): Professional antigen-presenting cells that link the innate and adaptive immune systems by capturing and then presenting antigen to T cells.

FORKHEAD BOX PROTEIN 3 (FOXP3): A transcription factor responsible for the development and function of regulatory T cells.

PLATELET-ACTIVATING FACTOR (PAF): A potent mediator of inflammatory responses that is a regulator of anaphylaxis. Studies have indicated that blocking the effects of PAF prevents fatal anaphylaxis.

REGULATORY T (TREG) CELLS: A subset of T cells that control inflammation and induce tolerance by secreting anti-inflammatory cytokines.

STAPHYLOCOCCAL ENTEROTOXIN B (SEB): A superantigen produced by the bacterium *Staphylococcus aureus* that elicits a massive cytokine release. This severe inflammatory response often serves as a model of inflammation in biological studies.

TGF-β: A cytokine produced by a variety of cells that is involved in the suppression of inflammation by regulating cellular proliferation and differentiation.

THYMIC STROMAL LYMPHOPOIETIN (TSLP): A cytokine that stimulates the maturation of T cells through activation of antigen-presenting cells, such as dendritic cells and macrophages.

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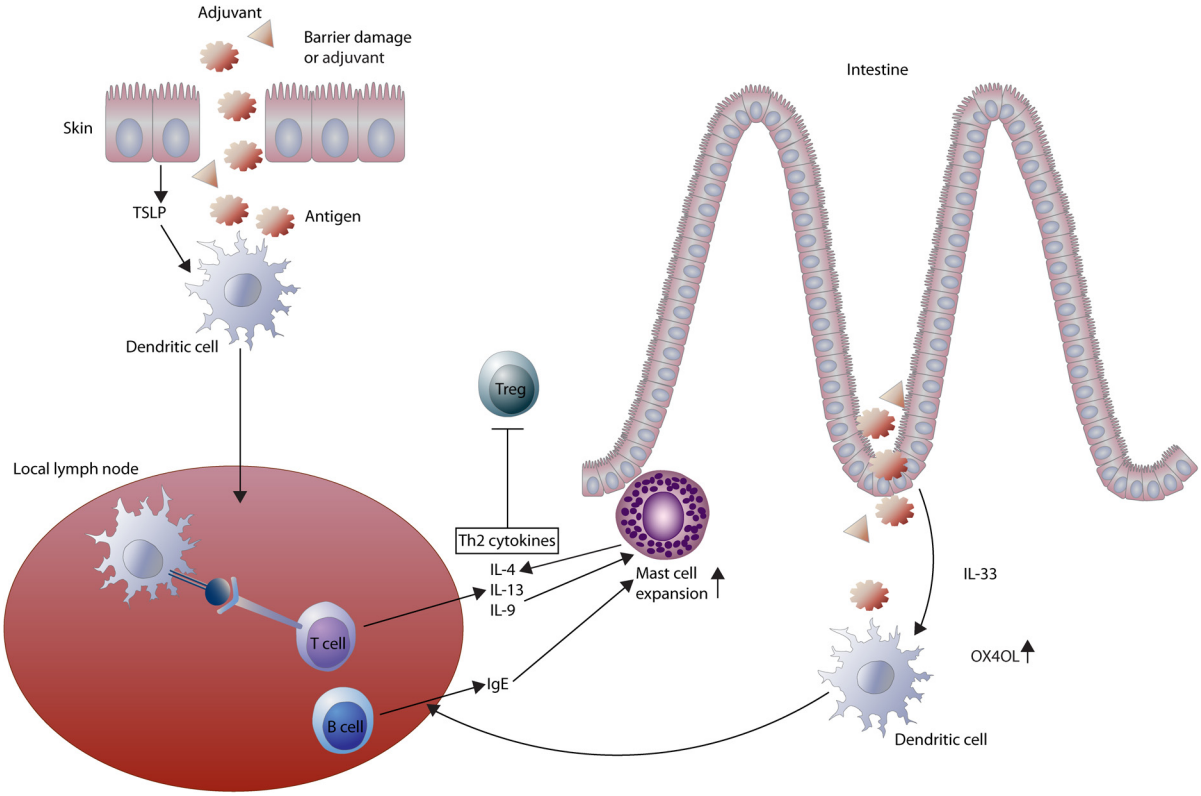

FIG 1. Possible mechanisms of allergic sensitization to food antigens. Altered skin barrier (or adjuvant) allows antigen entry and stimulates keratinocytes to produce thymic stromal lymphopoietin *(TSLP)*. This activates skin-derived DCs, which promote the differentiation of T_H2 cells and IgE-producing B cells in draining lymph nodes. Orally administered mucosal adjuvant induces IL-33 secretion by intraepithelial cells, which upregulates OX40 ligand *(OX40L)* expression on DCs that promote the T_H2 response in MLNs. Increased T_H2 cytokine and IgE levels mediate intestinal expansion of mast cells that might, in turn, recruit T_H2 cells to the intestine and increase intestinal permeability, which results in the development of gastrointestinal symptoms, including diarrhea. Increased T_H2 milieu, such as that seen in *Il4raF709* mice, might hinder Treg cell function, which leads to loss of oral tolerance to food antigens.

(MLNs), where they induce Treg cells that migrate back to the LP. Resident CX_3CR1^+ macrophages in the LP can expand Treg cells that suppress generation of type 2 cytokines and IgE, as well as the effector functions of mast cells and basophils, thus inhibiting allergic inflammation and food hypersensitivity. The importance of Treg cells in the development of tolerance has been demonstrated in both mice and human subjects, in which deficiency of ***forkhead box protein 3*** $(Foxp3)^+$ T cells leads to increased allergic disorders, such as AD and food allergy.[13] Transfer of Treg cells induces oral tolerance in mice,[14] and antigen-specific $CD4^+CD25^+Foxp3^+$ Treg cells are associated with the onset of clinical tolerance to milk.[15]

The mucosal adjuvants CT and SEB have been widely used to overcome oral tolerance to coadministered antigens. Oral sensitization to various food antigens in the presence of CT or SEB has been shown to be effective in inducing antigen-specific IgE and systemic anaphylaxis on antigen exposure.[6,16] Orally administered CT is thought to promote type 2 responses and food hypersensitivity through upregulation of the costimulatory molecule OX40 ligand on gastrointestinal $CD103^+$ DCs,[17] which are normally tolerogenic. Additionally, IL-33, but not ***thymic stromal lymphopoietin*** or IL-25, has been shown to upregulate OX40 ligand on DCs.[18] Although CT is unlikely to play a role in the etiology of human food allergy, these results raise the possibility that factors that stimulate intestinal epithelial cells to produce IL-33 might trigger type 2 responses to ingested foods. Polymorphisms in genes encoding IL-33 and/or its receptor, ST2, are highly associated with allergic diseases,[19] further supporting their potential roles in human food allergy. Although further studies are needed to determine whether these adjuvants also directly suppress the generation or function of Treg cells, dysfunction of Treg cells after SEB exposure has previously been shown in samples from patients with AD.[9] Oral SEB-driven sensitization resulted in a type 2 response and antigen-triggered anaphylaxis with decreased expression of intestinal ***TGF-β*** and Foxp3,[6] whereas transfer of Treg cells from unexposed mice was also sufficient to diminish food-induced allergic responses in this model.[20]

Enteral sensitization to food allergens can also be elicited in the absence of CT or SEB in mice genetically manipulated to enhance IL-4 responses. For instance, *Il4raF709* mice, in which IL-4 signaling is enhanced because of disruption of the inhibitory signaling motif in the IL-4 receptor α-chain, exhibit sensitization to food proteins, mast cell expansion, anaphylactic responses after food challenge, and a food allergy–specific gut microbiota.[8,21,22] Recent studies have revealed defective induction and function of *Il4raF709* Treg cells because of their T_H2 reprogramming (T. A. Chatila and H. C. Oettgen, manuscript in preparation). These findings implicate strong IL-4 signals, such as

TABLE I. Key points

- Animal models allow extensive investigation into the mechanisms of allergic sensitization or tolerance to specific allergens under controlled environmental conditions within a defined genetic background, which promotes a better understanding of the etiology of human food allergy.
- Animal models have identified key factors responsible for breakdown in oral tolerance, such as epithelial cytokines that activate DCs to promote a T_H2 milieu, altered microbiota, or antigen exposure through alternative routes, such as the skin.
- Animal models have defined effector mechanisms of food allergy, some of which might also play a role in human subjects: IgE- and IgG-mediated pathways of anaphylaxis, variable genetic susceptibility to food allergy, and T cell– and mast cell–dependent diarrhea.
- Animal models enable experimental investigation to delineate the associative or causal influences of epidemiologic findings in human subjects, which might facilitate prevention strategies.
- Animal models allow validation of the utility of existing therapeutics, as well as development of novel therapies, which can lead to significant improvements in therapy options for food allergy patients.

those that might be encountered in the T_H2 milieu of atopic patients, in subverting Treg cell responses to oral antigens and fostering the development of food-specific IgE, intestinal mast cell expansion, and susceptibility to anaphylaxis.

Emerging data suggest that allergic sensitization to foods can occur through routes other than the tolerance-promoting oral route, such as exposure through the skin or the respiratory tract. Mouse models have demonstrated that sensitization through skin successfully elicited allergic sensitization and anaphylaxis to various food antigens, including egg, peanuts, and hazelnuts.[23-25] Mice cutaneously exposed to hazelnut protein exhibited sustained hazelnut-specific IgE antibodies associated with memory IgE and IL-4 responses after 8 months of antigen withdrawal,[26] which might reflect the situation in human subjects with persistent clinical sensitivity to peanuts and tree nuts. Cutaneous exposure was more effective in triggering food sensitization than the intragastric, intranasal, or sublingual routes,[5] indicating that the skin might be a potent route of food sensitization. In contrast, antigen uptake through intact skin has also been shown to downregulate antigen-specific responses.[27] Data from these mouse models suggest that additional factors, such as adjuvant[5] or skin barrier disruption,[23] in addition to antigen entry are required for food sensitization. These factors might promote antigen sensitization by activating skin DCs because DCs derived from mechanically disrupted skin were shown to be programmed by keratinocyte-derived thymic stromal lymphopoietin[28] to bring antigen to the MLNs,[29] where they can induce local T_H2 responses. After subcutaneous immunization, retinoic acid might also be important for subsequent homing of T and B cells to the gut.[30] Conversely, antigen-specific gut-homing T cells can be reprogrammed after cutaneous antigen exposure to migrate to the skin and elicit allergic skin inflammation in the mouse,[29] suggesting a bidirectional cross-talk between the skin and gut. Possible mechanisms of allergic food sensitization are shown in Fig 1.

Microbiota regulation of tolerance and allergy

Alterations in the microbiota have now been implicated in the pathogenesis of AD, asthma, and food allergy.[31] Intestinal microbiota influence the network of the immune system and result in impaired regulatory functions and T_H2 skewing. While germ-free (GF) conditions are almost impossible in human studies, limiting the types of analysis that can be performed, a role for commensal microbiota in promoting oral tolerance has been clearly defined by using gnotobiotic mice, in which reconstitution of GF mice with well-characterized communities of microbiota or defined bacteria has been performed. Numbers of $CD4^+Foxp3^+$ Treg cells are reduced in antibiotic-treated mice or GF mice,[32,33] which exhibit a predisposition toward allergic sensitization.[33,34] Administration of defined commensal microbiota, such as *Clostridia* species and *Bacteroides fragilis*, or short-chain fatty acids (microbiota-derived products) to GF mice induced Treg cells[32,35-38] and reduced allergic sensitization,[32] supporting the notion that intestinal commensal microbiota promote Treg cells and limit allergic responses to foods. *Il4raF709* mice carrying a gain-of-function mutation in IL-4 receptor α-chain, which are susceptible to allergic sensitization and anaphylaxis,[8,21] exhibit an altered gut microbiota signature from that seen in control mice.[21] GF mice reconstituted with these microbiota exhibit allergic sensitization and anaphylaxis. Transfer of antigen-specific Treg cells to *Il4raF709* mice is capable of both restoring the normal microbiota and suppressing the allergic responses.[21] A recent study demonstrated a successful reconstitution of mice with human microbiota that resulted in an increase in Treg cell numbers and amelioration of allergic diarrhea.[39] Intriguingly, mice cohoused with or progeny of reconstituted mice with human microbiota also exhibited increased Treg cell numbers.[39] These findings suggest that susceptibility to or protection against food allergy might be a transmissible trait. These murine approaches are powerful tools for dissecting the interaction between the microbiota and disease pathogenesis, opening potential investigations into a myriad of human microbiota that are beneficial or harmful in the treatment and management of allergic conditions.

Effector mechanisms of food allergy

Once food sensitization is established, re-exposure to antigen can lead to local or systemic manifestations of food allergy. Systemic antigen sensitization with intraperitoneal adjuvant has been primarily performed to induce antigen sensitization and food hypersensitivity responses on antigen challenge and therefore provided important insights into the mechanisms of the effector phases of food allergy.[40] Early clinical evidence suggested that anaphylaxis was classically mediated by antigen cross-linking of antigen-specific IgE bound to FcεRI on mast cells. This induced the rapid release of mediators, such as histamine and leukotrienes, which act on responder cells to induce vasodilation, increased vascular permeability and hypotension, and bronchospasm, which commonly manifest as a shock.[41] Mouse models of anaphylaxis have well-defined alternative pathways of systemic anaphylaxis mediated by IgG, FcγRIII, neutrophils, macrophages, basophils, and ***platelet-activating factor*** (PAF),[40] some of which might also play a role in human systems. Subsequent findings showed human neutrophils activated through

IgG-mediated systemic anaphylactic shock in mice.[42] This was further defined by using mice engineered to express human FcγRs,[43] and taken together, the results shed new light on the role of neutrophils in human anaphylaxis. As in the mouse studies,[44] PAF levels were associated with the severity of anaphylaxis in human subjecrs,[45] whereas PAF acetylhydrolase levels were decreased in patients with fatal anaphylaxis,[45] suggesting that the failure of PAF inactivation might increase anaphylactic severity. Mouse studies have suggested that anaphylaxis caused by food allergen ingestion is IgE dependent, whereas anaphylaxis induced by systemically administered allergen is mediated by both the IgG and IgE pathways.[40] The IgE pathway is also more sensitive, requiring lower levels of antigen compared with IgG-mediated responses.[46] Possible markers that distinguish IgE- versus IgG-mediated anaphylaxis have been suggested in mouse models[47] but have not yet been extended to human studies.

As in human subjects, the susceptibility of mice to food-induced anaphylaxis seems to vary with antigen and strain influences. C3H/HeJ mice, but not BALB/c mice, sensitized orally with CT and antigen were susceptible to oral food-induced anaphylaxis.[48] C3H/HeJ mice lack a functional Toll-like receptor 4 that recognizes LPS,[49] but a requirement of Toll-like receptor 4 impairment for food-induced anaphylaxis was exclusive to mice on a C3H/HeJ background and peanut protein but not seen in mice on a BALB/c background or to cow's milk (CM) antigen.[16] Mouse studies have indicated that food antigens must be absorbed systemically to induce anaphylaxis[50] and that inhibiting antigen passage through the intestinal epithelium can prevent anaphylaxis.[51] Indeed, systemic antigen challenge induces anaphylaxis in typically resistant strains, such as C57Bl/6 mice.[52] Although the precise mechanisms underlying the variable genetic susceptibility to food allergy are not known, these results are consistent with the observations in human subjects that the predisposing genetic factors are important.[53]

Gastrointestinal symptoms, including diarrhea, are common symptoms of food-induced anaphylaxis in mice and have helped define key mechanisms of response. Repeated oral antigen challenge of mice intraperitoneally immunized with ovalbumin and alum induced dose-dependent acute diarrhea associated with increased intestinal permeability and mastocytosis.[54,55] This diarrhea was dependent on the IgE–mast cell pathway and on a combination of serotonin and PAF.[54] These results highlight the critical role for mast cells in allergic diarrhea, and intestinal mast cell numbers were associated with systemic anaphylaxis severity.[56] The role of T cells in allergic diarrhea was demonstrated by adoptive transfer of $CD4^+$ T cells purified from MLNs of sensitized mice, which transferred antigen-triggered diarrhea to the naive recipients.[57] Mast cells produce type 2 cytokines and T_H2 chemoattractants and might recruit T_H2 cells to the gut.[57] Conversely, type 2 cytokines (IL-4, IL-13, and IL-9) in the gut might promote mast cell expansion/recruitment in the gut.[8,22,58,59] The cross-talk between T_H2 cells and mast cells and its role in the development of food allergy might be an important aspect of intestinal pathogenesis and needs to be further investigated.

Antigen cross-reactivity

Several legumes, especially peanut, exhibit an extensive serologic cross-reactivity. Mouse models have helped define such cross-reactivity in controlled exposure environments that are impossible in human subjects because of the implicit problems in determining a cross-reactive sensitization versus multisensitization in patients. For example, lupin and fenugreek have been implicated as triggers of reactions in patients with peanut allergy.[60,61] Mice orally sensitized to lupin or fenugreek exhibited hypersensitivity reactions to challenge with peanut, soy, fenugreek, or lupin, providing direct experimental evidence of the physiologic relevance of this cross-reactivity among legumes. Similarly, mice sensitized with CM exhibited CM-specific IgE and IgG_1 antibodies that cross-reacted with soy proteins, which is analogous to the data obtained in human subjects.[62,63] These mice had anaphylaxis to oral challenge with soy protein.[64] Although it is not clear whether cross-reactive IgE and IgG_1 predict the elicitation of clinical symptoms to the cross-reactive allergens in human subjects, such studies will likely have important implications for further characterization of cross-allergenicity among food allergens.

INSIGHTS ON PREVENTION OF FOOD ALLERGY

Findings from clinical and epidemiologic research and results from animal models are mutually supportive in increasing their significance; epidemiological studies have identified possible causative factors associated with the onset of the disease, and animal models allow the inferences from these studies to be experimentally tested to directly assess causality. For example, clinical studies have suggested that cutaneous (environmental) exposure to antigen or maternal antigen transmission during pregnancy and breast-feeding might play a role in food sensitization. Similarly, the observations that patients treated with antiulcer medication had allergic responses to coingested foods led to the hypothesis that acid suppression is a risk factor for food allergy. Mouse models have enabled the testing of these hypotheses and provided insight into the molecular and cellular mechanisms.

Route of antigen exposure

The observations that oral exposure to foods is limited in infancy and that allergic reactions to foods are reported to occur on the first known ingestion suggest potential roles for other routes of allergen exposure. Epidemiologic data suggest that sensitization to peanut protein can occur in children through exposure to peanut in oils applied to inflamed skin,[65] whereas early oral exposure to food antigen induces tolerance.[66] Food allergen consumption at home correlates with the incidence of food allergy.[67] Furthermore, loss-of-function mutations in *FLG*, a gene that encodes the epithelial barrier protein filaggrin, conferred increased risk for AD and other allergies, including peanut allergy.[68,69] These observations led to the hypothesis that the altered barrier function in AD skin might facilitate cutaneous sensitization to food antigens, potentially leading to the development of food allergies. We have recently used a mouse model of allergic skin inflammation with many features of AD and AD-associated asthma[70] to demonstrate that epicutaneous sensitization with the food antigen results in IgE-dependent expansion of intestinal mast cells and IgE-mediated anaphylaxis on oral challenge.[23] Our findings support the hypothesis that cutaneous sensitization to food allergens plays an important role in the development of food allergy and show that IgE and intestinal mast cells are critical to this pathology. Further evidence is that

sensitization to ovalbumin occurred through the skin of flaky tail mice, which carry a mutation in the *Flg* gene, and resulted in production of antigen-specific IgE.[71,72] This provided conclusive evidence that filaggrin deficiency and consequent skin barrier dysfunction enhances antigen sensitization. Avoidance of cutaneous exposures might prevent the development of food anaphylaxis. Recovery of skin barrier function by increasing filaggrin expression in keratinocytes[73] might be potentially beneficial for patients with AD and AD-associated food allergy.

Maternal transmission

Maternal allergy is a risk factor for allergic disease in children; however, there is no direct evidence of maternal transmission of allergy susceptibility to children. It also remains controversial whether the antigen exposure during pregnancy predisposes the child to allergic disease. Peanut consumption during pregnancy associating with the development of peanut sensitization in infants has been supported[74] and refuted.[65] Mouse studies have convincingly shown that antigen exposure during pregnancy protected the offspring against allergic sensitization.[75-77] Mechanistically, this tolerance induction was due to TGF-β and antigen[77] or antigen-IgG immune complexes[76,78] transferred through breast milk. Additionally, exposure of pregnant mice to certain bacteria prevents the development of an allergic phenotype in the offspring,[79] implying protective effects by early-life microbial exposure. There is currently no supportive human study for the protective effect of maternal antigen ingestion, and further studies are needed to examine whether a similar approach would be amenable in human subjects.

Acid suppression

Alterations in gastric digestive capacity can affect the allergenicity of ingested food proteins.[80] The increased risk of food sensitization was first described as associating with the use of acid-suppressing medication in patients treated for peptic ulcers and their development of food allergen sensitization.[81] Antiulcer medication during pregnancy has been associated with a higher risk of asthma in childhood.[82] Similar to these findings in human subjects, antacid treatment promoted oral sensitization and hypersensitivity to hazelnut allergens in mice,[83] and concomitant feedings of pregnant mice with an antiulcer drug and codfish induced codfish-specific IgE in mothers and a T_H2 milieu in their offspring.[84] These examples highlight the utility of mouse models to define the associative or causal influences of epidemiologic factors identified in food allergy studies in human subjects.

TREATMENT

The requirements for strict allergen avoidance and the use of injectable epinephrine in emergency situations have been shown to contribute to the significant adverse effect food allergy can have on a patient's quality of life.[85] Consequently, providing improved therapeutic options has become an important avenue for food allergy research. Because the US Food and Drug Administration typically requires animal testing before issuing an Investigational New Drug label, preclinical animal models of food allergy will likely be a necessary step toward achieving this goal. Indeed, studies in animal models have already supported advancements of therapy in 3 key areas: (1) validation of existing therapeutic strategies, (2) utility of existing therapies for food allergy, and (3) development of novel therapies. Although there has been significant interest in the third point, it seems likely that the animal studies aimed at validation and utility of existing therapeutics can lead to relatively immediate and potentially significant improvements in therapy options for patients with food allergy.

Validation of existing therapeutic approaches

In the recent "Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel," the recommendations for treatment of food-induced anaphylaxis in a hospital setting included the use of H2 antihistamines (ranitidine, 1-2 mg/kg per dose) in addition to H1 antihistamines and other standard allergy treatment strategies.[86] Indeed, combination H1 and H2 antihistamines have shown efficacy for acute allergic reactions in a randomized, double-blind, placebo-controlled trial.[87] Despite this, the rationale for H2 antihistamine use seemed unclear because these readily available drugs are mainly used for their acid-suppressing abilities and the role of the H2 receptor in systemic anaphylactic reactions had not been shown. Taking advantage of genetically deficient mice and the ability to completely eliminate the contributions of each specific receptor, we recently demonstrated that IgE-dependent anaphylactic responses in the mouse were only partially ablated in the absence of either H1 or H2 receptors.[88] In contrast, deficiency in both H1 and H2 receptors provided substantial protection. This was also evident if intravenous histamine, which is sufficient to elicit a response, was used. Our study provides conclusive evidence to support the rationale of using H2 antihistamines in food allergy therapy.

Similarly, there have been substantial efforts to determine the efficacy and safety of oral immunotherapy (OIT) for several food allergens, including milk, egg, and peanut.[89] These have been approached mainly through relatively small-scale clinical trials, perhaps because of the risks associated with adverse reactions to food administration. Despite concluding that there is a measurable benefit to OIT therapy, a recent Cochrane meta-analysis of many of the peanut studies raised concerns over the lack of consistency in design and readouts that limited the proper determination of the efficacy and safety of this treatment.[90] The mechanistic understanding of the clinical benefits of OIT therapy also remains elusive, with desensitization versus tolerance still under investigation. By using a murine model of food allergy, Leonard et al[91] were able to clearly demonstrate significant reduction in food allergy–associated symptoms through a modified OIT strategy. Furthermore, they defined a unique protective mechanism that localized to the intestinal mucosal compartment rather than having a systemic influence over the $Foxp3^+$ Treg cell compartment, which has been the focus of many clinical studies. The use of mice allowed these investigators to examine the mechanisms of protection in a way that would be extremely difficult in human trials. In this way the use of murine models can provide focus and understanding that might help in the design of future clinical trials, particularly for decisions on measures of efficacy.

Application of existing therapies to food allergy

The global suppression of immune responses is a common therapeutic strategy applied to inflammatory diseases, such as allergic asthma, autoimmune diseases, or post-transplantation.

For allergic asthma, glucocorticoids have become a mainstay, and yet they are generally considered ineffective for food allergy. Work with a murine model of food allergy examined the potential effects of rapamycin in altering food-induced allergic responses.[92] Perhaps not surprisingly, given its potent abilities to suppress T-cell responses, rapamycin was able to diminish the generation of food allergy–associated pathology when administered during the sensitization window. In addition, treatment of fully sensitized mice was also sufficient to reduce the severity of diarrhea, symptoms, and core body temperature decreases seen on antigen challenge. Interestingly, the immediate responses to passive immunization with antigen-specific IgE or in cultured mast cells were unaffected, but instead, the IL-9–mediated survival of mast cells was diminished. Increasing evidence from animal models has supported the critical role for mast cells and the IL-9 pathway in the severity of food-induced allergic responses,[55,59] including the beneficial effects of mast cell stabilization in IL-9 transgenic mice with systemic cromolyn sodium treatment.[59] Interestingly, several case reports have shown therapeutic benefit from oral cromolyn sodium treatment for food-dependent exercise-induced anaphylaxis[93,94] and, taken together, the results suggest that existing therapies that limit mast cell numbers or enhance mast cell stability might be clinically effective for food allergy.

Similarly, recent work has demonstrated the potential efficacy of the tyrosine kinase inhibitor compound sunitinib malate (Sutent; Pfizer, New York, NY)[95] in food allergy models. Sunitinib malate inhibits several receptor systems, including that of the stem cell factor receptor, which is highly expressed on mast cells, and has been successfully used in the treatment of renal carcinoma and imatinib-resistant gastrointestinal tumors.[96] Although high doses were used, the findings demonstrated a clear diminishment of oral antigen–triggered anaphylactic responses in mice previously sensitized to ovalbumin. Importantly, inhibition of passively immunized mice, as well as primed *in vitro* mast cells, was shown, suggesting that the efficacy of this approach lies with inhibition of the immediate mast cell response to antigen.

These examples highlight how animal models of food allergy can serve as a screening tool to examine the potential biological efficacy of therapeutic compounds that are already approved for other uses. The obvious benefit to this approach lies with the existing safety information available from previous clinical trials that might generate therapeutic options faster than new developments.

Screening for efficacy of new therapies

During the last decade, there have been many examples of potential therapies for food allergy that have been demonstrated by using murine models. One of the most discussed is the use of Chinese herbal formulations, which has been the subject of previous reviews.[97] In particular, work on Food Allergy Herbal Formula-2 (FAHF-2) has demonstrated the potential for murine models as a tool to aid in the development of novel therapies. FAHF-2, a concoction of 9 herbal extractions, has been clearly demonstrated to limit the severity and progression of food-induced allergic responses to peanut in these models, and its effects were sustained over several months.[98] Importantly, although relatively large doses of the extracted formulation are necessary, there was no reported evidence of toxicity from this treatment strategy. In an initial phase 1 trial of 18 patients, FAHF-2 has been reported to be safe and to have reduced expression of CD63, an activation marker, on *ex vivo*–stimulated basophils from these patients.[99] Further studies have begun to be aimed at elucidating the mechanisms through which these effects might be mediated.

Schneider et al[100] recently demonstrated that the neutralizing anti-IgE antibody omalizumab can facilitate rapid oral desensitization in high-risk patients with peanut allergy, further supporting the potential of anti-IgE as a treatment of food allergy. The efficacy of antibodies specific for a segment of human membrane IgE on depleting IgE-producing B cells has been proved in humanized mice expressing the human M1′ domain,[101] strengthening the value of the animal model in development of a new treatment of food allergy.

We also reported a potential new therapy in antigen-coupled cell tolerance.[102] Drawing from numerous studies in autoimmunity and transplantation, chemical coupling of antigens to the surfaces of autologous cells has been shown to promote specific and sustained tolerance,[103] but it is unknown whether this would be effective in type 2 immunity, such as allergy. Additionally, this method requires intravenous antigen delivery, and particularly for food allergy, it is difficult to accept that this would not cause adverse reactions. Using murine models of allergy, we demonstrated that this approach was potently capable of reducing peanut-specific immune responses and could be delivered to peanut-sensitized animals without eliciting any reactions. The first phase 1 clinical trial of this type of tolerance induction has recently been reported for treatment of multiple sclerosis and established its tolerability and safety, as well as showing decreased myelin peptide-specific immune responses in several patients.[104]

SUMMARY

In summary, animal models of food allergy are invaluable tools for dissecting etiology, mechanisms, and preventive strategies, as well as assisting in the identification, validation, and development of therapies before they progress to patients. Although the application of animal models to human disease requires careful and thorough consideration and interpretation, their utility in facilitating truly translational discoveries has been demonstrated repeatedly and on many levels. Particularly in the setting food allergy, in which risks of adverse reactions to therapy are a major issue for patients, animal models will be indispensible to effectively and ethically develop new treatments. Mechanistically, recent discoveries on the role of the microbiota in the etiology of food allergy that have been derived from studies of animal models provide an excellent example of how lessons learned from experimental animals can provide new breakthroughs and educate future studies of host factors in human subjects with food allergy.

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