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REVIEW

Experimental Models for Studying Food Allergy

Cynthia Kanagaratham, Benjamin F. Sallis, and Edda Fiebiger

Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Boston Children's Hospital; and Department of Medicine, Harvard Medical School, Boston, Massachusetts

SUMMARY

Animal models have been invaluable tools for understanding the immunologic mechanisms of IgE-mediated food allergy and for testing novel treatment options. This review summarizes commonly used murine models and discusses their advantages and shortcomings with regard to how they phenocopy the human disease.

Immunoglobulin E–mediated food allergy is rapidly developing into a global health problem. Publicly available therapeutic intervention strategies are currently restricted to allergen avoidance and emergency treatments. To gain a better understanding of the disease pathophysiology so that new therapies can be developed, major research efforts have been put into studying food allergy in mice. Animal models should reflect the human pathology as closely as possible to allow for a rapid translation of basic science observations to the bedside. In this regard, experimental models of food allergy provide significant challenges for research because of discrepancies between the presentation of disease in humans and mice. The goal of this review is to give a summary of commonly used murine disease models and to discuss how they relate to the human condition. We will focus on epicutaneous sensitization models, on mouse strains that sensitize spontaneously to food as seen in humans, and on models in humanized animals. In summary, expanding the research toolbox of experimental food allergy provides an important step toward closing gaps in our understanding of the derailing immune mechanism that underlies the human disease. The availability of additional experimental models will provide exciting opportunities to discover new intervention points for the treatment of food allergies. *(Cell Mol Gastroenterol Hepatol 2018;x:x) (Cell Mol Gastroenterol Hepatol 2018;■:■–■; https://doi.org/10.1016/j.jcmgh.2018.05.010)*

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The prevalence of immunoglobulin (Ig) E–mediated food allergies has increased dramatically during the last decade, with a reported prevalence of 6%–8% of children in Western countries.[1,2] Because of the rapid rise in the number of patients with food allergies, it has become imperative that novel treatments are developed for patients with this condition. The disease is currently managed by allergen avoidance and treatment of accidental exposures with epinephrine. However, this management plan has its shortcomings, because approximately 40% of individuals with food allergies face accidental exposures each year, placing food anaphylaxis among the leading causes for emergency department visits in the United States.[3,4]

Leading emerging therapies for food allergies include oral (OIT) and epicutaneous (EPIT) allergen specific immunotherapy. Both methods aim to achieve tolerance by exposing patients to allergens at doses that stimulate an immune response without eliciting clinical symptoms of allergy. During OIT, patients are repeatedly exposed to increasing doses of allergens via the oral route. Although desensitization can be achieved, OIT patients are at risk of developing severe therapy-associated type I hypersensitivity reactions.[5–7] Furthermore, concerns have recently emerged with regard to the development of therapy-resistant eosinophilic esophagitis as a side effect of OIT in 2.7% of patients with IgE-mediated food allergies.[8] In EPIT, an allergen adsorbed epicutaneous delivery system placed on the skin is used to expose allergic individuals to the allergen. An example is Viaskin (DBV Technologies, Montrouge, France), a polyethylene membrane that has been demonstrated in mice to promote the diffusion of allergens from the surface of intact skin through to the stratum corneum and toward the epidermis.[9] The allergen is taken up by dermal dendritic cells and Langerhans cells, processed, and presented to T cells in the lymph nodes to elicit an immune response.[10] Repeated application of the allergen has been demonstrated to decrease reactivity to the allergen and to increase effector memory and naive regulatory T cells (Tregs) in the spleen.[11] Tregs induced from EPIT maintain their suppressive properties for a longer period after the end of the treatment than those generated from OIT. This may be because although both routes of immunotherapy promote effector memory Tregs, EPIT also

Abbreviations used in this paper: **EPIT, epicutaneous immunotherapy; FCER1A, high-affinity immunoglobulin epsilon receptor subunit alpha; FcεRI, high-affinity immunoglobulin E receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSC, hematopoietic stem cell; Ig, immunoglobulin; IL, interleukin; LCT, long chain triglycerides; MCPT, mouse mast cell protease; MCT, medium chain triglycerides; OIT, oral immunotherapy; PBMC, peripheral blood mononuclear cell; Th, T helper; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin; WASP, Wiskott–Aldrich syndrome protein.**

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promotes induction of naive Tregs that are more capable of proliferating and surviving than effector cells.[11] In patients with peanut allergies, 1 year of daily EPIT using 250 μg peanut protein applied by using Viaskin increased the dose needed to elicit an allergic response by at least 10-fold from their baseline tolerable dose.[12] Nonetheless, there are limitations to EPIT. For some patients a 10-fold increase in tolerable challenge dose is still a minor amount of allergen that can be tolerated, treatment responses were different between adults and children, and long-term benefits of EPIT remain to be investigated. Undoubtedly, additional research is needed to improve the current immunotherapy protocols as well as to develop novel intervention strategies. For this purpose, murine models will be invaluable tools because experimental interventions in humans are unethical.

In general, mouse models have been invaluable tools to gain a better understanding of the root cause of food allergies, mediators, and effectors of the immune reaction. The great degree in overlap of the genetics and the immune system between mice and humans has allowed researchers to gain a better understanding of the pathophysiology of food allergies.[13] The assortment of inbred strains with varying susceptibility to the disease and the generation of gene and cell type specific knockouts have helped uncover some of the key defects in the host that promote the development of food allergies.

Ideally, murine models of food allergy should be as homologous as possible to the human disease. In a recent review, Oyoshi et al[14] discuss isomorphic murine models of food allergies, which encompass most models of food allergy, in which the induction of disease is under the control of the investigator. Although the cause of the sensitization is not shared between human disease and isomorphic models, these models mimic clinical symptoms and can be used for developing treatments for food allergies. In this review, we will focus on 3 categories of recently investigated models: epicutaneous sensitization models, spontaneous sensitization models, and humanized mouse models.

Pathophysiology of Human Food Allergy as Reflected in Murine Models

There are many steps in the process of establishing oral tolerance that may be disturbed, resulting in the failure to develop oral tolerance or in the loss of oral tolerance. Epidemiologic and experimental studies have demonstrated that sensitization can occur through defects in the skin epithelium, resulting from disorders such as eczema and atopic dermatitis. This type of sensitization can be recapitulated in mice through dermal sensitization models discussed later in the review.[15–18] In addition to defects in the skin barrier, increase in baseline permeability of the gut due to decrease in tight junction integrity can promote the development of food allergies.[19] The acidic environment in the stomach helps in preventing sensitization by either degrading the allergen and/or by affecting the uptake of the allergen by immune cells.[20] Thus, alterations of stomach pH is a risk factor for food allergy induction as documented epidemiologically by a higher rate of sensitization among antacid users and elevated IgE titers and T-cell reactivity when allergens are administered in conjunction with antacids in mouse models.[21,22] The gut microbial community and its role in food allergy have been studied extensively.[23] Certain class of bacteria, such as Clostridia, have been associated with the promotion of oral tolerance and protection from allergen sensitization by increasing IgA production.[24]

In concert with defective mechanisms in the host, allergic patients fail to develop oral tolerance to their allergen because of interplay of intrinsic and extrinsic factors that allow antigens to maintain their structural integrity until processed and presented in the context of inflammatory signals. The allergen itself can have innate adjuvant properties that promote sensitization. For example, the major peanut allergen Ara h 1 can interact with CD209 on dendritic cells, promoting phagocytosis of the allergen and subsequently leading to antigen presentation to T cells.[25] The presence of disulfide bonds can help allergens maintain their structure by protecting them from proteolysis and thermal degradation.[26,27]

Clinical features of human food allergy, such as serum sensitization, mast cell expansion, and T helper 2 (Th2)-type tissue inflammation, are properly recapitulated, albeit to varying degrees, in mouse models of food allergy. The sensitization status of mice is commonly determined by measuring allergen-specific Igs, such as IgE and IgG1, in serum. When using alum as an adjuvant during sensitization, serum IgE has up to 80% specificity for the model antigen in mice; however, in patients only a small fraction (0.1%–15%) of total serum IgE is specific to a single food allergen.

Hallmark Th2 cytokines, interleukin (IL) 4 and IL13, promote the switch of Ig production by B cells to IgE, which, in combination with IL5 and IL13, induce mast cell expansion in the affected mucosal tissues. In murine models, the expression of these cytokines is typically measured at the mRNA level from small intestinal tissue samples or at the protein level from cell suspensions of the mesenteric lymph nodes or spleens. Expansion of the mucosal mast cell compartment of the small intestine is a measure of severity of food allergy in mice and in humans. In mice, mucosal mast cells are commonly quantified by chloroacetate esterase staining. Serum mast cell protease, MCPT1, is used as a systemic readout for mucosal mast cell activation on antigen-specific IgE cross-linking.[28–30] Unfortunately, no human equivalent for MCPT1 exists for monitoring IgE-mediated immune activation in patients with food allergies. Other in vivo markers of mast cell degranulation include histamine and serotonin, release of calcium stores, and induction of eicosanoid metabolism.[31]

Some pathophysiologic aspects of human food allergy are harder to recapitulate in murine models. For instance, in patients, anaphylaxis after exposure to an allergen causes rapid and acute hypotension coupled with skin, mucosal, gastrointestinal, respiratory, or cardiovascular symptoms.[32–34] Oral anaphylaxis is hard to achieve in most mouse models; therefore different challenge strategies are used, and systemic anaphylaxis is commonly monitored as