Asia Pac Allergy. 2019 Jan;9(1):e4
https://doi.org/10.5415/apallergy.2019.9.e4
pISSN 2233-8276·eISSN 2233-8268

Asia Pacific allergy

Current Review

Check for updates

Human *ex vivo* and *in vitro* disease models to study food allergy

Lisa Hung[1,2], Helena Obernolte[3], Katherina Sewald[3], and Thomas Eiwegger[1,2,4,*]

[1]Department of Immunology, University of Toronto, Toronto, ON, Canada
[2]Translational Medicine Program, Research Institute, The Hospital for Sick Children, Toronto, ON, Canada
[3]Department of Preclinical Pharmacology and In-Vitro Toxicology, Fraunhofer ITEM, Hannover, Germany
[4]Division of Clinical Immunology and Allergy, Food Allergy and Anaphylaxis Program, The Hospital for Sick Children, Toronto, ON, Canada

Received: Dec 5, 2018
Accepted: Jan 11, 2019

***Correspondence to**
Thomas Eiwegger
Division of Clinical Immunology and Allergy, The Hospital for Sick Children, Toronto, M5G 1X8, ON, Canada.
Tel: +1-416-813-7654 X1862
Fax: +1-416-813-8624
E-mail: thomas.eiwegger@sickkids.ca

ORCID iDs
Thomas Eiwegger
https://orcid.org/0000-0002-2914-7829

Conflict of Interest
T. Eiwegger is the site PI of a DBV sponsored global study; received research funds from the HSBC Bank Canada Catalyst Research Grant from The Hospital for Sick Children, and the Innovation Fund Denmark Grant no. 6159-00005A. The rest of the authors declare that they have no relevant conflicts of interest.

ABSTRACT

Food allergy is a growing global public health concern. As treatment strategies are currently limited to allergen avoidance and emergency interventions, there is an increasing demand for appropriate models of food allergy for the development of new therapeutics. Many models of food allergy rely heavily on the use of animals, and while useful, many are unable to accurately reflect the human system. In order to bridge the gap between *in vivo* animal models and clinical trials with human patients, human models of food allergy are of great importance. This review will summarize the commonly used human *ex vivo* and *in vitro* models of food allergy and highlight their advantages and limitations regarding how accurately they represent the human *in vivo* system. We will cover biopsy-based systems, precision cut organ slices, and coculture systems as well as organoids and organ-on-a-chip. The availability of appropriate experimental models will allow us to move forward in the field of food allergy research, to search for effective treatment options and to further explore the cause and progression of this disorder.

Keywords: Humans; Allergens; Anaphylaxis; Food hypersensitivity; Biological phenomena; Models

INTRODUCTION

The prevalence of food allergy has dramatically increased in the last two decades. While some studies suggest a peak prevalence of up to 10% in younger age groups in countries like Australia, estimates are often hampered by errors in self-diagnosis and reporting [1-3]. Despite the upsurge in both occurrence and awareness, much of the cause and progression of this disease remains unknown. There is no known cure for food allergy. Furthermore, there are no definitive prevention strategies in place. Currently, no standardized, approved treatments are available. Thus, management is limited to avoidance of the offending allergen and emergency interventions when required [4]. Symptoms range from mild urticarial reactions to life threatening anaphylaxis. Food induced reactions are reported to account for 20%–50% of hospital admitted anaphylaxis cases in Asia, Europe, North America, and Australia [3]. Notably, in the Republic of Korea alone, the incidence of anaphylaxis increased nearly 2 fold from 2008 to 2014 [5].

Author Contributions

Conceptualization: Lisa Hung, Thomas Eiwegger. Data curation: Lisa Hung, Helena Obernolte, Katherina Sewald, Thomas Eiwegger. Investigation: Lisa Hung, Helena Obernolte, Katherina Sewald, Thomas Eiwegger. Supervision: Thomas Eiwegger. Validation: Lisa Hung, Helena Obernolte, Katherina Sewald, Thomas Eiwegger. Writing - original draft: Lisa Hung, Thomas Eiwegger. Writing - review & editing: Lisa Hung, Helena Obernolte, Katherina Sewald, Thomas Eiwegger.

Food allergies generally manifest in early life, and while certain allergies such as milk, egg and soy tend to be lost with age, many allergies including peanut and tree nuts are rarely lost and often persist into adulthood [6]. Thus, patients must cope with the fear of experiencing a potentially fatal reaction throughout their lifetime. The complex nature of this affliction continues to challenge scientists, as both the cause and progression of food allergies is multifactorial. While genetic predisposition continues to be a considerable risk factor in the development of allergies, the rapid increase in prevalence suggests an additional component of environmental risk [7, 8]. Indeed, many recent studies have proposed roles for hygiene, diet, microbiome diversity, obesity and many other environmental and lifestyle factors in the development of food allergies [9]. Unique properties of food proteins and certain methods of food processing (e.g., dry-roasting of peanuts) may also contribute to their allergenicity [9, 10]. As such, there is a great need for appropriate experimental models that have the complexity to represent the human situation and help to translate animal data into novel therapies for food allergy. This review will discuss human *in vitro* and *ex vivo* disease models used to study aspects of IgE-mediated food allergy, as well as a few models with potential to be used for this application. While non-IgE mediated food allergies also exist, this review will be focusing exclusively on the severe, acute nature of IgE mediated food allergies.

FOOD ALLERGY DEVELOPMENT

Food allergies can broadly be defined as an adverse immune reaction that occurs reproducibly upon exposure to a given food [11]. Reponses involve both the innate and adaptive arms of the immune system and implicate multiple organ systems. The current understanding of the development of IgE-mediated food allergies involves 2 stages: sensitization and re-exposure [12]. During the symptom-free sensitization phase, the immune system of an individual first encounters the allergen which primes allergen specific Th2 type T cells. These cells then facilitate B-cell activation and are instrumental in promoting IgE isotype switching. This results in the development and release of allergen specific IgE antibodies. These antibodies go on to bind to the high-affinity IgE receptor FcεRI on tissue-resident mast cells and circulating basophils, otherwise known as the main effector cells of the allergic response. Although the low affinity receptor FcεRII present on eosinophils, B cells, T cells, monocytes, macrophages, platelets, and Langerhans cells also bind IgE antibodies, the exact role of this receptor in the allergic cascade is not entirely clear [13].

Upon re-exposure to the allergen, the specific IgE antibodies bound to FcεRI recognize and bind to the allergen, crosslink, and induce degranulation of the effector cells, releasing preformed inflammatory mediators, initiating an allergic response. This may result in systemic anaphylaxis, which can be fatal if not treated with epinephrine shortly after exposure (**Fig. 1**).

LIMITATIONS OF ANIMAL MODELS

Many food allergy studies have been performed in animal models [14]. Animals retain the physiological complexity required to mount an allergic response including an immune system, native microbiota and the integration of multiple organ systems. These models have been instrumental in our current understanding of food allergies and essential for the development and assessment of potential treatment options. However, *in vivo* experiments tend to be time-consuming, costly, and often limited by ethical constraints. Additionally,

Asia Pacific allergy

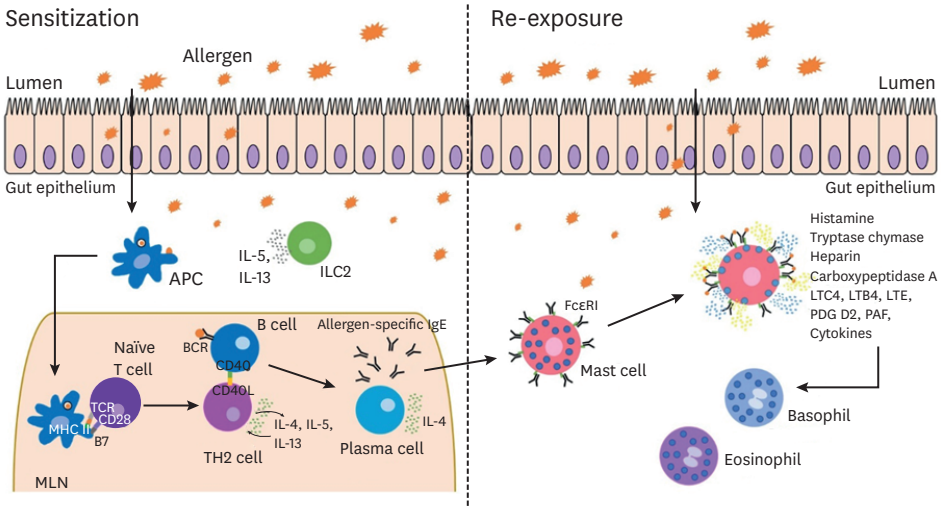

Fig. 1. Schematic of allergic sensitization and re-exposure. Sensitization: Food allergens can cross the luminal barrier by transcellular or paracellular transport, or through direct luminal antigen sampling by dendritic cells (DCs). These allergens are picked up and processed by DCs which can then migrate to mesenteric lymph nodes (MLN) and present the allergen to naïve CD4+ T cells in the context of MHC II. These T cells can then differentiate into Th2 cells that secrete pro-allergic cytokines that influence B cells to become IgE secreting plasma cells. These allergen-specific IgE antibodies can then bind to the FcεRI (high affinity IgE receptor) expressed on the main effector cells of the allergic response, including mast cells and basophils. Re-sensitization: Upon re-exposure to the allergen, the allergen-specific IgE on the surface of the effector cells can bind, crosslink and activate the cell leading to degranulation of pro-inflammatory mediators. The release of these factors can cause multiple downstream effects and result in the recruitment of other inflammatory cell subsets. APC, antigen-presenting cell; IL, interleukin; MHC, major histocompatibility complex; LTC4, leukotriene C4; LTB4, leukotriene B4; LTE, leukotriene E; PDG D2, prostaglandin D2; PAF, platelet-activating factor.

animal studies may fail to accurately represent human disease states. This may be due to subtle but relevant differences in the mammalian immune systems [15]. For example, unlike humans, rodents do not express the high affinity IgE receptor on dendritic cells (DCs) or monocytes under homeostatic conditions [16]. These cells are considered critical for the development and progression of food allergy in humans [17]. In particular, FcεRI$^+$ DCs have been proposed to have a key role in allergen presentation and priming naïve T cells to specific epitopes of IgE-reactive antigens which functions to amplify allergic responses as a whole [18]. In addition, certain treatments developed for atopic diseases that were highly efficacious when tested in animal models, do not always show the same results in human clinical trials, highlighting the substantial differences in the mammalian immune systems [15, 19-21].

In order to narrow this gap, humanized mouse models have been successfully created and tested. This approach allows the animal model to better reflect the human adaptive immune system. NSG-SGM3 mice engrafted with human hematopoietic stem cells (HSC), liver and thymus developed high numbers of human tissue-resident mast cells. These mice exhibited a passive cutaneous anaphylaxis (PCA) response measured by ear swelling as well as a passive systemic anaphylaxis response measured by a decrease in body temperature and increase in observable symptoms upon sensitization with a chimeric IgE-anti-NP antibody and challenge with NP conjugated bovine serum albumin [22]. Humanized mouse models of food-induced systemic anaphylaxis have also been generated. NSG mice engrafted with peripheral blood mononuclear cells from peanut allergic donors have been sensitized to peanuts via intraperitoneal injection of peanut extract. These mice expressed peanut-specific IgE and symptoms of an allergic reaction upon challenge with peanuts. Administration

https://doi.org/10.5415/apallergy.2019.9.e4

of omalizumab blocked peanut-induced anaphylaxis [23]. Similarly, NSG mice carrying a human *sfc* (stem cell factor) transgene engrafted with human HSCs and sensitized to peanuts via gavage feeding displayed peanut-induced systemic anaphylaxis. In this model, treatment with omalizumab also prevented anaphylaxis [24]. These models provide a useful tool to study food-induced anaphylaxis and test potential therapies for food allergy. However, the physiological and anatomical differences between species continue to make comparison and translation of data into human studies difficult. Furthermore, a recurring theme in the use of animal models in food allergy studies is the required induction of disease either through genetic or physical manipulation. The incidence of naturally developed food allergies in animals is uncommon, so it may be the case that these induced allergic responses do not accurately reflect the human situation.

Despite these limitations, animal models are an essential part of food allergy research and will continue to be used in the future. However, these restrictions in conjunction with ethical incentives encourage the reduction, refinement and replacement of animal studies with novel approaches.

Human *in vitro* and *ex vivo* models may be the most appropriate option for food allergy studies that precede the transition from rodent to human *in vivo* interventions. In addition to the highly relevant and directly translatable data produced, these models significantly reduce patient risk. Not only can these models be used to test hypotheses directly in a human system, but also to find new drug targets, test potential therapeutics before clinical trials to prevent adverse outcomes, and for use as potential diagnostic tools. They may also be used to prioritize drug testing in a more accurate and efficient manner.

Although single cell cultures are technically classified as human *in vitro* models, they will not be described in this review. While they are useful for studying certain aspects of food allergy, they do not necessarily reflect the complex interplay between the different cell types in the body.

TYPES OF *IN VITRO* AND *EX VIVO* ALLERGY MODELS

Biopsy based models

Biopsies are a straight forward and common approach to gather biological specimens for clinical assessment and diagnosis. These procedures are usually minimally invasive, and the procured samples contain all the different cell types involved in the disease model. Biopsy samples can then be cultured in specialized media and remain viable for short term experiments. Depending on the extraction procedure, tissue explants maintain the 3-dimensional structure of the organ and provide tissue-specific signals which are invaluable aspects of these models. This approach is also applied frequently to obtain site specific effector cell populations for means of phenotypic and functional characterization and expansion (**Fig. 2E**).

Bronchial biopsies taken from asthmatic patients are sources of fully differentiated lung tissue that contain the cellular repertoire required to study allergen specific responses [19]. When these samples are exposed to allergen in culture, they can reflect the allergic response of asthmatic lung tissue, predominantly by cytokine production including interleukin (IL)-5, IL-4, IL-13, IL-16, and RANTES (Regulated upon Activation, Normal T cell Expressed, and Secreted) as well as increased chemotactic activity of Th2 cells [25-29]. The importance of site-specificity has been demonstrated when comparing allergen-specific stimulation

Asia Pacific allergy

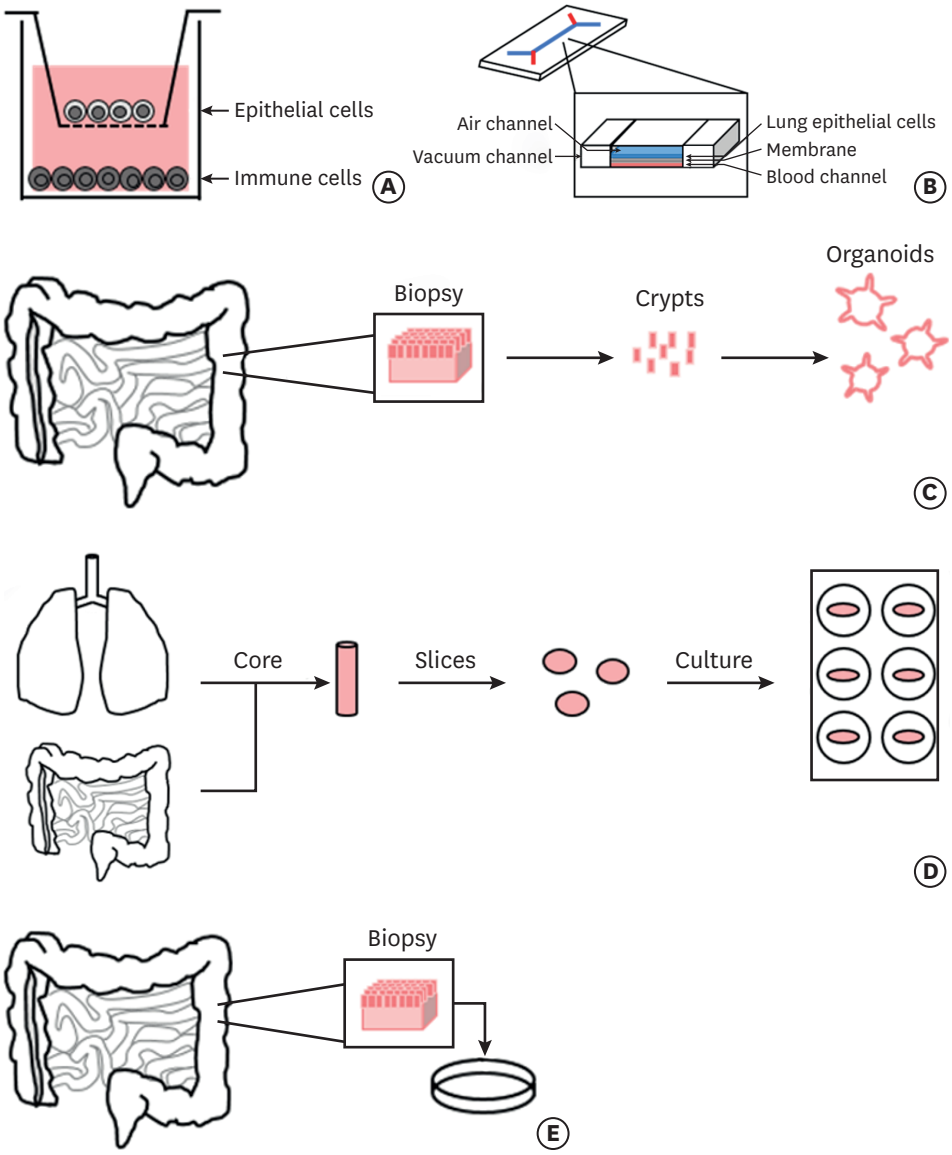

Fig. 2. Human *in vitro* and *ex vivo* models for food allergy research. Different types of human tissue and cell-based models potentially used to study food allergy in order of proximity to the human system. **(A)** *In vitro* coculture systems utilize Transwell inserts on which epithelial cells are cultured and allowed to polarize. Immune cells can be preloaded into the wells to examine cellular interactions. **(B)** Lung-on-a chip models consist of a membrane on which human lung epithelial cells line the top and are separated from human blood cells that line the bottom. Air flows over the epithelial cells and fluid that mimics blood flows along the bottom creating an environment reflective of the human lung. Vacuum channels on either side allow the cells to be stretched gently mimicking the mechanical movements of breathing. **(C)** Organoids can be generated using gut samples from human donors, the crypts are then isolated and used to form mini-gut cultures [57]. **(D)** Precision cut organ slices require the formation of tissue cores from agarose filled organs that are then cut into thin slices of fixed thickness. These slices are then incubated and used for experimentation. **(E)** Biopsy based models utilize tissue directly extracted from the organ of interest which is subsequently cultured and used for experimentation.

of bronchial biopsies to PBMC cultures, as it revealed differences in activation and co-stimulation requirements [27, 30]. Allergen stimulation of bronchial explants from asthmatic patients significantly increased production and release of IL-5 but did not affect granulocyte-monocyte colony-stimulating factor or IL-13 release, in contrast to the previously cited study. Additionally, treatment with a CD28 signalling blocker had no effect on IL-5 production.

https://doi.org/10.5415/apallergy.2019.9.e4

However, PBMCs from the same patients exhibited increased IL-5 and IL-13 production upon allergen stimulation, and was effectively inhibited by the CD28 signalling blocker [27]. Similarly, asthmatic bronchial biopsies treated with anti-CD80 and anti-CD86 mAbs blocked allergen-induced cytokine release, whereas cytokine production from asthmatic PBMCs was unaffected by anti-CD80 mAbs [30]. Both studies cite the presence or absence of costimulatory molecules as explanations for the differences seen in cytokine production. Thus, they demonstrate the importance of the tissue microenvironment in the development of the disease as a whole.

Gut biopsy samples have also been used for short-term culture to study food allergy. Duodenal biopsy samples from food allergic patients exposed to isolated protein fractions from wheat and apple resulted in an upregulation of histamine and tryptase release signifying mast cell degranulation [31]. Moreover, a decreased expression of tight junction proteins suggesting altered intestinal barrier function after allergen exposure was observed as compared to healthy controls [31]. These findings are in line with previous *in vivo* human studies. Exposing allergens directly to the gastric mucosa of food allergic patients resulted in swelling, hyperemia, and a decrease of tissue histamine and mast cells, presumably due to degranulation [32-34]. However, there is no study available that directly compares the 2 approaches, likely due to current ethical constraints.

Using biopsy samples as *ex vivo* models also has several limitations, the foremost being scarcity of tissue availability. While this sampling procedure is relatively easy to perform, the logistics surrounding tissue collection, including sedation or even anaesthesia is often difficult to justify purely for research associated purposes. Additionally, the size and number of samples is very limited. The viability of the samples themselves can only be maintained for a short period of time, depending on the organ from which the sample is taken, as well as the cultivation method [31]. Therefore, long-term experiments are not possible with the currently available technology. Biopsy sampling generally affects both the luminal and basal sides of the tissue and therefore site-specific investigations cannot be performed. An additional limitation is the relative isolation of the system itself. Since the tissue is extracted from the body, it cannot be used to observe the migration of cells in or out of the organ of interest.

Precision cut organ slices

Similar to the biopsy models, precision cut organ slices (PCOS) utilize pieces of cultivated human tissue from various sources. This can be an inventive use of otherwise discarded tissue. PCOS are created using a specialized tissue slicer to generate 50- to 400-μm-thick slices. The thickness is important as it affects the nutrient and gas exchange which is key for viability [35]. Depending on the organ from which the samples are derived, PCOS can maintain their viability for several days up to weeks [36]. PCOS contains all relevant cells of interest (structural cells such as heterogeneous epithelial cells, smooth muscle cells, fibroblasts and immune cells including macrophages and mast cells embedded in organ-specific extracellular matrix) and maintains the 3-dimensional structure of the organ. As in the biopsy models, it is also possible to obtain tissue directly from allergic individuals. However, due to the complexity of tissue sampling, many groups have used a passive sensitization approach with serum from allergic individuals before allergen provocation is performed. This allows for the comparison of sera from multiple, well characterized donors against the same background. Thus, disease specific serological differences can be assessed (**Fig. 2D**).

https://doi.org/10.5415/apallergy.2019.9.e4

Precision cut lung slices (PCLS) have been used to study many different disease models including asthma, chronic obstructive pulmonary disease, respiratory infections and fibrosis [37]. PCLS passively sensitized with sera from allergic individuals can be stimulated with relevant allergens which causes immediate macroscopic changes in the airway tissue [38]. Bronchoconstriction is a key feature of asthma that can be observed using PCLS with conventional low magnification microscopy and can be blocked by targeting certain receptors (leukotriene/thromboxane) or the addition of other clinically used allergy medications [38, 39]. The viability of PCLS during long-term cultivation has been extensively assessed; structural integrity and inducible bronchoconstriction was shown to last up to 15 days in culture [37]. In addition to gene expression analysis and proteomics, PCLS have also been used to study lung inflammation and cell surface marker expression in models of allergic asthma [40]. Due to the robust characteristics of PCLS, they are currently being used by pharmaceutical and chemical companies for safety and efficacy testing. This will allow for the assessment of new anti-inflammatory and anti-obstructive drugs and acts as a valuable model for research [37, 41].

Notably, a similar procedure can be done using gut tissue. Precision cut intestinal slices (PCIS) have been utilized for drug metabolism and toxicity studies, in addition to disease models such as intestinal fibrosis [42-44]. Although this system has not yet been reported in the context of food allergy, it could certainly be a promising model. PCIS have been described to maintain viability for up to 24 hours when cultured, and retain the multicellularity and three dimensional structure of gut tissue which is ideal for an acute allergy model [37, 45, 46].

Once again, the availability of these tissues represents a considerable barrier for these systems [39]. These models also require substantial time and effort to determine the optimal thickness of slices and culturing conditions, which tends to vary between organs. Since these tissues are extracted from the body, they are considered to be isolated systems, and will not be able to represent the importance of circulation and migration of cells and factors from blood and other tissues or into lymph organs [37]. Additionally, in standard immersion cultures, both sides of the tissue are exposed to the media and added stimulants which limits barrier and resorption related factors that contribute to allergen specific tissue responses.

Coculture systems

As noted, the ideal allergy model for acute allergen response includes all components of the human system which is why human tissue is essentially the best source for these samples. However, the complexity of human tissue models can be overwhelming and difficult to standardize. Therefore, a frequently used alternative to human tissue is to utilize human tumour cell lines. These are not limited by availability and can be tested and observed under very specific conditions. Monocultures of either epithelial cells or immune cells allow for the investigation of individual mechanistic aspects of IgE or non-IgE mediated responses. However, the interplay between cell types is crucial to the allergic response. Thus, coculture models that incorporate both epithelial cells and immune cells integrate barrier related components with immune cell function and provide a more comprehensive approach. Coculture systems can be very effective, especially in the context of permeability, barrier function, and immune cell migration studies after allergen stimulation (**Fig. 2A**).

Bronchial epithelial cells from patients with allergic asthma were tested for their ability to recruit DCs after exposure to Der p 1 (house dust mite allergen). They were shown to

secrete chemokines CCL2, CCL5, and CXCL10 following allergen challenge that enhanced the recruitment of mature monocyte-derived DC precursors into the epithelial layer in a chemotaxis assay [47].

Caco-2 cells (human intestinal epithelial cells) and RBL-2H3 cells (rat basophilic leukemia cells) were used to test the antiallergic effects of two lactic acid bacterial strains [48]. The bacteria caused an inhibition of mast cell degranulation in the coculture system but failed to show this response during direct interaction with the RBL-2H3 cells. This result suggested the bacterial antiallergic effects work indirectly through interactions with intestinal epithelial cells, which was confirmed via a PCA *in vivo* mouse model [48].

Similarly, T84 cells (human intestinal epithelial cells) were cocultured with PBMCs from atopic patients or healthy controls in order to test the effects of Toll-like receptor (TLR) ligands on preventing allergic responses. PBMCs from food allergic patients caused significantly reduced barrier integrity in the epithelial cell layer compared to the control cells during the coculture process. However, exposure of the epithelial cells to a TLR9 ligand prevented this PBMC-induced barrier disruption by increasing the ratio of anti-inflammatory cytokines and reducing pro-inflammatory cytokine production [49].

Of course, these systems are limited by the fact that not every cell is represented. Moreover, it lacks the structure and movement of live tissue. However, permeability and barrier function experiments are notoriously difficult to do *in vivo*, especially in humans, thus the coculture systems are a valuable resource for this kind of experiment.

FUTURE DIRECTIONS

There are many other potentially relevant models that have not yet been used in the context of food allergy studies but are worth mentioning in this review.

Lung organoids are 3-dimensional structures that can be created from human progenitor cells derived from different areas of the airway. They have been used to assess the effect of various cytokines on the development of different cell types (ciliated/secretory cells). However, current technology lacks the ability to mimic the complexity of the human lung. Culture conditions for lung organoids are still under review, but this model holds a lot of future potential [50].

Similarly, adult gastrointestinal stem cells can be used to grow mini gut epithelial organoids [51]. As organoids retain the morphological characteristics of the tissue from which they are derived, they represent a promising 3-dimensional model for allergy development in gut tissue. It has been shown that gut organoids can include all relevant intestinal cells from all 3 germ layers [52]. Intestinal function in terms of peptide absorption and bowel movement in response to histamine has also been shown [52]. They have previously been used to study host-microbial interactions, which would be a very interesting in the context of allergy development as many bacterial species have been proposed to play a role [53] (**Fig. 2B**). However, they do not mimic the mechanically active microenvironment of a living intestine (peristalsis and fluid flow), which is where organ-on-a-chip technology may be a more suitable alternative.

Lung-on-a-chip are three dimensional models of human lungs created on microchips that have the capacity to contain both immune cells and epithelial cells. Air and flowing liquid can also be introduced to mimic blood flow [54]. A model of asthmatic bronchoconstriction and bronchodilation has been created by using bronchial smooth muscle tissue engineered on elastomeric thin films. The muscle layer contracts in response to a cholinergic agonist, and exposure to IL-13 causes hypercontractility that mimics asthmatic inflammation. The hypercontraction was also shown to be reversed by using a beta agonist that is clinically used to treat asthmatic patients. This model already shows remarkable potential and could be extremely relevant for treatment development in the near future [55] (**Fig. 2C**).

Gut-on-a-chip technology can also mimic peristaltic motions and flowing liquid that recapitulates the physiology of a living intestine. Additionally, all the different intestinal epithelial cell types can be represented and induced to grow 3-dimensional villi while connected by tight junctions [56]. They have already been used to study host-microbe interactions, for an extended period of time so they could also potentially be used to look at the importance of the microbiome in the development and progression of food allergy [57].

Organ-on-a chip technology represents a promising new avenue of *in vitro* research. However, the complexity of the human system is extremely difficult to reproduce in a miniaturized system. Due to this, there is still much progress to be made, as optimization and validation strategies of these systems remain undefined.

CONCLUSION

Food allergy costs the United States healthcare system approximately $24.8 billion each year due to the morbidities associated with this disorder [57]. No standardized, approved treatments are available. It is imperative to focus resources towards finding good treatment options for these individuals. In order to do this, appropriate human models are necessary. The ideal preclinical model needs to be representative of the human system and maintains the multicellularity and structural integrity of the organ. All currently available models have their own specific benefits and limitations (**Table 1**).

Table 1. Comparison of the different human *in vitro* and *ex vivo* models of food allergy

	Biopsy based models	Precision cut organ slices	Coculture systems	Organoids	Organ-on-a-chip
Advantages	· Minimally invasive · Can be derived from food allergic subject · Contain all relevant cells and maintains tissue specific signals	· Generated from otherwise discarded tissue · Economical (many slices from one sample) · Contains all relevant cells and maintains tissue specific signals	· Widely available · Easily manipulated · Includes epithelial cells and effector cells · Works well for permeability, barrier function and cell migration studies	· Comprised of organ specific cell types · Simulates 3-dimensional (3D) structure similar to organ · Simplified organ system	· Simulates 3D structure · Can include epithelial cells and immune cells · Air and flowing liquid can be represented · Mimics muscle contraction
Disadvantages	· Lack of donors · High organizational demand · Limited viability · All sides of sample exposed to culture media and stimulant · Isolated system	· Lack of donors · Limited viability · Complex to determine appropriate conditions · All sides of sample exposed to culture media and stimulant · Isolated system	· Not all relevant cells represented · Lacks structure, movement, and costimulatory signals from tissue · Potentially too simplistic	· Variability of starter cells · Lack of validation markers · Does not mimic organ activity or fluid flow	· Difficult to generate · Cannot yet reflect complexity of human tissues · Difficult to validate · Limited multicellularity
Food allergy model	Yes	Yes (lung)	Yes	No	No

https://doi.org/10.5415/apallergy.2019.9.e4

REFERENCES

1. Savage J, Johns CB. Food allergy: epidemiology and natural history. Immunol Allergy Clin North Am 2015;35:45-59.
PUBMED | CROSSREF
2. Yu W, Freeland DMH, Nadeau KC. Food allergy: immune mechanisms, diagnosis and immunotherapy. Nat Rev Immunol 2016;16:751-65.
PUBMED | CROSSREF
3. Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn JKh, Fiocchi A, Ebisawa M, Sampson HA, Beyer K, Lee BW. A global survey of changing patterns of food allergy burden in children. World Allergy Organ J 2013;6:21.
PUBMED | CROSSREF
4. Benedé S, Blázquez AB, Chiang D, Tordesillas L, Berin MC. The rise of food allergy: environmental factors and emerging treatments. EBioMedicine 2016;7:27-34.
PUBMED | CROSSREF
5. Yang MS, Kim JY, Kim BK, Park HW, Cho SH, Min KU, Kang HR. True rise in anaphylaxis incidence: Epidemiologic study based on a national health insurance database. Medicine (Baltimore) 2017;96:e5750.
PUBMED | CROSSREF
6. Valenta R, Hochwallner H, Linhart B, Pahr S. Food allergies: the basics. Gastroenterology 2015;148:1120-31.e4.
PUBMED | CROSSREF
7. Hong X, Hao K, Ladd-Acosta C, Hansen KD, Tsai HJ, Liu X, Xu X, Thornton TA, Caruso D, Keet CA, Sun Y, Wang G, Luo W, Kumar R, Fuleihan R, Singh AM, Kim JS, Story RE, Gupta RS, Gao P, Chen Z, Walker SO, Bartell TR, Beaty TH, Fallin MD, Schleimer R, Holt PG, Nadeau KC, Wood RA, Pongracic JA, Weeks DE, Wang X. Genome-wide association study identifies peanut allergy-specific loci and evidence of epigenetic mediation in US children. Nat Commun 2015;6:6304.
PUBMED | CROSSREF
8. Portelli MA, Hodge E, Sayers I. Genetic risk factors for the development of allergic disease identified by genome-wide association. Clin Exp Allergy 2015;45:21-31.
PUBMED | CROSSREF
9. Barcik W, Untersmayr E, Pali-Schöll I, O'Mahony L, Frei R. Influence of microbiome and diet on immune responses in food allergy models. Drug Discov Today Dis Models 2015;17-18:71-80.
PUBMED | CROSSREF
10. Han Y, Kim J, Ahn K. Food allergy. Korean J Pediatr 2012;55:153-8.
PUBMED | CROSSREF
11. Conrad DH, Ford JW, Sturgill JL, Gibb DR. CD23: an overlooked regulator of allergic disease. Curr Allergy Asthma Rep 2007;7:331-7.
PUBMED | CROSSREF
12. Hussain M, Epstein MM, Noti M. Experimental food allergy models to study the role of innate immune cells as initiators of allergen-specific Th2 immune responses. Drug Discov Today Dis Model 2016;17-18:55-62.
CROSSREF
13. Fujiwara S. Humanized mice: A brief overview on their diverse applications in biomedical research. J Cell Physiol 2018;233:2889-901.
PUBMED | CROSSREF
14. Shin JS, Greer AM. The role of FcεRI expressed in dendritic cells and monocytes. Cell Mol Life Sci 2015;72:2349-60.
PUBMED | CROSSREF
15. Platzer B, Baker K, Vera MP, Singer K, Panduro M, Lexmond WS, Turner D, Vargas SO, Kinet JP, Maurer D, Baron RM, Blumberg RS, Fiebiger E. Dendritic cell-bound IgE functions to restrain allergic inflammation at mucosal sites. Mucosal Immunol 2015;8:516-32.
PUBMED | CROSSREF
16. Maurer D, Fiebiger S, Ebner C, Reininger B, Fischer GF, Wichlas S, Jouvin MH, Schmitt-Egenolf M, Kraft D, Kinet JP, Stingl G. Peripheral blood dendritic cells express Fc epsilon RI as a complex composed of Fc epsilon RI alpha- and Fc epsilon RI gamma-chains and can use this receptor for IgE-mediated allergen presentation. J Immunol 1996;157:607-16.
PUBMED
17. Blume C, Davies DE. In vitro and ex vivo models of human asthma. Eur J Pharm Biopharm 2013;84:394-400.
PUBMED | CROSSREF

18. Wang J, Jones SM, Pongracic JA, Song Y, Yang N, Sicherer SH, Makhija MM, Robison RG, Moshier E, Godbold J, Sampson HA, Li XM. Safety, clinical, and immunologic efficacy of a Chinese herbal medicine (Food Allergy Herbal Formula-2) for food allergy. J Allergy Clin Immunol 2015;136:962-70.e1.
PUBMED | CROSSREF

19. Wood RA, Sicherer SH, Burks AW, Grishin A, Henning AK, Lindblad R, Stablein D, Sampson HA. A phase 1 study of heat/phenol-killed, E. coli-encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) for the treatment of peanut allergy. Allergy 2013;68:803-8.
PUBMED | CROSSREF

20. Bryce PJ, Falahati R, Kenney LL, Leung J, Bebbington C, Tomasevic N, Krier RA, Hsu CL, Shultz LD, Greiner DL, Brehm MA. Humanized mouse model of mast cell-mediated passive cutaneous anaphylaxis and passive systemic anaphylaxis. J Allergy Clin Immunol 2016;138:769-79.
PUBMED | CROSSREF

21. Pagovich OE, Wang B, Chiuchiolo MJ, Kaminsky SM, Sondhi D, Jose CL, Price CC, Brooks SF, Mezey JG, Crystal RG. Anti-hIgE gene therapy of peanut-induced anaphylaxis in a humanized murine model of peanut allergy. J Allergy Clin Immunol 2016;138:1652-62.e7.
PUBMED | CROSSREF

22. Burton OT, Stranks AJ, Tamayo JM, Koleoglou KJ, Schwartz LB, Oettgen HC. A humanized mouse model of anaphylactic peanut allergy. J Allergy Clin Immunol 2017;139:314-22.e9.
PUBMED | CROSSREF

23. Jaffar ZH, Stanciu L, Pandit A, Lordan J, Holgate ST, Roberts K. Essential role for both CD80 and CD86 costimulation, but not CD40 interactions, in allergen-induced Th2 cytokine production from asthmatic bronchial tissue: role for alphabeta, but not gammadelta, T cells. J Immunol 1999;163:6283-91.
PUBMED

24. Hidi R, Riches V, Al-Ali M, Cruikshank WW, Center DM, Holgate ST, Djukanovic R. Role of B7-CD28/CTLA-4 costimulation and NF-kappa B in allergen-induced T cell chemotaxis by IL-16 and RANTES. J Immunol 2000;164:412-8.
PUBMED | CROSSREF

25. Lordan JL, Davies DE, Wilson SJ, Dent G, Corkhill A, Jaffar Z, Roberts K, Djukanović R, Holgate ST. The role of CD28-B7 costimulation in allergen-induced cytokine release by bronchial mucosa from patients with moderately severe asthma. J Allergy Clin Immunol 2001;108:976-81.
PUBMED | CROSSREF

26. Vijayanand P, Durkin K, Hartmann G, Morjaria J, Seumois G, Staples KJ, Hall D, Bessant C, Bartholomew M, Howarth PH, Friedmann PS, Djukanovic R. Chemokine receptor 4 plays a key role in T cell recruitment into the airways of asthmatic patients. J Immunol 2010;184:4568-74.
PUBMED | CROSSREF

27. Jaffar Z, Roberts K, Pandit A, Linsley P, Djukanovic R, Holgate S. B7 costimulation is required for IL-5 and IL-13 secretion by bronchial biopsy tissue of atopic asthmatic subjects in response to allergen stimulation. Am J Respir Cell Mol Biol 1999;20:153-62.
PUBMED | CROSSREF

28. Pizzuti D, Senzolo M, Buda A, Chiarelli S, Giacomelli L, Mazzon E, Curioni A, Faggian D, De Lazzari F. In vitro model for IgE mediated food allergy. Scand J Gastroenterol 2011;46:177-87.
PUBMED | CROSSREF

29. Reimann HJ, Lewin J. Gastric mucosal reactions in patients with food allergy. Am J Gastroenterol 1988;83:1212-9.
PUBMED

30. Reimann HJ, Ring J, Ultsch B, Wendt P. Intragastral provocation under endoscopic control (IPEC) in food allergy: mast cell and histamine changes in gastric mucosa. Clin Allergy 1985;15:195-202.
PUBMED | CROSSREF

31. Bischoff SC, Mayer J, Wedemeyer J, Meier PN, Zeck-Kapp G, Wedi B, Kapp A, Cetin Y, Gebel M, Manns MP. Colonoscopic allergen provocation (COLAP): a new diagnostic approach for gastrointestinal food allergy. Gut 1997;40:745-53.
PUBMED | CROSSREF

32. Bach PH, Vickers AE, Fisher R, Baumann A, Brittebo E, Carlile DJ, Koster HJ, Lake BG, Salmon F, Sawyer TW, Skabinsky G. The use of tissue slices in pharmacotoxicology studies. The report and recommendations of ECVAM workshop 20. Altern Lab Anim 1996;24:893-923.

33. de Kanter R, Tuin A, van de Kerkhof E, Martignoni M, Draaisma AL, de Jager MH, de Graaf IA, Meijer DK, Groothuis GM. A new technique for preparing precision-cut slices from small intestine and colon for drug biotransformation studies. J Pharmacol Toxicol Methods 2005;51:65-72.
PUBMED | CROSSREF

34. Sewald K, Braun A. Assessment of immunotoxicity using precision-cut tissue slices. Xenobiotica 2013;43:84-97.
PUBMED | CROSSREF

35. Wohlsen A, Martin C, Vollmer E, Branscheid D, Magnussen H, Becker WM, Lepp U, Uhlig S. The early allergic response in small airways of human precision-cut lung slices. Eur Respir J 2003;21:1024-32.
PUBMED | CROSSREF

36. Sanderson MJ. Exploring lung physiology in health and disease with lung slices. Pulm Pharmacol Ther 2011;24:452-65.
PUBMED | CROSSREF

37. Henjakovic M, Sewald K, Switalla S, Kaiser D, Müller M, Veres TZ, Martin C, Uhlig S, Krug N, Braun A. Ex vivo testing of immune responses in precision-cut lung slices. Toxicol Appl Pharmacol 2008;231:68-76.
PUBMED | CROSSREF

38. Lamb DJ, Wollin SL, Schnapp A, Bischoff D, Erb KJ, Bouyssou T, Guilliard B, Strasser C, Wex E, Blum S, Thaler E, Nickel H, Radmacher O, Haas H, Swantek JL, Souza D, Canfield M, White D, Panzenbeck M, Kashem MA, Sanville-Ross M, Kono T, Sewald K, Braun A, Obernolte H, Danov O, Schaenzle G, Rast G, Maier GM, Hoffmann M. BI 1002494, a novel potent and selective oral spleen tyrosine kinase inhibitor, displays differential potency in human basophils and B cells. J Pharmacol Exp Ther 2016;357:554-61.
PUBMED | CROSSREF

39. Groothuis GM, de Graaf IA. Precision-cut intestinal slices as in vitro tool for studies on drug metabolism. Curr Drug Metab 2013;14:112-9.
PUBMED | CROSSREF

40. Graaf IA, Groothuis GM, Olinga P. Precision-cut tissue slices as a tool to predict metabolism of novel drugs. Expert Opin Drug Metab Toxicol 2007;3:879-98.
PUBMED | CROSSREF

41. Pham BT, van Haaften WT, Oosterhuis D, Nieken J, de Graaf IA, Olinga P. Precision-cut rat, mouse, and human intestinal slices as novel models for the early-onset of intestinal fibrosis. Physiol Rep 2015 Apr;3(4). pii: e12323. https://doi.org/10.14814/phy2.12323.
PUBMED | CROSSREF

42. Li M, de Graaf IA, Groothuis GM. Precision-cut intestinal slices: alternative model for drug transport, metabolism, and toxicology research. Expert Opin Drug Metab Toxicol 2016;12:175-90.
PUBMED | CROSSREF

43. de Graaf IA, Olinga P, de Jager MH, Merema MT, de Kanter R, van de Kerkhof EG, Groothuis GM. Preparation and incubation of precision-cut liver and intestinal slices for application in drug metabolism and toxicity studies. Nat Protoc 2010;5:1540-51.
PUBMED | CROSSREF

44. Pichavant M, Charbonnier AS, Taront S, Brichet A, Wallaert B, Pestel J, Tonnel AB, Gosset P. Asthmatic bronchial epithelium activated by the proteolytic allergen Der p 1 increases selective dendritic cell recruitment. J Allergy Clin Immunol 2005;115:771-8.
PUBMED | CROSSREF

45. Yamashita S, Yokoyama Y, Hashimoto T, Mizuno M. A novel in vitro co-culture model comprised of Caco-2/RBL-2H3 cells to evaluate anti-allergic effects of food factors through the intestine. J Immunol Methods 2016;435:1-6.
PUBMED | CROSSREF

46. de Kivit S, Tobin MC, DeMeo MT, Fox S, Garssen J, Forsyth CB, Keshavarzian A, Landay AL. In vitro evaluation of intestinal epithelial TLR activation in preventing food allergic responses. Clin Immunol 2014;154:91-9.
PUBMED | CROSSREF

47. Barkauskas CE, Chung MI, Fioret B, Gao X, Katsura H, Hogan BL. Lung organoids: current uses and future promise. Development 2017;144:986-97.
PUBMED | CROSSREF

48. Merker SR, Weitz J, Stange DE. Gastrointestinal organoids: how they gut it out. Dev Biol 2016;420:239-50.
PUBMED | CROSSREF

49. Uchida H, Machida M, Miura T, Kawasaki T, Okazaki T, Sasaki K, Sakamoto S, Ohuchi N, Kasahara M, Umezawa A, Akutsu H. A xenogeneic-free system generating functional human gut organoids from pluripotent stem cells. JCI Insight 2017;2:e86492.
PUBMED | CROSSREF

50. Hill DR, Spence JR. Gastrointestinal organoids: understanding the molecular basis of the host-microbe interface. Cell Mol Gastroenterol Hepatol 2016;3:138-49.
PUBMED | CROSSREF

51. Nichols JE, Niles JA, Vega SP, Cortiella J. Novel in vitro respiratory models to study lung development, physiology, pathology and toxicology. Stem Cell Res Ther 2013;4 Suppl 1:S7.
PUBMED | CROSSREF

52. Nesmith AP, Agarwal A, McCain ML, Parker KK. Human airway musculature on a chip: an in vitro model of allergic asthmatic bronchoconstriction and bronchodilation. Lab Chip 2014;14:3925-36.
PUBMED | CROSSREF

53. Kim HJ, Ingber DE. Gut-on-a-Chip microenvironment induces human intestinal cells to undergo villus differentiation. Integr Biol (Camb) 2013;5:1130-40.
PUBMED | CROSSREF

54. Kim HJ, Huh D, Hamilton G, Ingber DE. Human gut-on-a-chip inhabited by microbial flora that experiences intestinal peristalsis-like motions and flow. Lab Chip 2012;12:2165-74.
PUBMED | CROSSREF

55. Kim HJ, Li H, Collins JJ, Ingber DE. Contributions of microbiome and mechanical deformation to intestinal bacterial overgrowth and inflammation in a human gut-on-a-chip. Proc Natl Acad Sci U S A 2016;113:E7-15.
PUBMED | CROSSREF

56. Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. JAMA Pediatr 2013;167:1026-31.
PUBMED | CROSSREF

57. Date S, Sato T. Mini-gut organoids: reconstitution of the stem cell niche. Annu Rev Cell Dev Biol 2015;31:269-89.
PUBMED | CROSSREF