REVIEW

Developing food allergy: a potential immunologic pathway linking skin barrier to gut [version 1; peer review: 2 approved]

Yui-Hsi Wang

Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, 45299-3026, USA

V1 First published: 10 Nov 2016, 5(F1000 Faculty Rev):2660
<https://doi.org/10.12688/f1000research.9497.1>

Latest published: 10 Nov 2016, 5(F1000 Faculty Rev):2660
<https://doi.org/10.12688/f1000research.9497.1>

Abstract

Immunoglobulin E (IgE)-mediated food allergy is an adverse reaction to foods and is driven by uncontrolled type-2 immune responses. Current knowledge cannot explain why only some individuals among those with food allergy are prone to develop life-threatening anaphylaxis. It is increasingly evident that the immunologic mechanisms involved in developing IgE-mediated food allergy are far more complex than allergic sensitization. Clinical observations suggest that patients who develop severe allergic reactions to food are often sensitized through the skin in early infancy. Environmental insults trigger epidermal thymic stromal lymphopoietin and interleukin-33 (IL-33) production, which endows dendritic cells with the ability to induce CD4⁺TH2 cell-mediated allergic inflammation. Intestinal IL-25 propagates the allergic immune response by enhancing collaborative interactions between resident type-2 innate lymphoid cells and CD4⁺TH2 cells expanded by ingested antigens in the gastrointestinal tract. IL-4 signaling provided by CD4⁺TH2 cells induces emigrated mast cell progenitors to become multi-functional IL-9-producing mucosal mast cells, which then expand greatly after repeated food ingestions. Inflammatory cytokine IL-33 promotes the function and maturation of IL-9-producing mucosal mast cells, which amplify intestinal mastocytosis, resulting in increased clinical reactivity to ingested food allergens. These findings provide the plausible view that the combinatorial signals from atopic status, dietary allergen ingestions, and inflammatory cues may govern the perpetuation of allergic reactions from the skin to the gut and promote susceptibility to life-threatening anaphylaxis. Future in-depth studies of the molecular and cellular factors composing these stepwise pathways may facilitate the discovery of biomarkers and therapeutic targets for diagnosing, preventing, and treating food allergy.

Keywords

IgE-mediated food allergy , epidermal TSLP , mucosal mast cells , intestinal mastocytosis

Open Peer Review

Approval Status

	1	2
version 1
10 Nov 2016		

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **Cecilia Berin**, Icahn School of Medicine at Mount Sinai, New York, USA
2. **Anne Marie Singh**, Northwestern University Feinberg School of Medicine, Chicago, USA
Lurie Children's Hospital of Chicago, Chicago, USA

Any comments on the article can be found at the end of the article.

Corresponding author: Yui-Hsi Wang (yui_hsi.wang@cchmc.org)

Competing interests: The author declares that he has no competing interests.

Grant information: This work is supported by the National Institutes of Health (AI090129-1, AI112626-01, and 2U19AI070235-11), the US Department of Defense (W81XWH-15-1-0517), the Digestive Health Center (P30DK078392), and the American Partnership for Eosinophilic Disorders.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2016 Wang YH. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Wang YH. **Developing food allergy: a potential immunologic pathway linking skin barrier to gut** [version 1; peer review: 2 approved] F1000Research 2016, 5(F1000 Faculty Rev):2660 <https://doi.org/10.12688/f1000research.9497.1>

First published: 10 Nov 2016, 5(F1000 Faculty Rev):2660 <https://doi.org/10.12688/f1000research.9497.1>

Introduction

Food allergy has emerged as a major health problem worldwide because of the rapid increase in prevalence over the past decade. Food-induced allergic reactions can cause clinical symptoms ranging from mild mouth itching and abdominal pain to life-threatening anaphylaxis, characterized by hypotension, vascular collapse, cardiac dysrhythmias, and diarrhea¹. Among the 15 million people who are affected by food allergy in the US, only some individuals develop food-induced, life-threatening anaphylaxis, resulting in 30,000 emergency room visits per year². In the healthy gastrointestinal (GI) tract, the epithelial lumen and GI immunity develop active immune tolerance to dietary antigens, combat invading microbes, and limit their persistence in the mucosa. It is unclear why some individuals fail to establish oral tolerance toward innocuous food allergens and develop allergic reactions to food allergens at the mucosal sites of the GI tract. Importantly, it is perplexing why only some of the individuals with food allergy who have high levels of dietary allergen-specific serum immunoglobulin E (IgE) acquire susceptibility to developing life-threatening anaphylactic reactions^{3,4}. Clinically, individuals with atopy and skin sensitization in infancy often develop an allergic response to ingested food in the GI tract later in life⁵⁻⁷. Although this observation has led to the “dual-allergen exposure” hypothesis, the molecular and cellular mechanisms that support this plausible hypothesis remain to be established. The focus of this review is to discuss recent advances in understanding the molecular and cellular factors that contribute to allergic disease progression and promote susceptibility to life-threatening, IgE-mediated food allergy.

Epidermal thymic stromal lymphopoietin and interleukin-33 induce allergic sensitization

Recent clinical studies reveal that some patients with atopic dermatitis (AD) in early life may have a higher risk of developing food allergy⁶⁻⁹. Infants with atopic eczema are prone to be sensitized to egg at only 4 months of age¹⁰. In the population-based study of pediatric food allergy, eczema and filaggrin gene loss-of-function mutations, which are associated with reduced skin barrier integrity, are identified as the risk factors for food sensitization⁷. Evidence from murine studies demonstrates that epicutaneous applications of food proteins can trigger sensitization, which results in the development of IgE-mediated food allergy after repeated food ingestions¹¹⁻¹⁴. These findings support the notion that the skin barrier is an important route in initiating allergic sensitization to food antigens and evading oral tolerance.

After injury, stress, or environmental insults, the skin epithelium loses its barrier function and orchestrates inflammatory responses and tissue remodeling by producing a myriad of cytokines, chemokines, and growth factors¹⁵. Indeed, the idea that skin epithelium can trigger the onset of allergic diseases is supported by the findings that thymic stromal lymphopoietin (TSLP) can endow dendritic cells (DCs) with the ability to create a type 2-permissive microenvironment and drive a T-cell-mediated allergic immune response^{16,17}. Strong TSLP production is associated with the accumulation of large numbers of DCs activated by DC-lysosome-associated membrane protein-positive and of CD3⁺ T cells in the apical layers of the epidermis of patients with AD but not in normal or non-lesional skin¹⁸. Mechanistically, keratinocyte-derived TSLP can potentially induce the maturation and activation of

infiltrated myeloid DCs. These TSLP-activated DCs can produce large amounts of chemokines to recruit inflammatory cells, induce CD4⁺ T helper type 2 (TH2) cell differentiation, and maintain functional attributes of CD4⁺TH2 memory/effector cells¹⁸⁻²⁰. In concert with eliciting a DC-mediated TH2 immune response, a recent study showed that TSLP could also promote interleukin-3 (IL-3)-dependent basophil hematopoiesis, resulting in basophil-mediated allergic inflammation^{11,21}. Perhaps early exposure to food proteins accompanied by environmental insults or genetic predisposition factors that result in epidermal TSLP production may provoke DC/basophil/CD4⁺TH2 cell-mediated allergic sensitization via skin barrier before establishing tolerance to ingested foods during infancy.

Several factors have been demonstrated to induce epidermal TSLP production. Topical application of vitamin D3 analogs, the ligand for the vitamin D receptor, induces strong TSLP production by keratinocytes, resulting in the development of an AD-like phenotype in mice²². Since the binding of vitamin D receptor and retinoid X receptor alpha (RXR α) or RXR β heterodimers can form the transcriptional repressor of *Tslp* gene, the treatments of vitamin D3 analogs which alleviate the formation of such transcription repressor result in the induction of *Tslp* gene expression in the mouse skin keratinocytes²². The activation of Toll-like receptors by viral, bacterial, and fungal ligands can also induce TSLP production in epithelial cells²³. Accumulating evidence from recent animal studies has further substantiated the roles of TSLP and allergic sensitization via skin barrier in the development of experimental food allergy. Mice that develop AD after repeated topical applications of ovalbumin (OVA) plus vitamin D3 analog lose tolerance to ingested OVA and eventually develop symptoms of experimental food allergy¹¹⁻¹³. Conversely, mice deficient in TSLP receptor specifically in DCs also fail to develop antigen-specific IgE after epicutaneous sensitization and are resistant to developing experimental food allergy²⁴. Overexpression of TSLP can activate intradermally reconstituted basophils to promote cutaneous allergic inflammation, resulting in the development of experimental food allergy¹¹. By contrast, ablation of basophils in mice that are sensitized after topical application of vitamin D3 analogs results in resistance to developing experimental food allergy^{11,25}. These studies underscore the pivotal role of epidermal TSLP production in orchestrating the DC/basophil-mediated TH2 immune response that initiates the allergic sensitization to food antigens in the skin barrier, leading to the propensity to develop a food allergy (Figure 1).

In addition to aberrant epidermal TSLP induction, the loss of skin barrier function due to filaggrin gene mutation or injury after repeated skin picking (excoriation) also increases the risk for peanut allergy²⁶. Indeed, direct epicutaneous applications of cashew peanut extract, not soy extract, are sufficient to trigger adjuvant-independent allergic sensitization, possibly mediated by the skin-draining DCs that express ST2, the receptor for the inflammatory cytokine IL-33, also termed alarmin¹⁴. In another study, repeated tape stripping, which imitates the excoriation of skin observed in AD patients, can also trigger the production of the epithelial-derived inflammatory cytokine IL-33 and promote the development of experimental food allergy²⁷. Perhaps mechanical skin injury can induce an increase in circulating IL-33, which

Figure 1. Schematic overview of the stepwise mechanisms involved in the development of immunoglobulin E (IgE)-mediated food allergy. In the allergic sensitization phase, environmental or mechanical triggers (or both) may induce skin keratinocytes to produce thymic stromal lymphopoietin (TSLP), which recruits and activates dendritic cells (DCs) or basophils. Injured epithelial cells may also release interleukin-33 (IL-33) to activate ST2-expressing skin DCs. TSLP-activated DCs migrate to draining lymph nodes to induce naïve CD4⁺T cells to differentiate into CD4⁺TH2 cells and maintain CD4⁺TH2 effector/memory pools. In the allergy propagation phase, these CD4⁺TH2 cells migrate to the intestine and interact with resident type-2 innate lymphoid cells (ILC2s) to produce large amounts of IL-13 in response to intestinal IL-25 stimulation. In the amplification-of-mastocytosis phase, IL-4 signals provided by CD4⁺TH2 cells induce emigrated mast cell progenitors (MCPs) to become multi-functional IL-9-producing mucosal mast cells (MMC9s), which then expand greatly after ingested antigens cross-link with MMC9 surface IgE/FcεR complex. The inflammatory cytokine IL-33 enhances IL-9 production by MMC9s, resulting in MMC9 maturation and the amplification of intestinal mastocytosis in an autocrine loop. Thus, MMC9 induction may serve as a key cellular checkpoint to amplify and propagate allergic inflammation, resulting in the development of IgE-mediated food allergy. MMC, mucosal mast cell; STAT6, signal transducer and activator of transcription 6; TH2, T helper type 2 cell.

enhances IgE-mediated mucosal mast cell (MC) degranulation in the gut, resulting in the development of anaphylactic response to ingested antigens²⁷. Thus, in addition to TSLP, the epithelial-derived cytokine IL-33 and the allergenic property of certain food allergens can serve as the alternative factors to induce allergic sensitization to food antigens after skin injury occurred. These findings also broaden our understanding of the factors and immunologic pathways underlying the initiation of skin allergic sensitization that may potentiate the development of food allergy.

Interleukin-25, type-2 innate lymphoid cells, and CD4⁺TH2 cells perpetuate allergic reactions

In addition to allergic sensitization to food antigens via a damaged skin barrier, other factors at the mucosal site of the GI tract may confer susceptibility to food allergy later in life. After the occurrence of allergic sensitization induced by administering epicutaneous TSLP plus OVA antigen, blocking TSLP activity by using anti-TSLP antibody does not prevent skin-sensitized mice from developing experimental food allergy²⁴. This finding implies that the perpetuation and amplification of allergic reactions from skin to small intestine in the GI tract are essential for the development of IgE-mediated food allergy^{24,25}.

The GI mucosa is the largest immunologic site that constantly encounters numerous varieties of food antigens present in the daily

diet. Antigen sampling, processing, and presenting at the mucosal sites of the GI tract are complex processes involving intestinal epithelial cells, M cells, goblet cells, and DCs^{28,29}. It is postulated that tolerogenic CD103⁺ DCs present luminal food antigens to naïve CD4⁺ T cells to induce food antigen-specific regulatory CD4⁺ T cells, leading to a state of unresponsiveness to ingested antigens or oral tolerance^{30,31}. Considerable evidence demonstrates that the intestinal epithelial-derived cytokine IL-25 (IL-17E), a distinct IL-17 cytokine member, is a key factor in promoting protective type-2 immunity to parasitic infection^{32,33} (for example, helminth) and limits TH1- and TH17-mediated inflammation induced by commensal flora^{34,35}. Endogenous intestinal IL-25 produced constitutively by tuft cells, one of the five intestinal epithelial cell lineages, can sustain the homeostasis of type-2 innate lymphoid cells (ILC2s) and activate ILC2s to secrete IL-13 after helminth infection³⁶. These studies suggest that intestinal IL-25 may regulate the balance of the immune response to dietary proteins in the GI tract after the occurrence of allergic sensitization. Indeed, allergic sensitization results in the increase of intestinal IL-25 expression, which potentiates the development of allergic reactions to ingested antigens³⁷. Compared with their wild-type controls, genetically modified murine strains that produce intestinal-specific IL-25 constitutively or that lack the IL-25 receptor, IL-17RB, are more susceptible or resistant, respectively, to developing IgE-mediated experimental food allergy³⁷. Although intestinal ILC2s are the

primary TH2 cytokine producers in response to IL-25 stimulation, ILC2s alone are insufficient to drive anaphylactic reactions to ingested antigens in naïve or sensitized transgenic mice that produce IL-25 constitutively³⁷. Notably, CD4⁺TH2 cells that are induced after allergic sensitization and then amplified after repeated ingested antigen challenge are required for ILC2s to produce large amounts of IL-5 and IL-13 in response to IL-25 stimulation, resulting in the development of experimental food allergy³⁷. Possibly, IL-2 production by ingested antigen-induced CD4⁺TH2 cells promotes the capabilities of ILC2s to produce IL-5 and IL-13 in response to intestinal IL-25 stimulation^{37–40}. These findings may also explain the observation that IL-25-deficient mice infected with *Trichuris muris*, a GI parasite, fail to develop lymphocyte-dependent protective type-2 immunity to expel chronic parasitic infection³³. In another study using mice expressing a gain-of-function mutation of IL-4 receptor α chain (*Il4raF709*), ILC2s are found to produce some IL-4 in response to IL-33 stimulation in a mouse model of food allergy sensitized with staphylococcal enterotoxin B⁴¹. ILC2-derived IL-4 promotes the development of experimental food allergy by dampening regulatory T cell function, which can directly suppress mucosal MC function⁴¹. Together, these studies substantiate the role of IL-25 in promoting intestinal allergic reaction to ingested antigens by enhancing the concerted interactions between ILC2s, antigen-induced CD4⁺TH2 cells, or regulatory T cells (or a combination of these) after the occurrence of allergic sensitization²⁵. Furthermore, the findings support the view that IL-25 may bridge the crosstalk between the skin and gut by mediating collaborative interactions between ILC2s and CD4⁺TH2 cells to amplify the cascade of allergic reactions to ingested antigens at the effector phase of IgE-mediated food allergy (Figure 1).

Interleukin-33 and type-2 mucosal mast cells amplify hypersensitivity reactions

Food-induced anaphylaxis is an immediate, adverse reaction triggered predominantly by cross-linking of antigen-specific IgE bound to the high-affinity IgE receptor Fc ϵ R on MCs after re-exposure to allergen^{42–44}. Mechanistically, Fc ϵ R cross-linking activates a downstream signaling cascade that causes rapid release of vasoactive and preformed mediators, including histamine, trypsin, carboxypeptidase A, leukotrienes, and platelet-activating factor, resulting in physiological alternations that cause shock (anaphylaxis)^{45,46}. However, it is perplexing why only some, rather than all, individuals who are competent to generate MCs and have high levels of dietary allergen-specific IgE develop life-threatening anaphylaxis^{3,4}. Similar to humans, sensitized murine strains that have normal MC development and acquire high amounts of antigen-specific IgE vary in their susceptibility to developing severe systemic anaphylaxis¹³. This enigma hints that in addition to IgE and MCs, other molecular and cellular factors may also participate in driving the development of life-threatening anaphylaxis. Considerable evidence from clinical and animal studies demonstrates that elevated levels of IgE-positive MCs in the small intestine are associated with food allergy^{42,47–49}, suggesting a pivotal role of GI MCs in the development of food-induced, life-threatening anaphylaxis^{43,50}. Taking advantage of the differences in their susceptibility to food allergy, comparative analyses of intestinal mucosal cellular components among examined murine strains led to the identification of the novel, multi-functional IL-9-producing mucosal MCs (MMC9s)¹³. MMC9s function as type-2-promoting innate myeloid cells by producing prodigious

amounts of the TH2 cytokines IL-9 and IL-13 and exert MC function by secreting histamine and MC proteases¹³. Unlike conventional MCs, MMC9s display innate helper cell-like morphology with few metachromatic granules in their scanty cytoplasm. It appears that MMC9s are scarce in the small intestines of immunologically naïve mice. After allergic sensitization via the skin barrier or TH2-promoting adjuvant, the atopic IL-4 signaling provided by ingested antigen-induced CD4⁺TH2 cells can induce Fc ϵ R-expressing MC progenitors from bone marrow to develop into MMC9s¹³. Thus, mice expressing a gain-of-function mutation of IL-4 receptor α chain (*Il4raF709*) are more prone to developing experimental food allergy because of a cell-intrinsic effect of IL-4 in intestinal MC homeostasis⁵¹. Furthermore, MMC9s expand greatly in the small intestine of wild-type mice, but not mice deficient in Fc ϵ R α , after repeated exposure to ingested antigens, indicating that cross-linking of the surface IgE/Fc ϵ R complex by ingested antigens promotes the proliferation of MMC9s¹³. Reciprocally, ingested antigen-induced MMC9s amplify CD4⁺TH2 cell immune responses, which drive the concomitant increase of MMC9 and CD4⁺TH2 cell occurrence (unpublished observation). Furthermore, robust IL-9 production by MMC9s is essential for effective MMC9 expansion, which promotes intestinal mastocytosis in an IL-9-dependent autocrine manner, resulting in the development of severe systemic anaphylaxis¹³. Notably, intestinal epithelial-derived IL-33 can enhance the function of MMC9s by inducing robust IL-9 production, which can amplify intestinal mastocytosis, resulting in the development of anaphylactic response to ingested antigens¹³. It appears that in addition to promoting allergic reactions to ingested foods, intestinal MCs can provide an IL-4 signal to induce a TH2 cell program in regulatory T cells, resulting in the impairment of regulatory T-cell function and the loss of tolerance⁵². Given their anatomical location, characteristics, and function, MMC9s may be a key player that bridges the crosstalk between the skin and gut by perpetuating allergic reactions and amplifying anaphylactic responses to dietary proteins. Indeed, among sensitized murine strains, MMC9 occurrence is positively associated with their susceptibility to experimental food allergy¹³. Ablating MMC9s results in resistance to developing experimental food allergy¹³. In human studies, increased duodenal MMC9 frequency and expression levels of *Il9* and MC-specific transcripts are associated with atopy patients who developed comorbid allergic diseases, such as eczema and food allergy¹³. Thus, MMC9 induction may represent a pivotal cellular checkpoint in acquiring susceptibility to developing life-threatening anaphylaxis. Furthermore, these findings represent a new conceptual paradigm by linking atopic status (IL-4), dietary antigen and IgE/Fc ϵ R complex interactions, and inflammatory cues (exemplified by IL-33) with MMC9 biology and food allergy (Figure 1).

Conclusions

Although our knowledge of the pathways underpinning the development of allergy has increased, current evidence does not yet fully explain why life-threatening anaphylaxis occurs in only some individuals among those who are allergic to food allergens. Over the past decade, considerable evidence has led to a plausible hypothesis that details the stepwise mechanisms involved in the development of food allergy (illustrated in Figure 1): (i) in the allergic sensitization phase, exogenous molecules (lectins, proteases, or chitins) acting as mucosal TH2 adjuvants and filaggrin as a genetic predisposing factor may initiate inflammatory reactions to induce the

production of epidermal TSLP or IL-33 (or both) that triggers allergic sensitization to contacted food allergens before the establishment of oral tolerance^{53–56}. TSLP endows DCs and potentiates basophil function to promote a TH2-permissive microenvironment, which induces CD4⁺TH2 cells to differentiate and maintain antigen-specific CD4⁺TH2 memory/effector cells^{16,18,19,57}, which migrate to a draining lymphoid node and induce antigen-specific IgE generation. (ii) In the allergy propagation phase, re-exposure to ingested food antigens activates emigrated antigen-specific CD4⁺TH2 memory/effector cells in the small intestine to produce IL-13, resulting in the increase of intestinal IL-25 production. In the presence of CD4⁺TH2 memory/effector cells and IL-25 stimulation, resident ILC2s produce large amounts of IL-13, which creates a TH2-permissive environment that prevents tolerance. (iii) In the amplification-of-mastocytosis phase, repeated food antigen ingestion induces the increase of CD4⁺TH2 cells, which provide the IL-4 signaling that induces MC progenitors to develop into MMC9s, which expand greatly after ingested antigens cross-link with MMC9 surface IgE/FcεR complex. IL-33, a potent inflammatory cytokine, enhances IL-9 production by MMC9s, resulting in MMC9 maturation and the amplification of intestinal mastocytosis in an autocrine loop. Thus, it is possible that local accumulation of IgE-bearing MMC9s will impose the potent reactivity to ingested food antigens and is the prerequisite for developing life-threatening anaphylaxis. The proposed model provides paradigm-shifting insight into the immunologic mechanisms composing the progression of allergic reactions to food allergens from the skin to gut. Indeed, our proposed notion mirrors recent changes in the guidelines of the American Academy of Pediatrics, including the recommendation for early oral

exposure to food allergens during infancy for children at risk of atopic diseases⁵⁸. Future in-depth studies of human MMC9 and MMC9-associated molecules involved in the clinical reactivity of food allergy will provide the basis to translate the mechanistic findings from murine studies to further our understanding of human food allergy and the clinical application of this knowledge.

Abbreviations

AD, atopic dermatitis; DC, dendritic cell; GI, gastrointestinal; IgE, immunoglobulin E; IL, interleukin; ILC2, type-2 innate lymphoid cell; MC, mast cell; MMC9, interleukin-9-producing mucosal mast cell; OVA, ovalbumin; RXR, retinoid X receptor; TH2, T helper type 2; TSLP, thymic stromal lymphopoietin.

Competing interests

The author declares that he has no competing interests.

Grant information

This work is supported by the National Institutes of Health (AI090129-1, AI112626-01, and 2U19AI070235-11), the US Department of Defense (W81XWH-15-1-0517), the Digestive Health Center (P30DK078392), and the American Partnership for Eosinophilic Disorders.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

I thank Shawna Hottinger for editorial assistance.

References

- Sicherer SH, Sampson HA: **Food allergy: recent advances in pathophysiology and treatment.** *Annu Rev Med.* 2009; **60**: 261–77.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Gupta RS, Springston EE, Warrier MR, *et al.*: **The prevalence, severity, and distribution of childhood food allergy in the United States.** *Pediatrics.* 2011; **128**(1): e9–17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Faria AMC, Weiner HL: **Oral tolerance.** *Immunol Rev.* 2005; **206**(1): 232–59.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Vickery BP, Scurlock AM, Jones SM, *et al.*: **Mechanisms of immune tolerance relevant to food allergy.** *J Allergy Clin Immunol.* 2011; **127**(3): 576–84; quiz 585–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Lack G: **Update on risk factors for food allergy.** *J Allergy Clin Immunol.* 2012; **129**(5): 1187–97.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Calvani M, Cardinale F, Martelli A, *et al.*: **Risk factors for severe pediatric food anaphylaxis in Italy.** *Pediatr Allergy Immunol.* 2011; **22**(8): 813–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Koplin JJ, Wake M, Dharmage SC, *et al.*: **Cohort Profile: The HealthNuts Study: Population prevalence and environmental/genetic predictors of food allergy.** *Int J Epidemiol.* 2015; **44**(4): 1161–71.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Hill DJ, Hosking CS, de Benedictis FM, *et al.*: **Confirmation of the association between high levels of immunoglobulin E food sensitization and eczema in infancy: an international study.** *Clin Exp Allergy.* 2008; **38**(1): 161–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Lack G, Fox D, Northstone K, *et al.*: **Factors associated with the development of peanut allergy in childhood.** *N Engl J Med.* 2003; **348**(11): 977–85.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Palmer DJ, Metcalfe J, Makrides M, *et al.*: **Early regular egg exposure in infants with eczema: A randomized controlled trial.** *J Allergy Clin Immunol.* 2013; **132**(2): 387–92.e1.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Noti M, Kim BS, Siracusa MC, *et al.*: **Exposure to food allergens through inflamed skin promotes intestinal food allergy through the thymic stromal lymphopoietin-basophil axis.** *J Allergy Clin Immunol.* 2014; **133**(5): 1390–9, 1399.e1–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Mathias CB, Hobson SA, Garcia-Lloret M, *et al.*: **IgE-mediated systemic anaphylaxis and impaired tolerance to food antigens in mice with enhanced IL-4 receptor signaling.** *J Allergy Clin Immunol.* 2011; **127**(3): 795–805.e1–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Chen CY, Lee JB, Liu B, *et al.*: **Induction of Interleukin-9-Producing Mucosal Mast Cells Promotes Susceptibility to IgE-Mediated Experimental Food Allergy.** *Immunity.* 2015; **43**(4): 788–802.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Tordesillas L, Goswami R, Benedé S, *et al.*: **Skin exposure promotes a Th2-dependent sensitization to peanut allergens.** *J Clin Invest.* 2014; **124**(11): 4965–75.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Holgate ST: **The epithelium takes centre stage in asthma and atopic dermatitis.** *Trends Immunol.* 2007; **28**(6): 248–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Liu YJ, Soumelis V, Watanabe N, *et al.*: **TSLP: an epithelial cell cytokine that regulates T cell differentiation by conditioning dendritic cell maturation.** *Annu Rev Immunol.* 2007; **25**: 193–219.
[PubMed Abstract](#) | [Publisher Full Text](#)

17. **F** Wang YH, Liu YJ: **Thymic stromal lymphopoietin, OX40-ligand, and interleukin-25 in allergic responses.** *Clin Exp Allergy.* 2009; **39**(6): 798–806.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
18. Wang YH, Ito T, Wang YH, *et al.*: **Maintenance and polarization of human T_H2 central memory T cells by thymic stromal lymphopoietin-activated dendritic cells.** *Immunity.* 2006; **24**(6): 827–38.
[PubMed Abstract](#) | [Publisher Full Text](#)
19. **F** Soumelis V, Reche PA, Kanzler H, *et al.*: **Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP.** *Nat Immunol.* 2002; **3**(7): 673–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
20. **F** Ito T, Wang YH, Duramad O, *et al.*: **TSLP-activated dendritic cells induce an inflammatory T helper type 2 cell response through OX40 ligand.** *J Exp Med.* 2005; **202**(9): 1213–23.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
21. **F** Siracusa MC, Saenz SA, Hill DA, *et al.*: **TSLP promotes interleukin-3-independent basophil haematopoiesis and type 2 inflammation.** *Nature.* 2011; **477**(7363): 229–33.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
22. Li M, Hener P, Zhang Z, *et al.*: **Topical vitamin D3 and low-calcemic analogs induce thymic stromal lymphopoietin in mouse keratinocytes and trigger an atopic dermatitis.** *Proc Natl Acad Sci U S A.* 2006; **103**(31): 11736–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
23. Lee HC, Ziegler SF: **Inducible expression of the proallergic cytokine thymic stromal lymphopoietin in airway epithelial cells is controlled by NFκB.** *Proc Natl Acad Sci U S A.* 2007; **104**(3): 914–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
24. Han H, Thelen TD, Comeau MR, *et al.*: **Thymic stromal lymphopoietin-mediated epicutaneous inflammation promotes acute diarrhea and anaphylaxis.** *J Clin Invest.* 2014; **124**(12): 5442–52.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
25. **F** Muto T, Fukuoka A, Kabashima K, *et al.*: **The role of basophils and proallergic cytokines, TSLP and IL-33, in cutaneously sensitized food allergy.** *Int Immunol.* 2014; **26**(10): 539–49.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
26. **F** Brown SJ, Asai Y, Cordell HJ, *et al.*: **Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy.** *J Allergy Clin Immunol.* 2011; **127**(3): 661–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
27. Galand C, Leyva-Castillo JM, Yoon J, *et al.*: **IL-33 promotes food anaphylaxis in epicutaneously sensitized mice by targeting mast cells.** *J Allergy Clin Immunol.* 2016; pii: S0091-6749(16)30369-4.
[PubMed Abstract](#) | [Publisher Full Text](#)
28. Mowat AM: **Anatomical basis of tolerance and immunity to intestinal antigens.** *Nat Rev Immunol.* 2003; **3**(4): 331–41.
[PubMed Abstract](#) | [Publisher Full Text](#)
29. **F** McDole JR, Wheeler LW, McDonald KG, *et al.*: **Goblet cells deliver luminal antigen to CD103⁺ dendritic cells in the small intestine.** *Nature.* 2012; **483**(7389): 345–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
30. **F** Schulz O, Jaensson E, Persson EK, *et al.*: **Intestinal CD103⁺, but not CX3CR1⁺, antigen sampling cells migrate in lymph and serve classical dendritic cell functions.** *J Exp Med.* 2009; **206**(13): 3101–14.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
31. Coombes JL, Siddiqui KR, Arancibia-Carcamo CV, *et al.*: **A functionally specialized population of mucosal CD103⁺ DCs induces Foxp3⁺ regulatory T cells via a TGF-β and retinoic acid-dependent mechanism.** *J Exp Med.* 2007; **204**(8): 1757–64.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
32. **F** Fallon PG, Ballantyne SJ, Mangan NE, *et al.*: **Identification of an interleukin (IL)-25-dependent cell population that provides IL-4, IL-5, and IL-13 at the onset of helminth expulsion.** *J Exp Med.* 2006; **203**(4): 1105–16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
33. **F** Owyang AM, Zaph C, Wilson EH, *et al.*: **Interleukin 25 regulates type 2 cytokine-dependent immunity and limits chronic inflammation in the gastrointestinal tract.** *J Exp Med.* 2006; **203**(4): 843–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
34. **F** Zaph C, Du Y, Saenz SA, *et al.*: **Commensal-dependent expression of IL-25 regulates the IL-23-IL-17 axis in the intestine.** *J Exp Med.* 2008; **205**(10): 2191–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
35. Caruso R, Sarra M, Stolfi C, *et al.*: **Interleukin-25 inhibits interleukin-12 production and Th1 cell-driven inflammation in the gut.** *Gastroenterology.* 2009; **136**(7): 2270–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
36. **F** von Moltke J, Ji M, Liang HE, *et al.*: **Tuft-cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit.** *Nature.* 2016; **529**(7585): 221–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
37. Lee JB, Chen CY, Liu B, *et al.*: **IL-25 and CD4⁺ T_H2 cells enhance type 2 innate lymphoid cell-derived IL-13 production, which promotes IgE-mediated experimental food allergy.** *J Allergy Clin Immunol.* 2016; **137**(4): 1216–25.e1-5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
38. **F** Mirchandani AS, Besnard AG, Yip E, *et al.*: **Type 2 innate lymphoid cells drive CD4⁺ Th2 cell responses.** *J Immunol.* 2014; **192**(5): 2442–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
39. **F** Oliphant CJ, Hwang YY, Walker JA, *et al.*: **MHCII-mediated dialog between group 2 innate lymphoid cells and CD4⁺ T cells potentiates type 2 immunity and promotes parasitic helminth expulsion.** *Immunity.* 2014; **41**(2): 283–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
40. Liu B, Lee JB, Chen CY, *et al.*: **Collaborative interactions between type 2 innate lymphoid cells and antigen-specific CD4⁺ Th2 cells exacerbate murine allergic airway diseases with prominent eosinophilia.** *J Immunol.* 2015; **194**(8): 3583–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
41. Noval Rivas M, Burton OT, Oettgen HC, *et al.*: **IL-4 production by group 2 innate lymphoid cells promotes food allergy by blocking regulatory T-cell function.** *J Allergy Clin Immunol.* 2016; **138**(3): 801–811.e9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
42. Stenton GR, Vliagoftis H, Befus AD: **Role of intestinal mast cells in modulating gastrointestinal pathophysiology.** *Ann Allergy Asthma Immunol.* 1998; **81**(1): 1–11; quiz 12–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
43. Peavy RD, Metcalfe DD: **Understanding the mechanisms of anaphylaxis.** *Curr Opin Allergy Clin Immunol.* 2008; **8**(4): 310–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
44. **F** Brandt EB, Strait RT, Hershko D, *et al.*: **Mast cells are required for experimental oral allergen-induced diarrhea.** *J Clin Invest.* 2003; **112**(11): 1666–77.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
45. Stone SF, Cotterell C, Isbister GK, *et al.*: **Elevated serum cytokines during human anaphylaxis: Identification of potential mediators of acute allergic reactions.** *J Allergy Clin Immunol.* 2009; **124**(4): 786–92.e4.
[PubMed Abstract](#) | [Publisher Full Text](#)
46. Galli SJ, Tsai M: **IgE and mast cells in allergic disease.** *Nat Med.* 2012; **18**(5): 693–704.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
47. Ahrens R, Osterfeld H, Wu D, *et al.*: **Intestinal mast cell levels control severity of oral antigen-induced anaphylaxis in mice.** *Am J Pathol.* 2012; **180**(4): 1535–46.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
48. Bengtsson U, Rognum TP, Brandtzaeg P, *et al.*: **IgE-positive duodenal mast cells in patients with food-related diarrhea.** *Int Arch Allergy Appl Immunol.* 1991; **95**(1): 86–91.
[PubMed Abstract](#) | [Publisher Full Text](#)
49. Caffarelli C, Romanini E, Caruana P, *et al.*: **Clinical food hypersensitivity: the relevance of duodenal immunoglobulin E-positive cells.** *Pediatr Res.* 1998; **44**(4): 485–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
50. **F** Kurashima Y, Kiyono H: **New era for mucosal mast cells: their roles in inflammation, allergic immune responses and adjuvant development.** *Exp Mol Med.* 2014; **46**(3): e83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
51. **F** Burton OT, Darling AR, Zhou JS, *et al.*: **Direct effects of IL-4 on mast cells drive their intestinal expansion and increase susceptibility to anaphylaxis in a murine model of food allergy.** *Mucosal Immunol.* 2013; **6**(4): 740–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
52. **F** Noval Rivas M, Burton OT, Wise P, *et al.*: **Regulatory T cell reprogramming toward a Th2-cell-like lineage impairs oral tolerance and promotes food allergy.** *Immunity.* 2015; **42**(3): 512–23.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
53. Berin MC, Shreffler WG: **T_H2 adjuvants: implications for food allergy.** *J Allergy Clin Immunol.* 2008; **121**(6): 1311–20; quiz 1321-2.
[PubMed Abstract](#) | [Publisher Full Text](#)
54. **F** Eisenbarth SC, Colegio OR, O'Connor W, *et al.*: **Crucial role for the Nalp3 inflammasome in the immunostimulatory properties of aluminium adjuvants.** *Nature.* 2008; **453**(7198): 1122–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
55. **F** Reese TA, Liang HE, Tager AM, *et al.*: **Chitin induces accumulation in tissue of innate immune cells associated with allergy.** *Nature.* 2007; **447**(7140): 92–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
56. **F** Margolis DJ, Kim B, Apter AJ, *et al.*: **Thymic stromal lymphopoietin variation, filaggrin loss of function, and the persistence of atopic dermatitis.** *JAMA Dermatol.* 2014; **150**(3): 254–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
57. **F** Wang Q, Du J, Zhu J, *et al.*: **Thymic stromal lymphopoietin signaling in CD4⁺ T cells is required for T_H2 memory.** *J Allergy Clin Immunol.* 2015; **135**(3): 781–91.e3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
58. **F** Greer FR, Sicherer SH, Burks AW, *et al.*: **Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas.** *Pediatrics.* 2008; **121**(1): 183–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

Open Peer Review

Current Peer Review Status:

Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1. **Anne Marie Singh**

¹ Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

² Department of Pediatrics, Lurie Children's Hospital of Chicago, Chicago, IL, USA

Competing Interests: No competing interests were disclosed.

2. **Cecilia Berin**

Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research