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Mouse models of allergic diseases

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The increasing prevalence of allergic diseases worldwide is posing significant socio-economic challenges. The pathogenesis of these diseases reflects a complex interaction of genetic and environmental factors. The heterogeneity of disease phenotypes challenges the concept of single mechanisms of disease. As human experimentation is limited, animal models have been developed to provide insights into pathogenesis and potential for discovery of novel therapeutics. Mice have served in models of many of the allergic diseases including asthma, allergic rhinitis, food allergy, atopic dermatitis (AD), and allergic conjunctivitis. Although much has been learned from these investigations, there are limitations when these models are translated to the human diseases.

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Introduction

Allergic diseases, often termed the ‘allergy epidemic’, represent an increasing concern worldwide. Initially most prevalent in Westernized countries, these diseases are now increasing in developing countries in parallel to changes in socio-economic conditions. The contributing factors result in a complex and somewhat variable pathogenesis between individual patients and in the same patient at different stages of their disease. This variability, as well as ethical considerations, makes it difficult to investigate these conditions in patients. As a surrogate, animal models of allergic disease have been developed with literally thousands of papers published in the last decade. Concerns have been expressed whether these animal studies are truly models of human disease, especially in light of the failure to directly translate the findings and potential therapeutic targets to the clinic. Early studies of allergy in mice were conducted with the notion that allergy is the consequence of T helper 2 (Th2)-type inflammation. Most clinical studies demonstrated that

human T cells were not as obviously polarized in this way, and the concept that atopic diseases reflect a Th2/Th1 imbalance is probably too simplistic [1].

Mouse models have been developed for almost all of the allergic diseases. Here, studies with mouse models of the most prevalent allergic diseases are reviewed: asthma, allergic rhinitis, food allergy and anaphylaxis, AD, and allergic conjunctivitis. In addition to the many important advances gained from investigation of these models, there are several limitations that preclude simple translation of the findings in mice to human disease. Most of these allergic disease models are acute and transient following initial allergen sensitization and challenge. Unlike their human disease equivalents, they do not develop spontaneously and chronic models have been difficult to establish in the mouse. There are many important differences between humans and mice in terms of the anatomical, physiological, and immunological contributors [2,3]. Caution in interpretation of the results of the studies in mice is necessary and knowledge and limitations of the various approaches used is essential [4]. Nonetheless, although no mouse model fully mimics the full range of clinical manifestations of the human allergic diseases, many do reproduce a collection of the features that characterize its most common forms, that is, they provide a basic core of phenotypic consequences.

Asthma

Mice are the most common species studied in animal models of asthma. In the majority of studies, mice are systemically sensitized to allergen with alum as an adjuvant and challenged to allergen via the airways for one to nine days in acute models and for five to nine weeks in ‘chronic’ models [5]. Results achieved in the primary sensitization and challenge model, which is so unlike the human disease, have probably been overinterpreted accounting for many of the failures to translate the findings or targets to the clinic. Unlike humans, mice do not exhibit intrinsic airway hyperresponsiveness (AHR) but they share many other features of asthma (Table 1). The most characteristic feature in mice is the development of airway dysfunction with development of AHR. The most accepted measures are changes in airway resistance and dynamic compliance, detected in tracheostomized and ventilated animals (invasive approach) following graded aerosolized methacholine challenge [6]. In the induction of allergen-induced AHR and airway eosinophilic inflammation, it has been widely accepted that Th2-type CD4⁺ T helper cells and related cytokines (IL-4, IL-13) play a central role. Thus, mice genetically deficient, for

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Table 1

Shared features between human and mouse allergic airway disease

Human asthma	Mouse allergen-induced
- Airway hyperresponsiveness to numerous stimuli	- Airway hyperresponsiveness to numerous stimuli—not histamine
- Airway inflammation	- Airway inflammation
- Reversible airway obstruction	- Reversible airway obstruction
- Airway/tissue eosinophilia	- Airway/tissue eosinophilia
- Increased CD4+ T lymphocytes	- Increased CD4+ T lymphocytes
- Increased CD8+ T lymphocytes	- Increased CD8+ T lymphocytes
- Mucus hyperproduction	- Mucus hyperproduction
- Increased allergen-specific IgE	- Increased allergen-specific IgE
- Increased Th2 cytokines	- Increased Th2 cytokines
- Early and late phase responses	- Early and late phase responses

example, in IL-4 or IL-5 fail to develop these lung allergic responses. However, clinical studies targeting these Th2 cytokines have met with little success [7], highlighting the complexity of the human disease. In both mice and asthmatics, the role of eosinophils in mediating AHR and asthma has been controversial with clear associations and dissociations of the two processes described in both species [8].

In light of these inconsistencies between species and in the different models, more recent studies in mice have explored mechanisms in addition to classic Th2-mediated responses. One focus has been on the recently described Th17 subset of T cells, a subset of CD4+ T cells releasing a number of cytokines (IL-17A, IL-17F, IL-22). Th17 polarized DO11.10 cells were shown to induce AHR and airway inflammation that was resistant to corticosteroids [9]. Conversely, IL-17 was shown to negatively regulate AHR and airway inflammation, and CD1d-restricted iNKT cells producing IL-17 appeared to play a role in ozone-induced AHR and airway inflammation but not in an allergen-induced model [10,11]. Thus, the role of IL-17 remains controversial in experimental models of asthma, with perhaps an inverse relationship between Th17-mediated neutrophil accumulation and Th2-mediated airway eosinophilia [12]. Similarly, the role of iNKT cells, as primary sources of Th2 cytokines, is also controversial in both mice and asthmatics [13].

Regulatory T cells (Tregs) have been shown to negatively regulate development of allergen-induced AHR and airway eosinophilia. Naturally occurring Tregs (CD4+CD25+FoxP3+) (nTregs) function has been studied in mice. Adoptive transfer of naive nTregs inhibited the development of allergen-induced AHR and airway inflammation through secretion of IL-10 and TGF- β [14]. Moreover, the suppressive function of this T cell subset was initiated following ligation of MHCI on the Tregs by CD8. In the absence of MHCI-CD8 interaction, these nTregs exhibited a plasticity in which they enhanced responses rather than suppressed them and this was

accompanied by reduced IL-10/TGF- β production and increased IL-13 release [15,16^{••}].

CD8+ T cells have also been demonstrated to play a crucial role in the development of AHR and eosinophilic airway inflammation and these findings have been supported in clinical studies. These CD8+ T cells were characterized by expression of the high affinity receptor for leukotriene B₄, BLT1, which was essential to the accumulation of CD8+ T cells in the lungs [17]. Moreover, these CD8+ T cells were shown to be corticosteroid-insensitive [18^{••},19]. Activation of these CD8+ T cells was shown to be dependent on IL-4-secreting CD4+ T cells in the initial sensitization phase [20]. In asthmatics, a similar population of CD8+BLT1+ T cells has been demonstrated in bronchoalveolar lavage fluid and in lung tissue [21]. Further, the annual decline in lung function in asthmatics was correlated with numbers of bronchial wall CD8+ T cells and not reticular basement membrane thickness or infiltrating eosinophils [22]. In addition, human CD8+ T cells, similar to mouse CD8+ T cells, were shown to be steroid-insensitive compared with CD4+ T cells [23].

Allergic rhinitis

Allergic rhinitis (AR) is the most prevalent atopic disease, affecting 20–35% of the population, and unlike asthma, the prevalence appears to be increasing. Following allergen exposure, symptoms occur rapidly (early phase response, EPR) and may persist, especially nasal obstruction (late phase response, LPR). Many of the factors leading to alterations in upper and lower airway function overlap. Despite the emerging concept of ‘one airway, one disease’, the two compartments do differ. The upper airways are derived from a different germ layer, and importantly the upper airway has no smooth muscle but is highly vascularized [24].

The majority of studies in mouse models of AR, similar to asthma models, were designed as acute triggers of symptoms. The response to nasal allergen challenge in previously sensitized mice is characterized by both an EPR

and LPR. In animal models, early responses have been quantitated by nasal rubbing and sneezing scores for 3–5 min following allergen challenge. As mice are obligate nasal breathers, decreases in respiratory frequency have been used as a surrogate marker in the EPR and LPR [25]. Direct measures of nasal resistance have now been used to monitor LPR [25]. Early studies showed that IgE–Th2 immune responses play a central role in the development of AR. However, recent studies have questioned these findings; FcεR1-deficient mice were shown to be capable of developing nasal eosinophilia, and IL-5-deficient mice that lack eosinophils developed AR [26]. Mice with a genetic deficiency of STAT1, a crucial component in IFN-γ signaling developed less nasal eosinophilia and histamine-induced nasal hyperresponsiveness [27]. Other studies have identified the role of H1, H3, and H4 histamine receptors and T regulatory cells in the regulation of AR [28–30]. Analysis of the mechanisms underlying the EPR and LPR demonstrated that the EPR was dependent on the interaction of IgE, the high affinity receptor for IgE and FcεR1-expressing mast cells, whereas the LPR, detected by increases in nasal resistance were mediated by IL-13, independent of nasal eosinophilia [25,31,32*].

Food-related allergy and food-induced anaphylaxis

The prevalence of food allergy has increased significantly in recent decades, including reports of life-threatening anaphylactic reactions. As studies in allergic individuals are necessarily limited, animal models of food allergy have helped understand the underlying mechanisms of the disease, the potential for new therapeutic targets, and to determine the allergenicity and risks of emerging transgenic crop plants containing newly synthesized proteins [33]. As most of the proteins contained in food are digested in the gut lumen before absorption in the intestine, it is important to recognize that ingestion of the majority of food proteins induce tolerance despite or perhaps because of daily exposures. The molecular structure of food proteins may be altered in the gastrointestinal tract, reducing their allergenicity, unlike the routes of allergen exposure in other allergic diseases. Studies in food allergy models in mice, similar to models of asthma and AR, have utilized systemic sensitization to allergen (often together with alum), followed by oral challenges [34]. The experimental endpoints include appearance of systemic anaphylaxis such as fall in body temperature, symptoms, loss of body weight, or diarrhea. Allergen-specific IgE–mast cell interactions associated with Th2-type immune responses, including IL-9, have been linked to the allergic response to foods such as rice or cow's milk [35–37]. Other studies demonstrated the essential role of T cells in the development of food allergy; CD4+ T cells from Peyer patches were shown to be the prominent effector cells as a source of Th2 cytokines, whereas CD8+ T cells or T regulatory cells

played potent suppressive roles in allergic enterocolitis [38,39]. Protective roles for allergen-specific IgA or IL-10 have been shown in food allergy. Disease-specific therapeutic approaches with oral IL-10 transfected *Lactococcus lactis* reduced food-induced anaphylactic reactions and serum levels of IgE antibodies [40*].

Atopic dermatitis

Similar to some of the other atopic diseases, the prevalence of AD is steadily increasing. The pathogenesis of AD is also believed to be mediated by Th2-driven inflammatory responses, often associated with high IgE levels. An important factor in AD may be skin barrier dysfunction as has been shown in association with mutations in filaggrin, an important class of the intermediate filament-associated proteins that interact with keratin intermediate filaments of terminally differentiating mammalian epidermis [41]. Bacterial superinfection of the skin is an important contributor to persistent and refractory disease.

True mouse models of AD are difficult to establish. Nc/Nga mice spontaneously develop AD-like skin lesions under conventional conditions. Skin lesions exhibit marked accumulation of mast cells and eosinophils, with epithelial hyperparakeratosis, hyperplasia, and spongiosis accompanied by upregulated Th2–IgE responses and skin barrier abnormalities [42]. However, studies with STAT6-deficient Nc/Nga mice demonstrated comparable levels of skin lesions to STAT6-sufficient Nc/Nga mice, accompanied by higher levels of Th1-type immune responses [43].

Other disease models in common strains or gene-targeted mice have utilized epicutaneous or systemic allergen sensitization followed by topical allergen challenges. These studies demonstrated the association or role for eosinophils, thymic stromal lymphopoietin (TSLP)-Th2 cytokines, and toll-like receptor-linked induction of IFN-γ [44–46].

The potent pro-inflammatory cytokine IL-17 has also been suggested to play a role in AD [47,48]. This is of interest as IL-17 is highly pro-neutrophilic, whereas AD patients show little neutrophil infiltration of the skin lesions. In one study, following development of AD-like disease with epicutaneous but not systemic sensitization, AHR was induced in an IL-17-dependent fashion [49*].

Allergic conjunctivitis

To elicit allergic conjunctivitis in mice, allergen is administered topically following systemic sensitization [50]. Pollens such as birch, ragweed, or house dust mite have been used. The EPR is thought to be mediated through allergen-specific-IgE–mast cell interactions. A variety of mediators released by mast cells in the EPR including eosinophilic chemotactic factor and platelet activating

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factor, can sustain subsequent allergic reactions in the LPR. However, some studies have shown less dependence on allergen-specific IgE or the crucial role of allergen-specific T cells in the development of LPR [51]. The central role of Th2-driven responses in allergic conjunctivitis is supported by studies of cytokine levels from allergen-specific lymphocytes, suppressor of cytokine signaling protein levels, Notch ligand (Delta-like4), or OX40 interactions [52–54]. Recent studies in mice and humans indicated that IFN- γ may also play a crucial role in the development of allergic conjunctivitis [55–57], highlighting the role of both Th1 and Th2 cytokines in the pathogenesis of many of the allergic diseases.

Conclusions

Although mouse models cannot entirely duplicate human asthma, AR, AD, food allergy, or allergic conjunctivitis, they have been invaluable in defining the requirements for sensitization, IgE and cytokine production, and mucus hyperproduction. These studies have also revealed how different mechanisms and pathways can lead to the same outcomes, similar to the heterogeneity seen in the human allergic diseases. The caveat is that there are limitations to each of these models and findings must be critically analyzed. Despite the many failures to translate findings to the clinic, animal studies still offer the potential for defining new therapeutic approaches. Earlier studies were based on the hypothesis that ‘allergy is a genetically regulated Th2-type inflammatory response’. This in many ways was biased by the approaches taken to elicit the responses. Increasingly, the complexity of the responses is being recognized including the involvement of Th1-mediated immune responses. Man remains the best model of human disease. But, even clinical studies are confronting the issues of disease heterogeneity and the potential for different pathways leading to similar clinical phenotypes. Together, this may account for the limited clinical success of many recently introduced therapies. To investigate chronic allergic diseases, chronic disease models are necessary. Finally, early sensitization to allergen in the very young is typical of virtually all allergic diseases. There is probably a very narrow window of opportunity for early intervention with the goals of preventing disease before the disease becomes established. Once established, the maintenance or progression phase is probably mediated by multiple pathways, pathways that are different from those involved in the inception or sensitization phase.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Heaton T, Rowe J, Turner S, Aalberse RC, de Klerk N, Suriyaarachchi D, Serralha M, Holt BJ, Hollams E, Yerkovich S *et al.*: **An immunoepidemiological approach to asthma: identification of *in vitro* T cell response patterns associated with different wheezing phenotypes in children.** *Lancet* 2005, **365**:142–149.
 2. Finkelman FD, Wills-Karp M: **Usefulness and optimization of mouse models of allergic airway disease.** *J Allergy Clin Immunol* 2008, **121**:603–606.
 3. Wenzel S, Holgate ST: **The mouse trap: it still yields few answers in asthma.** *Am J Respir Crit Care Med* 2006, **174**:1173–1176.
 4. Taube C, Dakhama A, Gelfand EW: **Insights into the pathogenesis of asthma utilizing murine models.** *Intl Arch Allergy Immunol* 2004, **135**:173–186.
 5. Nials AT, Uddin S: **Mouse models of allergic asthma: acute and chronic allergen challenge.** *Dis Model Mech* 2008, **1**:213–220.
 6. Glaab T, Taube C, Braun A, Mitzner W: **Invasive and noninvasive methods for studying pulmonary function in mice.** *Respir Res* 2007, **8**:63.
 7. Holgate ST: **Novel targets of therapy in asthma.** *Curr Opin Pulm Med* 2009, **15**:63–71.
 8. Hogan SP, Rosenberg HF, Moqbel R, Phipps S, Foster PS, Lacy P, Kay AB, Rothenberg ME: **Eosinophils: biological properties and role in health and disease.** *Clin Exp Allergy* 2008, **38**:709–750.
 9. McKinley L, Alcorn JF, Peterson A, Dupont RB, Kapadia S, Logar A, Henry A, Irvin CG, Piganelli JD, Ray A, Kolls JK: **TH17 cells mediate steroid-resistant airway inflammation and airway hyperresponsiveness in mice.** *J Immunol* 2008, **181**:4089–4097.
 10. Schnyder-Candrian S, Togbe D, Couillin I, Mercier I, Brombacher F, Quesniaux V, Fossiez F, Ryffel B, Schnyder B: **Interleukin-17 is a negative regulator of established allergic asthma.** *J Exp Med* 2006, **203**:2715–2725.
 11. Pichavant M, Goya S, Meyer EH, Johnston RA, Kim HY, Matangkasombut P, Zhu M, Iwakura Y, Savage PB, DeKruyff RH *et al.*: **Ozone exposure in a mouse model induces airway hyperactivity that requires the presence of natural killer T cells and IL-17.** *J Exp Med* 2008, **205**:385–393.
 12. Schmidt-Weber CB, Akdis M, Akdis CA: **TH17 cells in the big picture of immunology.** *J Allergy Clin Immunol* 2007, **120**:247–254.
 13. Bendelac A, Savage PB, Teyton L: **The biology of NKT cells.** *Ann Rev Immunol* 2007, **25**:297–336.
 14. Joetham A, Takeda K, Taube C, Miyahara N, Matsubara S, Koya T, Rha YH, Dakhama A, Gelfand EW: **Naturally occurring lung CD4(+)CD25(+) T cell regulation of airway allergic responses depends on IL-10 induction of TGF- β .** *J Immunol* 2007, **178**:1433–1442.
 15. Joetham A, Takeda K, Miyahara N, Matsubara S, Ohnishi H, Koya T, Dakhama A, Gelfand EW: **Activation of naturally occurring lung CD4(+)CD25(+) regulatory T cells requires CD8 and MHC I interaction.** *Proc Natl Acad Sci USA* 2007, **104**:15057–15062.
 16. Joetham A, Matsubara S, Okamoto M, Takeda K, Miyahara N, Dakhama A, Gelfand EW: **Plasticity of regulatory T cells: subversion of suppressive function and conversion to enhancement of lung allergic responses.** *J Immunol* 2008, **180**:7117–7124.
- The authors showed that CD8 and glucocorticoid-induced TNFR-related protein reciprocally control the function of naturally occurring CD4(+)CD25(+) regulatory T cells. This study defined receptor-induced activation or suppression of nTreg function and the functional plasticity of nTreg cells.
17. Miyahara N, Swanson BJ, Takeda K, Taube C, Miyahara S, Kodama T, Dakhama A, Ott VL, Gelfand EW: **Effector CD8+ T cells mediate inflammation and airway hyperresponsiveness.** *Nat Med* 2004, **10**:865–869.
 18. Ohnishi H, Miyahara N, Dakhama A, Takeda K, Mathis S, Haribabu B, Gelfand EW: **Corticosteroids enhance CD8+ T cell-mediated airway hyperresponsiveness and allergic inflammation by upregulating leukotriene B4 receptor 1.** *J Allergy Clin Immunol* 2008, **121**:864–871.

Corticosteroids upregulated functional leukotriene B4 receptor-1 expression on effector memory CD8+ T cells, increasing LTB4-induced signaling pathways, chemotaxis, and potentiated allergic airway inflammation and AHR induced by these cells. This study also showed that activated CD8+ T cells are steroid-insensitive.

19. Ohnishi H, Takeda K, Domenico J, Lucas JJ, Miyahara N, Swasey CH, Dakhama A, Gelfand EW: **Mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2-dependent pathways are essential for CD8+ T cell-mediated airway hyperresponsiveness and inflammation.** *J Allergy Clin Immunol* 2009, **123**:249-257.
 20. Koya T, Miyahara N, Takeda K, Matsubara S, Matsuda H, Swasey C, Balhorn A, Dakhama A, Gelfand EW: **CD8+ T cell-mediated airway hyperresponsiveness and inflammation is dependent on CD4+IL-4+ T cells.** *J Immunol* 2007, **179**:2787-2796.
 21. Gelfand EW, Dakhama A: **CD8+ T lymphocytes and leukotriene B4: novel interactions in the persistence and progression of asthma.** *J Allergy Clin Immunol* 2006, **117**:577-582.
 22. van Rensen ELJ, Sont JK, Evertse CE, Willems LNA, Mauad T, Hiemstra PS, Sterk PJ, The AMPUL Study Group: **Bronchial CD8 cell infiltrate and lung function decline in asthma.** *Am J Resp Crit Care Med* 2005, **172**:837-841.
 23. Ling-bo L, Leung DYM, Strand MJ, Goleva E: **ATF2 impairs glucocorticoid receptor-mediated transactivation in human CD8+ T cells.** *Blood* 2007, **110**:1570-1577.
 24. Wagner JG, Harkema JR: **Rodent models of allergic rhinitis: relevance to human pathophysiology.** *Curr Allergy Asthma Rep* 2007, **7**:134-140.
 25. Miyahara S, Miyahara N, Takeda K, Joetham A, Gelfand EW: **Physiologic assessment of allergic rhinitis in mice: Role of the high-affinity IgE receptor (FcεpsilonRI).** *J Allergy Clin Immunol* 2005, **116**:1020-1027.
 26. Roa J, Morikawa H, Crawford L, Baatjes A, Duong M, Denburg JA: **The effects of montelukast on tissue inflammatory and bone marrow responses in murine experimental allergic rhinitis: interaction with interleukin-5 deficiency.** *Immunology* 2007, **122**:438-444.
 27. Hattori H, Rosas LE, Okano M, Durbin JE, Nishizaki K, Satoskar AR: **STAT1 is involved in the pathogenesis of murine allergic rhinitis.** *Am J Rhinol* 2007, **21**:241-247.
 28. Yokota E, Kuyama S, Sugimoto Y, Ogawa M, Kamei C: **Participation of histamine H3 receptors in experimental allergic rhinitis of mice.** *J Pharmacol Sci* 2008, **108**:206-211.
 29. Takahashi Y, Kagawa Y, Izawa K, Ono R, Akagi M, Kamei C: **Effect of histamine H4 receptor antagonist on allergic rhinitis in mice.** *Int Immunopharmacol* 2009, **9**:734-738.
 30. Winkler B, Hufnagl K, Spittler A, Ploder M, Kállay E, Vrtala S, Valenta R, Kundi M, Renz H, Wiedermann U: **The role of Foxp3+ T cells in long-term efficacy of prophylactic and therapeutic mucosal tolerance induction in mice.** *Allergy* 2006, **61**:173-180.
 31. Miyahara S, Miyahara N, Matsubara S, Takeda K, Koya T, Gelfand EW: **IL-13 is essential to the late-phase response in allergic rhinitis.** *J Allergy Clin Immunol* 2006, **118**:1110-1116.
 32. Miyahara S, Miyahara N, Lucas JJ, Joetham A, Matsubara S, Ohnishi H, Dakhama A, Gelfand EW: **Contribution of allergen-specific and nonspecific nasal responses to early-phase and late-phase nasal responses.** *J Allergy Clin Immunol* 2008, **121**:718-724.
- The authors developed a model to assess early- and late-phase nasal responses using direct and indirect measurements. In this model, early-phase nasal responses may be antigen-nonspecific and mast-cell-dependent, whereas late-phase responses induced by repeated allergen exposure are antigen-specific and mast-cell-independent.
33. Dearman RJ, Kimber I: **Animal models of protein allergenicity: potential benefits, pitfalls and challenges.** *Clin Exp Allergy* 2009, **39**:458-468.
 34. Dearman RJ, Kimber I: **A mouse model for food allergy using intraperitoneal sensitization.** *Methods* 2007, **41**:91-98.
 35. Forbes EE, Groschwitz K, Abonia JP, Brandt EB, Cohen E, Blanchard C, Ahrens R, Seidu L, McKenzie A, Strait R *et al.*: **IL-9- and mast cell-mediated intestinal permeability predisposes to oral antigen hypersensitivity.** *J Exp Med* 2008, **205**:897-913.
 36. Feng BS, Chen X, He SH, Zheng PY, Foster J, Xing Z, Bienenstock J, Yang PC: **Disruption of T-cell immunoglobulin and mucin domain molecule (TIM)-1/TIM4 interaction as a therapeutic strategy in a dendritic cell-induced peanut allergy model.** *J Allergy Clin Immunol* 2008, **122**:55-61.
 37. Knight AK, Blázquez AB, Zhang S, Mayer L, Sampson HA, Berin MC: **CD4 T cells activated in the mesenteric lymph node mediate gastrointestinal food allergy in mice.** *Am J Physiol Gastrointest Liver Physiol* 2007, **293**:G1234-G1243.
 38. Yamada A, Ohshima Y, Yasutomi M, Ogura K, Tokuriki S, Naiki H, Mayumi M: **Antigen-primed splenic CD8+ T cells impede the development of oral antigen-induced allergic diarrhea.** *J Allergy Clin Immunol* 2009, **123**:889-894.
 39. Takayama N, Igarashi O, Kweon MN, Kiyono H: **Regulatory role of Peyer's patches for the inhibition of OVA-induced allergic diarrhea.** *Clin Immunol* 2007, **123**:199-208.
 40. Frossard CP, Steidler L, Eigenmann PA: **Oral administration of an IL-10-secreting *Lactococcus lactis* strain prevents food-induced IgE sensitization.** *J Allergy Clin Immunol* 2007, **119**:952-959.
- Oral treatment with nonpathogenic IL-10-producing microorganisms in the gut may prevent systemic food-induced anaphylaxis by reducing allergen-specific antibodies. This study provides a possible intervention with non-pathogenic microorganisms that could prove to be easy and safe.
41. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, Goudie DR, Sandilands A, Campbell LE, Smith FJ *et al.*: **Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for severity of atopic dermatitis.** *Nat Genet* 2006, **38**:441-446.
 42. Jin H, He R, Oyoshi M, Geha RS: **Animal models of atopic dermatitis.** *J Invest Dermatol* 2009, **129**:31-40.
 43. Yagi R, Nagai H, Iigo Y, Akimoto T, Arai T, Kubo M: **Development of atopic dermatitis-like skin lesions in STAT6-deficient NC/Nga mice.** *J Immunol* 2002, **168**:2020-2027.
 44. He R, Oyoshi MK, Garibyan L, Kumar L, Ziegler SF, Geha RS: **TSLP acts on infiltrating effector T cells to drive allergic skin inflammation.** *Proc Natl Acad Sci USA* 2008, **105**:11875-11880.
 45. Elkhail A, Pichavant M, He R, Scott J, Meyer E, Goya S, Geha RS, Umetsu DT: **CD1d restricted natural killer T cells are not required for allergic skin inflammation.** *J Allergy Clin Immunol* 2006, **118**:1363-1368.
 46. Jin H, Kumar L, Mathias C, Zurakowski D, Oettgen H, Gorelik L, Geha R: **Toll-like receptor 2 is important for the T(H)1 response to cutaneous sensitization.** *J Allergy Clin Immunol* 2009, **123**:875-882.
 47. Iguchi T, Kawata A, Watanabe T, Mazumder TK, Tanabe S: **Fermented barley extract suppresses the development of atopic dermatitis-like skin lesions in NC/Nga mice, probably by inhibiting inflammatory cytokines.** *Biosci Biotechnol Biochem* 2009, **73**:489-493.
 48. Kawakami Y, Tomimori Y, Yumoto K, Hasegawa S, Ando T, Tagaya Y, Crotty S, Kawakami T: **Inhibition of NK cell activity by IL-17 allows vaccinia virus to induce severe skin lesions in a mouse model of eczema vaccinatum.** *J Exp Med* 2009, **206**:1219-1225.
 49. He R, Oyoshi MK, Jin H, Geha RS: **Epicutaneous antigen exposure induces a Th17 response that drives airway inflammation after inhalation challenge.** *Proc Natl Acad Sci USA* 2007, **104**:15817-15822.
- Epicutaneous allergen sensitization but not intraperitoneal sensitization-induced IL-17-dependent allergic airway inflammation following airway allergen challenge. This study provides a possible link between allergic airway and skin disease, and the role of IL-17.
50. Niederkorn JY: **Immune regulatory mechanisms in allergic conjunctivitis: insights from mouse models.** *Curr Opin Allergy Clin Immunol* 2008, **8**:472-476.

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51. Fukushima A, Ozaki A, Jian Z, Ishida W, Fukata K, Ueno H, Liu FT: **Dissection of antigen-specific humoral and cellular immune responses for the development of experimental immune-mediated blepharoconjunctivitis in C57BL/6 mice.** *Curr Eye Res* 2005, **30**:241-248.
52. Kubo M, Ozaki A, Tanaka S, Okamoto M, Fukushima A: **Role of suppressor of cytokine signaling in ocular allergy.** *Curr Opin Allergy Clin Immunol* 2006, **6**:361-366.
53. Fukushima A, Sumi T, Ishida W, Ojima A, Kajisako M, Koyanagi A, Koyama N, Yagita H: **Notch ligand Delta-like4 inhibits the development of murine experimental allergic conjunctivitis.** *Immunol Lett* 2008, **121**:140-147.
54. Fukushima A, Yamaguchi T, Ishida W, Fukata K, Yagita H, Ueno H: **Roles of OX40 in the development of murine experimental allergic conjunctivitis: exacerbation and attenuation by stimulation and blocking of OX40.** *Invest Ophthalmol Vis Sci* 2006, **47**:657-663.
55. Giavina-Bianchi P, Kalil J, Rizzo LV: **Development of an animal model for allergic conjunctivitis: Influence of genetic factors and allergen concentration on immune response.** *Acta Ophthalmol* 2008, **86**:670-675.
56. Fukushima A, Sumi T, Fukuda K, Kumagai N, Nishida T, Tsuru E, Ueno H: **Analysis of the interaction between IFN-gamma and IFN-gammaR in the effector phase of experimental murine allergic conjunctivitis.** *Immunol Lett* 2006, **107**:119-124.
57. Leonardi A, Fregona IA, Plebani M, Secchi AG, Calder VL: **Th1- and Th2-type cytokines in chronic ocular allergy.** *Graefes Arch Clin Exp Ophthalmol* 2006, **244**:1240-1245.