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Advances and novel developments in mechanisms of allergic inflammation

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ABSTRACT

In the past decade, research in the molecular and cellular underpinnings of basic and clinical immunology has significantly advanced our understanding of allergic disorders, allowing scientists and clinicians to diagnose and treat disorders such as asthma, allergic and nonallergic rhinitis, and food allergy. In this review, we discuss several significant recent developments in basic and clinical research as well as important future research directions in allergic inflammation. Certain key regulatory cytokines, genes, and molecules have recently been shown to play key roles in allergic disorders. For example, interleukin-33 (IL-33) plays an important role in refractory disorders such as asthma, allergic rhinitis, and food allergy, mainly by inducing T helper (Th) 2 immune responses. Further, the cytokine TSLP has been shown to be a key factor in maintaining immune homeostasis and regulating inflammatory responses at mucosal barriers and targeting TSLP-mediated signaling is considered an attractive therapeutic strategy. We discuss interleukin 4 receptor pathways, which recently has shown to play a critical role among the allergic inflammatory pathways that drive allergic disorders and pathogenesis. The alarmin IL-33 has found to play a major role in type-2 immune responses in allergic diseases and clinical trials with IL33 inhibitors are underway in food allergy. Further, the cytokine Thymic Stromal Lymphopoietin (TSLP) has recently been shown a factor in maintaining immune homeostasis and regulating type-2 inflammatory responses at mucosal barriers in allergic inflammation. Also, new immune and genetic studies found that IL-4R pathways play a critical role among the allergic inflammatory pathways that drive allergic disorders and pathogenesis. In addition, new findings establish an important T cell-intrinsic role of Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) proteolytic activity in the suppression of autoimmune responses. We have seen how mutations in the filaggrin gene are significant risk factor for allergic diseases such as atopic dermatitis, asthma, allergic rhinitis, food allergy (FA), and contact allergy and hand eczema. We are only beginning to understand the mechanisms by which the human microbiota may be regulating the immune system, and how sudden changes in the composition of the microbiota may have profound effects, linked with an increased risk of developing chronic inflammatory disorders, including allergies. New research has shown the important but complex role monocytes play in such disorders as food allergies. Finally, we

discuss some of the new directions of research in this area, particularly the important use of biologicals in oral immunotherapy, advances in gene therapy, multi-food therapy, novel diagnostics in diagnosing allergic disorders, and the central role that OMICS plays in creating molecular signatures and biomarkers of allergic disorders such as food allergy. Such exciting new developments and advances has significantly moved forth our ability to understand the mechanisms underlying allergic diseases for improved patient care.

INTRODUCTION

The specialties of allergy and clinical immunology have entered the era of precision medicine by the stratification of diseases into distinct disease subsets, specific diagnoses, and targeted treatment options, including biologicals and small molecules. Especially, in the past decade, much progress has been made in untangling the cellular and molecular underpinnings of allergic diseases, particularly in understanding the complex regulation of inflammatory disorders. In this review, we present some of the more notable milestone discoveries as well as the future important directions of research in the mechanisms and treatment of allergic inflammation.

Milestone Discoveries

MAJOR MILESTONE DISCOVERIES

- **anti-IL33 for severe hypersensitivity**
- **Thymic Stromal Lymphopoietin (TSLP)**
- **IL-4R α**
- **Mucosa-associated lymphoid tissue lymphoma translocation protein 1(MALT1)Filaggrin and skin barrier**
- **Microbiota contribution to allergic pathways**
- **Monocytes and food allergy contributions**

Anti-IL-33 for Severe Hypersensitivity

The alarmin IL-33 plays a central role in initiating type-2 immune cytokine and chemokine responses that exacerbate allergic diseases such as allergic rhinitis, asthma, atopic dermatitis, and food allergy¹⁻³. In a mouse model of dust exposure, increased IL-33 levels drove a self-perpetuating amplification loop that maintained the lung in a state of lasting inflammation and remodeled tissue primed for exacerbations, suggesting blockade might ameliorate symptoms and prevent exacerbations by quelling persistent inflammation and airway remodeling⁴.

Clinical studies of IL-33 pathway inhibitors in allergy and asthma are underway. One recent 6-week placebo-controlled phase-2 study tested the safety and desensitizing capacity of the anti-IL33 antibody etokimab in peanut-allergic adults (NCT02920021)⁵. Investigators found 73% and 57% increases in the tolerated threshold allergen dose of the etokimab group (day 15 and 45, respectively), but 0% in the placebo group on either of the 2 days. The self-reported atopy-related events (asthma, eczema, food allergy, and allergic rhinitis) were more common in the placebo group than the etokimab-treated group (60% vs. 7%, respectively). Blood analysis revealed a reduction of peanut-specific IgE at day 15 in the etokimab group ($P=0.014$), and CD4⁺ cells had reduced IL-4, IL-13, IL-9, IL-5, and ST2 expression compared with placebo. The authors concluded that a single etokimab dose has the potential to desensitize peanut-allergic patients⁵.

Thymic Stromal Lymphopoietin (TSLP)

The cytokine Thymic Stromal Lymphopoietin (TSLP) has shown to be a key factor in maintaining immune homeostasis and regulating type 2 inflammatory responses at mucosal barriers in various allergic diseases⁶⁻⁸. Accumulating evidence suggests TSLP is a critical upstream cytokine in immune cells such as dendritic cells (DCs), T cells, basophils, group-2 innate lymphoid cells (ILC2s), and more recently, mast cells⁶⁻⁸. TSLP-mediated signaling has been studied primarily in DCs and T lymphocytes, in which signaling occurred primarily through JAK/STAT pathways^{9,10}. TSLP and IL-33 are consistently associated with adaptive Th2 immune responses⁸. Expression of the TSLP receptor TSLPR does not require the activation of Th2 cells and can be identified on naive CD4⁺ T cells¹¹, while expression of the IL-33 receptor ST2 on Th2 cells requires prior cell activation, suggesting that TSLP plays a role earlier in T-cell activation. TSLP has also been shown to be a significant regulator of innate lymphoid cell (ILC) function¹². Data from a human study suggest that TSLP could mediate resistance to corticosteroids in ILC2 cells from human PBMCs and bronchoalveolar lavage (BAL), and TSLP concentrations in BAL fluid from asthmatic patients were inversely correlated with corticosteroid-mediated inhibition of IL-5 production by ILC2s from BAL fluid¹³. The role of TSLP in activating basophils is controversial¹⁴, but basophils appear to have an essential role in the induction of TSLP-mediated Th2 inflammation⁷. A recent study showed that when the skin barrier is damaged, TSLP-

elicited basophils can promote epicutaneous sensitization to food allergens and subsequent IgE-mediated food allergy through IL-4⁷. TSLP was found as a novel survival factor of dermal mast cells, by interfering with apoptosis via a dual strategy involving STAT5/Mcl-1 and JNK/Bcl-x(L)¹⁵, suggesting that mast cells are a crucial responder to TSLP in TSLP-driven disorders^{15,16}. Interestingly, Kabata et al. found that TSLP activates distinct immune cell cascades in a different context: TSLP directly stimulated ILC2s, but not basophils in papain-induced innate immune-mediated type-2 airway inflammation, while TSLP principally acted on DCs and CD4 + T cells during the sensitization phase, but not basophils or ILC2s in OVA-induced adaptive immune-mediated type 2 airway inflammation¹⁷. Lai et al. recently reported that TSLP drives Th2-cell differentiation in the lung, independent of the draining lymph nodes¹⁸.

Accordingly, TSLP had been often referred to as “alarmins” and known to promote allergic inflammation. Targeting of TSLP and TSLP-mediated signaling is considered an attractive therapeutic strategy^{19,20}.

Interleukin-4 receptor alpha (IL-4R α)

Immunological and genetic studies show that the interleukin 4 receptor (IL-4R) pathway plays a critical role among the allergic inflammatory pathways that drive allergic disorders and pathogenesis²¹. The importance of this pathway in allergic inflammation stems from the critical role played by IL-4 and its heterodimeric cytokine-binding receptor chain IL-4R α in orchestrating the allergic response²². Efforts to therapeutic target IL-4/IL-4R α signaling have been developed as a promising strategy for T helper 2 (Th2)-mediated allergic disease.

A recent study found that inducible deletion of IL-4R α after allergic sensitization did not induce Th17, a neutrophilic inflammatory response as observed in IL-4R α -deficient mice after intranasal allergen challenge, and suppression of IL-4R α signaling after allergic sensitization would have significant therapeutic benefit for Th2-type allergic asthma²³. Another group demonstrated that IL-4 receptor α blockade prevents sensitization and alters acute and long-lasting effects of allergen-specific

immunotherapy of murine allergic asthma by beneficially affecting immunological key parameters such as immunoglobulin and cytokine secretion immediately after allergen immunotherapy and long-term priming of immune memory. The number of potentially disease-triggering Th2-biased Treg cells was further significantly decreased by IL-4 and IL-13 antagonist IL-4 mutein (IL-4M) treatment even two weeks later²⁴. As shown in Table 1, dupilumab, a fully humanized IgG4 monoclonal antibody targeting the IL-4R α subunit^{25,26} inhibits IL-4 signaling by binding to IL-4R α , and/or inhibit the recruitment of γ c to IL-4R α chain and/or inhibits the recruitment of the IL-4R α to IL-13R α 1, and therefore downregulates Th2 inflammation in allergic disorders²⁷. The suppression of allergic tissue inflammation by dupilumab, such as seen in eczema, would suggest inhibition of IL-4R type II receptor signalling²⁸. Dupilumab reduces local type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyposis²⁹. This drug has emerged as one of the most successful therapies targeting this axis³⁰ and has demonstrated efficacy and acceptable safety in atopic dermatitis, asthma, and other allergic diseases²⁵.

Mucosa-associated lymphoid tissue lymphoma translocation protein 1(MALT1)

Mucosa-associated lymphoid tissue lymphoma translocation protein 1(MALT1) regulates innate and adaptive immune signaling by acting as a scaffold protein to control signaling of NF- κ B, a protein complex that controls transcription of DNA, cytokine production, and cell survival. MALT1 is a cysteine protease that refines proinflammatory signaling by cleaving specific substrates. Because many of the substrates are involved in regulating inflammatory responses, the protease activity of MALT1 has emerged as a possible therapeutic target. Deregulated MALT1 activity has been associated with immunodeficiency, autoimmunity, and cancer in mice and humans³¹. Genetically engineered mice expressing catalytically inactive MALT1, which still have a scaffold function, were shown to spontaneously develop autoimmunity due to a decrease in Treg cells associated with increased effector T-cell activation. In contrast, complete absence of MALT1 does not lead to autoimmunity, which has been explained by the impaired effector T-cell activation due to the absence of MALT1-mediated signaling. However, MALT1-deficient mice develop atopic-like dermatitis upon aging, which is preceded by Th2 skewing, an increase in serum IgE, and a decrease

in Treg and surface expression of the Treg functionality marker CTLA-4³¹. In addition, MALT-1 protease-deficient mice display B cell hyperactivation to environmental antigens driving atopic disease³². These findings suggest a mechanism explaining the allergic responses in patients carrying *MALT1* mutation. Frizinsky et al. reported two patients harboring a novel *MALT1* mutation presented with signs of immune deficiency and dysregulation and were found to have an abnormal T-cell receptor repertoire³³, reinforcing the link between MALT1 deficiency and combined immunodeficiency. In fact, MALT1 has a T cell-intrinsic role in regulating the homeostasis and function of thymic and peripheral T cells³⁴. T cell-specific ablation of MALT1 proteolytic activity phenocopies mice in which MALT1 proteolytic activity has been genetically inactivated in all cell types. *Malt1*-PDT mice have a reduced number of Treg cells in the thymus and periphery, although the effect in the periphery is less pronounced compared with full-body *Malt1*-PD mice, indicating that other cell types may promote Treg induction in a MALT1 protease-dependent manner. Despite the difference in peripheral Treg number, both T cell-specific and full-body *Malt1*-PD mice similarly develop ataxia and multi-organ inflammation. Furthermore, reconstitution of the full-body *Malt1*-PD mice with T cell-specific expression of wild-type human *MALT1* eliminated all signs of autoimmunity³⁴. Together, these findings establish an important T cell-intrinsic role of MALT1 proteolytic activity in the suppression of autoimmune responses.

In the Learning Early about Peanut Allergy (LEAP) trial of dietary peanut for the prevention of peanut allergy, Winters et al. found a strong association between peanut allergy and the *MALT1* locus in peanut avoidance group of patients³⁵. Further, in two cousins harboring a *MALT1* mutation showed signs of immune deficiency and dysregulation and were found to have an abnormal T-cell receptor repertoire, reinforcing the link between MALT1 deficiency and immunodeficiency³³. The catalytic activity of the protease MALT1 is required for adaptive immune responses and regulatory T (Treg)-cell development, while dysregulated MALT1 activity can lead to lymphoma³⁶ and recent patients were found with t(11;18)-positive MALT lymphoma, suggesting a distinct clinical entity of MALT lymphoma³⁷.

Filaggrin and epithelial barrier

A dysfunctional epithelial barrier, which allows allergens and microbes to penetrate, leads to the release of type 2 cytokines that drive allergic inflammation and development of anaphylaxis to allergic disease^{38,39}. Filaggrin is crucial to the structure and function of the stratum corneum (SC)⁴⁰, which provides the physical barrier, and has been shown to be a key player in the pathogenesis of a variety of allergic diseases⁴¹, and filaggrin gene (*FLG*) mutations has also been found to be a significant risk factor for allergic diseases such as atopic dermatitis (AD)⁴², asthma, allergic rhinitis, food allergy^{43,44}, contact allergy, and hand eczema^{45,46}. Also filaggrin gene loss-of-function variants modify the effect of breast feeding on eczema risk in early childhood⁴⁷. Although filaggrin has been widely known as a key genetic risk factor for AD⁴², it is known to modify AD disease⁴¹. A recent study revealed that filaggrin deficiency as well as skin injury and dysbiosis trigger keratinocyte intracellular IL-1 α release that drive chronic skin inflammation. That finding that has implications for AD pathogenesis and potential therapeutic targets⁴⁸. More recently, The *FLG* null mutations increase circulating thymic-derived Treg cells and limit expansion of both memory and effector T cells, further promoting Treg abnormalities seen in AD. *FLG* null mutations also heightened the immune imbalance between Th-1, Th-2, and Th-17 like Tregs in AD⁴⁹.

Microbiota contribution to allergic pathways

Studies have consistently demonstrated that dysregulation of resident microbial communities in gut, lung, or skin microbiome is associated with allergic sensitization and inflammation^{50,51} as well as cancer⁵². A recent study showed that the composition and function of upper airway microbiome could influence asthma pathogenesis in young adults and the elderly⁵³. Further, variation in the differential abundance of specific bacterial genera was found in children who develop IgE-associated allergic disease⁵⁴ and early changes in oral microbial composition appear to influence immune maturation and allergy development during the first 7 years of life⁵⁵. Despite increasing awareness of the importance of microbiome in allergy, the molecular basis contribution of the microbiota to allergic inflammation pathway is only beginning to be described. Mice housed under germ-free

conditions display significantly more pronounced type-2 inflammation and allergic sensitization, compared with conventionally colonized mice, showing that commensal microbiota protects against the development of allergic inflammation^{56,57}. In fact, laboratory mice born to wild mice have natural microbiota and model human immune responses⁵⁸. Similarly, antibiotic-driven dysbiosis in germ-free mice leads to impaired maturation of Tregs, increased numbers of IL-4 producing T follicular helper (TFH) cells, a subclass of CD4⁺ T cells that regulate memory B-cell and plasma cell differentiation. This was critical for the elevated IgE phenotype, and thus enhanced Th2 responses, which promotes proinflammatory colonic iNKT cells⁵⁹. Conversely, specific bacterial strains, their components or metabolites can successfully induce a variety of anti-inflammatory responses in the gut and in the lung⁶⁰.

Accumulating evidence supports an essential role for the commensals in mediating immune tolerance through the generation of peripheral antigen-experienced Treg cells⁶¹⁻⁶³. Ohnmacht et al. identified a subset of antigen-experienced Foxp3⁺ Treg cells that express the transcription factor retinoic acid–related orphan receptor γ t (ROR γ t)⁺, which are dependent on the intestinal microbiota and effectively suppress T_H2-skewed immune responses by modifying the phenotype of intestinal dendritic cells⁶⁴. Another group showed that the bacteriotherapy induced expression by Treg cells of the transcription factor ROR- γ t in a MyD88-dependent manner, which was deficient in food allergy infants and mice and ineffectively induced by their microbiota. Deletion of Myd88 or Rorc in Treg cells abolished the protective effect of the microbiota in susceptible mice⁶⁵. However, different outcomes have been described as a consequence of Treg cell-specific deletion of floxed *Rorc* allele, encoding Ror- γ t^{66,67}.

The link between the microbiota and protection from food allergy is not well understood. Macia et al. reported that dysfunctional microbiota with reduced capacity to produce butyrate is a basis for allergic disease⁶⁸. Butyrate, one of the short-chain fatty acids (SCFAs) generated by the microbiota through the metabolism of dietary fiber, was recently shown to inhibit ILC-2 proliferation as well as IL-5 and IL-13 production. Feeding of exogenous SCFAs to mice can expand ROR- γ t⁺ Treg cells⁶⁴ and

increase the percentage of Treg cells in the lungs, affording protection from airway inflammation⁶⁹. In addition to SCFAs, the microbiota can produce a wealth of products, such as the monohydroxy fatty acid 12,13-diHOME, which increased in neonates at risk of asthma, and drove Th2 skewing by acting on dendritic cells and T cells⁷⁰.

Monocytes and food allergy contributions

Infants who develop food allergy display a proinflammatory immune profile in cord blood, but how this relates to interleukin-4 (IL-4)/T helper 2 (Th2)-type immunity characteristic of allergy is unknown. In a general population-derived birth cohort, Zhang et al.⁷¹ found that in infants who developed food allergy, cord blood displayed a higher monocyte-to-CD4⁺ T-cell ratio and a lower proportion of natural regulatory T cell (nT_{reg}) in relation to duration of labor. CD14⁺ monocytes of food-allergic infants secreted higher amounts of inflammatory cytokines (IL-1 β , IL-6, and tumor necrosis factor- α) in response to lipopolysaccharide. In the presence of the mucosal cytokine transforming growth factor- β , these inflammatory cytokines suppressed IL-2 expression by CD4⁺ T cells. In the absence of IL-2, inflammatory cytokines decreased the number of activated nT_{reg} cells and diverted the differentiation of both nT_{reg} and naïve CD4⁺ T cells toward an IL-4-expressing nonclassical Th2 phenotype. These findings explain the susceptibility to food allergy in infants and suggest anti-inflammatory approaches to its prevention.

Future Directions with Big Ideas

IMPORTANT FUTURE DIRECTIONS WITH BIG IDEAS

- **Gene therapies**
- **Prevention**
- **Mono therapy With biologicals**
- **Simultaneous Multi-food therapy**

- **New diagnostics**
- **-OMICs**

Gene therapies

The next-generation approaches using gene therapy for treating allergies is a major future direction for treatment of allergic disorders. ARA-LAMP-Vax is one such agent⁷². This novel compound is a single plasmid multivalent (Ara h1, h2, h3) lysosomal associated membrane (LAMP) DNA vaccine that is designed to radically shift the immune response to peanut allergens in sensitized patients. DNA encoding the peanut allergens Ara h1, h2 and h3 are inserted in tandem in a single plasmid containing the coding sequence for LAMP. Upon intradermal or intramuscular administration, uptake of the plasmid by antigen presenting cells results in the synthesis of an allergen-LAMP fusion protein. The LAMP component directs the fusion protein to cellular lysosomes, where the allergen is processed and added to major histocompatibility complex (MHC)-II antigens, which then stimulate a CD4+ helper T-cell response. Given that the peptide allergen is not released from the antigen presenting cells, it is anticipated that these immunoregulatory effects can be achieved with minimal or no risk of systemic allergic reactions to the vaccine. Another vaccine, PVX108 uses fragments of the allergen protein specifically engineered to avoid mast cells and basophils to desensitize the immune system⁷³. The vaccine has passed safety testing and the next phase of clinical trials is now under way.

Another example of genetically modifying allergens was seen with Fel d1 that produces cat allergy strongly associated with asthma. Fel d1 is the most important allergen from cats and is produced primarily in saliva and spread to the haircoat during grooming and then transferred to the environment via hair and dander. Fel d1 cat allergen causes IgE-mediated sensitization in most cat-

allergic individuals. Gene editing using the major cat allergen, Fel d1 using CRISPR-Cas9 can delete the cat allergen Fel d1 from cat cells⁷⁴. Satyaraj et al.^{75,76} studied a novel approach to reducing allergenic Fel d1 exposure involving binding the Fel d1 with an anti-Fel d1 polyclonal egg IgY antibody. They hypothesized that hair from cats who had been fed foods containing anti-Fel d1 IgY would show a significant reduction in active Fel d1 (aFel d1). From week 3, there was a significant reduction in mean aFel d1 with an overall average decrease of 47% by week 10, ranging from a 33% to 71% decrease vs baseline. Cats with the highest baseline aFel d1 showed the greatest decrease in aFel d1. Thus, feeding anti-Fel d1 IgY to cats successfully reduced aFel d1 on their haircoat, with the greatest decreases observed in cats with initially high levels.

Monotherapy with Biologics

Allergen-specific immunotherapy has several limitations, including cost, long treatment periods, recurring clinic visits, adverse responses to treatment, and lack of persistent desensitization⁷⁷. Furthermore, the allergen-specific nature of food allergy limits the effectiveness of single allergen immunotherapy, providing no cross-reactive desensitization for patients with multiple food allergies. Non-allergen-specific treatments for FA, particularly for those with multiple food allergies, are desirable. Biologics bypass many of these limitations of immunotherapy because they can rapidly inhibit and suppress the immunologic pathways inherent to many food allergies, therefore increasing the allergen threshold required to initiate an allergic reaction⁷⁷. The Food and Drug Administration (FDA) and European Medicines Agency have approved five biologics for a variety of atopic disorders; however, none are currently approved for FA treatment. Several biologics are currently being evaluated for FA in clinical trials, both as monotherapy and as adjunctive therapy in combination with oral immunotherapy (OIT). Below, we discuss several of the recent advances in biological therapy for FA.

IL-4 and IL-13 targeted therapy.

Dupilumab (Dupixent®) is a recombinant human IgG4 monoclonal antibody directed against the α -chain of the IL-4 receptor (IL-4R α). Both IL-4 and IL-13 bind to IL-4R α , resulting in a signaling cascade that promotes allergic inflammation. Shown in Table 1, dupilumab prevents the initiation of this inflammatory cascade and potentially may mitigate the upstream pathophysiological events leading to FA. Dupilumab is currently approved for treating moderate-to-severe atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis.⁷⁸ The first reported use of dupilumab in FA was in a case report from a patient receiving dupilumab for severe atopic dermatitis (AD). The patient was incidentally found to tolerate foods to which she was previously allergic and was originally diagnosed with corn allergy (anaphylactic shock and positive testing) and pistachio allergy (positive testing and positive oral food challenge). After starting dupilumab, the patient subsequently passed two oral challenges to corn and pistachio.⁷⁹ In a phase 2 trial of patients with active EoE, dupilumab reduced dysphagia, histologic features of disease (including eosinophilic infiltration and a marker of type 2 inflammation), and abnormal endoscopic features compared with placebo⁸⁰.

There are currently 4 ongoing clinical trials evaluating the safety and potential efficacy of dupilumab in FA: (1) NCT03793608 dupilumab monotherapy for treating peanut allergy; (2) NCT03682770 dupilumab as adjunctive therapy with OIT for peanut allergy; (3) NCT03679676 dupilumab as adjunctive therapy with OIT for multiple food allergies; and (4) NCT04148352 dupilumab as an adjunctive therapy with OIT for cow's milk allergy.

IL-5 targeted therapy

As part of the pathogenic mechanism of FA, the release of IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) induces IL-5 production. Specifically, ILC2 cells may be activated by IL-25, which, in turn, increases levels of IL-5, an interleukin that promotes eosinophil production, maturation, proliferation, and migration.⁷⁷ Currently, three anti-IL-5 products have been approved by the FDA for treatment of eosinophilic asthma: mepolizumab (Nucala®), reslizumab (Cinqair®), and benralizumab (Fasenra®), as shown in Table 1. Mepolizumab and reslizumab bind to IL-5, blocking receptor interaction, and benralizumab binds to the α -chain of IL-5 receptor on eosinophils and basophils. This blockade depletes the production and activity of eosinophils.⁷⁷ Mepolizumab and reslizumab have demonstrated efficacy in reducing eosinophil counts in patients with eosinophilic esophagitis

(EOE)⁸¹ and benralizumab is currently being evaluated for treating eosinophilic gastrointestinal disease (NCT03473977).

Alarmin targeted therapy

Alarmins, including IL-25, IL-33, and TSLP, play a critical role in developing and maintaining FA. The release of alarmins can be induced in response to exposure of food allergens, and promote a shift away from a T helper 1 (Th1) tolerogenic state to a Th2-dominant proallergic state by inducing the activation and expansion of type 2 innate lymphoid cells (ILC2s) and production of cytokines IL-4, IL-5, and IL-13. TSLP has been shown to enhance the production of IgE from memory B cells via an IL-4- and/or IL-13-dependent mechanism^{82,83}.

Anti-alarmin agents have been evaluated for treating several atopic conditions. The inhibition of IL-33 using the humanized IgG1/kappa monoclonal antibody etokimab has been investigated for treating FA. Shown in Table 1, a phase II, double-blind, placebo-controlled study determined that 73% of patients receiving a single dose of etokimab were able to tolerate a cumulative dose of 275 mg peanut protein compared with 0% of patients receiving placebo⁸⁴.

Additional anti-alarmin agents are under similar evaluation in clinical trials. Tezepelumab, a human monoclonal antibody which binds to TSLP, has been evaluated for treating asthma and AD, but not yet for FA. Although trials investigating the blockade of IL-25 and TSLP in humans with FA are not yet underway, a murine model study showed that injecting a monoclonal antibody against IL-25, IL-33 receptor, and/or TSLP strongly inhibited FA development⁸⁵. Overall, antibodies toward alarmins are showing promise as treatments for atopic diseases. The safety and efficacy of anti-alarmin agents for treating FA patients has yet to be determined.

Simultaneous Multifood therapy

For patients with multiple food allergies, immunotherapy with only one food does not desensitize them from other food allergens. Moreover, patients with multiple food allergies report lower quality of life improvement after single food oral immunotherapy (OIT) partly because they need to avoid other foods⁸⁶. A strategy for treating these patients is to use multiple food allergen OIT.

Begin et al. reported that 22 out of 25 patients who received OIT with up to 5 foods simultaneously were able to reach daily doses of 10 times their original reaction thresholds for each food⁸⁷. More recently, Eapen et al.⁸⁸ reviewed the progress of patients 1.5 to 18 years undergoing multifoed OIT for up to 12 foods, including peanut, tree nuts, seeds, legumes, and egg. Of 45 patients, 4 completed OIT and were able to eat their allergenic foods three times weekly. The up-dosing phase of OIT was problematic for 49% of the patients who experienced oral itching, perioral hives, and abdominal pain. The authors reported these symptoms were mild and that 87% of the patients successfully increased their threshold for food mediated allergic reactions. These studies indicate that multifoed OIT has therapeutic potential for patients who can tolerate it.

Novel Diagnostics

Currently, the cornerstone of diagnosing IgE-mediated allergy is a clinical history followed by in-vitro or in-vivo tests, including Skin Prick Test (SPT), Specific-IgE (sIgE) test, cellular test and Oral Food Challenge (OFC)⁸⁹. Conventional allergy tests like SPT and sIgE to allergen extracts are unable to differentiate sensitization from clinical allergy, resulting in overdiagnosis. More advanced antigen-based tests like component-resolved diagnostics (CRD) may lead to a more accurate diagnosis and selection of therapeutic intervention^{90,91}, and becoming increasingly incorporated into routine diagnostics⁹². A recent systemic review suggested that sIgE to Ara h2 can enhance the accuracy of diagnosis and reduce the number of OFCs necessary to rule out clinical peanut allergy in unclear cases⁹³. A hazelnut allergy study suggested that combinations of CRD-based approaches with clinical history and extract data are superior to CRD alone⁹⁴. Another advanced technology for allergy diagnosis based on CRD is multiplex molecular allergens assays, such as MAdx ALEX⁹⁵ and Euroimmun Multiplex immunoblot assay⁹⁶, which enable clinicians to simultaneously detect multiple allergens in a single test that requires only a small amount of blood.

Cellular tests, such as Basophil activation test (BAT)^{97,98}, Histamine-release assays (HRA)⁹⁹, and more recently, the mast cell activation test (MAT)^{100,101} have been reported to add significant diagnostic value to SPT, IgE-based test methods and reduce the need for OFC testing. BAT was compared to

histamine release (HR) and passive HR and did not show a significant advantage but could diagnose subjects with low basophil numbers in contrast to HR⁹⁹. The reports on passive sensitization strategies using the mast cell lines¹² or mast cell precursors¹³ showed promising potential for distinguishing peanut allergy from peanut sensitization, but with lower sensitivity than BAT. However, MAT has the advantage of using serum instead of fresh blood, overcoming the limitation that BATs requires fresh blood. In addition, the MAT also provides results for patients whose basophils do not respond to the BAT.

Although many novel diagnostic techniques are improving the accuracy of food allergy diagnostics, OFC remains the only gold standard for definitive diagnosis and sometimes cannot be avoided ¹⁰². However, OFC is time-consuming, costly, and burdened by the risk of life-threatening anaphylactic reactions^{102,103}. Therefore, reliable prognostic markers for predicting the severity of allergic reactions during OFC are unmet needed^{104,105}. Chinthrajah et al. proposed an integrated approach combining lab-values (ratio of peanut-stimulated basophils to anti-IgE-stimulated basophils), along with clinical variables (exercise-induced asthma and FEV1/FVC ratio at the time of DBPCFC) to be incorporated into a novel algorithm for assigning challenge severity score (CSS) to predict the severity of reaction during peanut OFC¹⁰⁶. This decision rule is being investigated in a clinical trial (NCT02103270).

OMICS

Traditional approaches for treatment atopic diseases have focused on managing patients based on phenotype or the observable characteristics of disease, yet despite similar clinical symptoms and appearance, multiple patients may have different treatment response and disease trajectories. For example, atopic diseases may be manifestations of the same disease. This is seen in atopic dermatitis, which presents first during infancy with progression to food allergy, allergic asthma, and allergic rhinitis. Thus, pathophysiologic heterogeneity within each atopic phenotype has shifted our efforts away from treating groups of patients based on clinical observations towards identifying the underlying mechanistic pathways and biomarkers to better inform diagnosis, treatment, and

prognosis in individual patients. Toward this aim, exponential advances in bioinformatic technologies have allowed us to generate and analyze large-scale biological data sets¹⁰⁷. With personalized or precision medicine, the advent of technologies that identify genes or biomarkers for diagnosing or monitoring treatment efficacy has revolutionized many fields of medicine, especially allergic diseases. Precision medicine has been practiced in allergology for over a century since pollen-specific immunotherapy¹⁰⁸. Today, this is commonly referred to “omics”, one of the important driving platforms behind recent developments that enabled investigation of almost everything at the molecular level of proteins, lipids, and small molecules including innumerable DNA and RNA sequencings with a hypothesis-free approach. Omics is a collective set of high-throughput technologies designed to empirically analyze large sets of pathophysiologic data, including genetic makeup (genomics), epigenetic modifications (epigenomics), gene and protein expression (transcriptomics and proteomics, respectively), metabolite production (metabolomics), and microbial flora (microbiomics). Unlike traditional hypothesis-driven and reductionist approaches, the omics approach to biological studies is holistic, integrative, and hypothesis-generating, attempting to characterize and quantify a wide spectrum of analytes and cellular components from a single biological sample towards the goal of identifying complex patterns and associations that better define endotypes and allow for treatment decisions tailored toward the underlying pathologic mechanism(**Figure 1**)¹⁰⁹.

One area that omics has enabled new discoveries is the field of food allergy (FA). The increasing prevalence of FA, lack of robust biomarkers, and inadequate treatments has driven further research into the mechanism underlying food allergies. FA is a complex and heterogeneous disease, and multiple genetic variants play a role in the etiology of this disorder. In addition to genetic and epigenetic factors^{110,111}, the microbiome¹¹² and the exposome¹¹³ determine FA predisposition, disease progression, and the severity of reactions to offending foods. Omics technologies provide large amounts of data from different subjects and disease states, which enable the creation of detailed network maps representing physiologic pathways associated with health and disease¹¹⁴. To date in patients with FA, genome-wide association studies (GWAS) have uncovered several common

genetic variants contributing to risk¹¹⁵. Recent findings have indicated that *FOXP3* DNA methylation changes can influence FA or responses to treatment¹¹⁶. Research into other epigenetic changes, including those mediated by histone modifications, might be useful in improving our ability to diagnose FA and to monitor its evolution or response to therapy. It is also likely that targeted alteration of the epigenome might soon be possible with advances in epigenome editing and DNazymes¹¹¹.

Omics technologies have generated a wealth of data and have allowed us to create molecular signatures, disease susceptible genetic loci, and potential biomarkers in patients with FA. For example, transcriptomics has shown us the differences in gene expression between allergic and nonallergic patients and novel immune processes in FA. Proteomics has helped us identify and characterize allergens and evaluate food-processing techniques that could decrease the allergenic potential of allergic epitopes, as well as proteomic features associated with disease states or responses to therapy¹¹⁵. Identifying metabolites synthesized by human or resident microbes could help us to molecular fingerprint patients to improve FA prognosis, diagnosis, or targeted therapy. With these fast-growing efforts to generate and integrate data from different technologies, the application of precision medicine and targeted therapy in patients with FA is likely within the next 10 years.

Conclusion

During the past decade, we have experienced extraordinary progress in unraveling cellular and molecular mechanisms of immune regulation. Today, the specialties of allergy and clinical immunology are now part of precision medicine that stratifies diseases into specific subsets and diagnoses as well as new targeted therapy options such as biologics and small molecules. For example, drug development is now shifting from chemicals to biologicals. In past decades, there have been no significant treatment breakthroughs for many patients with allergic disorders, but today, we are experiencing the success of major biological drugs and novel allergen-specific

immunotherapy treatments. In this review, we have seen significant advances in our understanding of the complexities of immune and cellular reactions in allergic disorders, the role of microbiome and diet, treatment successes and failures, all of which have allowed us to take new approaches in diagnosing and treating disorders like food allergy, asthma, atopic dermatitis, eczema, and food allergy. Important future directions with big ideas will include additional advances in the development of new biologics, gene therapy, immunotherapy, and further discoveries with OMICs.

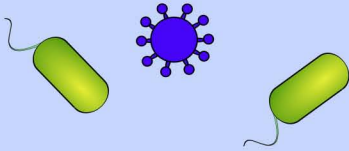
Table 1: Biologics and Targets for Atopic Disorders

Biologic	Target	Indication(s)
Omalizumab (Xolair®)	Anti-IgE	1. Moderate to severe persistent atopic asthma in patients 6 years of age or older inadequately controlled by inhaled corticosteroids 2. Chronic idiopathic urticaria in patients 12 years of age and older inadequately controlled by H1 antihistamine treatment.
Mepolizumab (Nucala®)	Anti-IL-5	Severe eosinophilic asthma in patients 12 and older as add-on maintenance treatment
Reslizumab (Cinqair®)	Anti-IL-5	Severe eosinophilic asthma in patients 18 and older as add-on maintenance treatment
Benralizumab (Fasenra®)	Anti-IL-5R	Severe eosinophilic asthma in patients 12 and older as add-on maintenance treatment
Dupilumab (Dupixent®)	Anti-IL-4R α	1. Moderate-to-severe atopic dermatitis in patients 12 years and older whose disease is inadequately controlled with topical prescription therapies or when those therapies are not advisable 2. Moderate-to-severe asthma in patients 12 years and older as add-on maintenance treatment with an eosinophilic phenotype or with oral corticosteroid dependent asthma 3. Chronic rhinosinusitis with nasal polyposis in adult patients as add-on
Etokimab	Anti-IL-33	1. Completed Phase 2a clinical trial for adults with peanut allergy (NCT02920021) 2. Completed Phase 2a clinical trial for adults with eosinophilic asthma (NCT03469934). Phase 2b clinical trial for eosinophilic asthma postponed pending results from chronic rhinosinusitis with nasal polyps trial (see below) 3. Completed Phase 2b clinical trial for adults with moderate-to-severe atopic dermatitis (NCT03533751)- failed to meet primary endpoint

Microbiomics



- Metagenomics
- Sequencing (MGS)



Epigenomics



- Chromatin remodelling
- DNA methylation
- Histone modification
- RNA interference

Proteomics

- MALDI-TOF
- Nano LC-MS/MS



Transcriptomics

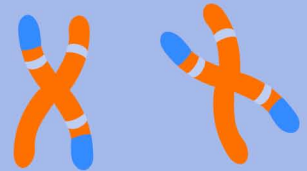
- Microarrays
- Single cell RNAseq



OMICS

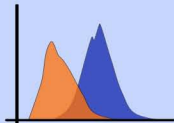
Genomics

- Whole Genome Sequencing



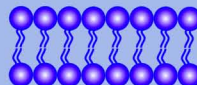
Immunophenotyping

- CyTOF
- Flow cytometry
- Single cell RNAseq



Lipidomics

- Liquid Chromatography Tandem Mass Spectrometry (LC-MS)



Metabolomics

- Nuclear Magnetic Resonance (NMR)
- Mass Spectrometry (MS)

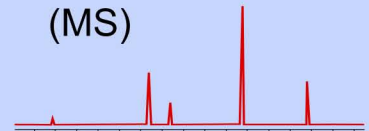


Figure 1. Omics technologies has enabled precision medicine and personalized care. Omics is based on platform technologies in genomics (by far the most robust), metabolomics, proteomics, epigenomics, transcriptomics, lipidomics, and microbiomics to generate vast datasets, and advanced bioinformatics to interrogate and interpret the datasets using machine learning and artificial intelligence.

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