

Advances and highlights in mechanisms of allergic disease in 2015

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This review highlights some of the advances in mechanisms of allergic disease, particularly anaphylaxis, including food allergy, drug hypersensitivity, atopic dermatitis (AD), allergic conjunctivitis, and airway diseases. During the last year, a mechanistic advance in food allergy was achieved by focusing on mechanisms of allergen sensitization. Novel biomarkers and treatment for mastocytosis were presented in several studies. Novel therapeutic approaches in the treatment of atopic dermatitis and psoriasis showed that promising supplementation of the infant's diet in the first year of life with immunoactive prebiotics might have a preventive role against early development of AD and that therapeutic approaches to treat AD in children might be best directed to the correction of a T_H2/T_H1 imbalance. Several studies were published emphasizing the role of the epithelial barrier in patients with allergic diseases. An impaired skin barrier as a cause for sensitization to food allergens in children and its relationship to filaggrin mutations has been an important development. Numerous studies presented new approaches for improvement of epithelial barrier function and novel biologicals used in the treatment of inflammatory skin diseases. In addition, novel transcription factors and signaling molecules that can develop as new possible therapeutic targets have been reported. (*J Allergy Clin Immunol* 2016;■■■■:■■■-■■■.)

Key words: Anaphylaxis, atopic dermatitis, asthma, eosinophilia, allergen immunotherapy

This review highlights key advances in mechanisms of anaphylaxis, systemic mastocytosis, drug hypersensitivity, and epithelial barrier dysfunction in patients with atopic dermatitis (AD) and asthma, particularly those reported in 2015. Some of the key advances are summarized in [Table I](#).¹⁻³⁷

EPIDEMIOLOGY, DIAGNOSIS, AND MECHANISMS OF ANAPHYLAXIS, INCLUDING FOOD ALLERGY

An increase in the prevalence of anaphylaxis has been reported in several studies. In a US-wide survey of physicians, an analysis of "Anaphylaxis in America" summarized results from data gathered from experience, knowledge, and attitudes among allergy/immunology specialists, primary care, and emergency physicians.¹ More pediatric allergy/immunology specialists than others believed that life-threatening allergic reactions today are more common than 10 years ago.

Data from national databases concerning anaphylaxis in England and Wales (1992-2012) showed increased incidence but not for fatal anaphylaxis. They also identified marked differences in the age distribution of anaphylaxis admissions and fatalities according to the trigger, which might offer important clues to the underlying pathophysiology.²

Studies performed in an Australian hospital focusing on a population with food-related anaphylaxis showed an increase from 5.6-fold in 2005-2006 to 8.2-fold in 2011-2012. The highest rates occurred in children aged 0 to 4 years, but the greatest proportional increase occurred in those aged 5 to 14 years.³ Acceleration in the rate of increase in food-related anaphylaxis in older children and teenagers has implications for management of food allergy, who are at greatest risk of fatal anaphylaxis.³

Another study also showed an increased rate of hospitalization (from 2001 to 2011) for food-induced anaphylaxis in Italian children.⁴ In addition, the prevalence of anaphylaxis was reported to be increasing in the European pediatric population, as well as in the United States and Australia.³⁸

Consequently, molecular research on mechanisms of anaphylaxis have been revisited and increased. Tryptase and histamine levels reportedly increase during anaphylaxis but seem to be inadequate to fully identify all anaphylactic responses. Accordingly, Gill et al³⁹ reviewed the role of platelet-activating factor (PAF) in anaphylaxis. Patients with acute allergic reactions have very high serum PAF levels, which correlated better than serum tryptase or histamine levels with anaphylaxis severity. Anaphylaxis grade significantly correlated with basal levels of

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Abbreviations used

AD:	Atopic dermatitis
ADR:	T cell–mediated adverse drug reaction
AIT:	Allergen immunotherapy
BATF:	Basic leucine zipper transcription factor
CHS:	Contact hypersensitivity
CRH:	Corticotrophin-releasing hormone
DP2:	D prostanoid receptor 2
EoE:	Eosinophilic esophagitis
FFx:	Fragility fracture
FOXP3:	Forkhead box P3
GARP:	Glycoprotein A repetitions predominant
GBP:	Glycan-binding protein
HMGB1:	High-mobility group box 1
IDEC:	Inflammatory dendritic epithelial cell
ILC2:	Group 2 innate lymphoid cell
IM-ADR:	Immune-mediated adverse drug reaction
JAK:	Janus kinase
LC:	Langerhans cells
NF-κB:	Nuclear factor κB
NP:	Nasal polyp
PAF:	Platelet-activating factor
PM:	Particulate matter
PMN-MDSC:	Polymorphonuclear myeloid-derived suppressor cells
PP2A:	Protein phosphatase 2A
PPI:	Proton pump inhibitor
PR-10:	Pathogenesis-related group 10 protein
RAGE:	Receptor for advanced glycation end products
Siglec:	Sialic acid-binding immunoglobulin-like lectin
SIP:	Sphingosine-1-phosphate
STAT3:	Signal transducer and activator of transcription
TJ:	Tight junction
Treg:	Regulatory T
TSLP:	Thymic stromal lymphopoietin

PAF-acetylhydrolase.^{39,40} Another recent report showed that the plasma protease cascade mediated by the factor XII–driven contact system critically contributes to the pathogenesis of anaphylaxis in both murine models and human subjects.⁴¹

Strategies have been evaluated for the consumption and avoidance of food allergens. A study has taken the attention of the scientific community, with early introduction of peanuts that decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts.⁴²

One of the unmet needs is to define a definitive diagnostic marker for food allergy. Martino et al⁵ performed genome-wide DNA methylation profiling on blood mononuclear cells from volunteers who had undergone objective oral food challenges, concurrent skin prick tests, and specific IgE tests. They discovered a DNA methylation signature of 96 CpG sites that predicted clinical outcomes. Diagnostic scores were derived from these 96 methylation sites, and cutoffs were determined in a sensitivity analysis. Methylation biomarkers outperformed allergen-specific IgE measurement and skin prick tests for predicting oral food challenge outcomes. Food allergy status was correctly predicted in a replication cohort with an accuracy of 79%. As such, DNA methylation biomarkers might offer promise for diagnosing food allergy and other allergic disorders.⁵

At present, the diagnosis of food-induced anaphylaxis is based on clinical history, determination of food-specific IgE

concentrations, and oral food challenges. The identification of the real food allergen responsible for anaphylaxis has always been debated. For example, it was shown that anaphylaxis after administration of inactivated trivalent influenza vaccines might be caused by specific IgE to an influenza vaccine component and not to contaminating egg protein.⁴³

An advance was achieved by Hofmaier et al.⁴⁴ The investigators focused on mechanisms of allergen sensitization, in particular the route and dose of allergen exposure to pathogenesis-related group 10 protein (PR-10), a family of allergenic proteins shared by many pollens (eg, birch and alder) and foods (eg, apple, peach, and soy). Notably, children are exposed to both pollen-derived (inhaled) and food-derived (ingested) PR-10 molecules. They investigated the role of route and dose of exposure in the evolution of IgG and IgE responses to recombinant PR-10 molecules. They found that nonallergic children have a default antibody response to PR-10 molecules, which is early, weak, and transient; does not involve IgE; and is initiated by foodborne PR-10. By contrast, atopic subjects have an antibody response to PR-10 molecules that is delayed, strong, and persistent; involves both IgG and IgE; and is initiated by airborne PR-10. These findings have implications for novel diagnosis, as well as considering ways to counterregulate the development of allergic sensitization.

Eschborn et al⁴⁵ studied a humanized mouse model of food allergy in which NOD/SCID/γc-deficient mice were reconstituted with peripheral blood cells from allergic subjects and immunized with the relevant allergen. Gastrointestinal allergen inoculation induced intestinal inflammation, which could be inhibited by inoculation with regulatory T (Treg) cells, particularly activated Treg cells, from the same human donor. Furthermore, blocking of the Treg cell–associated molecule, glycoprotein A repetitions predominant (GARP) blocked the suppressive effect of Treg cells, whereas treatment with soluble recombinant GARP amplified the suppressive effect. Based on these observations, the authors suggest that soluble GARP treatment can suppress human allergy, whereas blocking GARP can enhance cancer immunotherapy.⁴⁵

SYSTEMIC MASTOCYTOSIS

Mast cell disorders are associated with an increased number, increased activation, or both of mast cells and are broadly divided into those defined by expression of clonal mast cells and those defined by mast cell activation. Systemic mastocytosis can lead to potentially fatal anaphylactic reactions caused by excessive mast cell mediator release.^{46,47} The absence of urticaria or angioedema in patients with severe reactions to Hymenoptera stings with hypotension might represent a relevant factor in identifying patients with mastocytosis, regardless of their serum tryptase levels.⁶ Serum levels of 9α, 11β-prostaglandin F₂ were also reported as a useful biomarker of anaphylaxis.⁷ Type 2 cytokine–related immune responses associated with development of antigen-specific IgE antibodies can contribute to pathogenesis in patients with allergic diseases and to fatal anaphylaxis. However, recent findings in mice indicate that IgE also can enhance defense against honeybee venom. In a recent study mice lacking IgE or functional FcεRI could not survive challenge with a potentially lethal amount of viper venom. The extent to which type 2 immune responses against venoms can decrease pathology associated with envenomation is influenced by the type of venom, frequency of venom exposure, and the genetic background of the host.⁴⁸

TABLE I. Key advances

Advance	References
Anaphylaxis	
Increased prevalence of anaphylaxis	Altman et al, ¹ Turner et al, ² Mullins et al, ³ Nocerino et al, ⁴ Martino et al, ⁵ Sicherer et al ³⁸
Novel biomarkers and treatment for patients with mastocytosis	Zanotti et al, ⁶ Nassiri et al, ⁷ Weng et al, ⁸ Broesby-Olsen et al, ⁹ Vos et al, ¹⁰ Yip et al ¹¹
AD	
Therapeutic approaches in patients with AD and psoriasis	Noda et al, ¹² Czarnowicki et al, ¹³ Suarez-Farinas et al ¹⁴
Impaired skin barrier causes sensitization to food allergens in children	Brough et al ¹⁵
Novel biologicals used in treatment of inflammatory skin diseases	Krueger et al, ²⁰ Lin et al, ²¹ Li et al, ²² MacDonald et al ²³
Asthma	
Bronchial epithelial barrier function	Pellerin et al, ¹⁶ Kim et al, ¹⁷ Amano et al, ¹⁸ Czarnowicki et al, ¹⁹ Madritsch et al, ²⁶ Kubo et al ²⁷
<i>IL1RL1</i> gene has been implicated in the pathogenesis of asthma	Akhabir et al ²⁴
BATF as a possible therapeutic target in asthmatic patients	Ubel et al ²⁵
MicroRNA 9 regulates glucocorticoid signaling in steroid-resistant airway hyperresponsiveness	Li et al ²⁸
Eosinophilia	
Improved treatment focusing on EoE	Wen et al, ²⁹ Rothenberg et al ³⁰
Mucin proteins regulate eosinophil survival	Ilmarinen et al ³¹
Allergen immunotherapy	
ICON consensus on AIT	Jutel et al ³²
Treg cells achieve allergen tolerance and suppress airway inflammation	Tsai et al, ³⁴ Akdis and Akdis ³³
IL-10-overexpressing B cells and histamine exerts immune regulatory functions	Stanic et al, ³⁵ Ferstl et al ³⁶
Novel method to monitor the response to immunotherapy	Shamji et al ³⁷

In a recent study human LAD2 cells and umbilical primary human cord blood–derived cultured mast cells were stimulated with substance P or IgE/anti-IgE with or without preincubation with luteolin and its novel structural analog 3', 4', 5, 7-tetramethoxyluteolin (methlut) or cromolyn (1–100 μ mol/L) for 2 or 24 hours, after which mediator secretion was measured.⁸ Methlut appeared to be a promising mast cell inhibitor for the treatment of allergic and inflammatory conditions. It has been reported that patients with mastocytosis had high serum corticotrophin-releasing hormone (CRH) and bone marrow mast cell CRH receptor expression. In a recent study the authors demonstrated high serum CRH levels and bone marrow mast cell CRH receptor expression in a patient with mastocytosis and suggest that high serum or skin CRH expression could stimulate mast cells to secrete vascular endothelial growth factor, other mediators, or both to increase vascular permeability and promote tissue inflammation.⁴⁹

Broesby-Olsen et al⁹ have suggested that the KIT D816V mutation is a novel method to diagnose mastocytosis in patients with anaphylaxis. The authors present data on 4 adult patients with anaphylaxis in whom a positive KIT D816V mutation in peripheral blood was found despite normal or low basal serum tryptase levels and absent or inconspicuous urticaria pigmentosa skin lesions.

As discussed above, measurement of serum tryptase levels is the most commonly used test to estimate the need for bone marrow biopsy in patients suspected to have indolent systemic mastocytosis. In a retrospective study in patients with indolent systemic mastocytosis older than 50 years with a body mass index of greater than 25 kg/m², serum methylimidazole acetic acid was reported to be more useful than serum tryptase in determining the need for bone marrow biopsy.¹⁰ Fragility fractures (FFxs) and osteoporosis occur frequently in patients with indolent systemic mastocytosis. The Mast FFx score, which calculates these 5 parameters (ie, male sex, high levels of the bone resorption marker

serum type I collagen C-telopeptide, low hip bone mineral density, absence of urticaria pigmentosa, and alcohol intake), has been shown as an easy-to-use prediction model for the occurrence of FFxs in patients with systemic mastocytosis.⁵⁰

Sumpter et al⁵¹ identified a new pathway for mast cell activation mediated by autocrine secretion of hemokinin-1, which then ligates and signals through its receptor, neurokinin receptor 1; this pathway was shown to contribute to passive local and systemic anaphylaxis and airway inflammation. Because mast cells express the vitamin D receptor, Yip et al¹¹ studied the effects of 25-hydroxyvitamin D and its active metabolite, 1 α ,25-dihydroxyvitamin D, on mast cell functions *in vitro* and *in vivo*. Mouse and human mast cells were shown to express an enzyme, 25-hydroxyvitamin D-1 α -hydroxylase, which converts 25-hydroxyvitamin D to 1 α ,25-dihydroxyvitamin D. Both forms of vitamin D₃ suppressed mast cell mediator release *in vitro* and decreased the severity of mast cell–dependent passive cutaneous anaphylaxis when applied to the skin; these effects were vitamin D receptor and 25-hydroxyvitamin D-1 α -hydroxylase dependent. The authors suggest that these observations raise the possibility of developing vitamin D–related therapies to suppress mast cell–mediated disorders.

MECHANISMS OF DRUG HYPERSENSITIVITY

There was increasing evidence that specific HLA alleles influence the risk of drug hypersensitivity reactions. Several features of T cell–mediated adverse drug reactions (ADRs) are strikingly similar to those displayed by patients with autoimmune diseases.⁵²

In a recent review White et al⁵³ discussed the role of host genetics, microbes, and drugs in the development of immune-mediated adverse drug reactions (IM-ADRs). They focused on

expanding existing models of IM-ADR pathogenesis, as well as implications and future applications of this work in clinical practice. The authors highlighted the importance of T-cell immune responses in the mechanisms of both B cell-mediated and primary T cell-mediated IM-ADRs.

Munoz-Cano et al⁵⁴ showed gene ontology analysis in patients with a proved clinical history of nonsteroidal anti-inflammatory drug-dependent or nonsteroidal anti-inflammatory drug-independent anaphylaxis to lipid transfer protein-induced anaphylaxis. Their data suggest that differential regulation of the IFN- γ pathway, IgG receptors, and adenosine receptor 3 might provide the pathogenic basis of distinct responses between the 2 groups.

Anaphylaxis patient registries are accumulating data directly linked to patients. Recently, a study using a Charite-Berlin anaphylaxis registry database indicated a higher risk of severe anaphylaxis after monotherapy with β -blockers or angiotensin-converting enzyme inhibitors, which was more pronounced when both drugs were combined. Their findings were confirmed in a mouse model.⁵⁵ Another study showed that peroxisome proliferator-activated receptor-dependent dermal acute vascular hyperpermeability activation involves the activation of mitogen-activated protein kinase and Akt pathways and leads to downstream destabilization of endothelial cell-cell junctions and anaphylaxis.⁵⁶

MECHANISMS OF AD

AD is the most common chronic inflammatory skin disease and often precedes the development of food allergy and asthma.^{38,57,58} Major mechanisms include abnormalities in terminal differentiation of the epidermal epithelium leading to a defective stratum corneum, which allows enhanced allergen penetration and systemic IgE sensitization. Atopic skin is predisposed to colonization or infection by pathogenic microbes, most notably *Staphylococcus aureus* and *Herpes simplex* virus.

Noda et al¹² compared and reviewed the common inflammatory skin diseases psoriasis and AD, which are characterized by immune-mediated inflammation and abnormal keratinocyte differentiation. In patients with psoriasis, suppression of the IL-23/T_H17 pathway seems the best therapeutic approach, and novel developments in testing of targeted therapeutics against various immune axes (T_H2, T_H22, and IL-23/T_H17) are being pursued in patients with AD and psoriasis.¹² It was suggested that therapeutic approaches to treat AD in children might be best directed to the correction of a T_H2/T_H1 imbalance, whereas adults might also benefit from IL-22-targeted therapies.¹³

Suarez-Farinas et al¹⁴ have investigated the scalp transcriptome and associated biomarkers in comparisons of patients with AD and psoriasis with alopecia areata, a common T cell-mediated disorder. They showed that alopecia areata is associated with a combined T_H2, T_H1, IL-23 and IL-9/T_H9 signature, suggesting consideration of anti-T_H2-, anti-T_H1-, and anti-IL-23-targeting strategies.

Thymic stromal lymphopoietin (TSLP) is one of 3 cytokines in addition to IL-25 and IL-33 that are known to promote the generation and maintenance of a T_H2 cytokine response. Wang et al⁵⁹ used a mouse adoptive transfer model to show that TSLP was not required for ovalbumin plus alum-induced generation of a T_H2 response by ovalbumin-specific T cells but was required for the survival of ovalbumin-specific memory T cells in this model. TSLP signaling of CD4⁺ T cells also promoted the recall

response of mice with established T_H2 memory in a mouse model of AD and memory cell generation and maintenance after a secondary response.

A study performed in 228 European American patients with AD, who were selected according to their eczema herpeticum status and severity, provided evidence that genetic variants in the *IFNGR1* gene are implicated in susceptibility to eczema herpeticum.⁶⁰ Another RNA-sequencing approach was applied in patients with AD and a history of eczema herpeticum and in patients with AD without a history of eczema herpeticum. Patients with AD with a history of eczema herpeticum have a distinct immune response after *H simplex* virus exposure. The data suggest that the inhibition of interferon regulatory factors 3 and 7 innate immune pathways might contribute to increased susceptibility to disseminated viral infection in these patients.⁶¹

Using the Wayne County Health, Environment, Allergy and Asthma Longitudinal study birth cohort, Havstad et al⁶² investigated whether distinct and meaningful atopic phenotypes exist within a racially diverse birth cohort using 10 allergen-specific serum IgE measurements from children aged 2 years. The authors presented 4 different allergen sensitization patterns: "low to no sensitization" (76.9% of sample), "highly sensitized" (2.7%), "milk and egg dominated" (15.3%), and "peanut and inhalant(s)" (5.1%).

Comorbidities in patients with AD suggest more complex mechanisms open for further research. A study performed by the National Health Interview Survey showed in 2 adult cohorts that eczema in adults is a marker for cardiovascular risk, emphasizing the importance of behavioral modification and more aggressive interventions to better manage eczema.⁶³ In addition, an analysis of 19 US population-based studies demonstrated that eczema is associated with increased headaches in childhood, particularly in patients with severe disease accompanied by atopy, fatigue, and sleep disturbances.⁶⁴

Gruber et al⁶⁵ showed that supplementation of the infant's diet in the first year of life with immunoactive prebiotics might have a potential preventive role against early development of AD, but the effect was not sustained in infants at low risk of atopy.

Finally, Lee et al⁶⁶ examined the mechanism of itching, a process germane to AD. Focusing on eosinophil-deficient mice, they were able to show that itching and contact toxicant-induced edematous responses and histopathology were linked to the presence of eosinophils. The authors implicated substance P in this response. These findings, as commented on by Leiferman,⁶⁷ present compelling evidence that targeting eosinophils might be a useful strategy for pruritis.

Immune deficiencies linked to atopy

Gambineri et al⁶⁸ discussed a patient with X-linked immune dysregulation, polyendocrinopathy, enteropathy syndrome who presented with severe enteropathy, dermatitis, and other signs of autoimmunity since 3 to 4 weeks of age. The identified forkhead box P3 (*FOXP3*) gene mutation was associated with reduced expression of this protein in Treg cells. After unmanipulated and unrelated donor cord blood stem cell transplantation, the gut immune system recovered and functioned longer than the peripheral immune system. A whole-exome and targeted gene sequencing study showed LPS-responsive Beige-like anchor deficiency as a novel cause of X-linked immune dysregulation, polyendocrinopathy, enteropathy-like syndrome and Treg cell deficiency

associated with metabolic dysfunction and increased apoptosis of Treg cells.⁶⁹

Another type of X-linked immune deficiency, Wiskott-Aldrich syndrome, which is characterized by microthrombocytopenia, eczema, and immunodeficiency, was reported by Kharya et al.⁷⁰ The authors showed that haploidentical T-cell receptor $\alpha\beta$ and CD19-depleted hematopoietic stem cell transplant appears to be a promising treatment.

In addition, a study performed in a cohort of patients with hemophagocytic lymphohistiocytosis and X-linked lymphoproliferative disease 1 showed that the use of an assay for 2B4 receptor function in combination with signaling lymphocyte activation molecule-associated protein expression in peripheral blood lymphocytes might help to refine the selection of patients with hemophagocytic lymphohistiocytosis with X-linked lymphoproliferative disease 1 who are appropriate for mutation analysis.⁷¹

A study performed in Pediatric Immuno-Hematology Hospital in France showed that high circulating endothelial cell counts are associated with the occurrence of endothelial complications in children undergoing hematopoietic stem cell transplantation for primary immunodeficiencies.⁷²

de Inocencio et al⁷³ described the involvement of somatic *NOD2* mosaicism in the pathogenesis of Blau syndrome, which is characterized by the triad of granulomatous arthritis, dermatitis, and uveitis.

Human mutations in *ORAI1* are associated with severe combined immunodeficiency, myopathy, and ectodermal dysplasia with anhydrosis. Accordingly, a patient with opportunistic infections and hypotonia caused by a novel *ORAI1* mutation, who had combined immunodeficiency but residual T-cell function, was reported.⁷⁴

Mechanisms of skin barrier dysfunction in patients with AD

Skin barrier dysfunction plays a key role in the initiation of AD and is associated with both genetic susceptibility and environmental risk factors. The skin of patients with AD can exhibit not only loss-of-function mutation in filaggrin 1 but also defects in tight junction (TJ) function, all of which can contribute to decreased skin barrier function.⁷⁵ Diverse inherited and acquired abnormalities in epidermal structural and enzymatic proteins converge to produce defective permeability barrier function and antimicrobial defense in patients with AD.⁷⁶ Recent evidence suggests that children can become sensitized to food allergens through an impaired skin barrier. Brough et al¹⁵ showed that exposure to peanut antigen in dust through an impaired skin barrier in atopic inflamed skin is a possible route for peanut sensitization and allergy.

As was previously shown, filaggrin mutations have been found to be the strongest risk factor for AD.⁷⁷ IL-33 bears the potential to directly or indirectly promote epidermal barrier impairment and thereby plays a crucial role in sustaining and enhancing the local inflammatory responses in patients with AD. One relevant effect of this cytokine was shown to be downregulation of filaggrin.⁷⁸

Another study by Thyssen et al⁷⁹ showed the relationship between filaggrin mutations, AD, and food sensitization in adults. The authors were not able to evaluate the possible effects of current AD and disease severity, but the presence of filaggrin

mutations in patients with AD appeared to increase the prevalence of sensitization.

A whole-exome sequencing study of Ethiopian patients with AD and ichthyosis vulgaris, which is characterized by loss of filaggrin expression, suggested that no single gene is likely to be causative for this disease complex in these patients.⁸⁰ The data revealed several rare variants in both previously described and new candidate genes, especially those in the epidermal differentiation cluster on 1q21, suggesting heterogeneous disease pathogenesis among Ethiopian patients.

In another study, Pellerin et al¹⁶ reported a novel finding, showing downregulated bleomycin hydrolase gene expression in the epidermis of the lesional skin in atopic patients. Less bleomycin hydrolase can lead to reduced production of amino acids, which compose the natural moisturizing factor and affect stratum corneum dryness.

In another study that links immune response to filaggrin expression and barrier function in the skin, Kim et al¹⁷ investigated the presence of the TSLP receptor in human epidermis and keratinocytes. They demonstrated downregulation of filaggrin expression by TSLP, which is mediated by signal transducer and activator of transcription (STAT) 3-dependent pathways, extracellular signal-regulated kinase-dependent pathways, or both.

In another study Amano et al¹⁸ showed that topical application of a Janus kinase (JAK) inhibitor suppressed STAT3 activation and improved skin barrier function, permitting increases in levels of terminal differentiation proteins, such as filaggrin, and natural moisturizing factors in AD and dry skin.

Severe dermatitis, multiple allergies, and metabolic wasting syndrome is a recently recognized syndrome caused by mutations in the desmoglein 1 gene. To date, only 3 families have been reported. A recent study focused on severe dermatitis, multiple allergies, and metabolic wasting syndrome demonstrated that a novel *de novo* heterozygous missense c.1757A>C mutation in the desmoplakin gene, which predicts the amino acid substitution p.His586Pro in the desmoplakin polypeptide, has a role in heritable skin barrier defects.⁸¹

In addition, the first study to identify a combined effect of the gene-environment interaction between claudin 1 (*CLDN1*) polymorphism and mold exposure on the development of AD and IgE production has been reported. Mold exposure in early life is a risk factor for AD, and the *CLDN1* polymorphism might influence the development of AD and IgE production in children.⁸²

Czarnowicki et al¹⁹ defined molecular and structural effects in the skin that are induced by the common moisturizer petrolatum, which is often used to prevent skin infections in patients with AD. They showed that petrolatum robustly enhances expression of skin antimicrobial peptides and epidermal molecules that contribute to skin barrier function. This was accompanied by increased stratum corneum thickness and significantly reduced T-cell infiltrates in the setting of “normal-appearing” or nonlesional AD skin.

Immune effector mechanisms in patients with AD

Differences between Langerhans cells (LCs) and inflammatory dendritic epithelial cells (IDECs) were found in the epidermis of patients with AD.⁸³ LCs, but not IDECs, extend dendrites through the TJs, making them more likely to capture antigens from outside the TJ barrier. Langerin accumulated on LC dendrite tips, whereas

FcεRI was diffusely expressed on the cell membranes of LCs and IDECs in AD lesional skin.⁸³

A recent study depicts differences in skin-homing and systemic T-cell subsets in patients with AD versus those with psoriasis. Both types of patients showed increased T-cell infiltration in skin lesions; however, patients with AD were characterized by higher persistent and systemic activation of central and effector memory T-cell subsets. Pathologic T-cell activation in these patients extends to “skin-homing” and “systemic” central memory T-cell populations.⁸⁴

Correa da Rosa et al⁸⁵ investigated whether patients with AD have altered tissue immune responses on allergen challenge. The authors showed that allergic immune reactions were globally attenuated and differentially polarized in patients with AD, with significant decreases in levels of T_H1-related products, some increases in levels of T_H17-related products, and inconsistent upregulation of T_H2-related products. This suggests that strategies to boost T_H1 responses might be necessary to increase the effectiveness of protective immunologic responses.⁸⁵

As a proinflammatory cytokine mainly secreted by epithelial cells, TSLP has been associated with allergic reactions in the skin and lungs. In a recent study Fornasa et al⁸⁶ showed that a short isoform of TSLP is expressed in healthy skin and gut tissue, whereas a long TSLP isoform is present in inflammatory disease conditions. The TSLP isoform ratio is altered by several inflammatory disorders, which has implications for the treatment and prevention of AD.

The human skin-associated autoallergen thioredoxin induced IgE-dependent upregulation of the T_H2 cytokine IL-13 and impaired upregulation of IL-10 in sensitized patients with AD. Thioredoxin can be released from dermal or epidermal cells and might promote inflammatory responses by activating specific T cells, as well as other cells that express receptors for IgE.⁸⁷

Czarnowicki et al⁸⁸ demonstrated that patients with severe AD have selective expansion of skin-homing T_H2/T_C2 and T_H22/T_C22 subsets with lower T_H1/T_C1 frequencies in peripheral blood lymphocytes. The authors identify T-cell pathways warranting further investigation in cutaneous lymphocyte antigen–positive and negative cell subsets in children. These data create a critical basis for studying alterations in immune activation in peripheral blood of adults and pediatric patients with AD.

Several studies highlighted the involvement of IL-22 in patients with AD. A recent study by Mashiko et al⁸⁹ showed that human skin mast cells are major producers of IL-22 in patients with psoriasis and AD. The authors established that skin mast cells also produce IL-17, which could be important in the pathophysiology of chronic inflammatory skin disorders.

Noda et al⁹⁰ demonstrated that the Asian AD phenotype, which combines features of AD and psoriasis, is characterized by increased T_H17 polarization. These patients (even those with increased IgE levels) have a phenotype that blends characteristics of European American patients with AD and those with psoriasis, including increased hyperplasia, parakeratosis, higher T_H17 activation, and a strong T_H2 component. The relative pathogenic contributions of the T_H17 and T_H2 axes in creating the Asian AD phenotype need to be tested in future clinical trials with appropriate targeted therapeutics.

The studies were extended to comparison of B-cell populations and antibody-secreting cells in the peripheral blood of patients with AD, patients with psoriasis, and control subjects. The data suggest that AD is accompanied by a systemic expansion of

transitional and chronically activated CD27⁺ memory B cells, plasmablasts, and IgE-expressing memory B-cell subsets.⁹¹ CD19⁺CD24⁺⁺CD38⁺⁺ transitional and CD19⁺CD24[−]CD38[−] new memory B-cell counts were both higher in patients with AD.

Novel treatments linked to mechanisms of AD

Clinical trials with novel biologicals are being increasingly reported in the treatment of inflammatory skin diseases. A study performed in patients with moderate-to-severe plaque psoriasis treated with a human IgG₁ mAb specific for the IL-23 p19 subunit (BI 655066) demonstrated good drug tolerance and durable clinical improvement in these patients, supporting a central role for IL-23 in the pathogenesis of psoriasis. BI 655066 treatment resulted in reduced expression of lesional skin genes associated with IL-23/IL-17–signaling pathways and normalization of psoriatic lesion gene expression profiles to a profile close to that of nonlesional skin. A significant correlation between treatment-associated molecular changes and Psoriasis Area and Severity Index score improvement was observed.²⁰

Allopurinol is a commonly prescribed drug for symptomatic hyperuricemia and its complication, gout. A problem with allopurinol is that it is a frequent cause of severe cutaneous adverse reactions, including hypersensitivity syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Lin et al²¹ showed strong pharmacogenetic links between HLA-B*58:01 and allopurinol/oxypurinol and provided a molecular understanding of allopurinol-induced severe cutaneous adverse reactions associated with HLA-B*58:01.

In a different study of treatment of severe skin inflammation, lidocaine therapy was shown to ameliorate the severity of lesional skin in patients with AD. The authors demonstrated a critical role and molecular mechanism of lidocaine in Treg cell regulation.²² Lidocaine treatment improved the SCORAD severity scores of patients with AD and improved the numbers of FOXP3⁺ Treg cells to levels seen in healthy subjects. Treg cells have been investigated in another study showing that Treg cells isolated from affected skin of patients with systemic sclerosis produced significant amounts of IL-4 and IL-13 (a T_H2 response) and that the plasticity of Treg cells toward T_H2 can be tissue specific.²³

The mechanisms of AD have been frequently compared with those involved in contact hypersensitivity (CHS). Goldenberg et al⁹² addressed the problem involving allergic contact dermatitis, which has a complex relationship with AD and is a common pediatric problem that warrants attention, research, and action. The authors also discussed nickel-limiting directives active in many countries and the potential benefits deriving from collaborations between researchers, manufacturers, policymakers, and patients. In a recent study the investigation of the roles of M2 and M1 macrophages in patients with CHS showed that mannose receptor–positive M2 macrophages contribute to the development of CHS by producing matrix metalloproteinase 12.⁹³

ALLERGIC CONJUNCTIVITIS

Su et al⁹⁴ used an experimental allergic conjunctivitis model, in which mice are primed systemically with ragweed allergen in alum and then have their eyes exposed to a ragweed solution to evaluate the ability of a culture supernatant of TNF-stimulated bone marrow–derived mesenchymal stem cells to suppress disease induction. In keeping with other evidence for the

immunosuppressive effects of mesenchymal stem cells, the culture supernatant suppressed disease induction and, both *in vitro* and *in vivo*, inhibited IgE secretion, mast cell enrichment, activation and histamine release, and vascular permeability. Inhibitory effects were COX-2 dependent and partially reproduced by prostaglandin E₂. The authors suggest that culture supernatants of mesenchymal stem cells might be useful for treating allergic conjunctivitis; however, the ability of such supernatants to suppress established allergic conjunctivitis was not investigated.

IMMUNE EFFECTOR MECHANISMS IN AIRWAY DISEASES

Research performed by using multiple omics and systems biology approaches

Systems biology and multiple omics have been used during the last year in several studies of asthma and allergies to uncover the relationship among physiologic, biologic, epigenetic, and environmental processes. It was recently reviewed that deeper phenotypic and environmental profiles and wider implementation in system-wide profiling will elucidate connections that will uncover relevant biological pathways.^{95,96} The total pollen transcriptome, proteome, and allergome of *Panicoidae* Johnson grass pollen revealed quantitative differences in its allergenic components compared with temperate grass pollens.⁹⁷ This knowledge has the potential to improve specific diagnosis and allergen immunotherapy (AIT) for patients with grass pollen allergy in subtropical regions and reduce the burden of allergic respiratory disease globally.

Goldblum et al⁹⁸ showed that several conformational epitopes on Jun a 1 are major targets for the IgE response to mountain cedar pollen, which makes Jun a 1 good prototype for identifying the structural basis of allergenicity.

In another omics study transcriptomic and proteomic sequencing of house dust mite showed the full gene structures of 20 canonical and 7 noncanonical allergen homologs.⁹⁹ The Kyoto Encyclopedia of Genes and Genomes pathway analysis revealed a phototransduction pathway in *Dermatophagoides farinae*, as well as thiamine and amino acid synthesis pathways, which is suggestive of an endosymbiotic relationship between *D farinae* and its microbiome. The authors also found a novel major allergen, ubiquinol-cytochrome c reductase binding protein-like protein, which they designated as Der f 24.

In a recent genome-wide study, the authors evaluated 6706 cis-acting expression-associated variants identified through a genome-wide expression quantitative trait loci survey of CD4⁺ lymphocyte association with asthma.¹⁰⁰ The data presented new evidence to support the roles of fatty acid desaturase 2 (*FADS2*), N-acetyl-alpha-D-galactosaminidase (*NAGA*), and Factor XIII (*F13A1*) in asthma pathogenesis.

Obesity increases the risk of respiratory outcomes in children with asthma with a clear dose-response relationship between body mass index and asthma/wheeze. Authors found that children carrying the β_3 -adrenergic receptor gene *ADRB3* Arg allele were more susceptible to the adverse effects of obesity on childhood asthma.¹⁰¹

The IL-1 receptor-like 1 (*IL1RL1*) gene has been implicated in the pathogenesis of asthma and related phenotypes both in animal models and human studies, as well as in a variety of other diseases. Consistent with this, an important functional polymorphism was identified in the asthma-associated *IL1RL1* region in the lungs.²⁴

Biochemical and physiologic mouse model studies have also contributed to our understanding of effector mechanisms in allergic airway disease. Balenga et al¹⁰² used mouse models to demonstrate that defects in regulator of procontractile G protein-coupled receptor signaling 6, which is selectively expressed in airway smooth muscle and negatively regulates procontractile G protein-coupled receptor signaling, have little effect on allergic airway inflammation and lower IL-13 and IL-33 responses to allergen challenge but increase airway responsiveness to methacholine in unimmunized mice. The authors suggest that such defects can contribute to asthma in subjects without lack prominent airway inflammation.¹⁰²

Amison et al¹⁰³ studied the role of platelet purinergic receptors in mouse models of allergic airway inflammation. Platelet activation by ADP through the receptor P1Y1 stimulated RhoA signaling, which was important for the formation of platelet-leukocyte complexes and polymorphonuclear cell migration to the lungs in ovalbumin-primed and airway-challenged mice. Furthermore, ADP activation of platelets used a distinct signaling pathway from ADP-induced platelet aggregation. The authors suggest that this difference can be exploited to develop new anti-inflammatory/antiallergic drugs.

DNA-dependent protein kinase, which is important for repairing double-stranded DNA breaks, is also required for the expression of vascular cell adhesion molecule 1, as well as many other nuclear factor κ B (NF- κ B)-dependent genes that are downstream of TNF stimulation. Ghonim et al¹⁰⁴ used *in vitro* studies and mouse models to show that genetic or pharmacologic DNA-dependent protein kinase inhibition suppressed pulmonary allergy without inducing severe combined immunodeficiency. This suggested to the authors that this kinase might be a potential target for the treatment of asthma.

Advances in cytokines and cells

IL-25 secreted from sinonasal epithelium and infiltrating mast cells play a crucial role in the pathogenesis of chronic rhinosinusitis with nasal polyps (NPs). Shin et al¹⁰⁵ demonstrated that IL-25 expression was upregulated in NP mucosa from patients with chronic rhinosinusitis with NPs compared with uncinate process tissue from control subjects and those with chronic rhinosinusitis without NPs. Overexpression of epithelial IL-25 was confirmed by using immunohistochemistry, and double-immunohistochemistry staining showed that tryptase-positive cells were one of the main sources of IL-25 among immune cells. Accordingly, in a mouse model anti-IL-25 treatment reduced the number of polyps, mucosal edema thickness, collagen deposition, and infiltration of inflammatory cells, such as eosinophils and neutrophils.¹⁰⁵

Group 2 innate lymphoid cells (ILC2s) were shown to mediate helminth immunity, inflammation, and tissue repair and remodeling in mouse models.¹⁰⁶ The involvement of ILC2s in asthma was recently demonstrated with their increased numbers in peripheral blood. In contrast, there was no change in allergic rhinitis, suggesting differences in the immunopathogenesis of these diseases.¹⁰⁷

It has been demonstrated that IL-33 activated mast cells and ILC2 drive predominantly IL-13-regulated gene expression when cocultured with bronchial epithelial cells (Fig 1).¹⁰⁸⁻¹¹⁰ This mechanism seems to initiate a transcriptional program that can subsequently exacerbate airway pathology.

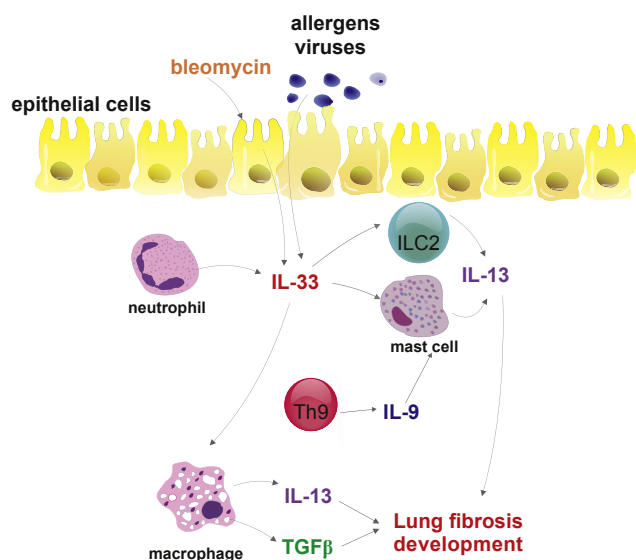


FIG 1. Role of cells and cytokines in allergic airway diseases. Epithelial cells are activated by external factors, such as allergens and viruses. IL-33 secreted from epithelial cells acts on mast cells and ILC2s, which results in a predominantly IL-13-regulated gene expression (Nagarkar et al¹⁰⁸). During the development of fibrosis, bleomycin induces IL-33 release by epithelial cells and stimulates a neutrophil-dependent processing of IL-33. IL-33 stimulates the production of IL-13 by ILC2s and macrophages and the production of TGF- β by macrophages. This currently acts as a major mechanism in the development of lung fibrosis (Li et al¹¹⁰). IL-9 secreted by Th9 cells is apparently important for the accumulation and activation of mast cells in the lungs (Sehra et al¹⁰⁹).

Ullah et al¹¹¹ studied mouse models of house dust mite- and cockroach-induced allergic airway disease by using gene-deficient mice and specific inhibitors to identify a pathway that leads to production of the pro-Th2 cytokines through IL-25, IL-33, and TSLP. They demonstrated that activation of TLR4 by LPS existing in the allergens leads to IL-1 α production, which stimulates epithelial cell secretion of the receptor for advanced glycation end-product (RAGE) ligand high-mobility group box 1 (HMGB1); HMGB1 activation of RAGE promoted IL-25 and IL-33 production and allergic sensitization. The HMGB1-RAGE pathway was suggested as a useful therapeutic target; however, the involvement of this pathway in maintenance of established allergic airway disease was not investigated.

ILC2s, mast cells, CD4⁺ T cells, and natural killer T cells produce IL-9 that regulate inflammation and affects many other cell types. The number of Th9 cells present in the draining lymph nodes and airways strongly correlates with asthmatic disease.¹¹² Sehra et al¹⁰⁹ used a house dust mite model of murine allergic airway disease to evaluate the importance of IL-9 and IL-9-secreting Th9 cells for pulmonary mast cell accumulation. Through the use of gene-deficient mice, specific inhibitors, and cell transfer experiments, IL-9 production by Th9 cells was shown to be important for the accumulation and activation of mast cells in the lungs; neither Th2 cells nor IL-13 had this effect. The authors suggest that IL-9 and Th9 cells might be appropriate targets to limit mast cell-dependent immediate hypersensitivity; however, IL-9 involvement in maintaining established pulmonary mast cell responses was not investigated.

Cytokine-induced JAK activation is upstream of STAT activation, which mediates many cytokine effects. Ashino et al¹¹³ demonstrated that a specific combined JAK1/3 antagonist inhibits

STAT5 and STAT6 activation and Th2 differentiation but neither Th1 nor Th17 differentiation *in vitro*. *In vivo* the same antagonist blocked a pulmonary Th2 response and the induction of allergic airway disease in mice when instituted during the sensitization phase of this model and allergic airway disease, but not Th2 cytokine expression, when instituted during the allergen challenge phase. This is consistent with previous evidence that STAT6 activation is critical for Th2 differentiation but not maintenance of cytokine secretion by polarized Th2 cells and is also required for IL-4 and IL-13 induction of goblet cell metaplasia, increased smooth muscle responsiveness, and airway eosinophilia.

Li et al¹¹⁰ studied the role of IL-33 in the development of bleomycin-induced pulmonary fibrosis in a murine model (Fig 1). Bleomycin induced epithelial cell IL-33 release and stimulated neutrophil-dependent processing of IL-33 to a more potent form, which promoted ILC2 and macrophage production of IL-13 and macrophage production of TGF- β , together promoting collagen secretion by fibroblasts and the development of lung fibrosis.

Increased airway deposition of the secreted extracellular matrix protein periostin is associated with human asthma. Bentley et al¹¹⁴ used a house dust mite model of allergic airway disease in C57BL/6 mice to study the importance of periostin in disease development. All disease features, including Th2 cytokine secretion, were reduced in periostin-deficient mice and in mice treated with a neutralizing anti-periostin mAb. Dendritic cells from periostin-deficient mice did not mature normally, and transfer of bone marrow-derived dendritic cells from wild-type mice promoted allergic responses in periostin-deficient mice. The authors suggest that periostin might be a useful therapeutic target in asthma but do not demonstrate periostin involvement in the maintenance of established disease in their model.

B cells and IgE regulation in the Th2 microenvironment have been studied also. Transcriptional expression profiling of B lymphocytes revealed increased IL-4 receptor expression in patients with allergic asthma.¹¹⁵ B-cell RNA sequencing transcriptome analysis was performed with 24 samples from patients with house dust mite-induced allergic asthma (to avoid seasonal variation) and 17 samples from control subject in this study. The authors suggest that IL-4 receptor might hold translational potential as both a biomarker and a therapeutic target in patients with allergic asthma to house dust mite. Naturally occurring IgG autoantibodies specific for IgE have been identified in patients with asthma and other diseases. A study performed in patients with atopic and nonatopic asthma demonstrated that naturally occurring IgG anti-IgE autoantibodies can inhibit, as well as induce, basophil activation. These data might explain in part why some of the atopic subjects who make allergen-specific IgE never have clinical symptoms and why omalizumab therapy shows a variable clinical benefit in patients with severe atopic asthma.¹¹⁶

Focusing on deep phenotyping of B-cell responses, Anzillotti et al¹¹⁷ explored the phenotype of B cells in patients with common variable immunodeficiency and found a substantial reduction of PreBII-large cells, suggesting a defect in a fundamental checkpoint during B-cell maturation in this diverse set of immunodeficiencies.

The D prostanoid receptor 2 (DP2), also known as chemoattractant receptor-homologous molecule expressed on Th2 cells, is implicated in the pathogenesis of asthma and was recently shown to be highly expressed by the bronchial epithelium in asthmatic patients. The activation of DP2 drives epithelial

differentiation, suggesting that in addition to its well-characterized role in inflammatory cell migration, DP2 might contribute to airway remodeling in asthma.¹¹⁸ Prostaglandin D₂ and cysteinyl leukotrienes are lipid mediators derived from mast cells; they have been shown to activate T_H2 cells.¹¹⁹

Xue et al¹²⁰ demonstrated that prostaglandin D₂ and cysteinyl leukotrienes activate T_H2 cells through different pathways, but act synergistically to promote multiple downstream effector functions, including neutrophil migration and survival. Combined inhibition of both prostaglandin E₂ and leukotriene E₄ might provide an effective therapeutic strategy for allergic responses, particularly in patients with severe asthma.

Endogenous prostanoids can suppress the development of allergic airway disease in mouse models. Zaslonka et al¹²¹ used an ovalbumin model of allergic airway disease, cell transfer studies, treatment with the synthetic prostaglandin misoprostol, and E prostanoid receptor 2-deficient mice to study the role of this receptor in limiting allergic airway disease. They demonstrated that prostaglandin E₂ signaling of CD4⁺ T cells through E prostanoid receptor 2 suppresses IL-13 secretion and, at least partly through this mechanism, the development of allergic airway disease. Although prostaglandin E₂ is consequently suggested as a possible therapeutic for asthma, no evidence is provided that prostaglandin E₂ can suppress established allergic airway disease.

Polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) infiltrate the lungs in mouse models of allergic airways disease and have an inhibitory effect on airway inflammation. Shi et al¹²² demonstrate that aspirin treatment and COX-1 deficiency inhibit PMN-MDSC accumulation in the lungs of allergen-immunized mice; this is associated with an increased T_H2 airway response. Two prostaglandin-related mechanisms were shown to be responsible for the interaction between COX-1 inhibition and PMN-MDSCs: COX-1-dependent prostaglandin E₂ acting on the prostanoid 2 and 4 receptors promoted bone marrow generation of PMN-MDSCs, whereas the prostaglandin E₂/EP4/cyclic AMP/protein kinase A pathway promoted PMN-MDSC expression of arginase 1, which was predominantly responsible for their suppressive effect on airway inflammation. Consistent with this, PMN-MDSCs from patients with aspirin-induced asthma were considerably less suppressive than the same cell population from patients with aspirin-tolerant asthma.¹²²

Traffic-related particulate matter (PM) has been linked to an increased incidence of asthma and allergic diseases. The molecular mechanisms through which PM exposure promotes allergic diseases was clarified in a recent study demonstrating that PM activates an aryl hydrocarbon receptor–Jagged 1–Notch cascade to promote allergic airway inflammation, especially in the context of the proasthmatic IL-4 receptor allele Il4raR576.¹²³ Another link to type 2 immune response and IL-4 has been recently reported. Perceived stress has been presented as a persistent precipitating effect in increasing T_H2 responses in asthmatic patients, and this effect might be mediated by peripheral blood levels of neuropeptide Y.¹²⁴ Neuropeptide Y levels consistent with a dampened response associated with chronic psychological stress were lower among young patients with acutely exacerbated and non-exacerbated asthma compared with healthy control subjects. Among asthmatic patients, neuropeptide Y appeared to play a role in the association between perceived stress and the persistently increased IL-4 levels of the type 2 immune response. Additional understanding of mechanisms involved in the type 2

immune response was provided by a recent study performed in patients with mild atopic asthma, which showed increased numbers of hematopoietic progenitor cells expressing receptors for TSLP and IL-33, which are important initiators of type 2 immunity. In asthmatic patients allergic inflammatory responses are associated with increased lung homing of bone marrow-derived CD34⁺ hematopoietic progenitor cells, which include eosinophil lineage-committed progenitor cells. TSLP and IL-33 promote lung homing of precursors of proinflammatory effector cells through an IL-13-dependent axis in patients with allergic asthma.¹²⁵

The integrin lymphocyte function-associated antigen 1 (CD11a/CD18) is required for efficient homing of T_H2 cells. Knight et al¹²⁶ demonstrated that the variant of the polymorphic CD11a allele in BALB/c mice encodes a protein that causes greater adhesion to the lymphocyte function-associated antigen 1 ligand ICAM-1 than the protein encoded by the C57BL/6 variant of the CD11a gene. This was shown to result in more severe allergic lung disease and *Leishmania major* infection in mice that bore the BALB/c allele. Furthermore, the authors identified a human CD11a polymorphism that was associated with atopy. This suggested that CD11a might be a useful susceptibility marker and therapeutic target in allergy.

Circadian rhythms in asthmatic patients

Allergic symptoms vary considerably with time of day under the control of a circadian clock that modulates IgE/mast cell reactions. Using mast cell-deficient mice, mice with a dominant negative mutation in the transcription factor Clock, and a mast cell reconstitution strategy, Nakamura et al¹²⁷ demonstrated that temporal variation in IgE-mediated mast cell degranulation is dependent on Clock and humoral factors produced by the adrenal glands.

Transcription factors and signaling molecules in asthmatic patients

The transcription factor basic leucine zipper transcription factor (BATF) is associated with B- and T-cell differentiation.¹²⁸ BATF-deficient mice were found by Ubel et al²⁵ to be resistant to the induction of allergic airway disease, whereas transgenic BATF overexpression enhanced the severity of experimental murine allergic airway disease. BATF expression was increased in PBMCs of children with allergic asthma who had not been treated with steroids; this increase was reversed by steroid therapy. This suggests that steroid therapy might, in part, suppress asthma through effects on BATF and that BATF might be an appropriate therapeutic target in asthmatic patients.

Pham et al¹²⁹ used mouse models to show that cytokine activation of STAT3 induces activity of the Ets-family transcription factor Etsv5, which activates IL-17a and IL-17f gene expression in T cells through histone modification. Furthermore, these effects were shown to contribute to a house dust mite-induced model of allergic airway disease in C57BL/6 mice, which is consistent with a role for IL-17 in this model.

Hatchwell et al¹³⁰ demonstrated that β -adrenergic agonists, such as salmeterol, partially suppress the development of house dust mite- and rhinovirus 1B-induced murine allergic airway disease by increasing protein phosphatase 2A (PP2A) levels. PP2A, in turn, suppressed the expression of relevant chemokines and chemokine receptors and reduced phosphorylated extracellular

signal-regulated kinase 1 and active NF- κ B levels in the lungs. The anti-inflammatory effects of salmeterol could be mimicked by an unrelated PP2A-activating drug and inhibited by small inhibitory RNA knockdown of PP2A. Thus PP2A activation can account for some of the clinical benefit of β_2 -adrenergic agonists in asthmatic patients.

Oskeritzian et al¹³¹ studied the role of the bioactive sphingolipid sphingosine-1-phosphate (S1P) and its receptors in airway disease induced by systemic IgE-mediated mast cell activation. Crosslinking of mast cell-associated IgE induced S1P secretion, which amplified mast cell degranulation and caused T cells to infiltrate the lungs in mice. S1P activation of mast cell S1P receptor 2 promoted induced STAT3-dependent mast cell chemokine release, which induced T-cell recruitment to the lungs. It is suggested that targeting this pathway might prevent the development of chronic allergic lung disease.

Endotypes of asthma

One recent focus of asthma research is the identification of asthma endotypes, which are defined as subsets of asthma driven by different pathophysiologic processes. A recent study showed that the T_H2/T_H17 -predominant pattern of cytokine expression was more common in asthmatic patients than in control subjects. Within the population of asthmatic patients, T_H2/T_H17 predominance was associated with more severe airway obstruction and hyperresponsiveness.^{132,133} A multicolor flow cytometric study that compared peripheral blood of patients with asthma during acute episodes, patients with stable asthma, and control subjects described higher numbers of Treg cells in patients with stable asthma compared with those in healthy control subjects. Treg cells gated as $CD3^+$, $CD4^+$, $CD25^+$, $CD127^+$, $FOXP3^+$, and $Helios^+$ exhibit a major change during asthma exacerbations.¹³⁴ Higher numbers of Treg cells in peripheral blood were found in subjects with stable asthma compared with healthy control subjects. In contrast, during asthma exacerbations, the number of Treg cells was significantly reduced compared with those in patients with stable asthma. Nonviral asthma exacerbation was characterized by increased frequency of IL-22- and IL-4-producing $CD3^+CD4^+$ T cells.

Xie et al¹³⁵ identified more IL-27 in combination with a type 2/CCL26 signature and suggested that the combined effects on IL-27 and IL-13 augmented STAT signaling in patients with severe asthma. Another study linked to IL-27 identified a novel tolerogenic circuit encompassing suppressive $CD1c^+$ DCs and Treg cells that might be implicated in impaired respiratory immunity in patients with chronic obstructive pulmonary disease. The same study further highlighted IL-10 and IL-27 as potent therapeutic targets.¹³⁶

In addition, Cagoni et al¹³⁷ demonstrated that fatal asthma is associated with the increased presence of eosinophils that express HLA-DR and costimulatory molecules in lymph nodes and large airways. The expression of Factor XIIIa⁺ monocyte-derived DCs, $CD4^+$ and $CD8^+$ T cells, $CD20^+$ B cells, and $CD23^+$ cells was increased in the large airways without a corresponding increase in expression of these cells in the bronchopulmonary lymph nodes.

Finally, a classification of asthmatic patients based on an endotype defined by blood and/or sputum eosinophils was reported. Fowler et al¹³⁸ showed that a cutoff of 0.45×10^9 cells/L for blood eosinophilia had a high sensitivity

and specificity for predicting sputum eosinophilia ($\geq 2\%$). This is valuable for determining the effect of certain biological therapies that target T_H2 pathways (eg, anti-IL-5). The authors propose that going forward with this relatively higher threshold would be useful for clinical trials, but patients should still be included if they have airway eosinophilia, regardless of the blood eosinophil count.

Epithelial barrier function in asthmatic patients

It is becoming increasingly evident that intact epithelial barrier function is important for preventing allergens from reaching tissues involved in allergic inflammation. Strategies that strengthen the epithelial barrier or block allergen migration toward epithelial function can have therapeutic potential. A recent study demonstrated the possibility of using antibody conjugates bispecific for ICAM-1 and a major respiratory allergen to inhibit allergen migration through respiratory cell layers and to reduce the activation of inflammatory cells below the mucosal epithelium. This approach might have also a synergistic protective effect in allergic patients with rhinovirus-induced asthma exacerbations.²⁶

In a study aiming to demonstrate a way to reconstitute an impact barrier,²⁷ it was demonstrated that CpG-DNA improved and restored the human bronchial barrier integrity in air-liquid interface cultures by increased expression of TJ-related molecules and their proper allocation, particularly in leaky asthmatic epithelium. This provided an additional hygiene hypothesis-compatible approach for preventing and treating asthma by restoring the impaired epithelial barrier through treatment with CpG-DNA. As evidence for the role for epithelial cells in extracellular matrix production in asthmatic airway inflammation, human lung fibroblasts cocultured with airway epithelial cells from asthmatic patients showed differential expression of the extracellular matrix constituents collagen I (COL1A1) and collagen III (COL3A1) and hyaluronan synthase.¹³⁹

Sialic acid-binding immunoglobulin-like lectins and related glycan-binding proteins

Sialic acid-binding immunoglobulin-like lectins (Siglecs) and related glycan-binding proteins (GBPs) play a role in immune regulation; defects in those molecules can lead to immunodeficiencies. This knowledge provides previously unanticipated opportunities for rational design of targeted therapies for immune dysfunction.^{140,141} The makeup of the human glycome, the GBPs that translate glycan recognition into function, and examples of glycan recognition events that are responsible for immune regulation have been reviewed recently.^{140,141}

A second review article has focused mainly on 2 families of GBPs: Siglecs and selectins that are involved in multiple steps of the immune response, including distinguishing pathogens from self, cell trafficking to sites of inflammation, fine-tuning of immune responses leading to activation or tolerance, and regulation of cell survival.^{140,141} Sialoglycan ligands for the immune inhibitory sialic acid-binding proteins Siglec-8 on eosinophils and Siglec-9 on neutrophils have been shown to be upregulated in chronically inflamed airways. Inflammatory mediators enhance the expression of Siglec-9 ligands, including MUC5B, on human Calu-3 cells through the NF- κ B pathway.

Enhanced biosynthesis of inhibitory Siglec ligands might be a tissue-level response to dampen ongoing inflammation.¹⁴²

Siglec-F is a proapoptotic receptor on mouse eosinophils that has a human homologue; constitutive expression of its ligand requires the enzyme $\alpha 2,3$ sialyltransferase. Kiwamoto et al¹⁴³ showed that mice lacking a functional allele for the gene that encodes this enzyme had lower levels of Siglec-F ligands compared with wild-type mice after sensitization and airway challenge with ovalbumin, along with higher levels of ovalbumin-specific serum IgG₁ (and total but not ovalbumin-specific serum IgE) and peribronchial and bronchoalveolar lavage eosinophils. These observations are compatible with the hypothesis that Siglec-F ligands downregulate eosinophil responses and that targeting Siglec-F or treatment with Siglec-F ligands might suppress airway eosinophilia.

In an additional article Kiwamoto et al¹⁴⁴ demonstrated that depleting a sialyltransferase that is required for constitutive synthesis of a pulmonary Siglec-F ligand increased airway eosinophil numbers, which is consistent with the possibility that Siglec-F ligand acts normally to restrain airway eosinophilia. The authors suggest the possibility of harnessing this relationship for the development of therapeutic modalities.

Mechanisms of steroid-resistant asthma

A recent study investigated the mechanisms underlying glucocorticoid responsiveness and systemic cysteine oxidation and its association with inflammatory and clinical features in patients with difficult-to-treat asthma. The association of cysteine oxidation with increased markers of oxidative stress and inflammation, increased features of asthma severity, decreased clinically defined glucocorticoid responsiveness, and impaired GR function were hypothesized. The study demonstrated that oxidation of the amino acid cysteine was associated with decreased responsiveness to systemic glucocorticoids in children with difficult-to-treat asthma.¹⁴⁵

Steroid-resistant asthma has been also linked to activation of innate immune cells. Recently, microRNA-9 has been shown to regulate glucocorticoid signaling in patients with steroid-resistant airway hyperresponsiveness, which suggests a novel mechanistic target for future therapies.²⁸

Viral infections and asthma

Viral infections play an essential role in asthma exacerbations. A recent study reported that after influenza A virus infection in bronchial epithelial cells, viral levels increased 2-fold in asthmatic patients compared with those in control subjects, and this increase occurred together with increased IFN- $\lambda 1$ levels.¹⁴⁶ The authors did not observe differences between the groups after respiratory syncytial virus infections but rather significantly decreased IFN- λ levels that correlated with a decrease in viral titers. As a second recent finding, induction of suppressor of cytokine signaling 1 has been reported in patients with asthma exacerbation by rhinovirus infection.¹⁴⁷

Vitamin D and mechanisms of asthma

Vitamin D insufficiency has been associated with asthma and its severity. As an interesting novel finding, it was reported recently that 100 nmol/L vitamin D is able to augment the

expression of the soluble decoy receptor sST2 by epithelial cells and lymphocytes, which in turn inhibits the actions of IL-33.¹⁴⁸ In an independent study it has been demonstrated that supplementation with vitamin D reduced eosinophilic airway inflammation in patients with nonatopic asthma but did not affect sputum neutrophils.¹⁴⁹

A prospective birth cohort study found no evidence of a protective programming effect of high maternal 25-hydroxyvitamin D concentrations on allergic airway disease and lung function, but it might be associated with an increased risk of allergic diseases in offspring.¹⁵⁰

NOVEL MECHANISMS RELATED TO EOSINOPHILIC DISORDERS

Eosinophilic esophagitis (EoE) is one of the most common chronic, immune, or antigen-mediated disease diagnosed during the assessment of feeding problems in children and during the evaluation of dysphagia and food impaction in adults. Esophageal epithelium, which is normally devoid of eosinophils, shows increased numbers of them, with aggregates and even microabscesses. Numbers of mast cells, lymphocytes, and basophils are also increased in the affected esophagus.¹⁵¹

Wen et al²⁹ aimed to understand why some patients with esophageal eosinophilia respond to proton pump inhibitor (PPI) therapy. The investigators reported that PPI-responsive esophageal eosinophilia was molecularly similar to EoE and that PPI therapy could reverse the hallmark features of the disease, including all markers of allergic inflammation. It will be important to understand the mechanism through which PPI therapy can modify allergic inflammation in the esophagus and the applicability of this to other diseases. In an unrelated study patients with classic EoE were shown to have symptom improvement after treatment with an anti-IL-13 humanized antibody, which was shown to improve the EoE transcriptome and lower esophageal eosinophil levels,³⁰ calling attention to the need to conduct larger-scale clinical trials in both patients with EoE and those with PPI-responsive esophageal eosinophilia.

Eosinophil accumulation in tissues is orchestrated by a balance between survival and apoptosis signals. Ilmarinen et al³¹ investigated the role of polyamines, cationic molecules (eg, spermine) with basic functions related to nucleic acid packaging, DNA replication, apoptosis, transcription, and translation. They show that polyamines (in particular spermine) prolong eosinophil survival by inhibiting apoptosis-related mitochondrial permeability transition. Furthermore, spermine was found to promote eosinophil activation. These effects are likely to have bearing on other eosinophilic diseases and might also open possibilities for novel therapeutic interventions.

In another study Kiwamoto et al¹⁴⁴ examined the ligands that bind to Siglec-F, a GBP selectively expressed on mouse eosinophils and homologous to human Siglec-9. Its engagement induces apoptosis, suggesting a pathway for ameliorating eosinophilia in the setting of asthma and other eosinophil-associated diseases. Siglec-F recognizes sialylated sulfated glycans in glycan-binding assays, but the identities of endogenous sialoside ligands and their glycoprotein carriers *in vivo* were unknown. The investigators detected mouse lung glycoproteins that bound to Siglec-F, and proteomic analysis identified Muc5b and Muc4 as the glycoproteins. Notably, purified mucin preparations carried sialylated and sulfated glycans bound to eosinophils and induced

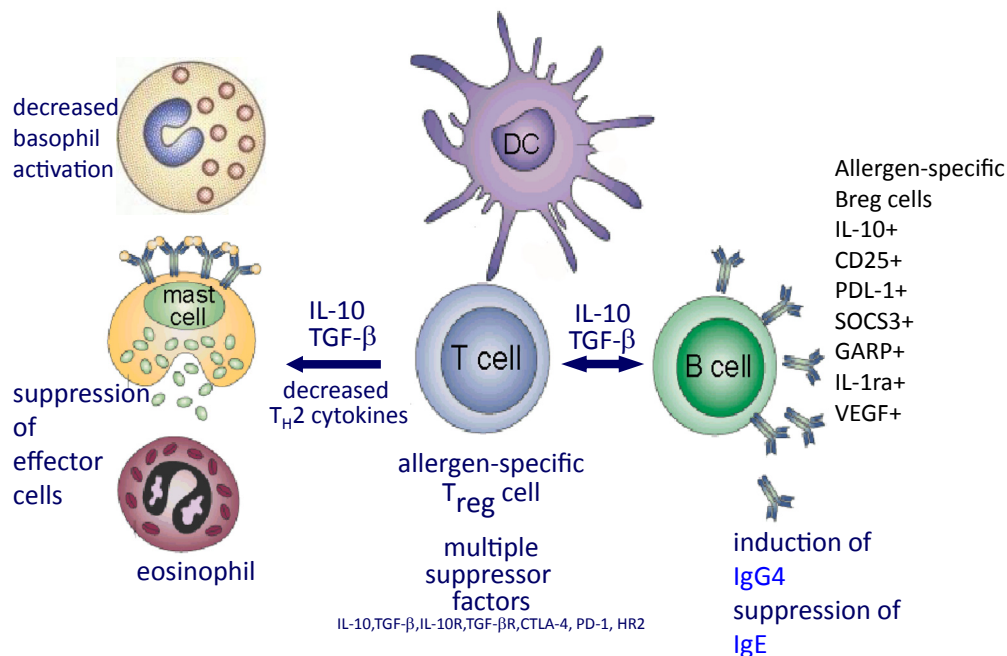


FIG 2. Mechanisms of allergen-specific immunotherapy. Allergen-specific immunotherapy induces Treg and regulatory B (Breg) cells. As a consequence, peripheral tolerance is induced, which in turn regulates the effector cells of allergy, in various ways. Treg cells suppress T_H2 cells and their cytokine production, which are indispensable for the differentiation, survival, and activity of mast cells, basophils, eosinophils, and mucus-producing cells and for tissue homing of T_H2 cells. IL-10 and TGF- β suppress IgE production, while inducing IgG₄, a noninflammatory immunoglobulin isotype. Allergen-specific Breg cells are characterized by high IL-10, CD25, programmed cell death 1 ligand 1 (PD-L1), GARP, IL-1 receptor antagonist (IL-1ra), and vascular endothelial growth factor (VEGF) expression.

their death *in vitro*. Furthermore, mice conditionally deficient in Muc5b displayed exaggerated eosinophilic inflammation. These findings identify mucin proteins as regulators of eosinophil survival.

In another study Mazzeo et al¹⁵² examined the mechanism by which eosinophils secrete granules. They reported that eosinophils secrete granules as exosomes, multivesicular bodies that were found to be increased in asthmatic subjects. It is interesting to speculate that these exosomes can be taken up by other cell types and remain functional.

MECHANISMS OF AIT, IMMUNE TOLERANCE, AND IMMUNODEFICIENCY

AIT has been used to treat allergic disease since the early 1900s. Despite numerous clinical trials and meta-analyses proving AIT efficacious, it is used in less than 10% of patients with allergic rhinitis or asthma worldwide.³² Mechanisms of AIT involve Treg and regulatory B cells and immune-regulatory functions of these cells on inflammatory cells in allergic tissues (Fig 2).³³ Induction of naturally occurring CD4⁺ Treg cells is associated with successful AIT.³³

In a recent study *Dermatophagoides pteronyssinus* subcutaneous immunotherapy enhanced the suppressive function of IL-10/IFN- γ in CD3/CD46-activated type 1 Treg-like cells from asthmatic patients.³⁴ In addition to Treg cells, regulatory B cells also seem to play a role in the suppression of allergen-induced immune activation. Distinct human IL-10-producing B-cell subsets with immunoregulatory properties have been described. IL-10-expressing B cells acquired a prominent immunoregulatory

profile comprising upregulation of suppressor of cytokine signaling 3, GARP, the IL-2 receptor α chain (CD25), and programmed cell death 1 ligand 1.³⁵ They showed significant reduction in levels of proinflammatory cytokines (TNF- α , IL-8, and macrophage inflammatory protein 1 α) and increased production of anti-inflammatory IL-1 receptor antagonist and vascular endothelial growth factor. IL-10-overexpressing B cells secreted less IgE and potentially suppressed proinflammatory cytokines in PBMCs, maturation of monocyte-derived dendritic cells (giving them a regulatory phenotype), and antigen-specific proliferation *in vitro*.³⁵ Histamine also exerts immune regulatory functions.

Recently, it was demonstrated that histamine released from enteric microbes might exert immunoregulatory effects *in vivo*. The amount of histamine secreted by a microbe might be critical in determining its pathological versus protective effects; however, it remains to be determined, on a case-by-case basis, whether these effects are protective or pathological.³⁶

Anaphylaxis has been one of the main side effects of AIT, and many efforts have been undertaken to develop novel AIT vaccines to overcome this.³² Recently, it was shown that developing a vaccine with synthetic peptides corresponding to B-cell epitopes of antigen 5 might provide a safe and effective strategy without allergic adverse effects.¹⁵³ These epitopes are potential candidates for developing vaccines, diagnostic tests, and immunotherapies against allergy caused by *Polybia paulista* wasp venom.

Shamji et al³⁷ worked to develop a novel tool to monitor the response to immunotherapy, such as studies of suppression of basophil activation in patients with grass pollen allergy who had been treated with sublingual or subcutaneous immunotherapy. Both treatments suppressed allergic symptoms, as well

as basophil activation, when basophil activation was tested by using conventional means or based on measurement of intracellular histamine through staining with fluorochrome-labeled diamine oxidase. The fluorochrome-labeled diamine oxidase was shown to correlate well with basophil histamine release and allergic symptoms, which were suppressed for at least 3 years by both forms of immunotherapy. The authors suggest that this assay might be useful for following the clinical response to immunotherapy.

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