CME Review

The origins of allergy from a systems approach

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Key Messages

- Allergy in its various manifestations is a systems disease consisting of networks among multiple organs.
- The epithelium plays a central role in allergic disorders, and allergic sensitization occurs through the skin unless tolerance is induced through the gastrointestinal tract.
- Filaggrin loss-of-function mutations result in impaired epithelial barrier integrity and are substantial genetic risk factors for atopic dermatitis, asthma, allergic rhinitis, and food allergy in children.
- Dysregulated growth and repair pathways and interplay between airway epithelium asthma gene loci and viral, allergen, or microbial exposure are substantial factors for early-onset asthma development and exacerbation.
- As a critical sensor of environmental stimuli, the epithelia of the lungs, gut, and skin are affected by an altered microbiome, air pollution, food allergens in a changed diet, and chemicals in modern detergents, all of which account for an increase in the prevalence of allergic diseases.
- A beneficial diverse microbiome is critical in protecting against allergic diseases, and early oral exposure to food allergens are effective at preventing specific food allergies.

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ABSTRACT

Objective: The origins of allergic diseases have traditionally been explained by immunoglobulin E–mediated immune responses to account for asthma, atopic dermatitis, atopic rhinitis, and food allergy. Research insights into disease origins support a broader array of factors that predispose, initiate, or exacerbate altered immunity in allergic diseases, such as (1) inherent epithelial barrier dysfunction; (2) loss of immune tolerance; (3) disturbances in the gut; and (4) organ-specific microbiomes, diet, and age. Here, we discuss these influences that together form a better understanding of allergy as a systems disease.

Data Sources: We summarize recent advances in epithelial dysfunction, environmental influences, inflammation, infection, alterations in the specific microbiome, and inherent genetic predisposition.

Study Selections: We performed a literature search targeting primary and review articles.

Results: We explored microbial-epithelial-immune interactions underlying the early-life origins of allergic disorders and evaluated immune mechanisms suggesting novel disease prevention or intervention strategies. Damage to epithelial surfaces lies at the origin of various manifestations of allergic disease. As a sensor of environmental stimuli, the epithelium of the lungs, gut, and skin is affected by an altered microbiome, air pollution, food allergens in a changed diet, and chemicals in modern detergents. This collectively leads to alterations of lung, skin, or gut epithelial surfaces, driving a type 2 immune response that underlies atopic diseases. Treatment and prevention of allergic diseases include biologics, oral desensitization, targeted gut microbiome alterations, and changes in behavior.

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Overall Purpose
Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives
At the conclusion of this activity, participants should be able to:

- Describe common cellular features at the origin of allergic diseases manifesting at different tissues.
- Discuss the impact of genetic and environmental factors on the epithelium and how they contribute to the development of allergic sensitization and tolerance.

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Conclusion: Understanding the spectrum of allergy as a systems disease will allow us to better define the mechanisms of allergic disorders and improve their treatment.

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Introduction

Since the first description of hay fever in 1870, waves of allergic diseases have risen to what is today being called an allergy epidemic; however, the specific underpinnings of abnormal immune responses underlying allergic disorders are still not clearly understood. From the mid-1960s, immunoglobulin E (IgE) was found to regulate a wide range of allergic diseases such as asthma, allergic rhinitis, atopic dermatitis (AD), and food allergy (FA). Recent studies have broadened our understanding of the influences that predispose, trigger, and perpetuate allergic diseases. These include genetic predisposition, epithelial barrier dysfunction, aberrant immune tolerance, exposure to pollution, and an altered diet and microbiome. However, such studies are predominantly interpreted from a single-disease or tissue-driven perspective rather than from a systems disease approach. In this narrow view, biological systems can be explained by the properties of their components. A systems-based approach toward disease is based on the concept that interactions among the many components of the entire system, such as between tissues and organs, are responsible for the overall behavior of the dynamic system. Approaching the complex nature of allergic diseases from a systems perspective allows us to integrate new technologies and form collaborations across several fields of study such as biology, bioinformatics, chemistry, and genetics. A systems approach, therefore, generates a more holistic and comprehensive view of the interconnecting tapestry of allergy as a systems disease that includes a broad array of influences such as exposure to air pollution and chemicals, inflammation and infection, alterations to the microbiome, food allergens, and inherent genetic predisposition (Fig. 1).

Support for the concept of allergy as a systems disease is found from observations exhibiting the importance of diverse microbiota, early oral exposure to an allergen, and vitamin D in the development of tolerance. Conversely, delaying oral exposure to food allergens and deficiency in either vitamin D or specific microbiota impedes the generation of immune tolerance. Thus, as illustrated in Figure 2, the influences from multiple systems produce damage to epithelial surfaces that underlies the various manifestations of an allergic disease. Skin, lungs, and gut function as critical sensors of environmental stimuli and are assaulted by a barrage of contemporary environmental stimuli including an altered microbiome, air pollution, food allergens in a changed diet, chemicals in modern detergents, and plastics. Collectively, this onslaught leads to alterations of lung, skin, or gut epithelial surfaces, driving a type 2 immune response that underlies most, if not all, atopic diseases, including asthma, AD, and FA.

In this review, we present current evidence that the spectrum of allergic diseases is a systems disease consisting of interconnected communication among multiple organs involving barrier homeostasis, the environment, and the microbiome. We evaluate specifically the interplay of multiple factors within the epithelium in allergic diseases, with an emphasis that oral tolerance prevents allergen-specific FA if it occurs before skin sensitization, and how a diverse microbiome protects against allergic diseases. Understanding the spectrum of allergy as a systems disease will allow us to better define the mechanisms of allergic disorders and improve their treatment.

Methods

Using available evidence, including that of our own research, this review intends to inform readers about the complex issue of the potential microbial-epithelial immune interactions underlying the early-life origins of allergic disorders and immune mechanisms that might suggest novel disease prevention or intervention strategies. Search terms and keywords included “allergy,” “atopic dermatitis,” “food allergy,” “asthma,” “microbiome,” and “epithelial barrier,” and also “pollution,” “PAH,” (polycyclic aromatic hydrocarbons) and “PM2.5” (atmospheric particulate matter with a diameter of less than 2.5 μm) concurrently with keywords including systems approach. We searched for exact phrases such as “allergic disease and origins.” Finally, to make our online searches more comprehensive, we conducted citation searches to determine whether the articles have been cited by other authors and to find more recent papers on the same or similar subjects. All citations were confirmed and entered using EndNote (Thomson Reuters, Ontario, Canada). We tried to include articles published since 2017.

Clinical Phenotypes and Endotypes of Allergic Diseases Shown by FA

The origins of allergic diseases are multivariable among patient populations, and therefore, stratifying the specific phenotypes and endotypes allowed us to predict how changes occur under varying conditions. Here phenotype refers to the clinically observable signs and symptoms, and endotype refers to the pathobiological mechanism underlying the phenotype. Applying the concepts of phenotype and endotype can be best illustrated using FA, for which both phenotype and endotype depend on the route of allergen exposure and factors influencing the mucosal barrier integrity, such as genotype, epigenetics, and the environment. Phenotypes and endotypes for IgE-mediated FA include the following: (1) classic IgE-mediated FA with 5 endotypes (persistent, transient, food-dependent and exercise-induced, aspirin- or nonsteroidal anti-inflammatory drugs–dependent, and alcohol-dependent); (2) aerosol-induced sensitization with 2 endotypes (local cross-reactions to aerosolized antigens and systemic and specific reactions to aerosolized food antigens); (3) intermittent and cross-reactive allergy; (4) α-Gal syndrome; and (5) sensitized nonreactive phenotype. Specific biomarkers and cluster analyses will be needed to further fine-tune phenotypes and endotypes for patients with FA, AD, and asthma. As phenotypes and endotypes of allergic diseases come into sharper focus, the potential for...
developing a precision medicine approach to treat the root causes of allergic symptoms increases.

**Epithelial Barriers and Allergic Diseases**

The primary tissues protecting us from exterior insults are the epithelia of the skin, airways, and gastrointestinal (GI) tract. The epithelium not only acts as a physical barrier; it actively responds to stimuli such as allergens, pollution, or microbes by releasing epithelial-derived cytokines that initiate and drive type 2 immune responses. Dysregulated epithelial barrier activity in allergic diseases such as AD, FA, and asthma increases the potential for allergen and microbe penetration and subsequent sensitization (Fig 2). Interactions among genetic, microbial, viral, environmental, and immune factors contribute to epithelial disruption, aberrant type-2 immune responses, and allergic disease.

**Genetic, Microbial, and Immune Influences of Epithelial Disruption**

The airway epithelium has been called “the gateway to allergic sensitization.” Multiple genomewide association studies have identified specific genes associated with asthma susceptibility, most notably the locus at chromosome 17q12-21, a region dense with epithelium-associated genes. Epithelial susceptibility genes, microbes, viruses, allergens, and type 2 immunity, alone or in combination, influence asthma development and exacerbation. There is a strong association of viral interactions with epithelial gene variants and the risk of respiratory illness and exacerbation of asthma for school-age children. Children with rhinovirus-related wheezing illnesses, who were also carriers of the epithelial-associated ORMDL3 gene variant, were at high-risk for early-life development of asthma. CDHR3, another asthma-associated susceptibility gene expressed in airway epithelium, encodes for cadherin-related family member 3, which is a receptor for rhinovirus C. The CDHR3 asthma-risk variant at SBP rs6967330 is not associated with a risk for respiratory syncytial virus severe bronchiolitis but does exhibit an association with a bronchiolitis subtype triggered by other infectious agents.

Viral interactions with airway microbiota also contribute to allergic sensitization. Examination of nasopharyngeal microbiota (NPM) and acute respiratory illnesses in children under 5 years of age revealed that viral pathogens account for more than 80% of infections and a shift in the NPM toward more pathogenic bacteria. This shift may facilitate acute respiratory illness, whether there is a viral infection or not. In addition, there is an association between the pathogenic NPM bacterial profile and persistent wheezing in allergen-sensitized school-age children. Investigations are underway to evaluate the mechanisms of NPM on allergen sensitization.

Another area of current research evaluates how epithelial factors contribute to the persistence of asthma symptoms. Altered expression of genes related to epithelial growth and repair pathways and type 2 pathway genes are associated with exacerbation of...
asthma. A continuous loop of dysregulation in epithelial growth and repair may contribute to further worsening of asthma symptoms. Overlapping with the type 2 and epithelial growth and repair pathways is 15-lipoxygenase, a lipid-metabolizing enzyme that generates the mediators of ferroptosis, a recently discovered form of cell death. Type 2 cytokines induce epithelial differentiation toward a goblet-cell phenotype, with 15-lipoxygenases pivotal to the process. This pathway may contribute to persistent disease aggravation in some types of asthma. After cell death, dysregulated epithelial repair pathways can change cell differentiation, elevate inflammatory responses, and increase cell death, all leading to repeated cycles of inadequate repair and aggravation of asthma symptoms.

Another intersection between epithelial-related genes and type 2 cytokines in allergic diseases is dectin-1 signaling. Epithelial-expressed dectin-1 inhibits the release of interleukin (IL)-33 and the ensuing recruitment of innate immune cells, thus, preventing type 2 allergic responses. IL-33 is expressed mainly by epithelial and endothelial cells that act both as a traditional cytokine and as an intracellular nuclear factor that functions as a transcription regulator. A single-nucleotide polymorphism in an intronic region of the dectin-1 gene locus was found to be associated with decreased lung function in patients with asthma. Furthermore, in respiratory epithelial cells from patients with asthma, the dectin-1 pathway was found to be deficient, which elevated IL-33. Individual having allergy with defective dectin-1 function may have substantially elevated IL-33 production, promoting type 2 allergic responses. Treatments restoring dysfunctional pathways driving certain types of asthma, such as lipoxgenase and dectin-1, are intriguing possibilities for future development.

Thymic stromal lymphopoietin (TSLP), an alarmin produced by epithelial cells at the mucosal surfaces of the lungs, skin, and GI tract, plays a crucial role in regulating type 2 immune responses in the airways. Notably, TSLP is a potent activator of innate immunity—the precursors to adaptive, allergen-specific Th2 responses. In mouse models, TSLP promoted type 2 immune responses by activating conventional dendritic cells and group 2 innate lymphoid cell responses. Interstitial macrophages expressing the TSLP receptor may also propagate TSLP-mediated acute airway inflammation. A mouse model of acute TSLP-dependent airway inflammation revealed attenuation of airway eosinophilia and Th2 differentiation with selective depletion of interstitial macrophages or deficient TSLP receptor signaling. Preliminary clinical trials using anti-TSLP therapy had shown promise in treating patients with severe, uncontrolled asthma.

The airway epithelium also has a protective feature against asthma with club cells, which are the primary secretory cells in the airway epithelium. Club cell secretory protein-16 (CC16) is the anti-inflammatory secretory product that protects children against asthma. Therapies that stimulate CC16 production may be an early-life therapeutic option to protect children from the disease.

Epithelial Barrier Dysfunction

The epithelial barrier is key in preventing or facilitating the atopic march from AD to asthma, rhinitis, and FA. The development of AD in infancy and subsequent allergic rhinitis and asthma in later childhood is known as the atopic march. This progressive atopy is dependent on various underlying factors such as the presence of filaggrin mutations and the time of onset and severity of AD. Clinical manifestations vary among individuals. Dysfunctional epithelial barrier integrity leads to allergic inflammation in patients with AD and eosinophilic esophagitis (EoE). A dysfunctional epithelial barrier is less successful at maintaining organ
homeostasis and suppressing inflammatory responses. Filaggrin loss-of-function (LoF) mutations, which impair epidermal tight junctions (TJs), are the most replicated genetic risk factors in developing AD and are associated with the most severe forms of AD. 25 Despite not being detected in the airway epithelium nor the digestive tract, filaggrin is also associated with other allergic diseases including asthma and FA. 25-27 Encoded by the FLG gene, the 400-kDa precursor profilaggrin filaggrin is proteolytically cleaved to form filaggrin in the stratum corneum, in which it regulates epidermal homeostasis and water retention. 26,29 FLG LoF mutations were found to lower epidermal barrier integrity. FLG LoF variants are widespread across many populations. Among people of European ancestry, 10% of heterozygous carriers of FLG LoF mutations reported a 50% reduction in filaggrin protein expression. 30 Furthermore, among people of Chinese, Malaysian, and Indian ancestries living in Singapore, FLG LoF mutations were common in addition to several previously unidentified variants. 31 Multiple FLG LoF variants associated with persistent AD have also been reported in Bangladeshi and African American populations. 32,33

Studies have found how skin barrier dysfunction leads to AD. When compared with skin from healthy individuals, both lesional and nonlesional skin from children with AD indicated decreased long-chain sphingolipids and an aberrant skin metabolism driven by type 2 cytokines. 54 Another study evaluated whether skin abnormalities can distinguish between children with AD and FA (AD/FA -) and children with AD without FA (AD/FA +). Lesional and nonlesional skin from children who were AD/FA +, AD/FA -, and nonatopic controls underwent comprehensive protein, transcriptome, and lipid analysis. 28 Results revealed that nonlesional skin from children who were AD/FA + had substantially lower filaggrin expression and a lower proportion of waxy lipid molecules such as sphingosine ceramide compared with AD/FA - children and nonatopic controls. Moreover, AD/FA - children also indicated increased transepidermal water loss compared with the control groups. Elevated gene expression of type 2 immune pathways was detected in the skin transcriptome of patients who are AD/FA+, along with elevated expression of skin proteins keratin 5, 14, and 16, suggesting hyperproliferative keratinocytes. 32 These studies indicate that nonlesional skin from children with AD are distinct from nonatopic children, and that genetic, protein, and lipid profiles of nonlesional skin from AD/FA - children are unique from AD/FA + children.

The dysfunctional epithelial barrier also plays a role in EoE, which occurs in a subset of patients with FA. Desmosomes are cell-to-cell junctions that contribute to cell barrier integrity, a component of which is the protein desmoglein-1, encoded by the DSG1 gene. Biopsies from patients with EoE revealed lower levels of DSG-1, indicating weakened epithelial integrity of the esophagus and impaired barrier function. The type 2 cytokine IL-13 has been found to exacerbate esophageal inflammation by inducing DSG1 downregulation. 32

Epithelial barrier deficiencies often lead to a state of constant inflammation, making it difficult for tissue repair. Deficient barrier integrity facilitates allergen entry and lowers the threshold for sensitization to innocuous substances because of the inflammatory environment, likely precipitating allergic sensitization at distal organs. 36

Epithelium and the Environment

In recent decades, the rate of industrialization has increased, exposing many populations to increasing amounts of diesel exhaust, automobile air pollution, and detergents, all of which disrupt epithelial TJs, reduce barrier integrity, and increase the prevalence of allergic disorders. 37,38 These concepts tie back to the studies on epithelial damage and dysfunction.

Studies have found that environmental pollutants such as nitrogen dioxide (NO2), carbon monoxide, and PM2.5 influence the development of asthma, even as early as in utero. It was found that PM2.5 from wildfires and pollution increases asthma attacks. 39 especially asthma hospitalization in children aged 0 to 5 years, 40 and increases inflammation and cardiovascular events. 41 Environmental exposures dramatically influence the phenotype of allergic diseases, including atopic eczema, FA, asthma, and allergic rhinitis. 42-45 Mechanisms linking air pollutants such as particulate matter, NO2, and ozone to the development and exacerbation of asthma include the induction of both eosinophilic and neutrophilic inflammation driven by stimulation of airway epithelium and increase of proinflammatory cytokine production, oxidative stress, and DNA methylation changes. Although exposure during fetal development is often reported as a crucial time frame, exposure to air pollution is detrimental to anyone of any age, thus, influencing asthma onset and increase in asthma prevalence, mortality, persistence, and exacerbation. 46

Epithelial activation barrier leakiness is also affected by pollution. As we have seen, epithelial cells are the first line of defense against pollution and are essential components of the innate immune response and tissue barriers. Upper and lower respiratory epithelial cells are exposed to air pollution, whereas GI epithelial cells are exposed to food and water pollution. Although stratum corneum has a stronger barrier function, the integrity of skin epithelium is important for almost any environmental exposure. The mucosal epithelium plays a role in mucociliary clearance—it produces antimicrobial peptides, cytokines, and chemokines; activates intraepithelial and subepithelial cells and recruits them to tissues; and supports the physical, chemical, and immunologic barriers. 47-52 The epithelial barrier in the airways and GI system consists of mucus, microbiota, surface liquids, and junctional complexes between adjacent epithelial cells that comprise TJs and adherens junctions. The ability of the epithelium to control the balance of tissue damage and repair signals is essential for the lifelong modulation of these responses to limit tissue injury when exposed to pollution. Epithelial cells respond to pollution, viral infections, and toxins with a group of cytokines such as IL-25, IL-33, and TSLP, which activate the epithelial cells and contribute to a type 2 inflammation by activating dendritic cells, T/h2 cells, type 2 innate lymphoid cells and mast cells. 35 These signals are the first-line of defense to initiate an inflammatory response to pollution in addition to IL-1 and inflammasome activation. Both type 1 and 2 inflammations in the bronchus, gut, skin, esophagus, and sinus have indicated an effect of the opening of the epithelial barrier. 49,55-65

Open epithelial TJ barrier in the mucosa allows pollutants, allergens, toxins, and any foreign substances to deeper tissues, 53 which eventually initiate local tissue inflammation. Currently, there are substantial data reporting that pollutants such as cigarette smoke, particulate matter, diesel exhaust, ozone, nanoparticles, microplastic, detergents, and cleaning agents and chemicals in household substances damage the epithelial barrier. 47,49,66-72 After the opening of the barrier, a local inflammation starts, and the tissue may become more vulnerable to inflammatory and tissue destructive effects of pollution. Most of these pollutants indicate synergistic effects, and the area is fully open for future research. Epithelial TJs regulate barrier integrity by modulating inflammatory triggers, which loosen barrier gaps and engage suppressive mechanisms that tighten the junction gaps. For example, histone deacetylases act to regulate the expression of distinct subsets of inflammatory or immune genes that, in turn, increase intestinal permeability and deacetylation blockade, tightening intestinal permeability. 60,76

Furthermore, epigenetic and environmental regulation in asthma and allergic disease is an exciting area that has recently gained scientific momentum. Exposure to environmental toxins is associated with asthma-related outcomes that may be explained by epigenetic regulation. For example, short- and long-term exposure to air pollutants (eg, NO2, carbon monoxide, PM2.5, polycyclic...
Many aspects of innate immunity targeted by microbes and their contributors to asthma, such as allergen sensitization and allergic defense mechanisms. These pollutant-driven epigenetic modifications of Tregs are critical in generating and maintaining tolerance to allergies, which may restrict tolerance to allergens, promoting an allergy-promoting Th2 immunity and increased susceptibility to allergic diseases. Targeting epigenetic processes that control chromatin remodeling and gene silencing to shift type 2 immunity enhances Treg activity and promotes a stronger epithelial barrier. Targeting epigenetic processes that control chromatin remodeling and gene silencing in airway cells may have future potential for novel asthma therapy.

**Microbiota and Metabolites**

Over the past 70 years, dietary changes, increasingly pure water supplies, overprescription of antibiotics, obesity, formula feeding for infants, and caesarian section birth have all likely contributed to an increase in allergic diseases. These changes all have major consequences to our commensal microbiomes, changes that are hypothesized to substantially contribute to an increase in allergic diseases. For example, children who lived on farms from birth have lower rates of allergic disease yet have no differences in lung function compared with children living in urban environments, suggesting that agricultural exposures protect children from asthma and atopy. Loss et al. found that, in children who live in rural Europe and were exposed to farm animal sheds, the high-risk 17q alleles were susceptible to environmental influences and therefore were associated with a lower risk of asthma and wheezing. Supporting this hypothesis, a study comparing Amish and Hutterite children found that despite similar genetic heritage, Amish children had substantially reduced risk of allergy, likely owing to observed differences in dust and bacteria found in the Amish households. Furthermore, the Protection Against Allergy: Study in Rural Environments study found that material exposure to farming activities and farm dairy products during pregnancy modulated cytokine production patterns of offspring and reduced the incidence of allergy at birth. Important contributors to asthma, such as allergen sensitization and allergic manifestations early in life, are being suppressed. Accordingly, the many aspects of innate immunity targeted by microbes and their compounds and metabolites might be a central switch for asthma and allergy protection.

The alarming increase in both the incidence and severity of food allergies has coincided with lifestyle changes in Western societies. The association between the gut microbial community changes and childhood food allergies has been confirmed in some epidemiologic studies. A Canadian Healthy Infant Longitudinal Development study found alterations in the gut microbial community in food-sensitized infants, in which Enterobacteriaceae were overrepresented in a less diverse microbial community in infants at 3 months of age, whereas Bacteroidaceae were underrepresented at 1 year. A Chinese infant cohort study found that infants with FA had a higher abundance of Firmicutes and a lower abundance of Bacteroidetes at 6 months, but no substantial difference in total microbial diversity was found. Stefa et al. described the role of mucosa-associated intestinal bacteria in the Clostridia class in protecting mice from allergic sensitization to peanuts. Translational studies found that the composition of the fecal microbiota is altered in infants with cow’s milk allergy. To understand how the microbiota regulates allergic disease in humans, germ-free mice were colonized with bacteria from the feces of healthy infants or infants with cow’s milk allergy (CMA). It was discovered that mice colonized with the microbiota of infants with CMA produced an anaphylactic response to the cow’s milk allergen β-lactoglobulin, whereas mice colonized with healthy infants’ microbiota were protected against such an allergic response. Analysis of the differences in composition among human fecal donors allowed investigators to develop a microbiota signature that distinguished the CMA from healthy populations in both human donors and colonized mice. Correlating ileal taxa with differentially expressed genes in the ileal epithelium from healthy-colonized mice allowed these investigators to identify a Clostridial species, *Aneurastipes caccae*, that mimicked the effects of the healthy microbiota, which proved the concept that bacteria and their products protect individuals against FA.

In addition, fiber consumption has decreased in our diets over recent years, which has been linked to reduced microbial diversity in mouse models. Certain Clostridia species have been reported to ferment dietary fiber into short-chain fatty acids that promote Treg differentiation, which helps generate immunologic tolerance. Short-chain fatty acids also induce the secretion of IL-22, which promotes gut barrier integrity. Accordingly, including dietary fiber may support a diverse microbiome profile, healthy epithelial barrier function, and immune tolerance.

Diet diversity is certainly important in preventing and managing FA. Roduit et al. found that in the first year of life, children with a lower diet diversity had an increased risk of sensitization to food allergens by the time they were aged 6 years. They also reported that introducing 0 to 6 items from any of the food groups of vegetables/fruits, cereals, bread, meat, cake, and yogurt within the first 6 or 12 months of life reduced prevalence of physician-diagnosed FA up to the age of 6 years.

**Route of Food Allergen Exposure**

The atopic march phenomenon provides compelling evidence that the local breakdown of barrier integrity at 1 organ such as the skin can cause a systemic collapse of immune tolerance at distant organs such as the lungs and the gut. This observation applies to FA, and because the route of initial exposure to food allergens is a substantial contributor to food sensitization. The current hypothesis of FA sensitization is that low-dose food allergen exposure to an infant’s skin increases the likelihood of FA. However, if eating the food allergen precedes skin sensitization, the child may avoid developing FA. The Learning Early About Peanut (LEAP) study found that early peanut protein consumption substantially reduced the prevalence of peanut allergy in high-risk infants. A follow-up of the LEAP children revealed that the prevalence of peanut allergy among the protected children remained low, even if they were instructed to avoid peanuts later in life, suggesting that sustained tolerance to peanut protein is induced when eaten early in life. LEAP investigators then asked whether 1 food allergen can protect against multiple food allergies. Children who consumed peanut protein were not protected from developing other food allergies, indicating that oral tolerance is allergen-specific and that numerous tolerance induction protocols help prevent FA. The question of whether oral exposure to 1 food allergen can prevent multiple food allergies was evaluated in the Enquiring About Tolerance study. Among children at high risk for allergy in whom peanuts had been introduced in the first year of life and continued until 5 years of age, a 12-month period of peanut avoidance was not associated with an increased prevalence of peanut allergy, suggesting that multiple tolerance induction protocols would help prevent FA.

LEAP and Enquiring About Tolerance studies underline the importance that early consumption of peanut proteins provides
sustained systemic protection from epicutaneous sensitization to peanut allergens, even in at-risk children. Recent guideline changes recommend the introduction of peanut-containing foods for infants considered a low-to-moderate risk at 6 months of age as an effective preventative strategy. However, consuming peanut-containing foods for high-risk children should only be attempted under physician supervision in children aged 4 months or older.  

**Therapeutic Options**

**Prevention**

As we have seen, changes in the function and composition of the human-associated microbiome have been implicated in the increasing global burden of noncommunicable diseases (allergic diseases, autoimmune diseases), exacerbating inflammation and metabolic dysregulation through multiple pathways across the lifespan. Addressing this with probiotic and prebiotic supplementation is a start, but we have barely scratched the surface of the microbiome’s complexity and its contributions to health. To establish and maintain a healthy microbiome, interventions focusing on changing aspects of our personal life, including a healthy and diverse diet, are essential to establishing and maintaining a healthy symbiosis. Societal and global interventions are also necessary for preventing a further decrease in the diversity of beneficial bacteria.

Another effective preventative measure is early oral exposure to food allergens, which provide protection from FA, even in at-risk children. Eczema severity and length of duration are associated with the increased risk of FA, and therefore, early identification of eczema would delay FA by use of emollients, allowing more time to induce oral tolerance.

**Biologics**

For IgE and type 2 allergic diseases, the development of biological therapies such as anti-IgE and anti-IL4Ra have the potential for improving care. One notable example is dupilumab, a human monoclonal antibody (mAb) targeting IL-4Ra, which reduces IL-4 signaling, effectively lowering severe asthma in patients with uncontrolled moderate-to-severe asthma with or without chronic rhinosinusitis. Dupilumab is currently approved by the Food and Drug Administration and European Medicines Agency for treating moderate-to-severe AD, asthma, and chronic rhinosinusitis with nasal polyposis. Dupilumab is also effective in reducing clinical signs and symptoms of AD and in moving the skin transcriptome of patients toward a nonlesional phenotype. In addition, this mAb can be effective in treating FA because of the key role IL-4 signaling plays in the development and persistence of FA. For patients with FA, dupilumab combined with oral immunotherapy (OIT) may increase desensitization to food allergens. It is well known that IgE plays a central role in allergy, in which allergen-specific IgE binds to the high-affinity IgE receptor on mast cells and basophils, releasing histamine from intracellular granules that lead to allergic symptoms. The anti-IgE mAb omalizumab (Xolair) inhibits IgE from binding to the high-affinity IgE receptor, preventing degranulation and subsequent inflammation.

**Immunotherapy**

The use of immunotherapy for aeroallergens has been used for many years but has only recently been used to treat FA. At present, there are following 3 types of immunotherapy for FA: epicutaneous, sublingual, and OIT. Epicutaneous and sublingual are considered safer than OIT but less effective at desensitizing patients, and there have been relevant safety concerns about OIT and uncertainty about how sustainable this therapy is. In addition, OIT was found to have high patient dropout rates, mostly owing to GI discomfort. However, combining OIT with omalizumab reduces the risk of these symptoms, facilitating rapid dosing, and lowering dropouts. Introducing OIT earlier in life might also improve its safety and efficacy.

Increasing the allergen-specific IgG/IgE ratio is believed to be important in reducing symptoms and desensitization. Treating patients with cat allergy indicates the benefits of shifting this antibody ratio. Oren et al treated cat allergy with monoclonal IgG antibodies that could bind the allergen and prevent IgE engagement. They used 2 potent, preselected allergen-blocking monoclonal IgG antibodies against the immunodominant cat allergen Fel d 1, and found that increasing the IgG/IgE ratio reduced the allergic response in mice and in patients with cat allergy. Constructing a mAbs library to other common allergens could be useful in reducing symptoms in other common allergies.

Mediating a shift from inflammatory IgE to the anti-inflammatory IgG4 is a key strategy for developing future immunotherapies. Successful immunotherapy models suggest that generating type-1 regulatory T cell and B regulatory cell responses consisting of the anti-inflammatory cytokines IL-10, transforming growth factor β, and IL-35 are essential in regulating the allergen-specific IgG/IgE ratio shift. B regulatory cells have additional benefits because they have been found to induce regulatory T cells, suppress Th2 effector responses, inhibit dendritic cell maturation, and even become sources of IgG4 once they differentiate into plasma cells.

**Conclusion**

Allergy in its various manifestations is a systems disease consisting of networks of communication among multiple organs (Fig 1). The epithelial barrier plays a crucial role in allergic disease sensitization and tolerance. Substantial evidence supports the hypothesis that epithelial barrier dysregulation underlies multiple allergic diseases such as asthma, AD, and FA, which can originate from several triggers acting alone or together. These include genetic mutations, changes to the microbiome, exposure to air pollutants and detergents, and initial route of exposure to certain foods (Fig 2).

In conclusion, we have reported how damage to epithelial surfaces lies at the origin of the many manifestations of allergic disease. The epithelia of the lungs, gut, and skin, which operate as critical sensors of environmental stimuli, are besieged by an onslaught of contemporary environmental forces including an altered microbiome, air pollution, food allergens in a changed diet, and chemicals in modern detergents. Collectively, this onslaught leads to alterations of lung, skin, or gut epithelial surfaces, driving a type 2 immune response that underlies many of the atopic diseases. Possible interventions to prevent the development and progression of allergic disease in the short term include early exposure to food allergens and a diverse, healthy microbiome. Probable therapies based on using pathways that normally provide protection from the allergic disease could be exploited to protect against allergic diseases, such as exposure to a diverse microbiome, immunotherapy with food allergens leading to desensitization, and targeted therapy (with biologics including mAbs) to enhance the modulatory effects of CC16 or dectin-1, or limit the effects of IL-4, IL-13, IgE, and even the allergens themselves. Identification of additional mechanisms and biomarkers of FA will facilitate an individualized precision medicine approach.

**References**


