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REVIEW

# Skin, gut, and lung barrier: Physiological interface and target of intervention for preventing and treating allergic diseases

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## Abstract

The epithelial barriers of the skin, gut, and respiratory tract are critical interfaces between the environment and the host, and they orchestrate both homeostatic and pathogenic immune responses. The mechanisms underlying epithelial barrier dysfunction in allergic and inflammatory conditions, such as atopic dermatitis, food allergy, eosinophilic oesophagitis, allergic rhinitis, chronic rhinosinusitis, and asthma, are complex and influenced by the exposome, microbiome, individual genetics, and epigenetics. Here, we review the role of the epithelial barriers of the skin, digestive tract, and airways in maintaining homeostasis, how they influence the occurrence and progression of allergic and inflammatory conditions, how current treatments target the epithelium to improve symptoms of these disorders, and what the unmet needs are in the identification and treatment of epithelial disorders.

**KEYWORDS**
biologics, IL-25, IL-33, tight junctions, TSLP

## 1 | INTRODUCTION

The epithelial barriers of the skin, gut, and respiratory tract are critical interfaces between the environment and the host, orchestrating both homeostatic and pathogenic immune responses.[1] Dysfunctional epithelial barriers are present in allergic and inflammatory disorders such as atopic dermatitis (AD), food allergy, eosinophilic oesophagitis (EoE), allergic rhinitis (AR), chronic rhinosinusitis (CRS), and allergic asthma.[1–3] Evidence supports the role of epithelial barrier dysfunction as a driver of the aberrant immune response to environmental triggers in many of these conditions, although it may also be considered a consequence of ongoing inflammation.[4] The "epithelial barrier hypothesis" proposes that the dramatically increased prevalence of allergic disorders in recent decades, as well as systemic autoimmune and metabolic conditions, and even neurodegenerative and psychiatric conditions, may be related to increased exposure to epithelial barrier-damaging agents linked to industrialization, urbanization, and modern life.[5,6]

This review provides an overview of the epithelial barriers of the skin, digestive tract, and airways, and explores how barrier

dysfunction could influence the disease course of allergic and inflammatory conditions. Clinical biomarkers and epithelium-targeted treatments for these conditions are also discussed, together with the unmet needs in this field.

## 2 | STRUCTURE AND FUNCTION OF THE EPITHELIUM

Epithelia form physical barriers of varying thickness and structure. The epithelium is composed of adjacent cells, with junctional complexes attaching neighbouring cells to each other and controlling paracellular transport. An extracellular basement membrane separates the epithelium from underlying tissues and acts as a scaffold for growth and regeneration after injury. Epithelial tissue is nourished by substances present in the lumen and diffusing from blood vessels in the underlying tissue.[1]

Normally, epithelia maintain the barrier between the host and the environment, regulate microbiome homeostasis and contribute to the development and maintenance of immune tolerance. Following pathogenic insult, epithelia alert neighbouring stromal and haematopoietic cells, recruit immune cells and initiate repair.

The epithelial structure in the skin, digestive tract, and airways is tailored to the physiological needs of the corresponding organ (Figure 1).[1] The epidermis (outer layer of the skin) differs from the epithelia of the digestive tract and airways in that it primarily serves as a physical barrier against the external environment. The epidermis is designed to be compact and impenetrable, with a highly stratified structure formed of squamous cells, covered in a lipid matrix that forms a water-resistant barrier.[2,7] Keratinocytes, the major cell type of the epidermis, proliferate in the basal layers and then progressively differentiate and migrate towards the skin surface where they lose their nuclei, cornify and flatten to form the stratum corneum.[2,8] Tight junctions in the central stratum granulosum form an additional component of the skin barrier, limiting penetration of allergens and microbes, facilitating paracellular transport of soluble mediators, and regulating water loss.[2,8] Other epidermal cell types include Langerhans cells, which are members of the tissue-resident macrophage family and regulate skin homeostasis and immune responses to environmental stimuli.[9]

The intestinal epithelium comprises a single layer of columnar cells, arranged in folds (villi) to maximize the surface area for nutrient absorption. Unlike the epidermis, the intestinal epithelium is designed to allow nutrients to pass through. Most intestinal epithelial cells are enterocytes, which are absorptive cells with microvilli. Others include goblet cells, which produce mucus to protect the epithelium from the contents of the intestinal lumen; Paneth cells, which produce antimicrobial peptides; tuft cells, which are chemosensory cells involved in the immune response; and stem cells, which reside in the base of villi crypts and proliferate continuously to replace the epithelium.[10] Intercellular junctional complexes, including tight junctions, control paracellular transport across the intestinal epithelium and maintain barrier integrity.[11]

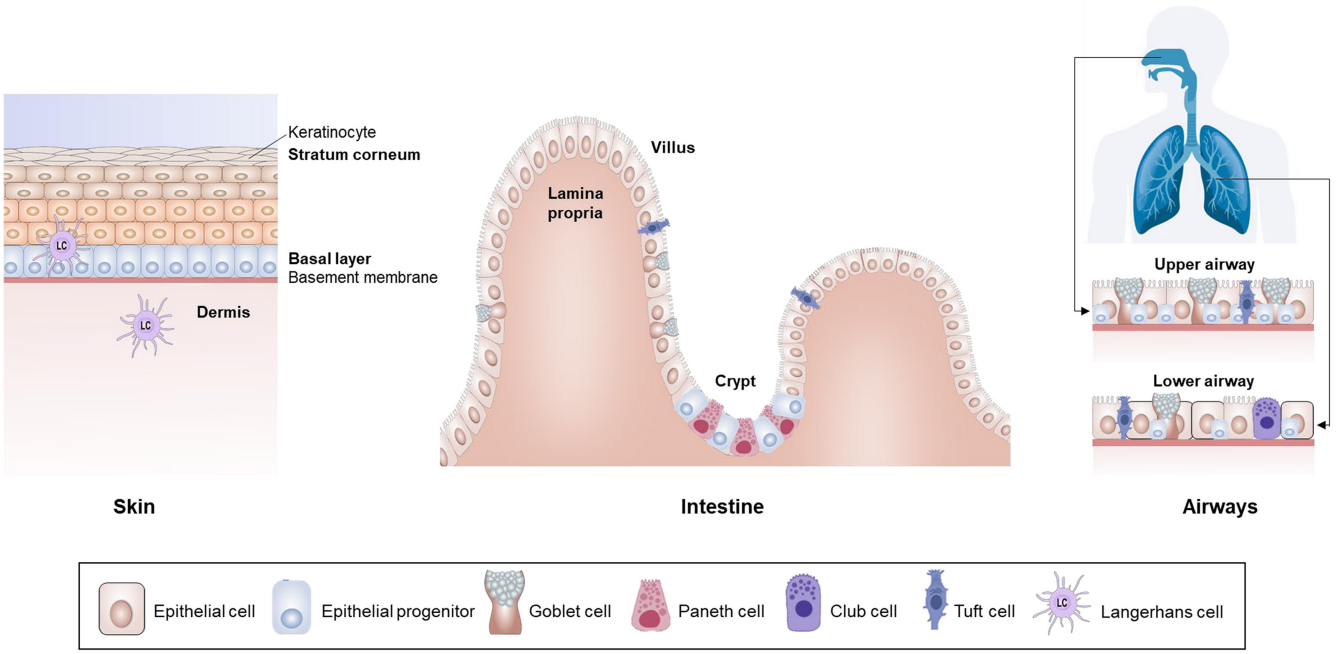


FIGURE 1 Simplified structure of the epithelia of the skin, intestine, and airways. The epidermis is the epithelium of the skin and has a stratified structure composed mainly of keratinocytes, which are replenished by a basal layer of epithelial progenitors that contact the basal lamina. Tissue-resident Langerhans cells regulate homeostasis and immune responses to environmental stimuli. The intestinal epithelium is composed of a single layer of ciliated epithelial cells arranged into villi. Other cells include goblet, Paneth and tuft cells, and epithelial progenitors reside within intestinal crypts. The epithelium of the upper airway has a pseudostratified structure that transitions to a simple epithelium in the lower airways. The airway epithelium is composed of ciliated epithelial cells, goblet cells (primarily in the upper airway), and club cells (primarily in the lower airways). It is replenished by basal progenitor cells, which abut the basal lamina.

Structurally, the airway epithelium shows intermediate features between the epidermis and the intestinal epithelium, being more permeable than the former and less permeable than the latter. The epithelium of the upper airway has a pseudostratified structure that transitions to a simple epithelium in the lower airways. It is composed predominantly of ciliated cells, which move mucus upward, goblet cells and basal stem cells. In the lower airways, other cell types are also present, including club (Clara) cells, which synthesize protective substances, neuroendocrine cells, which can sense airborne allergens, and chemosensory tuft cells.[1,12] The airway epithelium differs significantly from that of the lung parenchyma, where the alveoli feature a single layer of squamous epithelial cells that facilitate passive diffusion of gases between the blood and lungs. As in the intestine, tight junctions play a key role in maintaining epithelial barrier integrity.[13]

## 3 | ROLE OF THE EPITHELIAL BARRIER IN DYSREGULATED IMMUNE RESPONSES

Impaired immune responses are triggered by exposure of the epithelium to environmental stimuli, including physical (e.g., temperature change) and exposome (environmental exposures affecting living systems and their genomes) factors. In homeostasis, the immune response to allergens and other exposures does not activate inflammatory pathways. However, in allergic and nonallergic type 2 (T2) diseases, the anatomical and functional homeostatic balance of the epithelial barrier is skewed towards deleterious activation of the immune system, reduced junctional integrity, and impairment of epithelial barrier function (Figure 2).[7]

When the epithelial barrier is compromised, microorganisms, allergens, and other antigens can pass between epithelial cells through the basement membrane to the underlying tissue, triggering innate immune responses.[7] Innate T2 mechanisms involving T2 innate lymphoid cells (ILC2s) occur in both T2 allergic and T2 nonallergic diseases. In T2 allergic conditions, activation of adaptive immunity, with generation of allergen-specific T helper (Th) 2 cells and immunoglobulin E (IgE) synthesis, also occurs. T2 responses are initiated by epithelial cytokines, or "alarmins"—thymic stromal lymphopoietin (TSLP), interleukin (IL)-33 and IL-25—released from the epithelium in response to environmental exposures. These epithelial cytokines activate ILC2s and promote the maturation of resident myeloid dendritic cells, which prime naïve T cells for differentiation to Th2 cells.[14]

Th2 cells and ILC2s secrete key T2 cytokines: IL-5, IL-4, and IL-13.[14] IL-5 and the epithelial cytokines themselves activate and recruit eosinophils,[15–17] which secrete cytokines, lipid mediators, and oxygen radicals.[18] Eosinophil activation can cause tissue remodelling

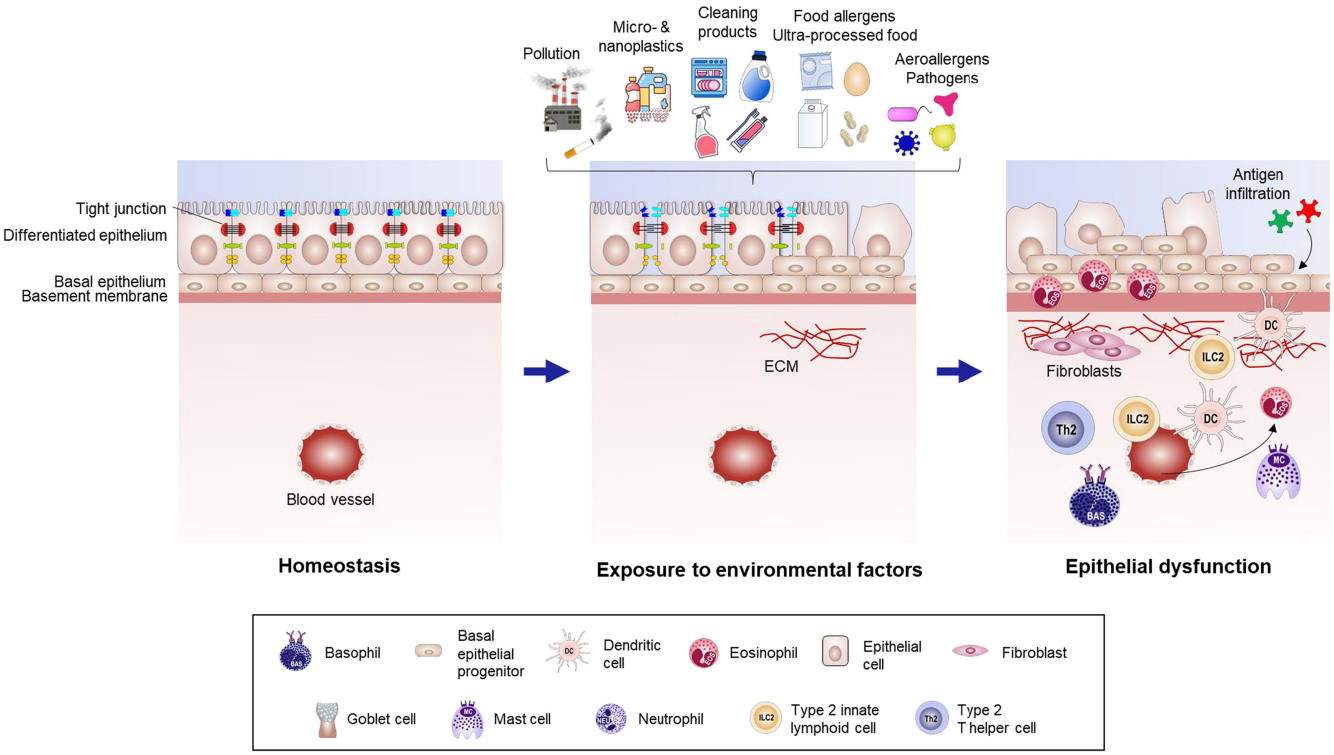


FIGURE 2 Development of epithelial dysfunction across allergic and inflammatory conditions. Exposure to allergens, pathogens, and environmental pollutants can harm the epithelium. These include house dust mite allergens, certain bacteria, fungus, and viruses; food allergens; emulsifiers and other additives found in ultra-processed food; detergents and surfactants found in laundry, dishwashing, domestic cleaning products, and toothpaste; and cigarette smoke, particulate matter, diesel exhaust, ozone, nanoparticles, and microplastics. Epithelia exposed to these factors are characterized by increased permeability, loss of differentiation, and a reduced homeostatic capacity. Infiltration of environmental antigens through a disrupted barrier can then drive sensitization and immune hyperreactivity, with consequent occurrence of allergic and inflammatory diseases. Over time, a cycle of injury and failed repair can lead to remodelling of the subepithelial tissue. ECM, extracellular matrix.

by damaging the endothelium, inhibiting repair, and stimulating fibrosis.[19,20] IL-4 causes B cells to produce IgE antibodies, which sensitize mast and dendritic cells.[14] IL-13 stimulates mucus production and smooth muscle contraction, and impairs the epithelial barrier by opening tight junctions.[14,21–23] Prolonged periods of inflammation can cause lasting structural changes in the epithelium.

In addition to T2 responses, epithelial barrier insults can trigger a variety of other immune reactions. Type 1 responses, directed primarily at intracellular pathogens, particularly viruses, involve ILC1s, natural killer cells, macrophages, and neutrophils, with interferon γ being the main effector cytokine.[24,25] Type 3 responses, directed primarily at extracellular microbial pathogens, including bacteria and fungi, involve Th17 cells, ILC3s, and neutrophils, and are mediated primarily by IL-17.[24,25] Further types of allergic hypersensitivity reactions and disease endotypes relevant to epithelial disorders have recently been defined.[25]

## 4 | CHARACTERISTICS OF ALTERED EPITHELIAL BARRIERS IN ALLERGIC AND INFLAMMATORY DISEASES

Epithelial barrier alteration is present in allergic and inflammatory diseases of the skin, digestive tract, and airways, with differing characteristics (Figures 3 and 4).

### 4.1 | Skin

AD is a systemic, inflammatory skin disease characterized by the interplay between an "outside-in" mechanism, where epidermal barrier dysfunction causes immune activation, and an "inside-out" mechanism, where cytokine release drives skin barrier dysfunction.[26–28] Inflammation in AD is heterogeneous.[28,29] While T2 immune signatures prevail, with increased expression of IL-4 receptor (R), IL-4, IL-13, IL-33, and TSLP,[28,29] an increased Th17 signature is also seen in the Asian endotype of AD.[30] Signalling through type II IL-4/IL-13 receptors on keratinocytes is particularly associated with barrier alterations.[31] AD is primarily driven by T cells, including cutaneous lymphocyte-associated antigen $(CLA)^+$ T cells,[32] whereas IgE is a bystander in most cases and eosinophil counts are variable.[29] Infiltration of mast cells, basophils, and Th2 cells leads to IL-13 and histamine release. These mediators act on their corresponding receptors to trigger pruritus. The resultant itch–scratch cycle of AD disrupts the stratum corneum, impairing the skin's barrier function and allowing further environmental damage and antigen penetration.[28,33]

Further to the T2-driven mechanisms of AD, type 1-driven keratinocyte apoptosis, mediated by T cells infiltrating the skin, also plays a key role.[34] Additionally, increased expression of IL-22, a cytokine that promotes keratinocyte proliferation and regulates type 3 innate immune responses, is associated with acute and chronic moderate-to-severe AD and correlates with epithelial barrier defects.[35,36]

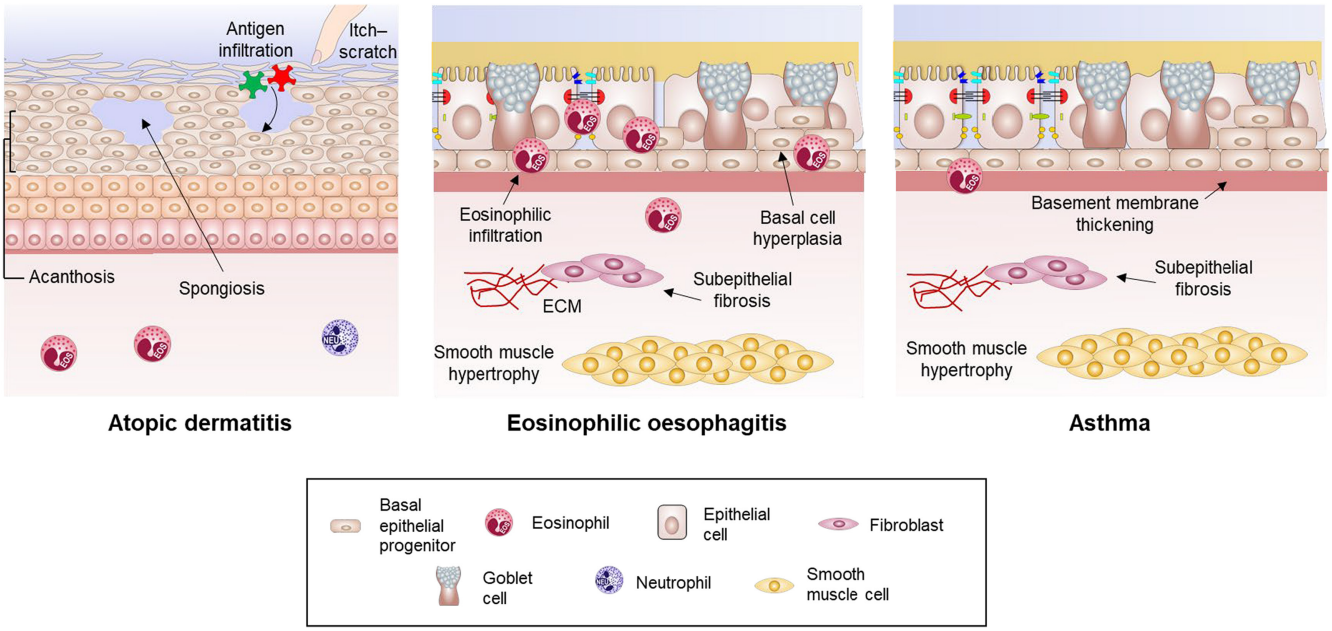


FIGURE 3 Key features of epithelial dysfunction in atopic dermatitis, eosinophilic oesophagitis, and asthma. Exposure of epithelia to harmful environmental factors and subsequent epithelial dysfunction can manifest in the skin, gastrointestinal tract, and airways as clinical conditions such as atopic dermatitis, eosinophilic oesophagitis, and asthma. In atopic dermatitis, inflammation and the itch–scratch cycle lead to an impaired skin barrier, allowing antigen infiltration and development of epidermal defects, such as spongiosis (intercellular oedema) and acanthosis (epidermal thickening). In eosinophilic oesophagitis, inflammation and epithelial/subepithelial defects are present, including barrier impairment, basal cell hyperplasia, fibrosis, and smooth muscle hypertrophy. In asthma, goblet and basal cell hyperplasia, and tissue remodelling occur, including basement membrane thickening, subepithelial fibrosis, and smooth muscle hypertrophy. ECM, extracellular matrix.

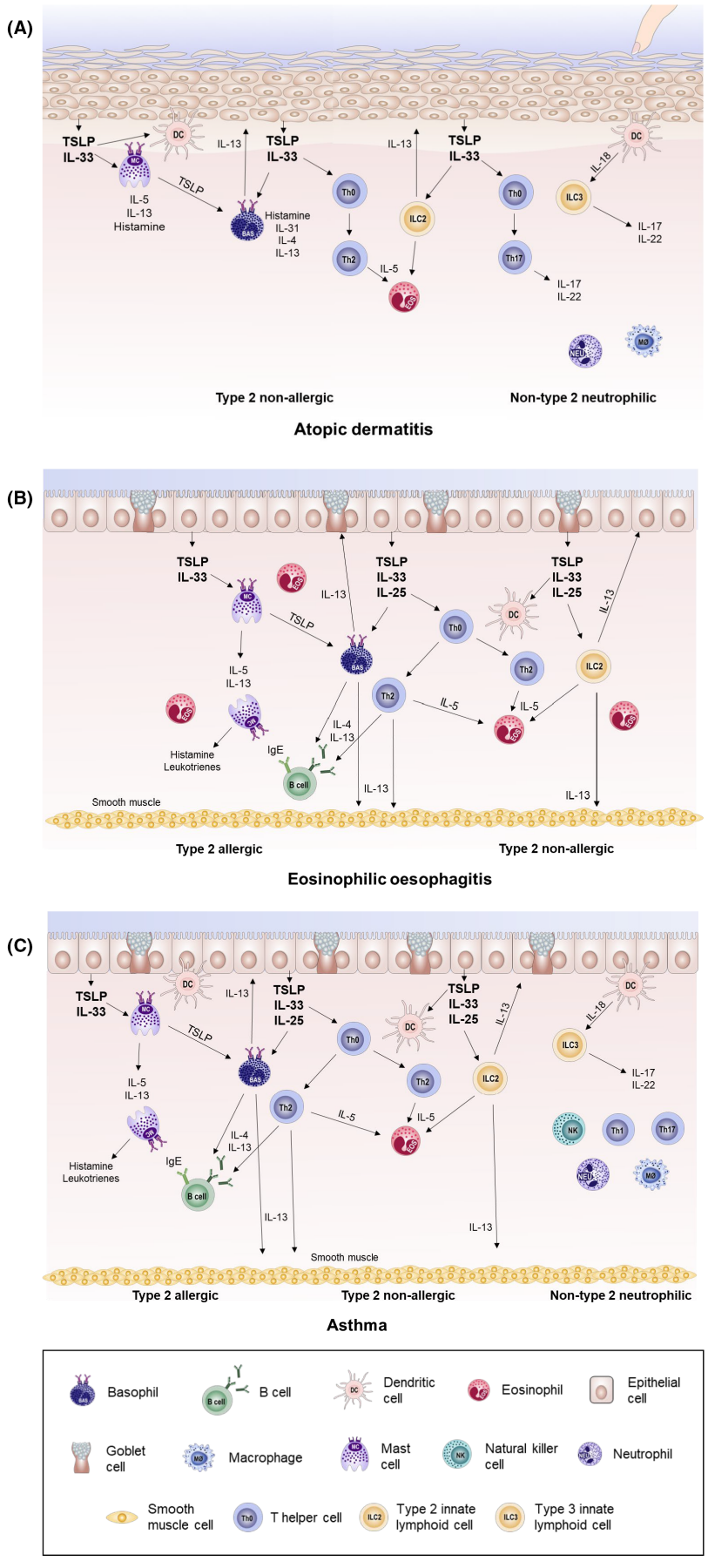


**FIGURE 4** Inflammatory cascades downstream of epithelial disruption in atopic dermatitis, eosinophilic oesophagitis, and asthma. Epithelial barrier disruption triggers the release of epithelial cytokines (TSLP, IL-33, and IL-25) that drive downstream inflammatory cascades potentially involving type 2 allergic, type 2 nonallergic, or non-type 2 neutrophilic inflammation. IL, interleukin; TSLP, thymic stromal lymphopoietin.

Genetic predisposition can contribute to AD. Some patients display loss-of-function mutations in the gene encoding filaggrin, a protein involved in the final differentiation of keratinocytes.[37] Mutations in claudins 1, 4, and 8 can affect the formation of tight junctions.[7] Both lesional and non-lesional skin in patients with AD exhibits terminal keratinocyte differentiation defects, resulting in hyperproliferation of the basal layer of the epidermis and barrier lipid abnormalities, compromising the skin barrier.[38] Histologically, AD is characterized by significant spongiosis and acanthosis.[39]

### 4.2 | Digestive tract

EoE is an immune-mediated disease characterized by infiltration of eosinophils into the oesophagus. EoE can be driven by sensitization to food allergens and involves a combination of T2 mechanisms.[40] Epithelial alterations include basal cell hyperplasia, dilated intercellular spaces, epithelial shedding (desquamation), and apical junction complex (AJC) defects.[41] Epithelial cytokines released following barrier disruption and subsequent IL-5, IL-4, and IL-13 secretion promote a Th2 immune response, leading to irreversible oesophageal remodelling, including strictures.[42,43] IL-13 further contributes to barrier disruption and can cause oesophageal dysfunction via collagen deposition, angiogenesis, and epithelial hyperplasia, independently of eosinophilic inflammation.[43–45]

Food allergy may also derive from alterations in intestinal barrier structure and function.[46–51] Environmental factors, acting directly on the gut barrier or indirectly on the microbiome, affect the integrity of tight junctions, and altered expression of tight junction proteins (and other defects) has been associated with intestinal sensitization to food allergens.[10,46] The interaction between the gut microbiome and intestinal eosinophils has also been associated with alterations to the epithelial barrier.[52]

Primary sensitization to food allergens is thought to occur through cutaneous or gut exposure via barrier impairment.[53,54] IL-33 release induced by mechanical skin injury triggers an expansion of IL-25-producing intestinal tuft cells. IL-25 drives activation of IL-5/IL-13-secreting ILC2s in the intestine, increasing mast cell numbers and intestinal permeability.[55] Following sensitization, subsequent exposure to the allergen triggers IgE-mediated release of preformed inflammatory mediators, such as histamine or heparin, from mast cells.[56] Rapid synthesis and release of lipid mediators (leukotrienes, platelet-activating factor, and prostaglandins) and the production of cytokines by activated mast cells follows. In genetically predisposed individuals, similar immunological pathways can be activated in the absence of an IgE-mediated reaction.[57,58]

### 4.3 | Airways

Bronchial asthma is a heterogeneous disorder of the lower airways, characterized by inflammation, hyper-responsiveness, and variable airflow obstruction. Although inflammation is predominately driven by T2 pathways, approximately 20% of patients with severe asthma have a T2-low phenotype, the underlying mechanisms of which remain poorly understood.[59,60] Asthma onset before 16 years of age is usually driven by T2 allergic mechanisms (IgE sensitization to aeroallergens), with T2-high and T2-low inflammation observed in adult-onset asthma.[61]

Epithelial dysfunction and the subsequent triggering of T2 inflammatory cascades are key features of asthma pathogenesis.[62] Epithelial shedding and/or the loss of functional ciliated cells is common,[61] and epithelial apoptosis may be induced by cooperating eosinophils and T cells.[63] Downregulation of junction proteins can occur owing to environmental stimuli or inflammatory processes, leading to a loss of epithelial integrity that can increase susceptibility to respiratory infections.[28] Alterations in cellular composition are also observed, with goblet cell hyperplasia (in large airways) and metaplasia (in small airways) combining with submucosal gland hypertrophy to result in excessive mucus production, driven by IL-13.[14] AJC disruption and other factors promote epithelial-to-mesenchymal transition (EMT), in which epithelial cells lose their polarity, adhesiveness, and anchorage to the basal membrane, and acquire mesenchymal features, such as migratory abilities. Features of airway remodelling, including thickening of the basement membrane, subepithelial fibrosis, angiogenesis, and smooth muscle hyperplasia, can also occur and contribute to persistent airway restriction.[61,64]

CRS is an inflammatory disease of the nose and paranasal sinuses. Although often classified phenotypically as CRS with nasal polyps (CRSwNP) or without nasal polyps (CRSsNP),[65] guidelines advocate for an endotypic classification based on the presence or absence of T2 inflammation.[66] In Western countries, most patients with CRSwNP display T2 features, whereas most patients with CRSsNP show a mixed eosinophilic–neutrophilic pattern.[65] In CRS, the upper airway epithelium undergoes many of the changes observed in asthma, including basal cell dysplasia, cilia loss, impaired secretory cell function, subepithelial extracellular matrix deposition, and EMT.[67] EMT has been more commonly observed in biopsied tissue from patients with CRSwNP than those with CRSsNP.[68] The epithelial barrier in patients with CRSwNP shows decreased expression of tight junction proteins compared with healthy controls, which may be regulated by IL-4 and interferon γ.[69] Epithelial apoptosis in CRS, characterized by submucosal infiltration of T cells, has also been shown to be regulated by interferon γ.[70]

AR is an IgE-mediated inflammatory response to aeroallergens. As in asthma, AJC impairment, T2 inflammation, eosinophilia, and mast cell and basophil involvement are key features.[71,72] Unlike asthma, tissue remodelling does not appear to be a consistent finding in AR.[72]

## 5 | CAUSES OF EPITHELIAL BARRIER DYSFUNCTION

Both environmental and genetic factors influence the epithelial barrier's anatomical and functional integrity, some of which may predispose it to disruption and, subsequently, inflammatory disease.

### 5.1 | Role of the exposome in epithelial barrier integrity

As already noted, changes in the exposome, particularly increasing exposure to environmental agents related to industrialization, urbanization, and modernization, may underly the increased incidence of allergic and inflammatory diseases worldwide.[3–6,73,74]

Air pollution, including particulate matter, ozone and diesel exhaust, disrupts epithelial integrity via tight junction damage, T2 and non-T2 inflammatory responses, and epigenetic changes in immune cells, and is associated with asthma and AD development.[73,75–77] Furthermore, air pollution alters both the airway microbiome, with a negative impact on lung function,[75,78,79] and the gut microbiome.[80] Micro- and nano-plastics, which individuals may be exposed to through contact, ingestion or inhalation, have been shown in preclinical models to penetrate epithelial barriers, disrupt cell membranes and denature proteins, triggering inflammation and apoptosis.[81–83]

Climate change and global warming are increasing both the concentration and the allergenicity of airborne pollens and fungi,[84–88] as well as the season length of airborne pollens.[89,90] These changes have subsequent effects on respiratory conditions and potentially other allergic disorders.[73] Proteases derived from pollens damage airway epithelial barriers by disrupting tight junctions and the anchorage of epithelial cells.[91–93]

Detergents and surfactants used in cleaning products, such as laundry and dishwasher products and toothpaste, induce epithelial barrier dysfunction and inflammation in the skin, oesophagus, intestine and airways, with recent preclinical studies identifying mechanisms including IL-33 release and tight junction disruption.[94–98] In humans, exposure to these substances is associated with asthma, AR and AD, and may also be linked to EoE.[99–102]

Consumption of a Western diet and ultra-processed foods negatively impacts intestinal epithelium integrity. Preclinical models have shown that high fat and sugar consumption increases transepithelial antigen uptake, reduces mucus thickness, and alters microbiota composition.[103–105] Low fibre intake alters bacterial metabolism, causing degradation of gut mucus glycoproteins and increasing susceptibility to inflammation.[106] Ultra-processed foods contain high levels of dietary advanced glycation end products, which may facilitate food allergy by impairing the gut barrier and by inducing immune dysfunction.[107] Furthermore, food emulsifiers induce a pro-inflammatory response in intestinal epithelial barriers and cause direct cell toxicity at high concentrations.[108] Food colourants have been shown to cause epithelial damage in mice via myosin light chain kinase activation.[109]

### 5.2 | Interactions between the microbiome and the epithelial barrier

The microbiome is integral to the regulation of immune tolerance mechanisms. Early exposure to microbes from the mother, wider family, and environmental sources contributes to microbiome development.

High consumption of ultra-processed foods and a low fibre intake negatively affect microbiome diversity and composition, microbial metabolism, and immunological tolerance.[110–112] Gut bacterial metabolites, including short-chain fatty acids, interact with immune cells and suppress the release of pro-inflammatory cytokines, promote barrier structure and function, and reduce epithelial permeability.[113] Children with high levels of the short-chain fatty acids butyrate and propionate in their stools at 1 year of age have significantly less atopic sensitization and are less likely to develop asthma between the ages of 3 years and 6 years than those with low levels; they also have lower risks of food allergy and AR.[114]

In the airways, *Haemophilus*, *Moraxella*, *Neisseria*, and *Streptococcus* overgrowth is associated with childhood asthma.[115,116] Colonization of the upper airways by *Pseudomonas* and *Staphylococcus* is often observed in CRS and is associated with asthma development.[116,117]

In the skin, reduced bacterial diversity and increased colonization by *Staphylococcus aureus* is seen in infants who subsequently develop AD.[118] *S. aureus* produces proteases that penetrate the epidermis and stimulate Th2 cytokine production. Of note, *S. aureus* induces activation of $CLA^+$ T cells, resulting in IL-13 production in particular, a key driver of eczema severity.[32,119] These activities promote further bacterial invasion by increasing *S. aureus* binding sites, inhibiting Toll-like receptor function, and decreasing antimicrobial peptide production.[2,120]

Bacterial metabolites from the gut exert an influence on the lungs either via the circulation or through migration of immune cells stimulated by bacterial factors.[121,122] Furthermore, gut–lung communication is bidirectional.[121] Disrupted gut or lung colonization can become a risk factor for the development of respiratory disease[123,124] through a variety of mechanisms, including inadequate training of immunotolerance, inefficient colonization resistance, and/or improper lung morphogenesis.[125–127] Gut dysbiosis has also been associated with AD development in children, suggesting that pathogenic colonization may drive systemic atopy.[28]

### 5.3 | Genetic and epigenetic influences on epithelial barrier function

Disorders of the immune response are strongly influenced by genetics, with many atopic susceptibility genes involved in the control of epithelial barrier homeostasis. Many genes associated with AD are located on chromosome 1q21 (referred to as the epidermal differentiation complex), including those encoding filaggrin, kinesin 3A, and other proteins important for keratinocyte maturation and skin barrier function.[128] Mutations in several asthma susceptibility genes are thought to be linked to aberrant epithelial remodelling, the unfolded protein response, and lipid biosynthesis.[7] Genome-wide association studies show that AD, AR, and asthma

also share genetic risk loci resulting in dysregulation of immune-related genes.[129] Polymorphisms of the *TSLP* gene are associated with increased risks of AD, asthma, airway hyperresponsiveness, nasal polyps, and EoE.[130–132] Overall though, disease-associated alleles have small effect sizes, highlighting the importance of complex gene–environment interactions in influencing disease processes.

Epigenetic mechanisms, including DNA methylation and post-transcriptional regulation by microRNAs (miRNAs), can induce immune system-level changes in gene expression that affect inflammatory disease prognosis.[133] *TSLP* is a methylation-sensitive gene, with epigenetic alterations associated with AD, asthma, and CRSwNP.[134,135] Hypomethylation of *KRT5* is one of the main epigenetic changes associated with asthma, resulting in upregulation of keratin 5 in basal airway epithelium and dysregulated epithelial differentiation.[7] DNA methylation in bronchial mucosa differs between patients with atopic and nonatopic asthma.[136] Differences in expression of miRNAs targeting immune-associated genes have been found in epithelial samples from patients with AD, AR, and asthma.[137] Children with IgE-mediated cow's milk allergy exhibit downregulation of miR193a-5, resulting in increased levels of IL-4,[133] as well as altered methylation status in Th1 and Th2 response mediator genes.[138–140] Pollution is a known driver of epigenetic alterations, with diesel exhaust and cigarette smoke altering bronchial epithelium DNA methylation and expression of miRNAs involved in several asthma-related processes, such as oxidative stress, apoptosis, autophagy, NF-κB signalling, EMT, and various inflammatory responses.[137,141]

## 6 | RELATIONSHIPS BETWEEN EPITHELIAL BARRIERS OF DIFFERENT ORGANS

The "allergic march" or "atopic march" refers to a progression of Th2-mediated immune conditions, with manifestations affecting multiple organ systems.[142] AD is often the first manifestation of the allergic march.[143] Children with AD are more likely to develop food and respiratory allergies, with the likelihood increasing with early-onset/persistent AD.[142] Cutaneous exposure to common food antigens (e.g., peanuts) together with impaired skin barrier function potentially drives sensitization in children with AD.[144] Repeated exposure to the same antigens stimulates epithelial release of IL-33 and TSLP, activating an immune cascade that triggers systemic dysregulation of immune tolerance, affecting the intestines and airways.[145,146] Mechanical skin injuries in AD also cause systemic release of IL-33, which activates intestinal mast cells and increases intestinal permeability, potentially increasing the likelihood of anaphylaxis in children with comorbid AD and food allergy.[55,147,148] Sensitization to food and inhaled allergens in infancy and early childhood is associated with higher risks of wheezing, asthma, and AR by 10 years of age.[128]

Evidence suggests that EoE could be a late manifestation of the allergic march. A paediatric virtual birth cohort study showed that children with IgE-mediated food allergy had a nine-fold increased risk of developing EoE, and that a personal history of AD, IgE-mediated food allergy, and asthma was independently and cumulatively associated with an increased risk of developing EoE.[149] Genetic and mechanistic studies have shown that TSLP promotes EoE, strengthening the link between the epithelium and the allergic march.[142]

Many patients do not follow a strict linear progression from AD to food allergy, EoE, asthma, and AR. Why some individuals develop certain atopic conditions and not others is poorly understood, and many children will experience only one atopic condition without further progression.[142] Twin and sibling studies indicate that the link between AD and allergic asthma may be independent of shared environmental factors.[150]

## 7 | CLINICAL BIOMARKERS OF EPITHELIAL BARRIER DISRUPTION

The identification of reliable biomarkers of susceptibility, diagnosis and disease monitoring, as well as predictors of the response to treatment, is key to providing personalized treatment. Although few accurate and easily obtainable biomarkers are available for epithelial-driven diseases, omics approaches are increasingly used for differential analysis and biomarker discovery.

### 7.1 | Atopic dermatitis

An unmet need remains for reliable biomarkers that can confirm AD among the heterogeneous eczema population.[151] Candidate diagnostic biomarkers include nitric oxide synthase 2/inducible nitric oxide synthase, human β-defensin-2, and matrix metalloproteinases 8 and 9. Squamous cell carcinoma antigen 2, thymus and activation-regulated chemokine, cutaneous T cell-attracting chemokine, eosinophil-derived neurotoxin, macrophage-derived chemokine, lactate dehydrogenase, and IL-18 may be useful biomarkers for monitoring disease severity. Lactate dehydrogenase, thymus and activation-regulated chemokine, pulmonary and activation-regulated chemokine, periostin, IL-22, eotaxin-1/3, and IL-8 may be biomarkers for monitoring treatment effects.[151]

### 7.2 | Eosinophilic oesophagitis

No validated, noninvasive biomarkers have been established for the diagnosis and monitoring of EoE.[152] Studies of patients with EoE-like disease but without eosinophilia suggest that conventionally defined EoE may be one phenotype on a broader "inflammatory dysphagia syndrome" spectrum. These patients exhibited an almost complete absence of oesophageal eosinophils but considerable

T-cell infiltration and could be differentiated from patients with EoE and healthy controls by mRNA expression of *eotaxin-3*, *MUC4*, and *CDH26*.[153]

### 7.3 | Food allergy

Food allergy screening tests (e.g., skin-prick tests, serum food-specific IgE levels, and atopy patch tests) are commonly used to identify sensitization to distinct foods. Nevertheless, the correlation between test positivity and clinical reactivity to foods is poor, and oral food challenge is generally required to confirm a diagnosis of food allergy.[154] The basophil activation test is a patient-friendly, in vitro alternative that can provide a definitive diagnosis without the need for an oral challenge.[154] Similarly, the mast cell activation test can support a diagnosis of plant food allergy.[155] Although biomarkers for food allergy are lacking, transcriptomic, epigenomic, microbiomic, and metabolomic biomarkers are being investigated.[156]

### 7.4 | Allergic asthma

Although biomarkers of asthma are available, not one of them univocally identifies and differentiates between phenotypes, although they can provide insight into inflammatory characteristics. The T2-high phenotype can be further subdivided into two phenotypes. First is a classical (typically early onset) allergic phenotype, identified through the presence of allergen-specific IgE in serum and demonstration of the clinical relevance of the sensitization. These patients typically have mild blood eosinophilia and high fractional exhaled nitric oxide (FeNO) and serum total IgE levels.[59] Second is a late-onset eosinophilic phenotype, characterized by eosinophilia and high FeNO levels, normal or mildly elevated serum total IgE levels, and high levels of serum IL-5 and IL-13.[59] The T2-low phenotype is less well defined; some patients display non-T2 haematopoietic inflammation, with elevated tumour necrosis factor α and IL-17 levels and neutrophilic airway inflammation,[157] whereas others show no haematopoietic infiltrate in the bronchi.[158] Currently, "epithelial dysfunction-driven" asthma cannot be easily identified. Increased asthma exacerbations in response to environmental triggers (e.g., pathogens, pollutants, pollens, and moulds) might be explored as a "fingerprint" of epithelial involvement, especially when poor asthma control persists despite targeting traditional T2 inflammatory drivers.[159–162]

### 7.5 | Chronic rhinosinusitis with nasal polyps

CRSwNP is usually characterized by intranasal eosinophilia and locally elevated IL-5, which correlate with disease severity and recurrence of nasal polyps after endoscopic sinus surgery.[163] Nasal nitric oxide correlates with eosinophilic upper airway inflammation. Nevertheless, nitric oxide levels tend to be lower in patients with CRSwNP than in healthy individuals, which may result from nasal congestion hindering nitric oxide exhalation.[164–166] Consistently elevated levels of periostin, an extracellular matrix protein secreted in response to IL-4 and IL-13, have been found in patients with CRSwNP relative to those with CRSsNP and healthy controls, and correlate with disease severity.[167] P-glycoprotein is upregulated in T2 inflammation, with secretion levels increased in the mucus of patients with CRS, and higher levels associated with CRSwNP and greater disease severity.[168]

### 7.6 | Allergic rhinitis

Positive skin-prick tests and/or serum specific IgE levels for seasonal and perennial aeroallergens are used to screen for AR, although confirmation of the diagnosis may require a nasal allergen challenge.[169] Nasal cytology can be used to support the differential diagnosis of rhinitis with and without inflammation and eosinophilia, and an association has been found between serum total IgE levels and the severity of nasal eosinophilia.[170] High nasal eosinophil levels also predict the clinical efficacy of subcutaneous immunotherapy.[171]

## 8 | TARGETING THE EPITHELIUM FOR THE TREATMENT OF ALLERGIC AND INFLAMMATORY DISEASES

Several biologic therapies for allergic and inflammatory diseases directly or indirectly target the epithelium of the skin, digestive tract, and airways (Figure 5).

### 8.1 | Anti-TSLP

Tezepelumab is a human monoclonal antibody (mAb) that blocks TSLP.[172] In addition to driving T2 inflammation, TSLP has been shown to mediate non-T2 interactions between epithelial cells, immune cells, and structural cells.[16] Tezepelumab is approved for severe, uncontrolled asthma without phenotypic restriction, having shown efficacy irrespective of baseline T2 biomarker levels (albeit with greater efficacy in patients with higher T2 biomarker levels),[173] and is being investigated in CRSwNP and EoE. Treatment with tezepelumab reduces levels of T2 inflammatory biomarkers (blood eosinophils, airway eosinophils, FeNO, IL-5, IL-13, and periostin) and exacerbations, and improves forced expiratory volume in 1 s, in patients with severe, uncontrolled asthma.[172–175] Tezepelumab also reduces airway hyperresponsiveness to mannitol, indicating that TSLP blockade might have additional benefits in asthma beyond reducing T2 airway inflammation.[176,177] The lack of efficacy of tezepelumab in AD[178] may reflect the mixed aetiology of the disease.

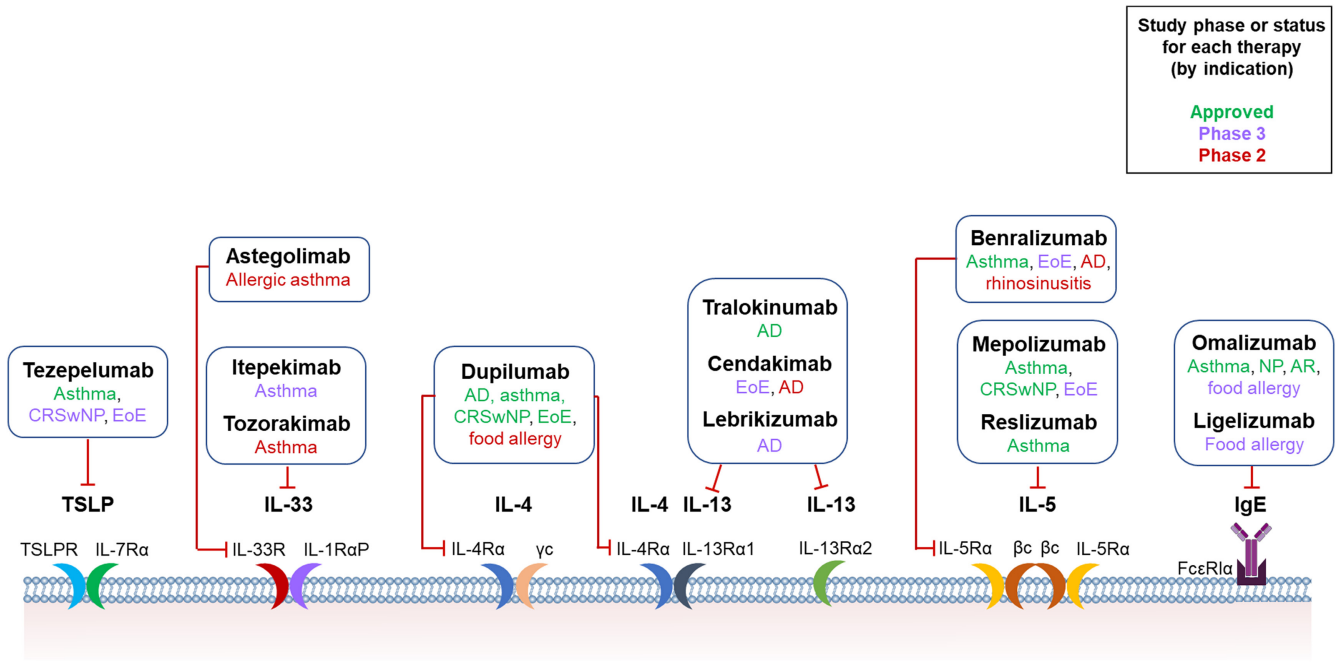


FIGURE 5 Approved and investigational biologic therapies for epithelial-driven allergic and inflammatory disease. AD, atopic dermatitis; AR, allergic rhinitis; CRSwNP, chronic rhinosinusitis with nasal polyps; EoE, eosinophilic oesophagitis; IgE, immunoglobulin E; IL, interleukin; NP, nasal polyps; R, receptor; TSLP, thymic stromal lymphopoietin.

## 8.2 | Anti-IL-33/anti-ST2

IL-33 activates cells of both the innate and adaptive immune systems.[179] Itepekimab, a mAb against IL-33, reduced the incidence of events indicating a loss of asthma control and improved lung function in a phase 2 study.[180] Astegolimab, a mAb targeting the IL-33 receptor ST2, has also shown efficacy in a phase 2 asthma study.[181] Tozorakimab is a dual-pharmacology anti-IL-33 mAb in a phase 2 trial for asthma.[182]

## 8.3 | Anti-IL-4Rα (anti-IL-4/IL-13)

Dupilumab inhibits IL-4 signalling via the type I receptor IL-4Rα/γc, and both IL-4 and IL-13 signalling through the type II receptor IL-4Rα/IL-13Rα. Blocking the IL-4/IL-13 pathway decreases many of the downstream mediators of T2 inflammation.[183] Dupilumab is approved for AD, asthma, CRSwNP, and EoE, and is being investigated in food allergy.[184,185] Dupilumab has also been shown to reduce *S. aureus* colonization and specific IgE levels of several food allergens in AD.[186–188]

## 8.4 | Anti-IL-13

In the skin, excess IL-13 reduces antimicrobial peptide production, facilitating *S. aureus* colonization in AD.[189] The anti-IL-13 mAb tralokinumab is approved for adults with moderate-to-severe AD. Tralokinumab treatment was shown to increase microbial diversity, reduce *S. aureus* levels and increase levels of commensal staphylococci.[190] The high-affinity anti-IL-13 mAb lebrikizumab also showed efficacy in AD in phase 3 trials.[191] In the oesophagus, IL-13 release results in eosinophil and mast cell infiltration, epithelial barrier disruption, and tissue remodelling.[41] Cendakimab is an anti-IL-13 mAb being investigated in EoE, with a phase 2 trial showing that it reduces eosinophil counts and improves histologic scores and mucosal appearance.[192]

## 8.5 | Anti-IL-5/IL-5Rα

Anti-IL-5/IL-5Rα mAbs attenuate T2 inflammation by reducing eosinophils in the airway and oesophageal epithelium, as well as mast cells in the oesophagus.[193] The anti-IL-5 mAbs mepolizumab and reslizumab have been approved for severe, uncontrolled asthma. Mepolizumab reduces airway eosinophils, deposition of subepithelial extracellular matrix (associated with airway remodelling) and production of IL-25 and TSLP.[194,195] Mepolizumab is also approved for the treatment of CRSwNP and is being investigated in EoE.[196,197] Benralizumab (anti- IL-5Rα mAb) is approved for severe eosinophilic asthma and is being investigated in CRSwNP, eosinophilic gastroenteritis, and other eosinophilic conditions.

## 8.6 | Anti-IgE

Anti-IgE treatment reduces serum free IgE and downregulates IgE receptor expression on circulating basophils, resident mast cells, and

B cells.[198–200] This inhibits IgE-mediated release of inflammatory mediators, attenuating the response to allergens.[200–202] Omalizumab, an anti-IgE mAb, has been shown to increase the allergen threshold needed to activate effector cells and inhibit IgE-mediated transport across epithelial barriers.[203] Omalizumab is approved for T2 allergic asthma, chronic spontaneous urticaria and CRSwNP, and is being investigated in AR.[204] Ligelizumab, an anti-IgE mAb with greater IgE-binding affinity than omalizumab, is being investigated in food allergy.[205]

### 8.7 | Nonbiologic treatments

Various nonbiologic treatments for allergic disorders exert their therapeutic effects through targeting the epithelium.

In AD, ceramide-based emollients can restore the skin's epithelial barrier, reducing susceptibility to irritants, normalizing skin pH, decreasing allergen protease activity, and ameliorating inflammation.[28] Topical calcineurin inhibitors or corticosteroids can further aid barrier repair.[28]

Probiotic consumption promotes Th1- versus Th2-mediated inflammation and reduces AD disease severity.[206,207] Topical creams containing prebiotics or bacterial lysate are effective in restoring microbiome diversity and reducing exacerbations in AD.[28] Early research into the use of probiotics for treating upper respiratory conditions has suggested that species associated with gut epithelial repair, such as *Lacticaseibacillus casei*, may improve epithelial integrity in AR and CRS.[208]

Inhaled corticosteroids may enhance airway epithelial integrity in asthma by improving tight junction assembly, as well as decreasing goblet cell hyperplasia and airway inflammation susceptibility.[61] Nasal corticosteroids are effective in restoring epithelial integrity in the upper airway in AR and CRS, by decreasing airway inflammation and upregulating tight junction proteins and protocadherin-1.[208]

## 9 | CONCLUSION

Epithelial barrier dysfunction is both a driver and consequence of immunological and inflammatory disorders, with underlying mechanisms that are complex and influenced by interactions between the exposome, microbiome, individual genetics, and epigenetics. An unmet need remains for treatments targeting epithelial impairment in AD, EoE, food allergy, AR, CRS, and asthma. An important first step will be identifying clinically applicable biomarkers and manifestations that differentiate patients with epithelial impairment as the main disease driver from those with inflammation-driven phenotypes. An interesting avenue of investigation is the possibility of system-level therapeutic targets for epithelial dysfunction, to prevent or treat the allergic march. Adult and paediatric allergy specialists trained in T2-driven diseases could play a key role in advancing this line of inquiry, in coordination with single-organ specialists.

## AUTHOR CONTRIBUTIONS

All authors were involved in conceiving the scope of the manuscript, drafting it and reviewing it critically for important intellectual content. Additionally, all authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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## CONFLICT OF INTEREST STATEMENT

Roberto Berni Canani, Marco Caminati, Laura Carucci, and Ibon Eguiluz-Gracia report no conflicts of interest.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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## REFERENCES

1. Izquierdo E, Rodriguez-Coira J, Delgado-Dolset MI, Gomez-Casado C, Barber D, Escribese MM. Epithelial barrier: protector and trigger of Allergic disorders. *J Investig Allergol Clin Immunol*. 2022;32(2):81-96.
2. Goleva E, Berdyshev E, Leung DY. Epithelial barrier repair and prevention of allergy. *J Clin Invest*. 2019;129(4):1463-1474.
3. Yazici D, Ogulur I, Pat Y, et al. The epithelial barrier: the gateway to allergic, autoimmune, and metabolic diseases and chronic neuropsychiatric conditions. *Semin Immunol*. 2023;70:101846.
4. Akdis CA, Akdis M, Boyd SD, Sampath V, Galli SJ, Nadeau KC. Allergy: mechanistic insights into new methods of prevention and therapy. *Sci Transl Med*. 2023;15(679):eadd2563.
5. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol*. 2021;21(11):739-751.
6. Pat Y, Ogulur I. The epithelial barrier hypothesis: a 20-year journey. *Allergy*. 2021;76(11):3560-3562.
7. Schleimer RP, Berdnikovs S. Etiology of epithelial barrier dysfunction in patients with type 2 inflammatory diseases. *J Allergy Clin Immunol*. 2017;139(6):1752-1761.
8. Lefevre-Utile A, Braun C, Haftek M, Aubin F. Five functional aspects of the epidermal barrier. *Int J Mol Sci*. 2021;22(21):11676.
9. Seneschal J, Clark RA, Gehad A, Baecher-Allan CM, Kupper TS. Human epidermal Langerhans cells maintain immune homeostasis in skin by activating skin resident regulatory T cells. *Immunity*. 2012;36(5):873-884.
10. Ali A, Tan H, Kaiko GE. Role of the intestinal epithelium and its interaction with the microbiota in food allergy. *Front Immunol*. 2020;11:604054.

11. Odenwald MA, Turner JR. The intestinal epithelial barrier: a therapeutic target? *Nat Rev Gastroenterol Hepatol*. 2017;14(1):9-21.
12. Wu M, Zhang X, Lin Y, Zeng Y. Roles of airway basal stem cells in lung homeostasis and regenerative medicine. *Respir Res*. 2022;23(1):122.
13. Wittekindt OH. Tight junctions in pulmonary epithelia during lung inflammation. *Pflugers Arch*. 2017;469(1):135-147.
14. Akdis CA, Arkwright PD, Bruggen MC, et al. Type 2 immunity in the skin and lungs. *Allergy*. 2020;75(7):1582-1605.
15. Pelaia C, Paoletti G, Puggioni F, et al. Interleukin-5 in the pathophysiology of severe asthma. *Front Physiol*. 2019;10:1514.
16. Gauvreau GM, Sehmi R, Ambrose CS, Griffiths JM. Thymic stromal lymphopoietin: its role and potential as a therapeutic target in asthma. *Expert Opin Ther Targets*. 2020;24(8):777-792.
17. Johnston LK, Bryce PJ. Understanding interleukin 33 and its roles in eosinophil development. *Front Med (Lausanne)*. 2017;4:51.
18. Carr TF, Berdnikovs S, Simon HU, Bochner BS, Rosenwasser LJ. Eosinophilic bioactivities in severe asthma. *World Allergy Organ J*. 2016;9:21.
19. Amin K, Janson C, Bystrom J. Role of eosinophil granulocytes in Allergic airway inflammation Endotypes. *Scand J Immunol*. 2016;84(2):75-85.
20. Ramirez GA, Yacoub MR, Ripa M, et al. Eosinophils from physiology to disease: a comprehensive review. *Biomed Res Int*. 2018;2018:9095275.
21. Schmidt H, Braubach P, Schilpp C, et al. IL-13 impairs tight junctions in airway epithelia. *Int J Mol Sci*. 2019;20(13):3222.
22. Sugita K, Altunbulakli C, Morita H, et al. Human type 2 innate lymphoid cells disrupt skin keratinocyte tight junction barrier by IL-13. *Allergy*. 2019;74(12):2534-2537.
23. Sugita K, Steer CA, Martinez-Gonzalez I, et al. Type 2 innate lymphoid cells disrupt bronchial epithelial barrier integrity by targeting tight junctions through IL-13 in asthmatic patients. *J Allergy Clin Immunol*. 2018;141(1):300-310 e311.
24. Johnston SL, Goldblatt DL, Evans SE, Tuvim MJ, Dickey BF. Airway epithelial innate immunity. *Front Physiol*. 2021;12:749077.
25. Jutel M, Agache I, Zemelka-Wiacek M, et al. Nomenclature of allergic diseases and hypersensitivity reactions: adapted to modern needs: an EAACI position paper. *Allergy*. 2023;78(11):2851-2874.
26. Facheris P, Jeffery J, Del Duca E, Guttman-Yassky E. The translational revolution in atopic dermatitis: the paradigm shift from pathogenesis to treatment. *Cell Mol Immunol*. 2023;20(5):448-474.
27. Elias PM, Wakefield JS. Could cellular and signaling abnormalities converge to provoke atopic dermatitis? *J Dtsch Dermatol Ges*. 2020;18(11):1215-1223.
28. Zhu TH, Zhu TR, Tran KA, Sivamani RK, Shi VY. Epithelial barrier dysfunctions in atopic dermatitis: a skin-gut-lung model linking microbiome alteration and immune dysregulation. *Br J Dermatol*. 2018;179(3):570-581.
29. Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. *J Allergy Clin Immunol*. 2019;143(1):1-11.
30. Noda S, Suarez-Farinas M, Ungar B, et al. The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization. *J Allergy Clin Immunol*. 2015;136(5):1254-1264.
31. Progneaux A, Evrard C, De Glas V, et al. Keratinocytes activated by IL-4/IL-13 express IL-2Rgamma with consequences on epidermal barrier function. *Exp Dermatol*. 2023;32(5):660-670.
32. Nicolas LSS, Czarnowicki T, Akdis M, et al. CLA+ memory T cells in atopic dermatitis: CLA+ T cells and atopic dermatitis. *Allergy*. 2024;79(1):15-25.
33. Nakashima C, Ishida Y, Kitoh A, Otsuka A, Kabashima K. Interaction of peripheral nerves and mast cells, eosinophils, and basophils in the development of pruritus. *Exp Dermatol*. 2019;28(12):1405-1411.
34. Trautmann A, Akdis M, Kleemann D, et al. T cell-mediated Fas-induced keratinocyte apoptosis plays a key pathogenetic role in eczematous dermatitis. *J Clin Invest*. 2000;106(1):25-35.
35. Gittler JK, Shemer A, Suarez-Farinas M, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol*. 2012;130(6):1344-1354.
36. Lopez DV, Kongsbak-Wismann M. Role of IL-22 in homeostasis and diseases of the skin. *APMIS*. 2022;130(6):314-322.
37. Thyssen JP, Kezic S. Causes of epidermal filaggrin reduction and their role in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol*. 2014;134(4):792-799.
38. Suarez-Farinas M, Tintle SJ, Shemer A, et al. Nonlesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalities. *J Allergy Clin Immunol*. 2011;127(4):954-964.e4.
39. Colmenero I, Torrelo A, Reyes-Múgica M. Skin. In: Scheimberg I, Cohen MC, eds. *Essentials of Surgical Pediatric Pathology*. Cambridge University Press; 2000:1-42.
40. Dellon ES, Kim HP, Sperry SL, Rybnicek DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest Endosc*. 2014;79(4):577-585 e574.
41. Nhu QM, Aceves SS. Tissue remodeling in chronic eosinophilic esophageal inflammation: parallels in asthma and therapeutic perspectives. *Front Med (Lausanne)*. 2017;4:128.
42. Aceves SS, Ackerman SJ. Relationships between eosinophilic inflammation, tissue remodeling, and fibrosis in eosinophilic esophagitis. *Immunol Allergy Clin N Am*. 2009;29(1):197-211.
43. Mavi P, Rajavelu P, Rayapudi M, Paul RJ, Mishra A. Esophageal functional impairments in experimental eosinophilic esophagitis. *Am J Physiol Gastrointest Liver Physiol*. 2012;302(11):G1347-G1355.
44. Zuo L, Fulkerson PC, Finkelman FD, et al. IL-13 induces esophageal remodeling and gene expression by an eosinophil-independent, IL-13R alpha 2-inhibited pathway. *J Immunol*. 2010;185(1):660-669.
45. Davis BP, Stucke EM, Khorki ME, et al. Eosinophilic esophagitis-linked calpain 14 is an IL-13-induced protease that mediates esophageal epithelial barrier impairment. *JCI Insight*. 2016;1(4):e86355.
46. Samadi N, Klems M, Untersmayr E. The role of gastrointestinal permeability in food allergy. *Ann Allergy Asthma Immunol*. 2018;121(2):168-173.
47. Andre C, Andre F, Colin L, Cavagna S. Measurement of intestinal permeability to mannitol and lactulose as a means of diagnosing food allergy and evaluating therapeutic effectiveness of disodium cromoglycate. *Ann Allergy*. 1987;59(5 Pt 2):127-130.
48. Dupont C, Barau E, Molkhou P, Raynaud F, Barbet JP, Dehennin L. Food-induced alterations of intestinal permeability in children with cow's milk-sensitive enteropathy and atopic dermatitis. *J Pediatr Gastroenterol Nutr*. 1989;8(4):459-465.
49. Jarvinen KM, Konstantinou GN, Pilapil M, et al. Intestinal permeability in children with food allergy on specific elimination diets. *Pediatr Allergy Immunol*. 2013;24(6):589-595.
50. Ventura MT, Polimeno L, Amoruso AC, et al. Intestinal permeability in patients with adverse reactions to food. *Dig Liver Dis*. 2006;38(10):732-736.
51. Konig J, Wells J, Cani PD, et al. Human intestinal barrier function in health and disease. *Clin Transl Gastroenterol*. 2016;7(10):e196.
52. Jimenez-Saiz R, Anipindi VC, Galipeau H, et al. Microbial regulation of enteric eosinophils and its impact on tissue Remodeling and Th2 immunity. *Front Immunol*. 2020;11:155.
53. DeLong JH, Simpson KH, Wambre E, James EA, Robinson D, Kwok WW. Ara h 1-reactive T cells in individuals with peanut allergy. *J Allergy Clin Immunol*. 2011;127(5):1211-1218 e1213.
54. Chan SM, Turcanu V, Stephens AC, Fox AT, Grieve AP, Lack G. Cutaneous lymphocyte antigen and alpha4beta7 T-lymphocyte

responses are associated with peanut allergy and tolerance in children. *Allergy*. 2012;67(3):336-342.
55. Leyva-Castillo JM, Galand C, Kam C, et al. Mechanical skin injury promotes food anaphylaxis by driving intestinal mast cell expansion. *Immunity*. 2019;50(5):1262-1275 e1264.
56. Benede S, Garrido-Arandia M, Martin-Pedraza L, Bueno C, Diaz-Perales A, Villalba M. Multifactorial modulation of food-induced anaphylaxis. *Front Immunol*. 2017;8:552.
57. Yu W, Freeland DMH, Nadeau KC. Food allergy: immune mechanisms, diagnosis and immunotherapy. *Nat Rev Immunol*. 2016;16(12):751-765.
58. Simon D, Cianferoni A, Spergel JM, et al. Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity. *Allergy*. 2016;71(5):611-620.
59. Kuruvilla ME, Lee FE, Lee GB. Understanding asthma phenotypes, Endotypes, and mechanisms of disease. *Clin Rev Allergy Immunol*. 2019;56(2):219-233.
60. Ricciardolo FLM, Sprio AE, Baroso A, et al. Characterization of T2-low and T2-high asthma phenotypes in real-life. *Biomedicine*. 2021;9(11):1684.
61. Carlier FM, de Fays C, Pilette C. Epithelial barrier dysfunction in chronic respiratory diseases. *Front Physiol*. 2021;12:691227.
62. Caminati M, Pham DL, Bagnasco D, Canonica GW. Type 2 immunity in asthma. *World Allergy Organ J*. 2018;11(1):13.
63. Trautmann A, Schmid-Grendelmeier P, Kruger K, et al. T cells and eosinophils cooperate in the induction of bronchial epithelial cell apoptosis in asthma. *J Allergy Clin Immunol*. 2002;109(2):329-337.
64. Hough KP, Curtiss ML, Blain TJ, et al. Airway Remodeling in asthma. *Front Med (Lausanne)*. 2020;7:191.
65. Cho SW, Kim DW, Kim JW, Lee CH, Rhee CS. Classification of chronic rhinosinusitis according to a nasal polyp and tissue eosinophilia: limitation of current classification system for Asian population. *Asia Pac Allergy*. 2017;7(3):121-130.
66. Kato A, Peters AT, Stevens WW, Schleimer RP, Tan BK, Kern RC. Endotypes of chronic rhinosinusitis: Relationships to disease phenotypes, pathogenesis, clinical findings, and treatment approaches. *Allergy*. 2022;77(3):812-826.
67. Bankova LG, Barrett NA. Epithelial cell function and remodeling in nasal polyposis. *Ann Allergy Asthma Immunol*. 2020;124(4):333-341.
68. Wang M, Sun Y, Li C, Qu J, Zhou B. Eosinophils correlate with epithelial-mesenchymal transition in chronic Rhinosinusitis with nasal polyps. *ORL J Otorhinolaryngol Relat Spec*. 2022;84(1):70-80.
69. Soyka MB, Wawrzyniak P, Eiwegger T, et al. Defective epithelial barrier in chronic rhinosinusitis: the regulation of tight junctions by IFN-gamma and IL-4. *J Allergy Clin Immunol*. 2012;130(5):1087-1096 e1010.
70. Basinski TM, Holzmann D, Eiwegger T, et al. Dual nature of T cell-epithelium interaction in chronic rhinosinusitis. *J Allergy Clin Immunol*. 2009;124(1):74-80.
71. London NR Jr, Ramanathan M Jr. The role of the Sinonasal epithelium in Allergic Rhinitis. *Otolaryngol Clin N Am*. 2017;50(6):1043-1050.
72. Corren J, Togias A. Remodeling in allergic rhinitis. Adding new data to an old debate. *Am J Respir Crit Care Med*. 2015;192(12):1403-1404.
73. Celebi Sozener Z, Ozdel Ozturk B, Cerci P, et al. Epithelial barrier hypothesis: effect of the external exposome on the microbiome and epithelial barriers in allergic disease. *Allergy*. 2022;77(5):1418-1449.
74. Mitamura Y, Ogulur I, Pat Y, et al. Dysregulation of the epithelial barrier by environmental and other exogenous factors. *Contact Derm*. 2021;85(6):615-626.
75. Tuazon JA, Kilburg-Basnyat B, Oldfield LM, et al. Emerging insights into the impact of air pollution on immune-mediated asthma pathogenesis. *Curr Allergy Asthma Rep*. 2022;22(7):77-92.
76. Gruzieva O, Xu CJ, Yousefi P, et al. Prenatal particulate air pollution and DNA methylation in newborns: an epigenome-wide meta-analysis. *Environ Health Perspect*. 2019;127(5):57012.
77. Fadadu RP, Abuabara K, Balmes JR, Hanifin JM, Wei ML. Air pollution and atopic dermatitis, from molecular mechanisms to population-level evidence: a review. *Int J Environ Res Public Health*. 2023;20(3):2526.
78. Vitte J, Michel M, Malinovschi A, et al. Fungal exposome, human health, and unmet needs: a 2022 update with special focus on allergy. *Allergy*. 2022;77(11):3199-3216.
79. Wang L, Cheng H, Wang D, et al. Airway microbiome is associated with respiratory functions and responses to ambient particulate matter exposure. *Ecotoxicol Environ Saf*. 2019;167:269-277.
80. Fouladi F, Bailey MJ, Patterson WB, et al. Air pollution exposure is associated with the gut microbiome as revealed by shotgun metagenomic sequencing. *Environ Int*. 2020;138:105604.
81. Xu M, Halimu G, Zhang Q, et al. Internalization and toxicity: a preliminary study of effects of nanoplastic particles on human lung epithelial cell. *Sci Total Environ*. 2019;694:133794.
82. Holloczki O, Gehrke S. Nanoplastics can change the secondary structure of proteins. *Sci Rep*. 2019;9(1):16013.
83. Jin Y, Lu L, Tu W, Luo T, Fu Z. Impacts of polystyrene microplastic on the gut barrier, microbiota and metabolism of mice. *Sci Total Environ*. 2019;649:308-317.
84. Buters J, Prank M, Sofiev M, et al. Variation of the group 5 grass pollen allergen content of airborne pollen in relation to geographic location and time in season. *J Allergy Clin Immunol*. 2015;136(1):87-95 e86.
85. Damialis A, Mohammad AB, Halley JM, Gange AC. Fungi in a changing world: growth rates will be elevated, but spore production may decrease in future climates. *Int J Biometeorol*. 2015;59(9):1157-1167.
86. Lang-Yona N, Shuster-Meiseles T, Mazar Y, Yarden O, Rudich Y. Impact of urban air pollution on the allergenicity of aspergillus fumigatus conidia: outdoor exposure study supported by laboratory experiments. *Sci Total Environ*. 2016;541:365-371.
87. Zhao F, Elkelish A, Durner J, et al. Common ragweed (Ambrosia artemisiifolia L.): allergenicity and molecular characterization of pollen after plant exposure to elevated NO2. *Plant Cell Environ*. 2016;39(1):147-164.
88. Ziska LH, Makra L, Harry SK, et al. Temperature-related changes in airborne allergenic pollen abundance and seasonality across the northern hemisphere: a retrospective data analysis. *Lancet Planet Health*. 2019;3(3):e124-e131.
89. Ziska L, Knowlton K, Rogers C, et al. Recent warming by latitude associated with increased length of ragweed pollen season in central North America. *Proc Natl Acad Sci USA*. 2011;108(10):4248-4251.
90. Kolarova E, Nekovar J, Adamik P. Long-term temporal changes in central European tree phenology (1946-2010) confirm the recent extension of growing seasons. *Int J Biometeorol*. 2014;58(8):1739-1748.
91. Vinhas R, Cortes L, Cardoso I, et al. Pollen proteases compromise the airway epithelial barrier through degradation of transmembrane adhesion proteins and lung bioactive peptides. *Allergy*. 2011;66(8):1088-1098.
92. Gaspar R, de Matos MR, Cortes L, et al. Pollen proteases play multiple roles in allergic disorders. *Int J Mol Sci*. 2020;21(10):3578.
93. Van Cleemput J, Poelaert KCK, Laval K, et al. Pollens destroy respiratory epithelial cell anchors and drive alphaherpesvirus infection. *Sci Rep*. 2019;9(1):4787.
94. Doyle AD, Masuda MY, Pyon GC, et al. Detergent exposure induces epithelial barrier dysfunction and eosinophilic inflammation in the esophagus. *Allergy*. 2023;78(1):192-201.
95. Rinaldi AO, Li M, Barletta E, et al. Household laundry detergents disrupt barrier integrity and induce inflammation in mouse and human skin. *Allergy*. 2023;79:128-141.
96. Saito K, Orimo K, Kubo T, et al. Laundry detergents and surfactants-induced eosinophilic airway inflammation by increasing IL-33 expression and activating ILC2s. *Allergy*. 2023;78(7):1878-1892.

97. Wang M, Tan G, Eljaszewicz A, et al. Laundry detergents and detergent residue after rinsing directly disrupt tight junction barrier integrity in human bronchial epithelial cells. *J Allergy Clin Immunol*. 2019;143(5):1892-1903.
98. Ogulur I, Pat Y, Aydin T, et al. Gut epithelial barrier damage caused by dishwasher detergents and rinse aids. *J Allergy Clin Immunol*. 2023;151(2):469-484.
99. Flindt ML. Pulmonary disease due to inhalation of derivatives of Bacillus subtilis containing proteolytic enzyme. *Lancet*. 1969;1(7607):1177-1181.
100. Adisesh A, Murphy E, Barber CM, Ayres JG. Occupational asthma and rhinitis due to detergent enzymes in healthcare. *Occup Med (Lond)*. 2011;61(5):364-369.
101. Guertler A, Moellhoff N, Schenck TL, et al. Onset of occupational hand eczema among healthcare workers during the SARS-CoV-2 pandemic: comparing a single surgical site with a COVID-19 intensive care unit. *Contact Derm*. 2020;83(2):108-114.
102. Wright BL, Masuda MY, Ortiz DR, et al. Allergies come clean: the role of detergents in epithelial barrier dysfunction. *Curr Allergy Asthma Rep*. 2023;23(8):443-451.
103. Guerville M, Leroy A, Sinquin A, Laugerette F, Michalski MC, Boudry G. Western-diet consumption induces alteration of barrier function mechanisms in the ileum that correlates with metabolic endotoxemia in rats. *Am J Physiol Endocrinol Metab*. 2017;313(2):E107-E120.
104. Volynets V, Louis S, Pretz D, et al. Intestinal barrier function and the gut microbiome are differentially affected in mice fed a Western-style diet or drinking water supplemented with fructose. *J Nutr*. 2017;147(5):770-780.
105. Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*. 2007;56(7):1761-1772.
106. Desai MS, Seekatz AM, Koropatkin NM, et al. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell*. 2016;167(5):1339-1353 e21.
107. Paparo L, Coppola S, Nocerino R, et al. How dietary advanced glycation end products could facilitate the occurrence of food allergy. *J Allergy Clin Immunol*. 2023;S0091-6749(23):1514-2.
108. Ogulur I, Yazici D, Pat Y, et al. Mechanisms of gut epithelial barrier impairment caused by food emulsifiers polysorbate 20 and polysorbate 80. *Allergy*. 2023;78(9):2441-2455.
109. Kwon YH, Banskota S, Wang H, et al. Chronic exposure to synthetic food colorant Allura red AC promotes susceptibility to experimental colitis via intestinal serotonin in mice. *Nat Commun*. 2022;13(1):7617.
110. Martinez Leo EE, Segura Campos MR. Effect of ultra-processed diet on gut microbiota and thus its role in neurodegenerative diseases. *Nutrition*. 2020;71:110609.
111. Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced extinctions in the gut microbiota compound over generations. *Nature*. 2016;529(7585):212-215.
112. Aitoro R, Paparo L, Amoroso A, et al. Gut microbiota as a target for preventive and therapeutic intervention against food allergy. *Nutrients*. 2017;9(7):672.
113. Hiippala K, Jouhten H, Ronkainen A, et al. The potential of gut commensals in reinforcing intestinal barrier function and alleviating inflammation. *Nutrients*. 2018;10(8):988.
114. Roduit C, Frei R, Ferstl R, et al. High levels of butyrate and propionate in early life are associated with protection against atopy. *Allergy*. 2019;74(4):799-809.
115. Bisgaard H, Hermansen MN, Buchvald F, et al. Childhood asthma after bacterial colonization of the airway in neonates. *N Engl J Med*. 2007;357(15):1487-1495.
116. Bagnasco D, Caminati M. Editorial: innate immunity and severe asthma: from microbiome to target therapy. *Front Immunol*. 2022;13:1114275.
117. Lan F, Zhang N, Gevaert E, Zhang L, Bachert C. Viruses and bacteria in Th2-biased allergic airway disease. *Allergy*. 2016;71(10):1381-1392.
118. Poh SE, Koh WLC, Lim SYD, et al. Expression of Staphylococcus aureus virulence factors in atopic dermatitis. *JID Innov*. 2022;2(4):100130.
119. Sans-De San Nicolas L, Figueras-Nart I, Bonfill-Orti M, et al. SEB-induced IL-13 production in CLA(+) memory T cells defines Th2 high and Th2 low responders in atopic dermatitis. *Allergy*. 2022;77(11):3448-3451.
120. Fölster-Holst R. The role of the skin microbiome in atopic dermatitis–correlations and consequences. *J Dtsch Dermatol Ges*. 2022;20(5):571-577.
121. Lunjani N, Walsh LJ, Venter C, et al. Environmental influences on childhood asthma-the effect of diet and microbiome on asthma. *Pediatr Allergy Immunol*. 2022;33(12):e13892.
122. Ni S, Yuan X, Cao Q, et al. Gut microbiota regulate migration of lymphocytes from gut to lung. *Microb Pathog*. 2023;183:106311.
123. Biesbroek G, Tsivtsivadze E, Sanders EA, et al. Early respiratory microbiota composition determines bacterial succession patterns and respiratory health in children. *Am J Respir Crit Care Med*. 2014;190(11):1283-1292.
124. Teo SM, Mok D, Pham K, et al. The infant nasopharyngeal microbiome impacts severity of lower respiratory infection and risk of asthma development. *Cell Host Microbe*. 2015;17(5):704-715.
125. Gollwitzer ES, Saglani S, Trompette A, et al. Lung microbiota promotes tolerance to allergens in neonates via PD-L1. *Nat Med*. 2014;20(6):642-647.
126. de Steenhuijsen Piters WAA, Jochems SP, Mitsi E, et al. Interaction between the nasal microbiota and *S. Pneumoniae* in the context of live-attenuated influenza vaccine. *Nat Commun*. 2019;10(1):2981.
127. Yun Y, Srinivas G, Kuenzel S, et al. Environmentally determined differences in the murine lung microbiota and their relation to alveolar architecture. *PLoS One*. 2014;9(12):e113466.
128. Maiello N, Comberiati P, Giannetti A, Ricci G, Carello R, Galli E. New directions in understanding atopic march starting from atopic dermatitis. *Children (Basel)*. 2022;9(4):450.
129. Ferreira MA, Vonk JM, Baurecht H, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. *Nat Genet*. 2017;49(12):1752-1757.
130. Ebina-Shibuya R, Leonard WJ. Role of thymic stromal lymphopoietin in allergy and beyond. *Nat Rev Immunol*. 2023;23(1):24-37.
131. Zhang Y, Wang X, Zhang W, Han D, Zhang L, Bachert C. Polymorphisms in thymic stromal lymphopoietin gene demonstrate a gender and nasal polyposis-dependent association with chronic rhinosinusitis. *Hum Immunol*. 2013;74(2):241-248.
132. Sherrill JD, Gao PS, Stucke EM, et al. Variants of thymic stromal lymphopoietin and its receptor associate with eosinophilic esophagitis. *J Allergy Clin Immunol*. 2010;126(1):160-165 e163.
133. D'Argenio V, Del Monaco V, Paparo L, et al. Altered miR-193a-5p expression in children with cow's milk allergy. *Allergy*. 2018;73(2):379-386.
134. Soliai MM, Kato A, Helling BA, et al. Multi-omics colocalization with genome-wide association studies reveals a context-specific genetic mechanism at a childhood onset asthma risk locus. *Genome Med*. 2021;13(1):157.
135. Liu T, Sun Y, Bai W. The role of epigenetics in the chronic sinusitis with nasal polyp. *Curr Allergy Asthma Rep*. 2020;21(1):1.
136. Kim YJ, Park SW, Kim TH, et al. Genome-wide methylation profiling of the bronchial mucosa of asthmatics: relationship to atopy. *BMC Med Genet*. 2013;14:39.
137. Weidner J, Bartel S, Kilic A, et al. Spotlight on microRNAs in allergy and asthma. *Allergy*. 2021;76(6):1661-1678.
138. Berni Canani R, Paparo L, Nocerino R, et al. Differences in DNA methylation profile of Th1 and Th2 cytokine genes are associated

with tolerance acquisition in children with IgE-mediated cow's milk allergy. *Clin Epigenetics*. 2015;7(1):38.
139. Hong X, Ladd-Acosta C, Hao K, et al. Epigenome-wide association study links site-specific DNA methylation changes with cow's milk allergy. *J Allergy Clin Immunol*. 2016;138(3):908-911 e909.
140. Paparo L, Nocerino R, Cosenza L, et al. Epigenetic features of FoxP3 in children with cow's milk allergy. *Clin Epigenetics*. 2016;8:86.
141. Clifford RL, Jones MJ, MacIsaac JL, et al. Inhalation of diesel exhaust and allergen alters human bronchial epithelium DNA methylation. *J Allergy Clin Immunol*. 2017;139(1):112-121.
142. Spergel JM, Du Toit G, Davis CM. Might biologics serve to interrupt the atopic march? *J Allergy Clin Immunol*. 2023;151(3):590-594.
143. Punekar YS, Sheikh A. Establishing the sequential progression of multiple allergic diagnoses in a UK birth cohort using the general practice research database. *Clin Exp Allergy*. 2009;39(12):1889-1895.
144. Lack G. Update on risk factors for food allergy. *J Allergy Clin Immunol*. 2012;129(5):1187-1197.
145. Ghezzi M, Pozzi E, Abbattista L, Lonoce L, Zuccotti GV, D'Auria E. Barrier impairment and type 2 inflammation in allergic diseases: the pediatric perspective. *Children (Basel)*. 2021;8(12):1165.
146. Ramsey N, Berin MC. Pathogenesis of IgE-mediated food allergy and implications for future immunotherapeutics. *Pediatr Allergy Immunol*. 2021;32(7):1416-1425.
147. Salo PM, Arbes SJ Jr, Jaramillo R, et al. Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. *J Allergy Clin Immunol*. 2014;134(2):350-359.
148. Mehta Y, Fulmali DG. Relationship between atopic dermatitis and food allergy in children. *Cureus*. 2022;14(12):e33160.
149. Hill DA, Grundmeier RW, Ramos M, Spergel JM. Eosinophilic esophagitis is a late manifestation of the allergic march. *J Allergy Clin Immunol Pract*. 2018;6(5):1528-1533.
150. Khan SJ, Dharmage SC, Matheson MC, Gurrin LC. Is the atopic march related to confounding by genetics and early-life environment? A systematic review of sibship and twin data. *Allergy*. 2018;73(1):17-28.
151. Yu L, Li L. Potential biomarkers of atopic dermatitis. *Front Med (Lausanne)*. 2022;9:1028694.
152. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128(1):3-20.e6.
153. Straumann A, Blanchard C, Radonjic-Hoesli S, et al. A new eosinophilic esophagitis (EoE)-like disease without tissue eosinophilia found in EoE families. *Allergy*. 2016;71(6):889-900.
154. Berni Canani R, Caffarelli C, Calvani M, et al. Diagnostic therapeutic care pathway for pediatric food allergies and intolerances in Italy: a joint position paper by the Italian Society for Pediatric Gastroenterology Hepatology and Nutrition (SIGENP) and the Italian Society for Pediatric Allergy and Immunology (SIAIP). *Ital J Pediatr*. 2022;48(1):87.
155. Santos AF, Couto-Francisco N, Becares N, Kwok M, Bahnson HT, Lack G. A novel human mast cell activation test for peanut allergy. *J Allergy Clin Immunol*. 2018;142(2):689-691.e9.
156. Patil SU, Bunyavanich S, Berin MC. Emerging Food Allergy Biomarkers. *J Allergy Clin Immunol Pract*. 2020;8(8):2516-2524.
157. Tiotiu A. Biomarkers in asthma: state of the art. *Asthma Res Pract*. 2018;4:10.
158. Hudey SN, Ledford DK, Cardet JC. Mechanisms of non-type 2 asthma. *Curr Opin Immunol*. 2020;66:123-128.
159. Wu YH, Lai AC, Chi PY, et al. Pulmonary IL-33 orchestrates innate immune cells to mediate respiratory syncytial virus-evoked airway hyperreactivity and eosinophilia. *Allergy*. 2020;75(4):818-830.
160. Ravanetti L, Dijkhuis A, Dekker T, et al. IL-33 drives influenza-induced asthma exacerbations by halting innate and adaptive antiviral immunity. *J Allergy Clin Immunol*. 2019;143(4):1355-1370 e1316.
161. Zaidi SR, Blakey JD. Why are people with asthma susceptible to pneumonia? A review of factors related to upper airway bacteria. *Respirology*. 2019;24(5):423-430.
162. McDowell PJ, Diver S, Yang F, et al. The inflammatory profile of exacerbations in patients with severe refractory eosinophilic asthma receiving mepolizumab (the MEX study): a prospective observational study. *Lancet Respir Med*. 2021;9(10):1174-1184.
163. Gevaert P, Han JK, Smith SG, et al. The roles of eosinophils and interleukin-5 in the pathophysiology of chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol*. 2022;12(11):1413-1423.
164. Zhou H, Fan W, Qin D, et al. Development, validation and comparison of artificial neural network and logistic regression models predicting eosinophilic chronic rhinosinusitis with nasal polyps. *Allergy, Asthma Immunol Res*. 2023;15(1):67-82.
165. Tang B, Tu J, Zhang M, et al. Diagnostic value and underlying mechanism of nasal nitric oxide in eosinophilic chronic rhinosinusitis with nasal polyps. *Mol Immunol*. 2023;159:1-14.
166. Colantonio D, Brouillette L, Parikh A, Scadding GK. Paradoxical low nasal nitric oxide in nasal polyposis. *Clin Exp Allergy*. 2002;32(5):698-701.
167. Danielides G, Lygeros S, Kanakis M, Naxakis S. Periostin as a biomarker in chronic rhinosinusitis: a contemporary systematic review. *Int Forum Allergy Rhinol*. 2022;12(12):1535-1550.
168. Nocera AL, Meurer AT, Miyake MM, Sadow PM, Han X, Bleier BS. Secreted P-glycoprotein is a noninvasive biomarker of chronic rhinosinusitis. *Laryngoscope*. 2017;127(1):E1-E4.
169. Auge J, Vent J, Agache I, et al. EAACI position paper on the standardization of nasal allergen challenges. *Allergy*. 2018;73(8):1597-1608.
170. Dodi G, Di Filippo P, Ciarelli F, et al. The role of nasal cytology and serum atopic biomarkers in paediatric rhinitis. *Diagnostics (Basel)*. 2023;13(3):555.
171. Jura-Szoltys E, Gawlik R, Branicka O, Stryjewska-Makuch G, Gluck J. Nasal cytology can predict clinical efficacy of subcutaneous immunotherapy in intermittent allergic rhinitis. *Postepy Dermatol Alergol*. 2022;39(6):1110-1115.
172. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med*. 2021;384(19):1800-1809.
173. Corren J, Pham TH, Garcia Gil E, et al. Baseline type 2 biomarker levels and response to tezepelumab in severe asthma. *Allergy*. 2022;77(6):1786-1796.
174. Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med*. 2017;377(10):936-946.
175. Gil EG, Parnes JR, Pham T-H, Griffiths JM. Tezepelumab treatment effect on annualized rate of exacerbations by baseline biomarkers in uncontrolled severe asthma patients: phase 2b PATHWAY study [abstract]. *Am J Respir Crit Care Med*. 2019;199:A2621.
176. Diver S, Khalfaoui L, Emson C, et al. Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med*. 2021;9(11):1299-1312.
177. Sverrild A, Hansen S, Hvidtfeldt M, et al. The effect of tezepelumab on airway hyperresponsiveness to mannitol in asthma (UPSTREAM). *Eur Respir J*. 2022;59(1):2101296.
178. Simpson EL, Parnes JR, She D, et al. Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: a randomized phase 2a clinical trial. *J Am Acad Dermatol*. 2019;80(4):1013-1021.
179. Drake LY, Kita H. IL-33: biological properties, functions, and roles in airway disease. *Immunol Rev*. 2017;278(1):173-184.

180. Wechsler ME, Ruddy MK, Pavord ID, et al. Efficacy and safety of Itepekimab in patients with moderate-to-severe asthma. *N Engl J Med*. 2021;385(18):1656-1668.
181. Kelsen SG, Agache IO, Soong W, et al. Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma: a randomized clinical trial. *J Allergy Clin Immunol*. 2021;148(3):790-798.
182. Study to assess the efficacy and safety of MEDI3506 in adults with uncontrolled moderate-to-severe asthma (FRONTIER-3). 2023 Accessed 30 May 2023. https://clinicaltrials.gov/ct2/show/NCT04570657
183. Harb H, Chatila TA. Mechanisms of dupilumab. *Clin Exp Allergy*. 2020;50(1):5-14.
184. Dellon ES, Rothenberg ME, Collins MH, et al. Dupilumab in adults and adolescents with eosinophilic esophagitis. *N Engl J Med*. 2022;387(25):2317-2330.
185. Braun C, Samaan K, Graham F, Paradis L, Roches AD, Begin P. Delayed-type hypersensitivity gastrointestinal symptoms induced by food oral immunotherapy and efficiently treated by dupilumab: a case report. *Pediatr Allergy Immunol*. 2023;34(3):e13935.
186. Spekhorst LS, van der Rijst LP, de Graaf M, et al. Dupilumab has a profound effect on specific-IgE levels of several food allergens in atopic dermatitis patients. *Allergy*. 2023;78(3):875-878.
187. Beck LA, Thaci D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med*. 2014;371(2):130-139.
188. Callewaert C, Nakatsuji T, Knight R, et al. IL-4Ralpha blockade by dupilumab decreases Staphylococcus aureus colonization and increases microbial diversity in atopic dermatitis. *J Invest Dermatol*. 2020;140(1):191-202 e197.
189. Napolitano M, di Vico F, Ruggiero A, Fabbrocini G, Patruno C. The hidden sentinel of the skin: an overview on the role of interleukin-13 in atopic dermatitis. *Front Med (Lausanne)*. 2023;10:1165098.
190. Beck LA, Bieber T, Weidinger S, et al. Tralokinumab treatment improves the skin microbiota by increasing the microbial diversity in adults with moderate-to-severe atopic dermatitis: analysis of microbial diversity in ECZTRA 1, a randomized controlled trial. *J Am Acad Dermatol*. 2023;88(4):816-823.
191. Blauvelt A, Thyssen JP, Guttman-Yassky E, et al. Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: 52-week results of two randomized double-blinded placebo-controlled phase III trials. *Br J Dermatol*. 2023;188(6):740-748.
192. Dellon ES, Collins MH, Rothenberg ME, et al. Long-term efficacy and tolerability of RPC4046 in an open-label extension trial of patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2021;19(3):473-483 e417.
193. Otani IM, Anilkumar AA, Newbury RO, et al. Anti-IL-5 therapy reduces mast cell and IL-9 cell numbers in pediatric patients with eosinophilic esophagitis. *J Allergy Clin Immunol*. 2013;131(6):1576-1582.
194. Flood-Page P, Menzies-Gow A, Phipps S, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. *J Clin Invest*. 2003;112(7):1029-1036.
195. Kalinauskaite-Zukauske V, Januskevicius A, Janulaityte I, Miliauskas S, Malakauskas K. Serum levels of epithelial-derived cytokines as interleukin-25 and thymic stromal Lymphopoietin after a single dose of mepolizumab in patients with severe non-allergic eosinophilic asthma: a short report. *Can Respir J*. 2019;2019:8607657.
196. Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2021;9(10):1141-1153.
197. Assa'ad AH, Gupta SK, Collins MH, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. *Gastroenterology*. 2011;141(5):1593-1604.
198. MacGlashan DW Jr, Bochner BS, Adelman DC, et al. Down-regulation of fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol*. 1997;158(3):1438-1445.
199. Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell Fce psilon RI expression and function. *J Allergy Clin Immunol*. 2004;114(3):527-530.
200. Lin H, Boesel KM, Griffith DT, et al. Omalizumab rapidly decreases nasal allergic response and FcepsilonRI on basophils. *J Allergy Clin Immunol*. 2004;113(2):297-302.
201. Schroeder JT, Bieneman AP, Chichester KL, et al. Decreases in human dendritic cell-dependent T(H)2-like responses after acute in vivo IgE neutralization. *J Allergy Clin Immunol*. 2010;125(4):896-901 e896.
202. Fahy JV, Fleming HE, Wong HH, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med*. 1997;155(6):1828-1834.
203. Gasser P, Tarchevskaya SS, Guntern P, et al. The mechanistic and functional profile of the therapeutic anti-IgE antibody ligelizumab differs from omalizumab. *Nat Commun*. 2020;11(1):165.
204. Salvati L, Liotta F, Annunziato F, Cosmi L. Therapeutical targets in allergic inflammation. *Biomedicine*. 2022;10(11):2874.
205. Wood RA, Chinthrajah RS, Eggel A, et al. The rationale for development of ligelizumab in food allergy. *World Allergy Organ J*. 2022;15(9):100690.
206. Raheem A, Liang L, Zhang G, Cui S. Modulatory effects of probiotics during pathogenic infections with emphasis on immune regulation. *Front Immunol*. 2021;12:616713.
207. Umborowati MA, Damayanti D, Anggraeni S, et al. The role of probiotics in the treatment of adult atopic dermatitis: a meta-analysis of randomized controlled trials. *J Health Popul Nutr*. 2022;41(1):37.
208. Zhang R, Zhang L, Li P, Pang K, Liu H, Tian L. Epithelial barrier in the nasal mucosa, related risk factors and diseases. *Int Arch Allergy Immunol*. 2023;184(5):481-501.


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