Epithelial Barrier: Protector and Trigger of Allergic Disorders

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Abstract

The epithelial barrier has classically been considered as the only first line of defense against irritants, pathogens, and allergens. However, it is now known to play an essential role in the immune response to exogenous agents. In fact, recent reports postulate the epithelial barrier hypothesis as a possible explanation for the increasing incidence and severity of allergic diseases.
The epithelial barrier preserves the isolation of internal tissues from potential external threats. Moreover, a coordinated interaction between epithelial and immune cells ensures the unique immune response taking place in mucosal tissues, which is reported to be dysregulated in allergic diseases.
We and others have demonstrated that in severe allergic phenotypes, the epithelial barrier undergoes several histological modifications, with increased infiltration of immune cells, leading to dysfunction. This is common in atopic dermatitis, asthma, and food allergy. However, the precise role of the epithelial barrier in mucosal biology during progression of allergic diseases is not well understood.
In this review, we aim to compile recent knowledge regarding the histological structure and immunological function of the epithelial barrier and to shed light on the role of this compartment in the onset and progression of allergic diseases.

Key words: Epithelium. Mucosal immunity. Allergy. Antigen. Immunoglobulin (Ig) switch. Inflammation.

Resumen

La barrera epitelial se ha considerado clásicamente sólo como la primera línea de defensa contra los irritantes, patógenos y alérgenos, pero ahora sabemos que el epitelio también desempeña un papel esencial en la respuesta inmunológica frente los agentes exógenos. De hecho, informes recientes postulan la hipótesis de la barrera epitelial como una posible explicación de la creciente incidencia y la gravedad de las enfermedades alérgicas.
La barrera epitelial preserva el aislamiento de los tejidos internos de las posibles amenazas exteriores. Se sabe que las células epiteliales, además de un papel meramente protector, también tienen una función esencial en el desarrollo de la respuesta inmune en las mucosas, favoreciendo un ambiente tolerogénico. Sin embargo, en enfermedades alérgicas, estas características se ven afectadas como demuestra una repuesta exagerada ante antígenos inocuos. De hecho, en los fenotipos alérgicos graves, la barrera epitelial experimenta varias modificaciones histológicas que se asocian con pérdida de integridad y aumento de los infiltrados celulares, lo que conduce a una disfunción de la misma. Este proceso es común en la dermatitis atópica, el asma y/o la alergia alimentaria. Aunque todavía no se conoce bien la función exacta de la barrera epitelial en la biología de la mucosa durante las enfermedades alérgicas.
En esta revisión, pretendemos recopilar los conocimientos recientes sobre la estructura histológica y la función inmunológica de la barrera epitelial, y arrojar luz sobre el papel de este compartimento en la aparición y la progresión de las enfermedades alérgicas.

Palabras clave: Epitelio. Inmunidad de las mucosas. Alergia. Antígeno. Cambio de Inmunoglobulina (Ig). Inflamación.

Introduction

The mucosa lines body cavities and passages (eg, in the gastrointestinal, respiratory, reproductive, and urinary tracts), which communicate directly or indirectly with the outside of the body. Mucosal tissues have 2 main features: (*1*) a specific histological conformation that preserves isolation of the inner tissues from external insult, and (*2*) privileged immunity. Together, these features enable specific and tight regulation of the immune response, which is essential for maintenance of homeostasis and participates in the development of several diseases, including allergic diseases and asthma [1].

Mucosal tissues are usually composed of conjunctive tissue and epithelium. Epithelial tissue in the mucosa is in contact with the external environment and underlined by a basal membrane and a lamina propria formed by connective tissue. This is highly vascularized and comprises different cell types (stromal and immune cells) and extracellular matrix proteins. Depending on its location in the body, mucosal tissue can be of several types, including oral, respiratory, and gastrointestinal. Each displays specific histological features [2-4].

The epithelium has classically been considered the first line of defense against inhaled irritants, pathogens, and allergens. However, in recent years, epithelial cells have been shown to play an essential role in the immune response and during the inflammatory process after tissue damage [5,6]. The epithelium consists of cells tightly attached to each other and arranged in several distinct layers. Junctional complexes such as tight junctions (TJs), adherent junctions, gap junctions, and desmosomes provide cohesion between cells. TJs form the closest cell-cell interactions in the apical area of oral epithelial cells, working as a restrictive gate for the passage of water, electrolytes, and other small molecules. They consist of transmembrane proteins, including occludin, claudin, and immunoglobulin-like surface proteins, as well as cytoplasmic molecules such as zonula occludens proteins [7]. Adherent junctions are protein complexes situated below TJs that bind strongly to cells. Adherent junctions are composed by cadherins that connect to the actin cytoskeleton [8]. Gap junctions are composed of hemichannels, called connexons, which are regulated by several factors including pH, calcium concentration, and posttranslational modifications. Thus, they provide direct communication between adjacent cells and regulate the exchange of small molecules and ions. Finally, desmosomes link 2 cells together by the intermediate filament cytoskeleton, becoming the adhesive bonds that give mechanical strength to tissues. Since the structure and functions of all the above-mentioned cell-cell junctions are key for preserving epithelial barrier integrity, their disruption has been linked to infections, autoimmune diseases, allergy, and cancer [9].

Respiratory System

The respiratory system is divided anatomically into structures of the upper and the lower respiratory tract, which correspond to 2 functional components, namely, the conductive component and the respiratory component.

The conductive component, which involves the nasal cavity, pharynx, larynx, and trachea, is lined by a mucosal tissue formed by ciliated pseudostratified columnar epithelium. Deeper into the respiratory system, the epithelium becomes thinner, and glands are less specialized and more abundant, passing from olfactory glands in the nasal cavity to seromucous glands in the trachea. These histological features in the upper airways enable isolation of the internal tissues and the humidification and conduction of the air into the lower respiratory tract, ie, the respiratory component.

The trachea bifurcates into the right and left primary bronchi, which enter the posterior side of each lung along with the pulmonary vessels, lymphatics, and nerves. Within each lung, the bronchus subdivides further to form the bronchial tree, the last component of the air conduction system. It is in the last parts of this component, the alveoli, where the gas exchange between air and blood occurs at the barrier membrane between an alveolus and the capillaries surrounding it.

The respiratory epithelium provides a physical barrier to infection, lining the respiratory tract from the nose to the alveoli with a wide range of cell types. Ciliated epithelial cells are important for propelling mucus up the airway, thereby removing particulate material. Ciliated cells line the respiratory tract down to the level of the respiratory bronchiole. The tracheobronchial glands are important sources of airway mucus, which serves to trap particulates. The respiratory epithelium also functions in the regulation of water and ion movement into the airway mucus. It secretes surfactant proteins A and D, lysozyme, lactoferrin, and antimicrobial peptides (β-defensins and cathelicidins) and releases reactive oxygen and nitrogen species to kill invading pathogens [5,10-13].

Oral and Gastrointestinal Tracts

The gastrointestinal track comprises the oral cavity, esophagus, stomach, intestine, and anus in addition to associated glands. Its main function is to obtain the molecules necessary for the maintenance, growth, and energy needs of the body from ingested food.

Histologically, it is formed by 4 main layers: the mucosa, submucosa, muscularis, and serosa. We focus on the epithelial tissue that forms the mucosa [11]. The entrance to the gastrointestinal tract is the oral cavity. Here, the mucosal structure varies along its location within the oral cavity, although 3 main types of mucosa can be distinguished based on their morphology and specific pattern of differentiation: (*1*) keratinized stratified squamous epithelium or masticatory mucosa, which covers the hard palate and gingiva; (*2*) nonkeratinized stratified squamous epithelium or lining mucosa, on the underside of the tongue, inside the lips and cheeks, on the floor of the mouth, and on the alveolar ridge; and (*3*) the specialized mucosa of the dorsal surface of the tongue [9,10,14]. The oral epithelium is the superficial layer that separates the environment from underlying tissues. It comprises a stratified squamous epithelium consisting of cells tightly attached to each other and arranged in layers. The oral epithelium possesses structural properties, such as stratification and cornification of keratinocytes, and specific cell-to-cell interactions to maintain its barrier function. The keratinized type contains 4 layers of cells: the basal layer, the spinous layer, the granular layer, and the superficial layer (keratinized layer). Keratinocytes are born and proliferate in the basal layer and undergo terminal differentiation as they migrate to the surface, where they die. Thus, the outermost

cell layers are composed of dead cells. Conversely, the surface cells of nonkeratinized epithelia are living cells without keratin. Besides, the nonkeratinized oral epithelium has no granular layer [10,15].

The oral cavity is connected with the pharynx (oropharynx), followed by the esophagus, both of which are characterized by stratified squamous epithelium, which ends in the stomach and is replaced by simple columnar epithelium in glands and the intestine [11].

The small intestine is the site where the digestive processes are completed and where nutrients (production of digestion) are absorbed by the cells of the epithelial lining. This site has been studied in depth owing to its immune-privileged features. In the small intestine, the epithelium of the mucosal layer is made up of simple columnar epithelium with microvilli, which increase the surface of absorption, and goblet cells, which are responsible for mucus secretion. However, in the large intestine, the mucosa lacks microvilli, although it still presents goblet cells and absorptive cells involved in absorption of water and electrolytes [16-18].

The Skin

The skin is the largest tissue in the body, comprising 3 layers: the epidermis, the dermis, and the hypodermis [11].

The epidermis presents a stratified squamous epithelium mainly formed by keratinocytes. It is the most external layer of the skin and displays a high regeneration rate in response to exogenous factors (eg, detergents, environmental pollutants). Other less abundant cell types in the epidermis include melanocytes and Langerhans cells. The former are involved in the immune response taking place in this tissue. The epidermis is organized in several layers. The most external layer is the stratum corneum, made up of dead keratinocytes. Next is the stratum lucidum, a very thin layer found mainly in areas such as the palms and soles. The third layer is the stratum granulosum, formed by rhomboid cells containing large granules of keratin, which is followed by the stratum spinosum, a layer formed by polygonal cells with remarkable intracellular adhesions. Finally, the inner layer is the stratum basale, which contains a few layers of cubic cells with a high proliferative potential [11].

The middle layer of the skin, the dermis, is located beneath the epidermis. This layer mainly comprises connective tissue fibers (eg, collagen, elastin).

The last layer of the skin is the hypodermis, which comprises mainly loose connective tissue, thus enabling the skin to slide over subjacent organs.

Mucosal Immune System

The need for permeability in the epithelial lining of mucous membranes (food absorption, gas exchange, reproduction) creates vulnerability to pathogens, making these

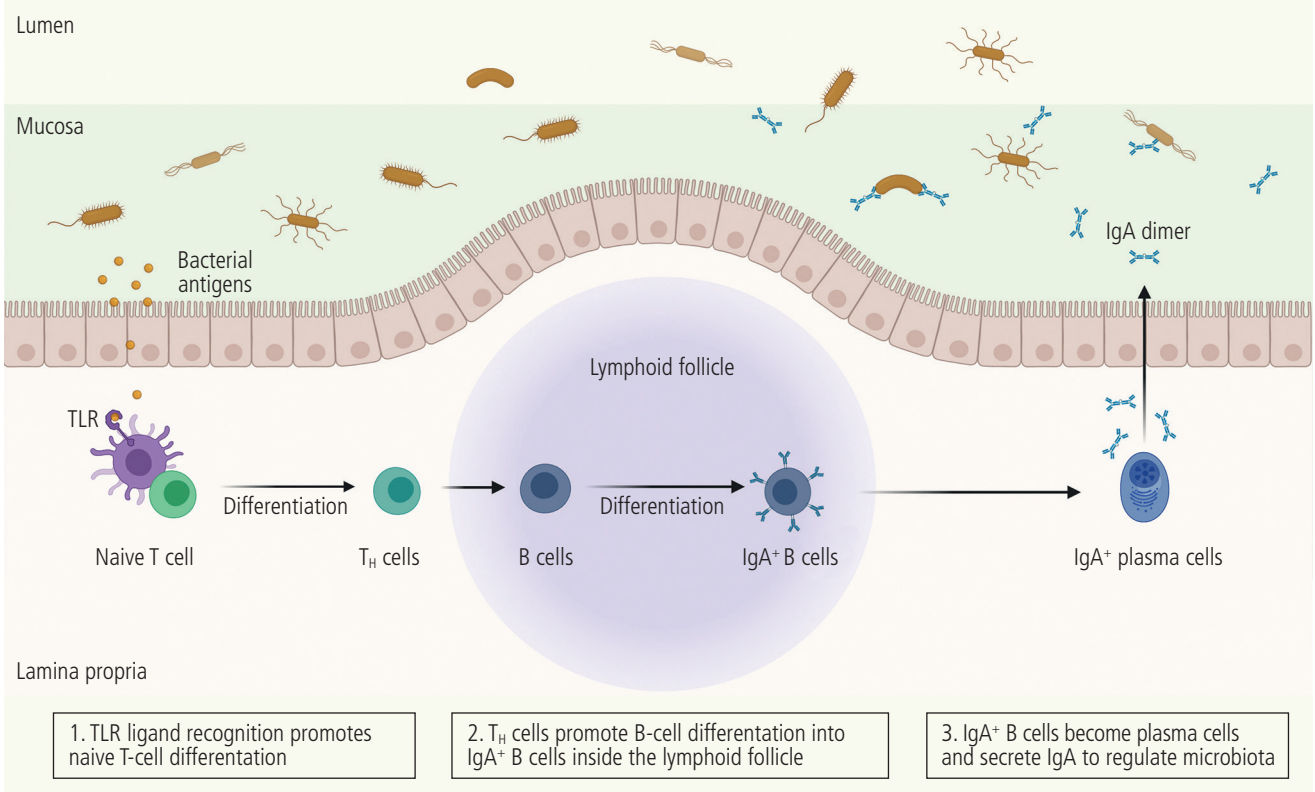

Figure 1. Immune protection by secretory IgA. (*1*) Antigen presenting cells of the mucosa can sense bacterial antigens through pattern recognition receptors such as toll-like receptors (TLRs) and induce naïve T-cell differentiation to T helper (T_H) cells. (*2*) T-cell activation can take place in special lymphatic tissue of the mucosa, where T_H cells promote class switching in germinal center B cells to produce IgA (IgA⁺ B cells). (*3*) The IgA⁺ B cells differentiate to plasma cells that produce dimeric IgA (Ig⁺ plasma cells), which becomes secretory IgA (sIgA) and is transported to the mucus to block entry of bacteria and regulate microbiota. Adapted from "IgA-mediated Gut Microbiota Regulation", by BioRender.com. Retrieved from https://app.biorender.com/biorender-templates.

regions a gateway for many infectious agents. Nonetheless, mucosal tissues rely on the larger part of the immune system (comprising mucus layers, epithelial cells, lymphoid tissues, and immune molecules situated in the mucosal membranes of the gut, the respiratory system, and the urogenital tract), thus providing a first line of defense for the internal body surfaces.

Mucosal tissues are continuously exposed to external stimuli, thus potentially leading to endless systemic proinflammatory responses. However, the mucosal immune system counts on 2 strategies to preserve homeostasis: (*1*) immune exclusion by secretory IgA antibodies, and (*2*) a confined tolerogenic immune response. Immunoglobulins (Igs) are the first barrier defense of mucosa tissues, in which polymeric IgA is the predominant isotype, except in the lower respiratory and genital tracts, where IgG is the major isotype [19,20]. Secreted IgA is synthesized by plasma cells derived from activated B cells in the lamina propria (Figure 1). Then, the antibody binds the polymeric Ig receptor expressed on the basolateral surfaces of epithelial cells, thus facilitating internalization of polymeric IgA, transport to the apical side, and release to the lumen. Subsequently, polymeric IgA blocks the access of antigens and pathogens to the epithelial barrier and enhances their agglutination [19,21]. Microorganisms become trapped in the mucus layer to be later eliminated by peristaltic and mucociliary events [22].

Alterations in epithelial barrier integrity could lead to invasion by pathogens. To avoid this, the mucosal immune system comprises inductive and effector sites, where the immune response is initiated and manifested, respectively. The response to microorganisms is initiated by epithelial cells and antigen-presenting cells (APCs). The epithelial barrier is situated underneath the mucus layer, and contains different types of specialized epithelial cells that vary according to the organ and contribute to mucosal immune regulation [16] (Figure 2). Goblet cells secrete mucins and antimicrobial peptides, which play a critical role in antigen transfer from luminal tissue to the lamina propria, contributing to food tolerance [23]. Additionally, the human airway epithelium contains another type of secretory cell, club cells, which produce glycoproteins, lipids, and peptides to provide chemical and physical protection in the airway [24,25]. Club cells have been shown to be altered in inflammatory diseases, such as allergy [26]. Besides, in response to epithelial injury, club cells differentiate into ciliated and goblet cells [24]. Paneth cells are located in the epithelium of the small intestine and sustain homeostasis by releasing antimicrobial peptides and proteins that regulate the amount of commensal and pathogenic microorganisms [27,28] (Figure 2). Additionally, endocrine cells (eg, enteroendocrine and neuroendocrine cells) are found along the epithelial barrier and may secrete a wide range of peptide hormones and neuropeptides, such as serotonin, vasoactive intestinal peptide, and γ-aminobutyric acid, which influence the function of immune cells [29,30] (Figure 2). Individual chemosensory cells called tuft cells (also known as brush cells or microvillus cells) (Figure 2), which help to expel helminths and generate a type 2 immune response, are distributed along the mucosal epithelium [31]. Tuft cells produce IL-25 and stimulate the development of type 2 innate lymphoid cells (ILC2s), which could lead to intestinal eosinophilia [32,33]. However, the specific role of tuft cells in allergy remains to be clarified. Another highly specialized cell is the microfold (M) cell, which is a unique epithelial subtype that overlies the lymphoid tissue and plays a role in transepithelial antigen transport (Figure 2). M cells take up luminal microbes through phagocytosis, endocytosis, or transcytosis and deliver them to dendritic cells (DCs) located in the lamina propria (Figure 2). Moreover, M cells can express IgA receptor on their apical surface to bind and transport secretory IgA-bound antigens [19,34]. This antigen-transport function suggest that M cells may contribute to the genesis of allergy. Finally, epithelial cells present supplementary immune-regulatory features, such as class I and II major histocompatibility complex expression [35], which enables them to present antigens to T cells. This occurs concomitantly with CD23 expression (the low-affinity receptor for IgE, FcεRII), which enables the epithelial cells to transport IgE and IgE-immune complexes across the epithelial monolayer [36]. Although robust evidence supports a role for epithelial cells in the mucosal immune response, studies focusing on the specific involvement of individual epithelial cell subtypes in allergy are scarce.

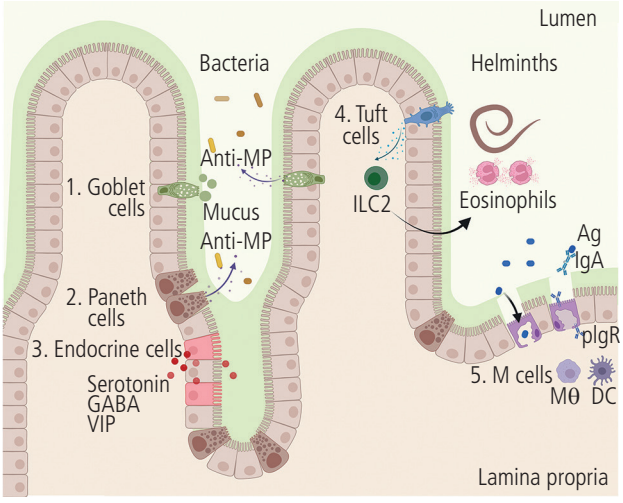

Figure 2. Mucosal epithelial cells. The epithelial cell barrier is home to specialized cell types with mucosa protective functions in the mucosa. The figure shows a section of the small intestine. (*1*) Goblet cells producing mucus and secreting antimicrobiobial peptides (Anti-MP); (*2*) Paneth cells releasing anti-MP; (*3*) Endocrine cells secreting neuropeptides such as serotonin, vasoactive intestinal peptide (VIP), and γ-aminobutyric acid (GABA); (*4*) Tuft cells participate in the response against helminths by stimulating type 2 innate lymphoid cells (ILC2s), which lead to intestinal eosinophilia; and (*5*) Microfold (M) cells capture luminal microbes and deliver them to dendritic cells (DCs) and macrophages (MΘ) located in the lamina propria. M cells express the polymeric IgA receptor (pIgR) to bind and transport secretory IgA-bound antigens (Ag). Adapted from "Intestinal Epithelium (Background)", by BioRender.com. Retrieved from https://app.biorender.com/biorender-templates.

Apart from the abovementioned luminal-antigen transference strategies of epithelial cells, antigens can be directly taken up by DCs with extending transepithelial dendrites and their own TJ proteins [37] (Figure 3). When the epithelial barrier is not damaged, antigens enter at specific sites underneath lymphoid follicles, composed mainly of clustered B-cell follicles interspersed with T-cell zones and a

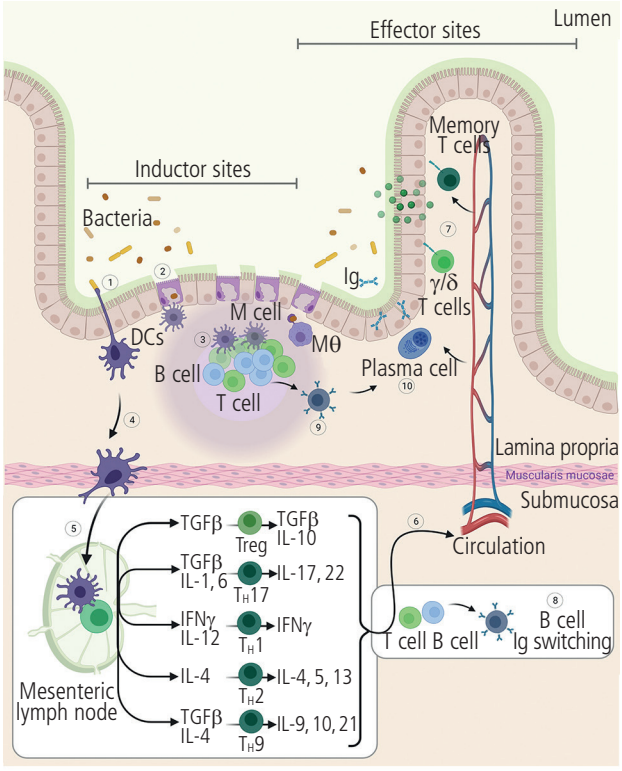

Figure 3. Mucosal inmmune system. The classic inductive sites consist of antigen-sampling M cells, T-cell areas, B-cell follicles, and antigen-presenting cells, which form mucosa-associated lymphoid tissue (MALT). Antigens can be captured by (*1*) dendritic cells (DCs) in the epithelium via dendrites extending directly into the lumen or (*2*) transported by M cells. Both cases induce DC maturation and migration to the T-cell zone (*3*) in MALT and (*4*) into draining mesentheric lymph nodes. (*5*) There, DCs trigger T-cell activation, which depends on the nature of the antigen and the local microenvironment. This results in T-cell differentiation and (*6*) homing to effector sites. (*7*) Activated T cells finish in the epithelium, where intraepithelial γδ-T cells are also situated. Class switching to IgA occurs in (*8*) mesenteric lymph nodes and in (*9*) MALT. (*10*) Then, primed B cells differentiate to plasma cells that migrate to the lamina propria, where they produce Igs, which can be secreted to the lumen. Adapted from "Intestinal Epithelium (Background)", by BioRender.com. Retrieved from https://app.biorender.com/biorender-templates.

variety of APCs. This organized structure is known as mucosa-associated lymphoid tissue (MALT), and, together with local lymph nodes, it is where the mucosal immune system is initiated (Figure 3) [38]. Mucosa-associated lymphoid tissue is classified according to its location as gut-associated lymphoid tissue, bronchial/tracheal-associated lymphoid tissue, nose-associated lymphoid tissue, and vulvovaginal-associated lymphoid tissue.

Epithelial cells and APCs are informed of the presence of microbes via pattern recognition receptors (Figures 1 and 3). Not all microorganisms are pathogenic (eg, microbiota). Thus, polar expression (apical versus basolateral side) of pattern recognition receptors is crucial for preventing unnecessary inflammatory responses. Under homeostatic conditions, interaction with microbiota induces transforming growth factor-β (TGF-β), retinoic acid, and thymic stromal lymphopoietin (TSLP), which promote tolerogenic APCs and, together with IL-10, the induction of regulatory T cells (Tregs) [39,40]. Tolerogenic APCs and Tregs stimulate B-cell class-switching to IgA production, which, after maturation, generates plasma cells able to migrate to the mucosa [41,42]. To achieve a successful IgA switch, ILC3s need to provide lymphotoxin-β receptor-dependent signals to DCs and stromal cells [43]. ILC3s play a major role in maintaining tolerance in the gut mucosa by stimulating B-cell differentiation, the development of isolated lymphoid follicles, and the production of IL-22, IL-17, and GM-CSF [44]. A newly identified regulatory ILC (ILCreg) has been shown to participate in preserving gut homeostasis via the secretion of IL-10 and TGF-β and relieving intestinal inflammation [45]. The role of ILC1s and ILC2s in the healthy gut is still unclear. In contrast, both subtypes are key to preservation of the epithelial barrier under pathogenic conditions [46,47].

Upon sampling antigens, conventional DCs migrate to draining lymph nodes to present them to naïve T lymphocytes (Figure 3). Depending on the antigen source and the cytokine environment, activated conventional DCs can polarize naïve T cells to T helper cell (T_H) phenotypes, namely T_H1, T_H17, T_H2, and T_H9 [48] (Figure 3). Pathogens that accumulate inside the vesicles of conventional DCs stimulate the differentiation of T_H1 cells, whereas the prototypical response to helminths is characterized as T_H2 [49]. Segmented filamentous bacteria lead to differentiation of T_H17 cells in the small intestine [50], and the commensal *Staphylococcus aureus* and the opportunistic fungus *Candida albicans* are thought to induce polarization of TH9 cells [51]. Then, polarized T cells, together with antigen-activated conventional DCs, promote class switching of B cells, which prevent the spread of the infection. B and T cells subsequently migrate to the mucosa effector sites, where they express their effector functions, mainly releasing immunomodulatory cytokines.

In the event of infection, different types of immune cells are recruited through specialized vascular structures that allow lymphocytes to migrate into the tissue [52]. Bacterial and viral infections trigger a type 1 response (activation of T_H1 cells, natural killer cells, ILC1, T_H17 cells, and ILC3), which includes the release of proinflammatory cytokines (IL-1β, IL-18, IFN-γ) [53] and cytokines with protective functions (IL-23, IL-22, and IL-17) [54,55]. Then, neutrophils are recruited to produce a wide range of proinflammatory and anti-inflammatory effector molecules [56], which in turn contribute to the recruitment of other immune cells to control pathogen spread and later release the factors necessary for the resolution of inflammation.

Tick, insect, and snake bites and stings and helminth invasions trigger a type 2 response (activation of ILC2, T_H2 cells, eosinophils, basophils, and mast cells). This is initiated by tuft cells, which release alarmins (TSLP, IL-25, and IL-33) that stimulate the production of IL-4, IL-5, and IL-13 and enhance B-cell class switching to IgE [57,58]. Similarly, allergic patients display a type 2 inflammatory response that is initiated after allergen exposure and results in the production of allergen-specific IgE, which might lead to airway hyperresponsiveness and mucus production [6,59].

The mucosal immune system also counts on intraepithelial γδ-T cells, ie, T cells that express the T-cell receptor γδ (TCR-γδ) and are located specifically in the epithelia of mucosal tissues. These T cells scan for signs of cellular stress

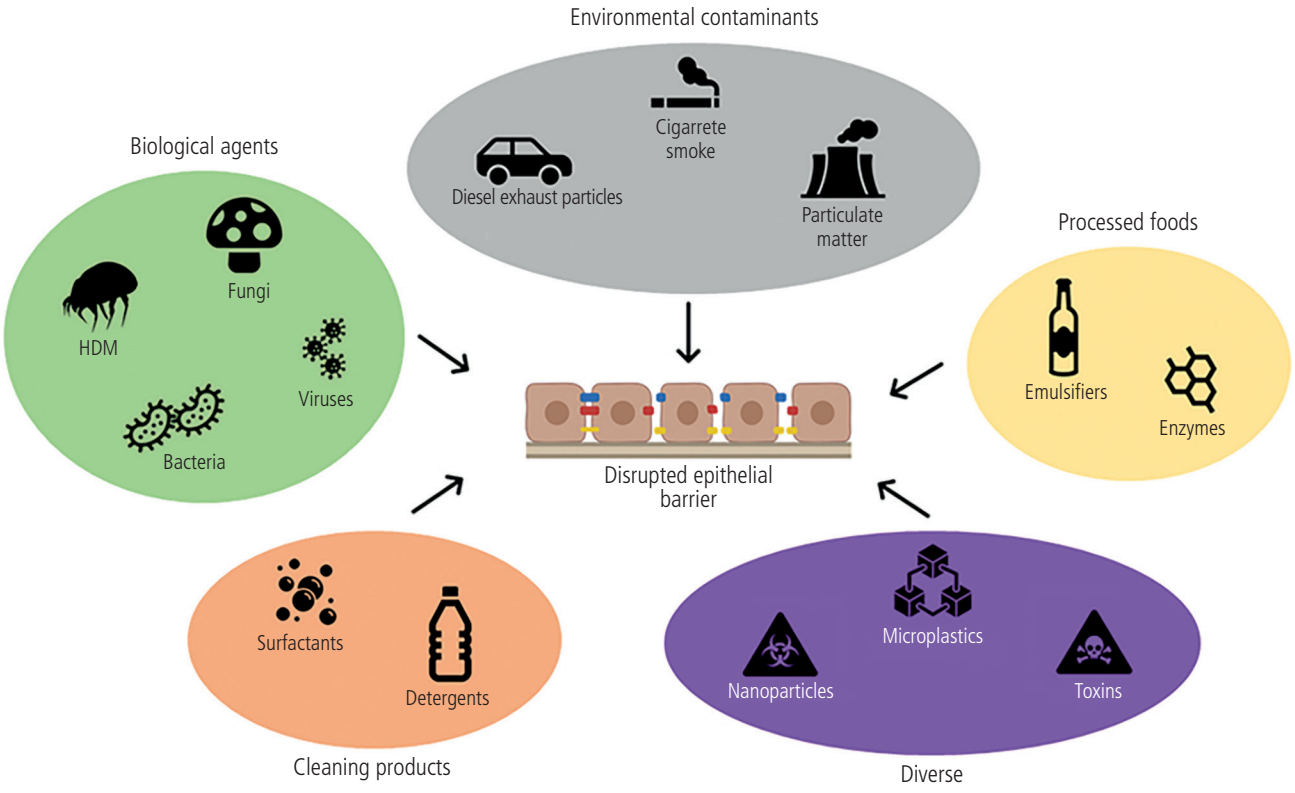

Figure 4. Environmental factors in epithelial barrier dysfunction. Human skin and mucosa are exposed daily to environmental contaminants (cigarette smoke, particulate matter, diesel exhaust particles, ozone, nanoparticles, and microplastics), airborne biological agents (house dust mites [HDM], bacteria, fungi, viruses) containing toxins and allergens, cleaning products containing surfactants and detergents, and processed food containing enzymes and emulsifiers, all of which have proven toxic for epithelial cells.

and respond with rapid effector functions (eg, lysing cells) when they detect infected or transformed host cells or if they sense critical information from other mucosal leukocyte populations. Recent data suggest that γδ T cells might be implicated in allergic airway diseases (asthma, rhinitis) and in intestinal hypersensitivity processes (food allergy, celiac disease), although the significance of this observation is not well known [60,61].

Epithelial Barrier Remodeling in Allergy

Common allergic diseases in industrialized areas include allergic rhinitis (already common in the late 19th century), allergic asthma, atopic dermatitis (which reached epidemic proportions after the 1960s) [62-64], food allergy, eosinophilic esophagitis, and drug-induced anaphylaxis (considered epidemic since 2000) [65-67]. Many allergens derived from environmental agents such as dust mites, bacteria, fungi, viruses, and toxins are encountered daily by humans as a consequence of industrialization. In addition, human skin and mucosa are exposed daily to substances commonly used for laundry and household cleaning (eg, detergents and surfactants), enzymes and emulsifiers in processed food, cigarette smoke, particulate matter, diesel exhaust fumes, ozone, nanoparticles, and microplastics. These agents have proven toxic for epithelial cells [68-71] (Figure 4).

The ability of the epithelium to control the balance between tissue damage and repair signals is essential if we are to limit epithelial damage, subsequent inflammation, and development of disease [72]. When the remodeling of epithelial barriers leads to increased leakiness, it also causes microbial dysbiosis and the translocation of bacteria to subepithelial areas, which induces tissue microinflammation [73] and sustained T-cell activation, with these alterations potentially underlying the onset of various allergic diseases [68].

Atopic dermatitis (AD) is an inflammatory skin disorder that affects 25% of children and 10% of adults and carries a higher risk of allergic rhinitis and asthma later in life. Filaggrin mutations and TJ protein deficiency (claudin-1, claudin-4, and claudin-6) have been described in the skin of patients with AD [74-80]. A recent gene expression analysis by RNA sequencing performed on matched lesional and nonlesional skin tissue biopsies from AD patients and healthy persons revealed that cell adhesion, cadherin signaling, and keratinization are the most differentially expressed gene groups in patients with AD. Of those, genetic expression levels of CLDN4 and TJP1 negatively correlated with *Staphylococcus aureus* in lesional samples [74]. A decrease in skin microbiota diversity due to an abundance of *S aureus* has been linked with the severity

of AD [74,81]. The role of *S aureus* in allergic diseases is controversial. A recent study on asthmatic patients showed that sensitization to *S aureus* enterotoxin B was associated with the presence of AD and with an increased risk of sensitization to common aeroallergens [82]. It is increasingly clear that the complex interaction between the skin microbiota, the epithelial barrier, and the immune system is key to our understanding of the development of AD.

AD is primarily a T_H2 cell–driven disease, with variable numbers of eosinophils and where IgE is considered only to play a bystander role. Targeting the T_H2 signature cytokines IL-4 and IL-13 with biological antagonists has proven effective for treatment of AD, indicating that both are major players in inducing skin inflammation in this disease [83-87]. In contrast, studies targeting the epithelial alarmins TSLP and IL-33 have not yet shown any effects on AD [88,89]. Emerging evidence shows that mast cells, eosinophils, and basophils are pivotal effector cells in causing pruritus in AD [90,91]. Chronic pruritus is a major clinical complaint in AD, since it considerably reduces quality of life and is difficult to treat [92]. Basophils and eosinophils infiltrate the skin in AD [93] and are located close to the nerves, thus providing a bridge between the neuronal and immune systems and amplifying local immune reactions [94]. Recent findings indicate that skin barrier defects support induction of pruritus [95]. In AD, chronic scratching worsens clinical symptoms. The impaired barrier function associated with the itch–scratch cycle further augments this positive feedback loop. IL-31 has recently emerged as one of the most effective approaches for treating pruritus in AD [96-99].

Allergic asthma is a heterogeneous lung disease characterized by chronic airway inflammation. It produces remodeling of the airway respiratory mucosa, causing airway obstruction and the subsequent loss of respiratory function [100,101]. Upon contact with a trigger (eg, viral infections, allergens, or pollution), asthma becomes exacerbated [102]. Given the ubiquitous presence of triggers and the heterogeneity of asthma patients, exacerbations cannot be fully prevented [103]. Airway mucosa remodeling in asthma can affect different layers of the epithelial barrier, namely, the airway smooth muscle below the epithelium, the extracellular matrix, the basal epithelial cell line, the epithelial layer itself, and even the lumen [101,104]. The airway smooth muscle tends to thicken with chronic inflammation, causing hypertrophy and hyperplasia, lowering the contractile potential of the airway tissue, and, hence, diminishing function [105,106]. This process often goes hand in hand with an increase in deposition of the extracellular matrix, which has been linked to an increase in arginase activity that releases precursors for synthesis of nitric oxide [107]. This process can be repressed by endogenous compounds such as asymmetric dimethylarginine, which inhibit nitric oxide synthase [107,108]. Interestingly, recent research has shown that in vitro culture of healthy epithelia incubated with Der p 1 produced higher amounts of asymmetric dimethylarginine than damaged epithelia [109]. Moreover, Der p 1 is a known proteolytic allergen that can cleave and disrupt TJs [110]. This disruption of TJs in the epithelial layer not only dysregulates epithelial cell differentiation, but also enables entry of other allergens and pathogens, which can then trigger continuous exacerbations [111-113]. This process is characterized by decreased expression of structural proteins forming the TJs such as occludin, zonula occludens proteins, and claudin-18 in the epithelial cells [113,114]. Nevertheless, continuous release of histamine, IL-4, and TNF-α by basophils and T cells also promotes epithelial permeabilization in primary human bronchial epithelial cells and mouse models, thus suggesting the chronic T_H2 allergic response as the main driver of the phenotype [115]. The loss of TJs is associated with changes in the type of cells that make up the epithelial layer. Remodeling is characterized by an increase in the number of goblet cells, which induces mucus overproduction and secretion to the airway lumen, reduces oxygen exchange, and obstructs the airway, thus impairing respiratory function [68]. It has recently been reported that microRNA 141 (miRNA141) may play a key role in this process. This miRNA is abundantly detected in the human airway epithelium, and its expression can be induced upon airway allergen challenge in asthma. Strikingly, inhibition of miRNA141 lowered airway hyperreactivity and suppressed mucus overproduction by IL-13 signaling [116].

Chronic inflammatory diseases can also influence the structure of the nasal mucosa. This is evident in chronic rhinosinusitis with nasal polyps (NP), in which the normal mucosa undergoes a remodeling process comprising rupture of the epithelial layer, proliferation of fibrotic tissue, deposition of the extracellular matrix, development of edema, and infiltration of immune cells and thin-wall vessels [117-119]. In this process, T_H2-related cytokines such as IL-4, IL-5, and IL-13 play a key role by recruiting eosinophils to the area; these would be responsible for causing edema and maintaining the inflammatory cascade over time [120,121]. Interestingly, recent research suggests that the basal epithelial cells may also play an important role in this process. Ordovas-Montanes et al [122] proposed that basal cells derived from NP may play a role in the reappearance of NP, in contrast with basal cells from healthy nasal mucosa, which constitutively maintain expression of the Wnt pathway in NP. Wnt genes are mostly induced by IL-4/IL-13 and limit basal cell differentiation to secretory cells. The authors showed that basal cells in NP could maintain Wnt expression without the presence of IL-4/IL-13 mirroring an inflammatory "memory" phenotype, inhibiting their differentiation, and promoting relapse of NP [122].

Remodeling also plays an important role in eosinophilic esophagitis, an antigen-driven T_H2 disease in which chronic eosinophilic inflammation causes esophageal dysfunction [122,123]. Eosinophilic esophagitis is driven mainly by food allergens, although certain aeroallergens can also initiate the disease [124-127]. Interestingly, IgG4, rather than IgE, appears to be the main driver of the disease, as treatment with omalizumab (anti-IgE) is not effective and deposits of IgG4 and IgG4-expressing plasma cells were observed in biopsies from patients with eosinophilic esophagitis [128]. Eosinophilic esophagitis is defined by edema, exudates, longitudinal furrows, and esophageal narrowing in advanced disease. All these changes ultimately cause epithelial barrier dysfunction. At the structural level, the loss of several structural proteins, such as desmoglein 1, E-cadherin, occludin, and claudins 1 and 7, leads to decreased numbers of desmosomes and other intercellular junctions [129-132]. This promotes an

epithelial-to-mesenchymal transition, in which epithelial cells transdifferentiate to fibrotic cells, leading to remodeling of the mucosal layer [133].

Finally, little is known about the effect of food allergy on the remodeling of the mucosal layers. Recent reports show that individuals with severe allergic respiratory disease living in areas of high allergen exposure present remodeling in the oral mucosa mediated by allergic reactions characterized by impaired TJ formation, immune cell infiltration, and overproduction of extracellular matrix [134,135]. This suggests that the oral mucosa might play a key role in allergic sensitization, tolerance, and mucosal remodeling. This notion is supported by the tolerogenic properties of the secondary organs linked to the oral mucosa (tonsils) and the success of oral allergen immunotherapy [136-138]. However, gut mucosal remodeling in food allergy is a very unexplored field, probably owing to the continuous avoidance of antigen exposure as a common treatment. Nevertheless, the interplay between gut microbiota and intestinal eosinophils has been hypothesized to cause intestinal alterations in the epithelial barrier [139]. In any case, these processes should be further investigated (Figure 5).

4. Effect of the Inflammatory Response on the Epithelial Barrier

Once inflammation has fulfilled its purpose, it must be controlled to prevent it from becoming chronic. Thus, there is a change in proinflammatory factors, which are responsible for activation of the immune response, towards a proresolving environment, which is achieved by the production of proresolving agents (Figure 6).

Proresolving agents are anti-inflammatory mediators that meet a series of requirements [140], as follows: (*1*) limiting the recruitment, infiltration, and activation of leukocytes (particularly neutrophils, which are the first to enter the site of inflammation and initiate phagocytosis

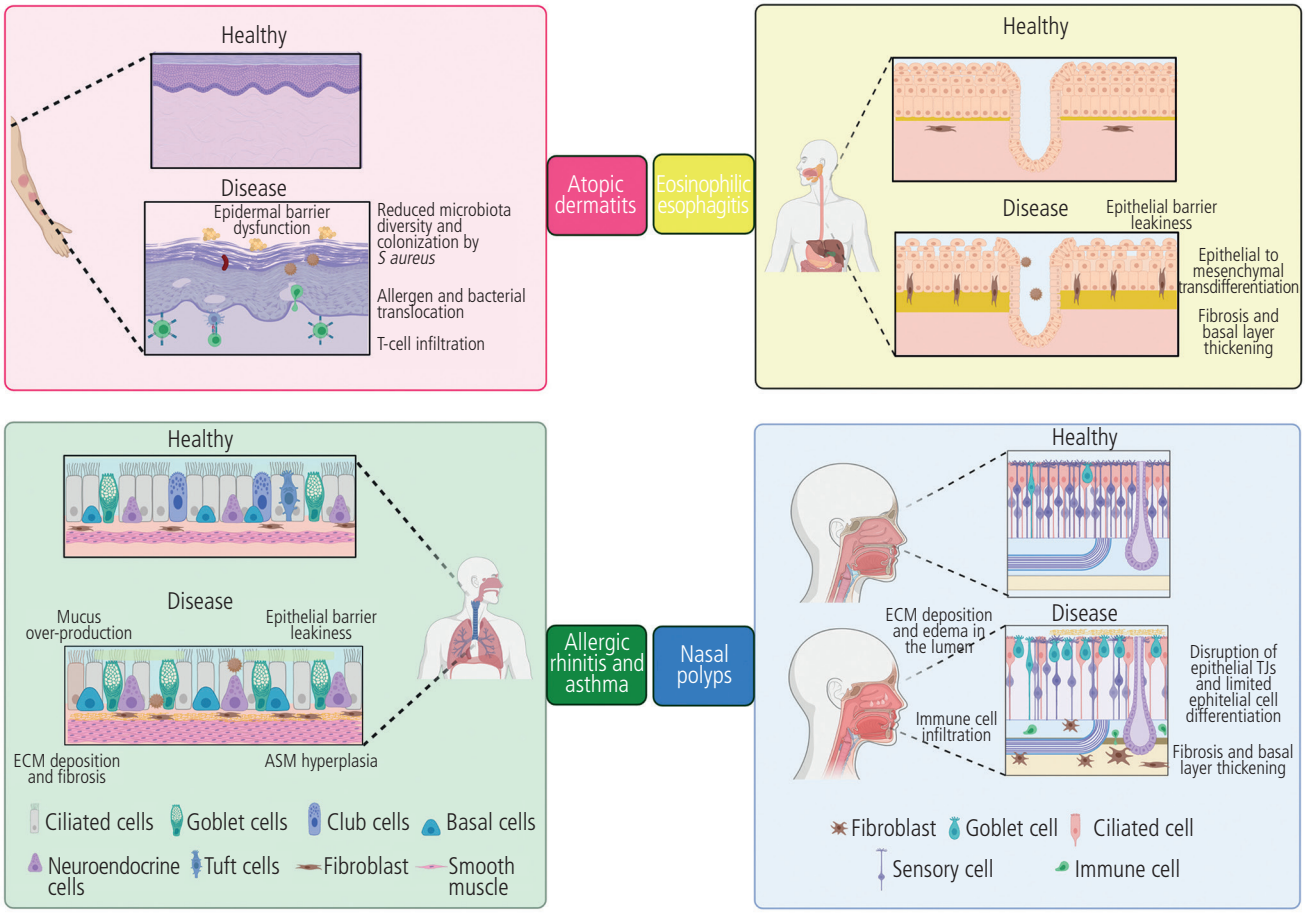

Figure 5. Epithelial remodeling in allergic diseases. Characteristic epithelial remodeling of mucosal surfaces in atopic dermatitis (top left, pink), eosinophilic esophagitis (top right, yellow), allergic rhinitis and asthma (bottom left, green), and nasal polyps (bottom right, blue). Remodeling in atopic dermatitis is characterized by dysfunction of the epithelial barrier, reduced diversity of skin microbiota, increased allergen translocation, and T-cell infiltration. Eosinophilic esophagitis is characterized by barrier leakiness, epithelial-to mesenchymal transdifferentiation, fibrosis, and basal layer thickening. Allergic rhinitis and asthma remodeling takes place in the airways and is defined by increased extracellular matrix (ECM) deposition and fibrosis, hyperplasia of the airway smooth muscle (ASM) layer, barrier leakiness, and overproduction of mucus. Nasal polyps are characterized by increased ECM deposition and edema in the lumen, limited cell differentiation and tight junction (TJ) disruption, immune cell infiltration, and basal layer thickening.

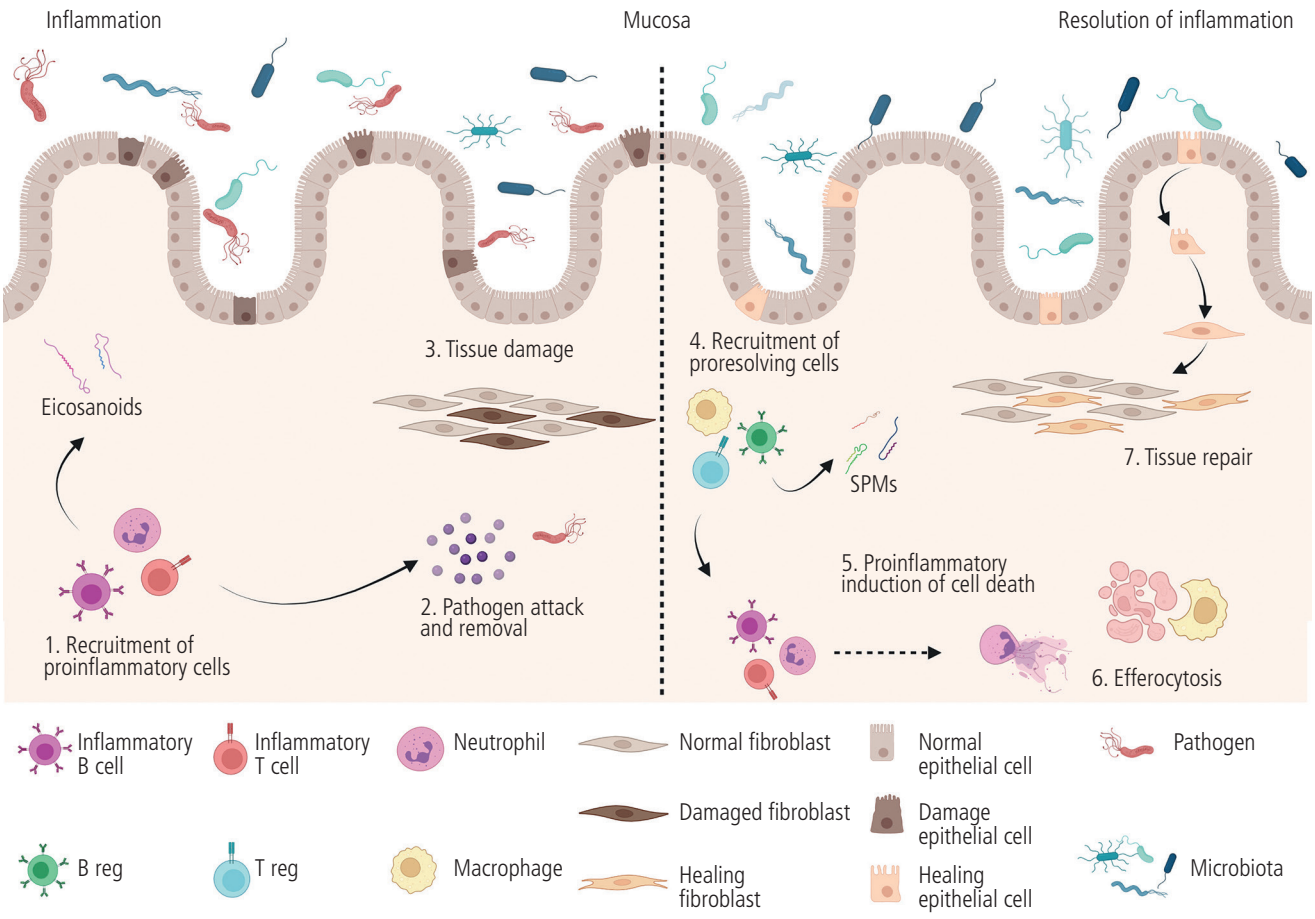

Figure 6. Comparison of the inflammatory response in the proinflammatory vs the resolution states. When a menace (eg, pathogens, injury, allergens) is encountered, a proinflammatory response ensues, starting with the recruitment of proinflammatory cells (*1*). These cells orchestrate the immune response using inflammatory mediators (eg, lipid mediators, such as eicosanoids and cytokines), with the aim of attacking and eliminating the threat (*2*). However, the inflammatory immune response might lead to tissue damage (*3*), which may remain chronic if inflammation is not appropriately resolved. Thus, after the threat is removed, the immune environment shifts towards a proresolving status via recruitment of regulatory immune cells (*4*). These cells ensure that homeostasis is restored using proresolving mediators (ie, anti-inflammatory cytokines and specialized proresolving mediators [SPMs]), which clear the inflammation site of proinflammatory cells, both by stopping recruitment and by activating cell death (neutrophil extracellular trap, apoptosis) (*5*). Cell debris is eliminated by phagocytic cells, such as macrophages, in a process called efferocytosis (*6*), which prevents re-establishment of inflammation. Finally, tissue needs to be repaired, a process that is largely regulated by epithelial-mesenchymal transition (*7*).

of microbes [141]); (*2*) promotion of the recruitment of noninflammatory (nonphlogistic) immune cells; (*3*) induction of apoptosis and clearance of neutrophils (efferocytosis); (*4*) inhibition of proinflammatory mediators such as cytokines; (*5*) induction of an anti-inflammatory status; and (*6*) activation of tissue regeneration and healing, restoration of homeostasis [142,143]. Resolution of inflammation is tissue-specific, with both general and organ-specific characteristics [141], thus explaining differences in regeneration between locations (eg, skin, which generates scars upon repair vs the liver, which regains total function) [144,145]. It is important to note that the resolution phase is bound to happen from the onset of the inflammatory reaction [146] and comprises, like inflammation itself, 5 "pillars" of resolution: removal (of microbes, dead cells, and cellular debris), restoration (of vascular integrity), regeneration (of tissue), remission (of fever and other inflammatory symptoms), and relief (of pain) [147].

First, proinflammatory cells and mediators must be depleted and substituted by others that can induce proresolving environments via nonphlogistic recruitment of cells, apoptosis of neutrophils, and evacuation of inflammatory cells from the tissue [148,149]. This process involves lipid mediators such as resolvins, protectins, and maresins, known as specialized proresolving mediators [140,150], which can target multiple cells (eg, neutrophils, macrophages, monocytes, T cells, and epithelial and endothelial cells) [140] and regulate apoptosis, efferocytosis, and tissue regeneration, thus preventing the activation of proinflammatory immune responses and fibrosis [140,147-152]. There is also evidence suggesting that proinflammatory mediators and cells play a role in the resolution of inflammation. For example, NFκB is a transcriptional factor that, during acute inflammation,

activates the production of proinflammatory cytokines; however, it also has a role in resolution of inflammation (eg, by increasing apoptosis of lymphocytes and neutrophils) [152], thus showing it to be a key regulator of the immune response.

The first steps in resolution of inflammation are directed towards stopping the recruitment of neutrophils and eliminating those that have already served their purpose. Neutrophils can undergo apoptosis, reverse migration, or lymphatic drainage [143]. Apoptosis is the main mechanism and is considered the desired form of cell death, being key in the regulation of resolution of inflammation. Other kinds of cell death, such as autophagy, pyroptosis, necrosis, and neutrophil extracellular traps usually lead to the maintenance of inflammation and tissue damage [143].

Efferocytosis of apoptotic neutrophils is essential for favorable resolution of inflammation. It is undertaken by phagocytic cells, especially monocytes and macrophages, which, upon recognition of apoptotic neutrophils, are skewed from a proinflammatory status towards an anti-inflammatory and proresolving status (from classic to alternately activated macrophages) [153]. Defects in efferocytosis usually delay resolution of inflammation and cause diseases such as systemic lupus erythematosus, where patients develop autoantibodies against intracellular components of the apoptotic cells released into the tissue [154].

Tissue repair is the next critical step in regaining homeostasis. It is directed mainly by the immune system (neutrophils and macrophages), although fibroblasts, epithelial and endothelial cells, and platelets are also needed for successful repair [155,156]. The numerous factors involved in resolution include growth factors and interleukins. Tissue repair requires proliferation and migration of epithelial cells, as well as proliferation of fibroblasts, usually through epithelial to mesenchymal transition [157], matrix deposition, and angiogenesis. While this process normally leads to remodeling of the tissue, final repair depends on the organ involved, as mentioned above [144,155].

Likewise, tissue repair mechanisms depend on the type of inflammation. For example, TGF-β is critical after type 1 and type 17 inflammation, whereas IL-13 is responsible for tissue repair in type 2 cases [155].

Recent studies propose that, at the end of inflammation, tissue does not return to previous homeostasis, but rather achieves an adapted homeostatic state in which, despite recovery of organ architecture and function, there are changes in cellular composition and phenotype, thus affecting the severity of future inflammatory responses [143,158,159]. Consequently, at this stage, the risk of developing chronic inflammation or autoimmune diseases may outweigh the potential benefit of rapid response in the case of a new infection [158].

Chronic infections caused by opportunistic pathogens such as *Staphylococcus aureus* might develop after achievement of adaptative homeostasis, potentially leading to diseases such as asthma [68].

Inflammatory responses are needed against insults that might produce disease, such as pathogens. Under normal conditions, inflammation is usually stopped on time thanks to proresolving and anti-inflammatory mediators and cells, which are released from initiation of the response. Both proinflammatory and proresolving states are needed to ensure successful tissue regeneration. However, it is necessary to strike a delicate balance, which is easily broken if any of the pieces are disturbed.

Epithelial Barrier and Allergic Sensitization

An altered epithelial barrier may be critical to our understanding of allergic sensitization. Early viral infection significantly increases the risk of developing asthma. In fact, Kusel et al [160] stated that children who develop viral infections in the first 6 months of life had an OR of 4.1 of having asthma. In the same study, mite exposure was only associated with an OR of 2.3. Interestingly, both risk factors combined increased the risk of asthma to an OR of 9.0. Lopez-Rodriguez et al [109] recently explained this effect. The proteolytic activity of Der p 1 affects epithelial maturation and consolidates inflammation only if the epithelium is not well established, as is the case during early viral infection. Moreover, the same authors demonstrated that high endogenous levels of glutathione S-transferase, a phenotype that has been associated with asthma, promote the enzymatic activity of Der p 1 [161]. Interestingly, Barber et al [162] demonstrated that the prevalence of sensitization to Der p 1 was higher in children than in adults, while sensitization and sIgE levels to Der p 2 were higher in adults, suggesting early sensitization to mites and subsequent progression governed by Der p 2.

A second frequent respiratory sensitizer in children is *Alternaria* species. The reason for this is unclear, as other naturally abundant mold species present a lower sensitization rate in the population. Recently Garrido-Arandia et al [163] demonstrated that Alt a 1, the major Alternaria allergen, interacts with the epithelial SLC22A17 receptor, thus promoting allergic sensitization. Remarkably, *Alternaria* spores colonize dead grass and are aerosolized together. It has been demonstrated that there are Phl p 1–like allergens in *Alternaria* spores and that Alt a 1 and Phl p 1 interact; this promotes cosensitization and potentially explains the progression of sensitization to grass pollen. Interestingly, despite being of relatively low abundance [164], Phl p 1 is the leading grass pollen allergen sensitizer [165]. As in the case of Der p 2 in mites, the Phl p 5 grass pollen allergen is usually a marker of progression of grass allergy, not an early indicator of sensitization. A similar interaction has been described between Alt a 1 and thaumatin, a relevant plant allergen [166], suggesting a pivotal role of *Alternaria* in the onset of food allergy. Notably, in most cases, early sensitization to *Alternaria* resolves spontaneously later in life, although its effect as a "gate opener" for allergic sensitization to other sources should not be neglected [167].

Allergic sensitization to aeroallergens in the presence [135] or absence [134] of food allergy was recently shown to alter the mucosal barrier, suggesting a systemic barrier defect and an association with severity of allergic disease. This process seems to be associated with systemic signatures [168] that point to factors such as T-cell proliferation [169], sphingolipids [170], arachidonic route signaling, and platelet function [171]. Such findings might prove relevant to our understanding of allergic sensitization and disease

progression and reinforce our approach to allergic diseases, where barrier function is pivotal.

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Conflicts of Interest

DB reports grants from ALK and Allero Therapeutics and personal fees from ALK and AIMMUNE. The remaining authors declare that they have no conflicts of interest.

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