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## Epithelial barrier hypothesis and the development of allergic and autoimmune diseases

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**Abstract** The “epithelial barrier hypothesis” proposes that genetic predisposition to epithelial barrier damage, exposure to various epithelial barrier-damaging agents and chronic periepithelial inflammation are responsible for the development of allergic and autoimmune diseases. Particularly, the introduction of more than 200,000 new chemicals to our daily lives since the 1960s has played a major role in the pandemic increase of these diseases. The epithelial barrier constitutes the first line of physical, chemical, and immuno-

logical defence against external factors. A leaky epithelial barrier initiates the translocation of the microbiome from the surface of affected tissues to interepithelial and even deeper subepithelial areas. In tissues with a defective epithelial barrier, colonization of opportunistic pathogens, decreased microbiota biodiversity, local inflammation, and impaired regeneration and remodelling takes place. A dysregulated immune response against commensals and opportunistic pathogens starts. Migration of inflammatory cells to other tissues and their contribution to tissue injury and inflammation in the affected tissues are key events in the development and exacerbation of many chronic inflammatory diseases. Understanding the underlying factors that affect the integrity of epithelial barriers is essential to find preventive measures or effective treatments to restore its function. The aim of this review is to assess the origins of allergic and autoimmune diseases within the framework of the epithelial barrier hypothesis.

**Keywords** Microbiota · Rhinitis · Sinusitis · Skin · Type 2 immunity

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### Introduction

The epithelial barrier is the primary contact between the host and the environment that plays a vital role in preserving the body's structural and functional integrity by shielding the host against pathogen invasion and foreign substance infiltration [1]. Physiological epithelial barrier functions are critical, since an impaired epithelial barrier is linked to a variety of chronic diseases, including allergies, autoimmune and metabolic diseases.

Since the 1960s, there has been a pandemic increase in the prevalence of allergic and autoimmune diseases, affecting more than 2 billion individuals

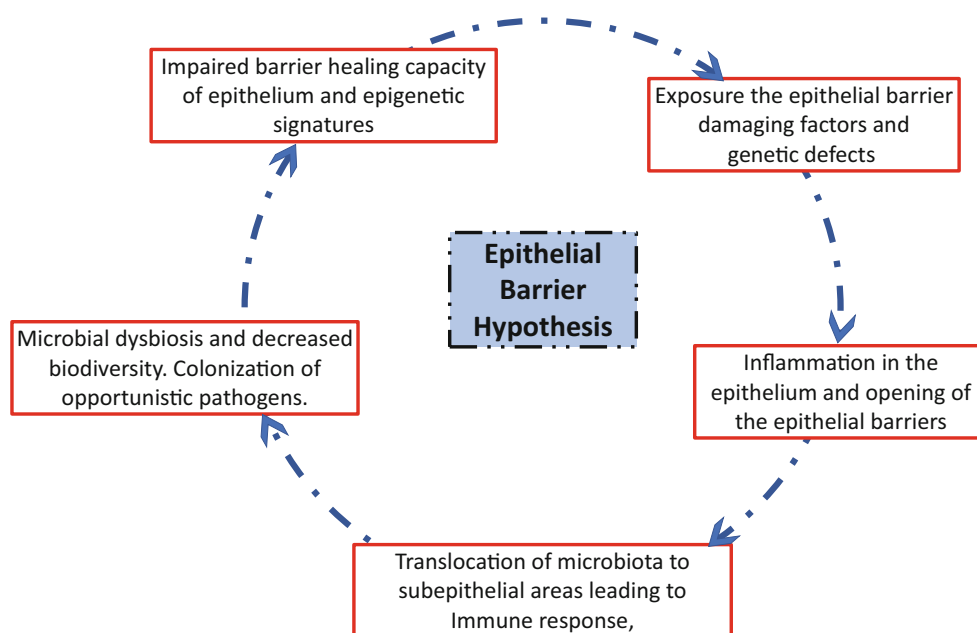
[2–4]. After 2000, a new wave of diseases emerged, including food allergies, eosinophilic esophagitis (EoE) and drug-induced anaphylaxis [5]. Environmental and genetic factors play a role in the pathogenesis of aforementioned diseases that are strongly associated with epithelial barrier defects [6, 7]. Studies on better understanding the epithelial barrier began with the first demonstration of keratinocyte apoptosis induced by activated T cells in the pathogenesis of atopic dermatitis (AD) [7, 8]. This was followed by the demonstration of epithelial barrier damage in asthma and chronic rhinosinusitis [6, 9, 10]. It was also shown that autophagy in intestinal epithelial cells acts to limit intestinal inflammation by protecting them from apoptosis during chronic colitis [11]. These diseases were characterized by apoptosis of highly activated local tissue epithelial cells with concomitant damage to the epithelial barrier. Spongiosis was evident in the skin of AD patients and epithelial desquamation was present in patients with asthma and sinusitis. The death of the highly activated epithelial cells ameliorated the local inflammatory burden. The damage of the epithelial barrier expulses local subepithelial inflammatory molecules to the lumens of mucosal surfaces. The spongiotic morphology facilitates the draining of the dermal inflammation away from the skin. Lesions of AD are characterized by an inflammatory signature and high transepidermal water loss. All of these events ameliorate the epithelial inflammatory burden related to the chronicity of these diseases with a continuous exacerbation and healing process.

The main functions of the mucosal barrier bring together the concepts of keep away, wash away and suppress that encompass multiple components of the immune system and tissue cell-related mechanisms [5]. The keep away function entails allergen ignorance

by acting as a physical barrier to external stimuli with an increased basement membrane (lamina reticularis) thickness [12], and secretion of IgA antibodies and antimicrobial peptides [13, 14]. The wash away function is responsible to drain inflammatory cells, small molecule mediators and cytokines away from the site of inflammation by mechanisms including the opening of the epithelial barriers. The aim of this type of tissue response is to drain the inflammatory cells and mediators away from the inflammation area. For example in asthma cells and mediators are found in the sputum by using the wash away mechanisms. They have left the tissues and are removed from the body after being mixed with sputum due to the opening of the epithelial barriers and molecular drainage and are removed from the inflammatory area to decrease the inflammatory burden. Cough and ciliary movement contribute to the wash away function and together these mechanisms clear away the unwanted threads as microbes, allergens, pollutants as well as inflammatory cells and mediators and decrease the inflammatory burden [15]. The epithelial cells have a suppressive role and regulate inflammation by the generation of regulatory dendritic cells, regulatory T and B cells and their anti-inflammatory cytokines [12, 16].

The epithelial barriers of the skin, lungs and gut can be impaired by exposure to environmental and toxic compounds recently introduced by industrialization, urbanization and modern lifestyle, as proposed by the “epithelial barrier hypothesis” (Fig. 1; Box 1; [4]). The epithelial barrier hypothesis is a collective concept that incorporates prior hypotheses such as the “hygiene”, “old friends”, and “biodiversity” [17]. Following the damage of the epithelial barrier, opportunistic pathogens, such as *S. aureus* may colonize the leaky barrier areas. The dysbiotic microbiota then translocate to interepithelial and subepithelial sites,

**Fig. 1** Epithelial barrier hypothesis: exposure to barrier-damaging agents or a genetic deficiency in barrier molecules leads to the colonization of opportunistic pathogens, translocation of the microbiome to the subepithelial area, immune response to dysbiotic microbiome and epithelial inflammation which causes chronic damage to the epithelial barrier integrity



### Box 1 Epithelial barrier affecting factors and their associated diseases

- A leaky gut epithelial barrier can contribute to the development of neurological diseases (e.g. multiple sclerosis) and joint diseases (e.g. rheumatoid arthritis) as the activated pathogenic immune cells in mucosal tissues with defective barriers can migrate to the affected organs [18, 19].
- Barrier leakiness precedes diabetes, a disease associated with poor gut microbiota biodiversity and altered composition [20].
- Epidemiological evidence collected from workers in detergent factories shows allergic and non-allergen-specific bronchial hyperreactivity in patients, allergen sensitizations [21].
- Exposure to household or professional cleaning agents is found to be correlated with the incidence of rhinitis [22, 23].
- Decreased occludin expression and barrier leakiness are observed when human and rat alveolar epithelial cells are exposed to diesel exhaust particulates [24, 25].
- Particulate matter affects the distribution of occludin and the alveolar barrier as shown in *ex vivo* experiments with human and rat alveolar epithelial cells [26].
- Respiratory barrier injury is promoted by ozone in mouse models [27].
- Polystyrene microplastics affect the gut barrier as shown in mouse models [28].
- Titanium dioxide nanoparticles which can be found in toothpaste amplify respiratory syncytial virus-induced airway epithelial barrier dysfunction [29].
- Damage to the structure of hamster small intestine *in vivo* and the translocation of *Escherichia coli* across M-cells *in vitro* are enhanced by emulsifiers [30].
- Ocular allergy development promotes the cycle of allergic inflammation by facilitating paracellular transport of allergens, pathogens, pollutants and other harmful triggers [31].

initiating a local or sometimes systemic immune and inflammatory response which is suspected as a culprit in many immune-related diseases. A cascade of events then follow to cause chronic periepithelial inflammation with barrier leakiness (Box 2; [4]). Currently, it is not fully understood whether the epithelial barrier damage occurs prior to or after the allergic/autoimmune response (Fig. 1). It is essential to understand the factors and molecular mechanisms that affect the epithelium barrier's integrity and find preventative measures or effective therapies to restore its physiological function. The aim of this review is to

### Box 2 Stepwise events describing the epithelial barrier hypothesis

- Genetic defects and/or exposure to epithelial-activating and barrier-damaging agents and opening of the skin and mucosal barriers.
- Colonization of opportunistic pathogens, *S. aureus*, *Moraxella*, *Haemophilus*, *Pneumococcus*.
- Translocation of microbiota to inter- and subepithelial areas.
- Immune response to commensals and opportunistic pathogens, together with systemic inflammation.
- Microbial dysbiosis and decreased biodiversity and commensals.
- Chronic inflammation in the periepithelial area.
- Defective epithelial barrier healing due to inflammation and epigenetic regulation of epithelial stem cells.

account for the alarming increase in the prevalence of allergic and autoimmune diseases through the framework of the epithelial barrier hypothesis. The barrier-damaging environmental and genetic factors and the concomitant inflammatory response are highlighted. Finally, the interplay between the epithelial barrier and microbial dysbiosis is discussed as a key driving force of allergic and autoimmune diseases.

### Factors affecting the epithelial barrier

#### Genetical factors: filaggrins and TJ polymorphisms

Studies have shown that environmental and genetic factors together play a role in the pathogenesis of diseases that are strongly associated with epithelial barrier defects such as AD [32] and inflammatory bowel disease (IBD) [33]. In addition, the fact that the strongest predictor of AD is a family history of allergy supports the importance of genetic factors in the pathogenesis of the disease [34].

Tight junctions (TJ), desmosome, and adherens junctions are the main structures involved in the formation of the mucosal epithelial barrier [35]. In addition, filaggrin protein, which binds to keratin fibres in epithelial cells in the epidermis, plays a role in the formation of the barrier [36]. One of the well-known genetic risk factors for the development of AD is loss-of-function mutations in the filaggrin gene (*FLG*) [37, 38]. The *FLG* protein is located in the stratum corneum and is essential for maintaining epidermal barrier integrity along with TJs in the stratum granulosum [32]. *FLG* loss-of-function mutations are associated with more severe AD [39] and food allergy development [40]. Furthermore, the presence of a *FLG* loss-of-function mutation predicts the development of asthma in AD patients who are sensitized to food

allergens [41]. In addition, copy number variation in *FLG* affects the AD development risk [42]. Deficiencies in other epithelial barrier-associated proteins such as *laminin alpha-3* [43], *TMEM79* [32], *filaggrin-2* [44] and *late cornified envelope-like proline-rich 1* [45] genes were also found to be associated with AD.

The TJ is a continuous, circumferential belt-like intercellular adhesion complex that regulates paracellular passage. Mouse studies have shown that the knock-out of various TJ components such as claudins (CLDN) and zonula occludens (ZO) proteins cause defects in the blood–brain barrier [46], blood–testis barrier [47], skin barrier [48] and even fatal embryonic anomalies [49, 50]. Mutations in *CLDN10B* and *CLND1* genes causing total absence or reduced protein expression of the respective claudin proteins leads to various syndromes associated with epidermal barrier impairment [51, 52]. The polymorphisms in the *CLDN1* gene were found to be associated with AD [53] and contact dermatitis [54]. The localization of the TJs on the cell membrane is essential for forming an efficient epithelial barrier structure. This is evidenced by the deficiencies in protein sorter adaptors that cause epithelial barrier impairment [55]. *Adaptor Related Protein Complex 1 Sigma 1 Subunit (AP1S1)* mutations altered localization of TJ proteins ZO-1 and claudin 3, resulting in an impaired intestinal epithelial barrier [56]. Single nucleotide polymorphisms of TJ-related proteins, membrane-associated guanylate kinase inverted (MAGI)-2 and MAGI3, are associated with IBD [57]. Moreover, loss-of-function mutations in the gene encoding desmosome protein desmoglein-1 cause impaired epidermal integrity and barrier function, resulting in severe skin dermatitis, multiple allergies and metabolic wasting (SAM) syndrome characterized by severe dermatitis, multiple allergies and metabolic wasting [58]. A recent study demonstrated the association between desmosome proteins desmoplakin and periplakin variants with eosinophilic esophagitis [59]. Protocadherin 1 gene variants, an adherence junction protein, have been shown to predispose an individual to bronchial hyperresponsiveness [60]. Lastly, single nucleotide polymorphisms of mucin (MUC)-19 and MUC22 are associated with Crohn's disease and MUC21 and MUC22 with ulcerative colitis [33].

### Environmental factors

The external exposome is a term used to describe the collection of chemical substances and environmental pollutants we are exposed to starting from conception until death. There is mounting epidemiological evidence indicating that pollution, alterations in dietary habits and exposure to toxic substances, such as dishwasher and laundry detergents, household cleaners, diesel exhaust, microplastics, nanoparticles, and food emulsifiers, possess severe epithelial barrier-damaging properties [39, 61]. More than 200,000 new chem-

icals have become excessively common especially in developing countries after the 1960s due to modernization, urbanization and globalization. In parallel, allergic and autoimmune diseases have become one of the main threats for mankind and a significant health-care burden [62].

Diesel exhaust particles (DEPs) harm the upper and lower respiratory tissues, causing serious damage to the nose, sinuses and lungs [24, 25]. Fukuoka et al. demonstrated that DEP disrupted TJs, thus leading to increased permeability of nasal epithelial cells [24] and facilitating the entry of allergens into subepithelial tissues causing the exacerbation of antigen-specific IgE-bearing mast-cell-mediated immediate allergic responses. Both in vitro and in vivo studies demonstrate that DEPs trigger the proliferation of eosinophils and increase secretion of interleukin (IL)-13 on lung epithelial cells causing fibrosis and tissue remodelling in the lungs [63]. Moreover, DEP stimulation on the primary human nasal epithelium modifies the basal secretome leading to inflammation with effusion of fluids [64, 65].

Laundry detergents and detergent residue after rinsing disrupt the TJ barrier integrity of human bronchial epithelial cells (HBEC). The toxicity of laundry detergents on HBECs has been demonstrated at relatively high concentrations (greater than 1:50,000 detergent dilution). While genes related to lipid metabolism, oxidative stress, cell survival, thymic stromal lymphopoietin (TSLP) and IL-33 are upregulated; genes related to cell adhesion, extracellular matrix organization and wound healing are downregulated in human bronchial cells after applying detergent at 1:50,000 dilution [23]. In the same study, the detergent residue remaining on clothes was demonstrated to be cytotoxic and induce epithelial barrier opening. Surfactants that are commonly used in various washing products and cosmetics, such as sodium lauryl sulfate and sodium benzenesulfonate, damage bronchial epithelial cultures even at 1:100,000 dilutions [22].

Ozone exposure plays a significant role in the pathogenesis of asthma and chronic obstructive pulmonary disease by disrupting the barrier integrity and inflammation. Similar to laundry detergents, ozone exposure also results in IL-33 upregulation in the human airways. IL-1 $\alpha$  and IL-17A are also overexpressed and cause hyperinflammation after ozone-induced lung injury in humans and mice [66].

Polystyrene microplastics are cytotoxic on human airway cells at a relatively low dose after prolonged exposure or at an acute dose. TJ genes, such as ZO-1, are downregulated after microplastic exposure on the human airway inducing an inflammatory response and barrier dysfunction which can contribute to the development of chronic obstructive pulmonary disease [67].

## Allergens

Proteolytic allergens cleave the TJs, enhancing epithelial permeability and disrupting barrier function. House dust mites (HDMs), *Aspergillus fumigatus*, and pollens are examples of allergens with intrinsic proteolytic activity. Antiviral airway responses were impaired in a mouse model of HDM-induced allergic bronchial inflammation by directly affecting toll-like receptor (TLR)-3 signalling [68]. Moreover, the nasal epithelial barrier function is compromised by the lower expression of epithelial cell TJ-related proteins, such as occludin and ZO-1 [69]. Another study indicated that the inhalation of *Aspergillus fumigatus* allergen by naïve mice induced airway eosinophilia that was dependent on protease-activated receptor-2 [70]. In addition, pollens have high molecular weight proteases with serine and/or aminopeptidase activity. It is generally accepted that transepithelial passage is increased due to the disruption of transmembrane junctional proteins by several allergen proteases [71].

## Microbiota

A healthy, diverse gut microbiota is known to be essential in maintaining gut epithelial barrier integrity. However, a disturbed and dysbalanced gut microbiota is associated with increased gut barrier permeability and translocation of microbial and food antigens, beneath the epithelium, which leads to a systemic inflammation. Of relevance, children with food allergies show an early onset of intestinal dysbiosis and impaired gut barrier function [72]. Furthermore, in a mouse model of autoimmune chronic kidney disease, systemic inflammation was associated with an increase of gut proteobacteria, leading to dysbiosis, bacterial translocation to the liver and increased serum endotoxin levels. However, eradication of facultative anaerobic bacteria with an antibiotic cocktail, reduced systemic inflammation in these mice by preventing bacterial translocation and reducing serum endotoxin levels, highlighting a causative relationship between dysbiosis and systemic inflammation in chronic kidney disease [73].

Intestinal epithelial cells (IECs) orchestrate communication between the gut microbes and the innate and adaptive mucosal immune cells. IECs can sense molecular patterns of commensal and pathogenic microbes and therefore initiate an adequate immune response. Furthermore, IECs can secrete molecules such as antimicrobial peptides or serotonin, which directly affect the function and composition of the gut microbiota [74].

The gut microbiota interacts with the host through metabolites produced including short-chain fatty acids, secondary bile acids and polysaccharide A. Short-chain fatty acids induce Treg cell differentiation and strengthen epithelial barrier integrity by inducing mucus secretion from goblet cells and IL-22 secretion

by innate lymphoid cells (ILCs) [72]. Secondary bile acids are known to inhibit IL-1 $\beta$  and IL-6 gene expression in IECs, whereas polysaccharide A induces IL-10 secretion in CD4+ T cells [75]. Together, microbial-derived metabolites are important immunomodulators and major players in maintaining the gut epithelial barrier.

## Food emulsifiers and dietary factors

Emulsifiers, also called surfactants, are amphipathic molecules, having both hydrophobic and hydrophilic regions that allow these molecules to interact with both oily and aqueous substances, and are commonly used in processed foods. There is accumulating evidence on the toxicity of emulsifiers as they increase TJ permeability [76, 77]. The detrimental impact of the widespread use of emulsifiers in processed food is now being widely studied [78, 79]. Ingestion of emulsifiers through processed food, ice cream and pastries has been speculated as an important factor behind the increase in inflammatory bowel disease (IBD) [78, 79]. The consumption of processed foods has been suggested to cause inflammatory changes leading to metabolic syndrome, particularly due to their high emulsifier content [80]. Food emulsifiers behave like surfactants and act similar to detergents. Interestingly, trace amounts have been demonstrated to increase bacterial translocation across epithelial cells [30, 81]. Several in vivo and in vitro studies have revealed such findings with increased weight gain and adiposity, changes in microbiome composition, elevated blood glucose, hyperphagia, hepatic steatosis and increased inflammatory markers. The use of emulsifiers in food products has significantly increased over the years to prevent phase separation and extend shelf life. Very recently, Khuda et al. reported that polysorbate-80, a well-known emulsifier, alters the function of TJs even at low cytotoxic levels [13]. Animal studies also showed that administration of polysorbate-80 and carboxymethylcellulose alter the microbiota composition and increase intestinal permeability [82, 83].

Gluten, the structural protein component of grains, has been reported to damage the epithelial barrier. Gliadin, the main fraction of gluten, has different effects on the gastrointestinal mucosa, including F-actin content reduction, cell growth inhibition and apoptosis induction [84]. In addition, it was reported that gliadin induces a rapid increase in intestinal permeability by rearrangement of the cytoskeleton through the zonulin pathway and TJ opening [85]. Gluten was demonstrated to increase intestinal permeability and translocation of bacteria in a dextran sulfate sodium-induced colitis mice model. The impaired desmosomes and adherence junctions led to worsening of colitis [82].

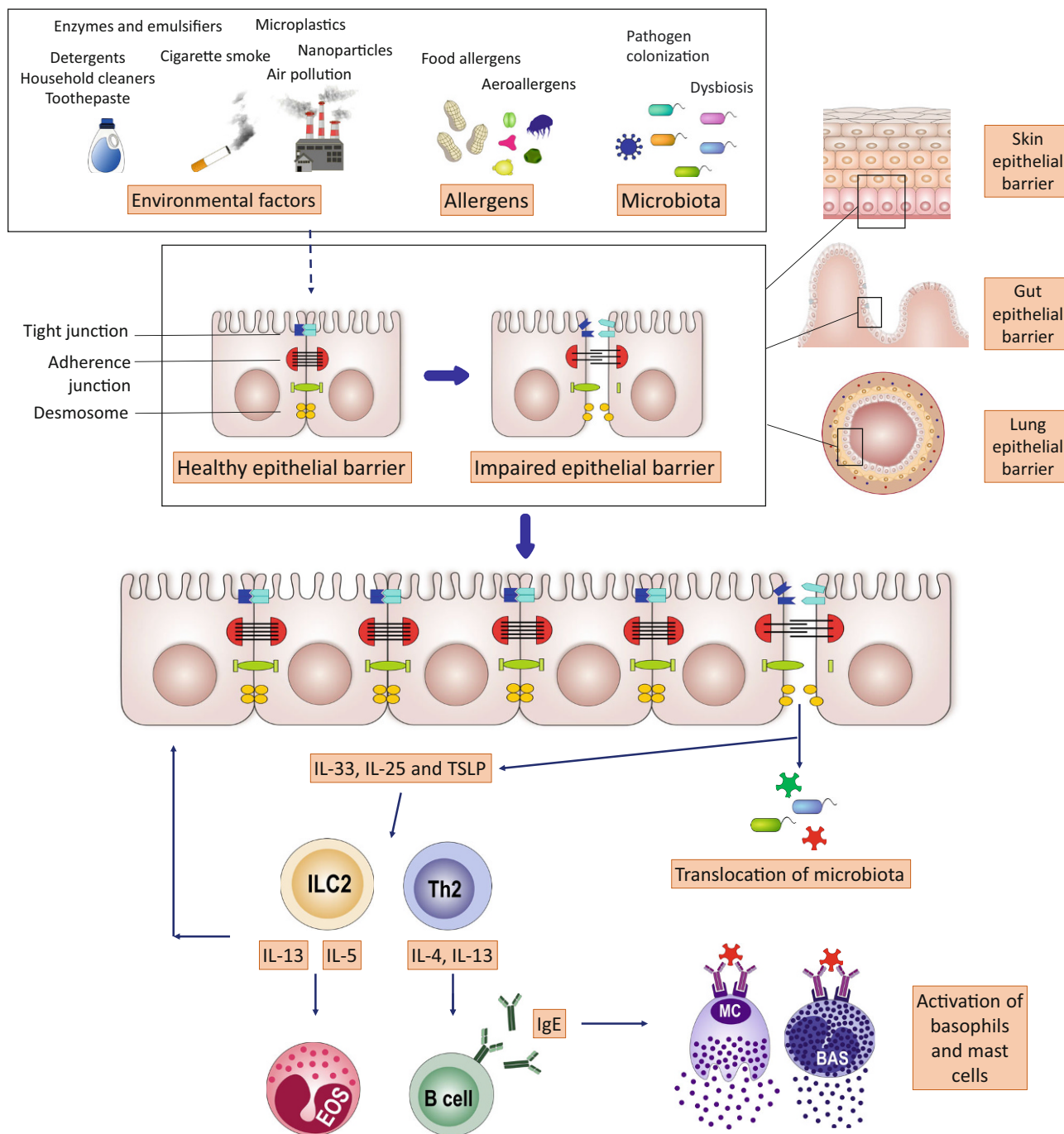
Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) are car-

bohydrates that are suspected to have a role in IBD symptoms [86]. In individuals with IBD, a high-FODMAP diet causes gastrointestinal symptoms [87]. Study shows that a high-FODMAP diet in mice promotes mast cell activation via lipopolysaccharide, which results in colonic barrier loss, and a low-

FODMAP diet restores these pathophysiologic mucosal alterations [86].

### Immune response to epithelial barrier damage

The immune response may vary depending on the site of the epithelial barrier (skin, upper and lower



**Fig. 2** Immune response to the epithelial barrier damage. Environmental factors, allergens and microbiota composition affect epithelial barrier function. A disrupted skin barrier eases the entry of allergens and activates the innate immune response. Damaged epithelial cells produce alarmins such as IL-25, IL-33, and TSLP, followed by activation of ILC2 and Th2.

Activated cells induce type 2 skewing and IgE production by B cells. Type 2 cytokines and degranulation of mast cells exacerbate the inflammation and further attenuate barrier function. ILC innate lymphoid cell, EOS eosinophil, MC mast cell, TSLP thymic stromal lymphopoietin

respiratory, oesophagus and gut). In general, epithelium-derived alarmins IL-25, IL-33 and TSLP, which are activated by allergens, pollutants, viruses, bacteria and toxins, lead to systemic inflammation characterized by activation of ILC2, exacerbated eosinophilia and IgE/IgG1 production and induce an immune response. Th2 cells and ILCs secrete type 2 cytokines such as IL-4, IL-5, IL-9 and IL-13. The signature type 2 cytokines IL-4 and IL-13 activate B cells to class-switch to IgE and also play a role in T-cell and eosinophil migration to allergic inflammatory tissues and the inflammation begins (Fig. 2; [88, 89]). IL-4 and IL-13 can also impair the epithelial barrier by reducing the expression of TJs and filaggrin. The dynamic crosstalk between the immune system, epithelial cells and their cytokines results in damage to skin and lung barriers [90].

Type 2 immune responses in skin are typically induced by defects in genes that make the epidermal layers relatively intact to release alarmins such as IL-33 and TSLP [88]. After inflammation, T cell migration is observed in the skin epithelium with variable numbers of eosinophils [91].

In airway epithelia, the type 2 immune response ultimately leads to infiltration of lung tissue with Th2 cells, ILC2s, M2 macrophages and eosinophils unlike the skin epithelia [92, 93]. This promotes nitric oxide production and differentiation of epithelia, production of mucus as well as smooth muscle contraction, and extracellular matrix generation, activation, recruitment and survival of eosinophils [17]. Environmental influences may be mediated via epigenetic processes like deacetylation. Mechanistic studies have demonstrated that barrier leakiness in asthma is induced by TH2 cells, IL-4 and IL-13 and histone deacetylase activity [94]. Moreover, increased histone deacetylase activity as a potential tissue-injury mechanism is found to be responsible for dysregulated epithelial cell repair, leading to defective epithelial barriers in allergic rhinitis [95].

Dysfunctions of intestinal epithelium lead to formation of several allergic, autoimmune and metabolic diseases. The majority of studies on the links between a leaky intestinal epithelial barrier, microbial dysbiosis, neuroinflammation, and neurodegeneration have been correlative, but a full causal relationship has yet to be shown [4].

### Epithelial barrier impairment on the development of allergic diseases

Many diseases, such as AD, asthma, chronic rhinosinusitis and EoE are associated with local epithelial tissue barrier dysfunction in the affected organ [96]. The skin barrier is the frontline defence against exogenous stimuli. Allergens passing through the skin barrier promote a local and systemic type 2-predominant inflammation, induced by IL-4, IL-5, IL-13 and IgE [88]. The allergen engages dendritic/Langerhans

cells in the skin, activating a local skin and systemic inflammatory response [39, 88]. Several invasive and non-invasive methods have been developed to study the skin barrier function. Non-invasive methods include the measurement of skin hydration, colorimetry, skin surface pH, and sebumetry. Recently, electrical impedance spectroscopy (EIS) has been introduced as a non-invasive tool to assess the integrity of the epidermal barrier *in vivo* [97, 98], as demonstrated in a mouse model of AD. After experimentally damaging the skin barrier by tape stripping and epicutaneous application of proteases and cholera toxin, a significant reduction in skin electrical impedance was observed, which is inversely correlated with transepidermal water loss, a well-known indicator of skin barrier function [97]. The clinical potential of EIS has been further investigated in patients with AD. Using artificial intelligence-based models, EIS can distinguish between the skin of controls without AD and the non-lesional skin of AD patients with good specificity and sensitivity. In addition, EIS can assess skin lesion healing in response to treatment, correlating with disease score, pruritus scores and inflammatory serum biomarkers that are significantly upregulated in patients and associated with inflammatory pathways that can affect the epithelial barrier [98].

An impaired airway epithelial barrier is a common characteristic of many asthmatic patients. The asthma susceptibility genes are expressed in the airway epithelium (e.g. IL1RL1, IL-33, TSLP). There is increasing evidence indicating that multiple genetic variants induced by environmental factors that increase the risk of asthma development regulate proteins associated with airway epithelial function [99]. Simultaneously, reduced expression of the TJ protein molecules occludin and ZO-1 has been found in nasal polyp biopsy specimens from patients with chronic rhinosinusitis [100]. In the mid-1960s, anionic surfactants and enzymes were added to laundry detergents to improve cleaning. However, these substances pose serious challenges to the epithelial barrier integrity of the skin and mucous membranes. Many cases of occupational asthma and rhinitis associated with workplace exposure to detergent enzymes and related occupational cases have been reported [101]. Studies in AD patients have shown that the expression of the TJ proteins claudin-1 and -23 is significantly reduced and epithelial barrier function is significantly impaired [53].

In addition, abnormal inflammatory or developmental signalling pathways may contribute to the establishment and worsening of epithelial barrier defects in allergies. It has been found that in EoE, pathological epithelial remodelling responses and an activated inflammatory response lead to an increase in the overall metabolic demand of the oesophageal epithelium. Thus, the oxygen-sensing transcription factor hypoxia-inducible factor (HIF)-1 $\alpha$  plays an important role in maintaining the barrier; at the same time,

high HIF has been shown to have a protective effect [102].

### Epithelial barrier effects on the development of autoimmune diseases

There is mounting evidence indicating that damaged epithelial barriers, its leakage and the resulting disturbance of the bacterial microflora composition contribute to the development of autoimmune diseases such as type I diabetes, multiple sclerosis, rheumatoid arthritis, ankylosing spondylitis, IBD and systemic lupus erythematosus [18, 19].

Intestinal membrane leakage is often discussed in the context of the epithelial barrier and autoimmune diseases. In healthy individuals, the integrity of the intestinal epithelium is preserved. Usually, bacteria that live in the gut do not translocate to internal organs. However, if the intestinal barrier is compromised, the intestinal commensals are exposed to the host's immune system in various organs. These observations have been well described in a murine model which described the link between intestinal barrier disruption and the pathogenesis of lupus. Intestinal epithelial TJ proteins are underexpressed in lupus-susceptible mice. In such individuals, commensal bacteria in the gut are transferred to the systemic tissues, activating antigen-presenting cells, which in turn migrate to the mesenteric lymph nodes. Subsequently, CD4+ T cells are activated, and inflammatory cytokines such as IL-6 are released. In rodents, IL-6 plays a vital role in the progression of lupus by inducing the production of autoantibodies by B cells and inhibiting the activity of regulatory T cells. Similar observations have also been made in humans. Dysbiosis, caused by a leaky gut, creates an inflammatory environment that results in an intense immune defence promoting the development of the disease or aggravating symptoms. Recognition of microbes or microbial products by lamina propria defences induces escalation of pro-inflammatory cytokines, including IFN- $\gamma$ , TNF- $\alpha$ , IL-1 and IL-13. These cytokines can aggravate the damage to the intestinal mucosa as in the case of IBD. Moreover, increased Th1 and Th17 cytokines and increased inflammatory activity of macrophages and dendritic cells can damage many tissues as observed in systemic lupus erythematosus [4, 103].

Experimental autoimmune encephalomyelitis (EAE) is a model of multiple sclerosis in rodents such that demyelination is produced by injection of brain extracts or proteins of central nervous system such as myelin basic protein. Moreover, pro-inflammatory cytokines can damage the blood–brain barrier by disrupting the myelin sheath, which directly contributes to the development of EAE. Studies also indicate that the relationship between the tightness of the intestinal epithelial membrane and the development of EAE is more complex because the intestinal barrier breakdown occurs depending on the model sometimes

shortly after the induction of EAE and sometimes before. It has also been shown that the degree of intestinal barrier breakdown is associated with the severity of EAE and with the immune dysfunction of the nervous system at many levels, from local to central. Interestingly, improving the tightness of the intestinal barrier in a mouse model ameliorates and postpones the development of EAE, which indicates a close relationship on the brain–gut axis. This is attributed to the intestinal nervous system, made up of the ganglia of the intestinal neurons and glial cells, which are capable of releasing important mediators influencing repair, cell proliferation, epithelial differentiation and TJ changes, regulating intestinal permeability and providing a communication pathway between the gut microenvironment and the central nervous system. [18, 104, 105].

Celiac disease is also an immune-mediated disease of the small bowel with histopathology showing dramatic changes in mucosal structure. A number of groups have reported an increase in the number of apoptotic intestinal epithelial cells in the peritoneal mucosa [106]. In addition, one-path impedance spectroscopy measurements of patients with celiac disease indicated an impaired epithelial barrier function. It is indicated that these patients can benefit from the zonulin-targeting drug, larazotide, as a supplement to a gluten-free diet [107]. Elevated serum zonulin levels signify a leaky intestinal barrier, which facilitates microbial dysbiosis and inflammation. It is also found that gut barrier leakiness is linked to rheumatoid arthritis development with the migration of the inflammatory cells from the gut to joints and the prevention of arthritis by healing epithelial barriers. The use of zonulin antagonists or therapies to restore the intestinal barrier integrity helps to inhibit the symptoms of certain diseases such as rheumatoid arthritis or ankylosing spondylitis. Several findings support the hypothesis that the onsets of rheumatoid arthritis and ankylosing spondylitis are associated with the intestinal microflora and zonulin levels, as cell wall fragments of various intestinal bacteria are arthritogenic. Current medical reports indicate the effectiveness of treatment with the use of larazotide acetate, a zonulin antagonist, which restores the integrity of the intestinal barrier and effectively inhibits the development of diseases by delaying the initial stage of arthritis [19, 108].

Translocation of microorganisms into the pancreatic lymph nodes has been observed, initiating pro-inflammatory cytokines IL-6 and TNF, thus enhancing the immune response of the Th1/Th17 type, which induces pancreatic cell damage, leading to pancreatic islet inflammation. These events are associated with the onset of type I diabetes as confirmed in a diabetic-resistant mouse model. However, diabetes is a much more complex disease as epithelial barriers are also regulated by metabolic mechanisms. It has been shown that high glucose levels in tissue due to



insulin resistance may negatively affect TJs by reducing the expression of protein genes responsible for their formation. When discussing the relationship between epithelial barrier continuity and autoimmune diseases, the haptoglobin protein zonulin, the human analogue of the *Vibrio cholerae* occludens toxin, should be mentioned. In a rodent model, a zonulin inhibitor has been demonstrated to reverse the symptoms of diabetes and microbial translocation in the intestine. Increased concentration of this protein was associated with the opening of tight junctions and dysbiosis, indirectly affecting the blood–brain barrier, which is also related to multiple sclerosis as discussed above [18, 19, 105].

**Table 1** Epithelial barrier dysfunction and the development of allergic and autoimmune diseases

Diseases	Associated epithelial barrier dysfunction
<b>Allergic diseases</b>	
<i>Asthma</i>	Multiple genetic variants, which regulate proteins associated with airway epithelial function are induced by environmental factors and consequently increase the risk for asthma development [86, 87, 89]
<i>Chronic rhinosinusitis</i>	Chronic rhinosinusitis patients with nasal polyps show defects in the epithelial barrier and reduced expression of tight junction proteins [88]
<i>Allergic rhinitis</i>	Occupational rhinitis is associated with exposure to detergents and their ingredients [89]
<i>Atopic dermatitis</i>	Immune dysregulation and epithelial barrier dysfunction characterized by impairment of epidermal TJ proteins are found in atopic dermatitis [60, 91]
<i>Eosinophilic esophagitis</i>	The oxygen-sensing transcription factor <i>HIF-1<math>\alpha</math></i> plays a crucial role in maintaining epithelial barrier integrity due to its ability to selectively control the tight junction <i>CLDN1</i> (claudin-1) [92]
<b>Autoimmune diseases</b>	
<i>Type 1 diabetes</i>	Epithelial breakdown associated with leaky gut may increase the translocation of microorganisms into the pancreatic lymph nodes. Consequently, production of pro-inflammatory cytokines is induced, which causes pancreatic cell damage. This was observed in a diabetic resistant mouse model [15, 16, 95]
<i>Multiple sclerosis</i>	Pro-inflammatory cytokines damage the blood–brain barrier by disrupting the myelin sheath, which was observed in an experimental model of MS in rodents [94, 95]
<i>Rheumatoid arthritis and ankylosing spondylitis</i>	The damaged epithelial barrier of the intestine may cause the penetration of microorganisms or their fragments into the bloodstream, and as it has been shown, intestinal bacteria and their components may be arthritogenic [16, 98]
<i>Inflammatory bowel disease</i>	Gut epithelial barrier dysfunction causes recognition of microbes or microbial products by lamina propria-inducing escalation of pro-inflammatory cytokines that cause significant damage to the intestinal mucosa, which is seen in inflammatory bowel disease [21]
<i>Systemic lupus erythematosus</i>	Dysbiosis, associated with a leaky gut, creates an inflammatory environment that results in an intense immune defence promoting the development of the disease or aggravating symptoms observed in systemic lupus erythematosus [93]
<i>Celiac disease</i>	An increase in the number of apoptotic intestinal epithelial cells in the peritoneal mucosa of patients has been reported [94]. In addition, the zonulin-targeting drug larazotide, a supplement to a gluten-free diet, could benefit CD patients [95]

## Conclusion

A defective epithelial barrier facilitates the absorption of foreign substances, inducing an inflammatory response, and subsequent systemic atopic reactions. Deciphering the underlying mechanisms involved in epithelial barrier disruption is vital for building novel strategies for the prevention and treatment of allergic and autoimmune diseases. Experimental models, organoids/spheroid models [109] and organ-on-a-chip systems should be developed to study the passage of allergens across a leaky epithelial barrier. There is clear evidence connecting barrier leakiness and allergic and autoimmune diseases, which can have systemic implications (Table 1). Several potential solutions have been proposed for reducing the incidence of diseases linked to a defective epithelial barrier: avoidance or dose control of all aforementioned substances, development of less toxic products, identification of biomarkers of a leaky barrier, novel therapies for restoring tissue-specific barrier components, inhibiting bacterial translocation, avoiding opportunistic pathogen colonization and interventions through diet and the microbiome.

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