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The epithelial barrier theory: Development and exacerbation of allergic and other chronic inflammatory diseases

Umut Can Kucuksezer[1,†], Cevdet Ozdemir[2,3,†], Duygu Yazici[4,5], Yagiz Pat[4], Yasutaka Mitamura[4], Manru Li[4], Na Sun[4], Paolo D'Avino[4], Xiangting Bu[4], Xueyi Zhu[4], Mubeccel Akdis[4], Kari Nadeau[6], Ismail Ogulur[4], and Cezmi A. Akdis[4,*]

ABSTRACT

It is now longer than half a century, humans, animals, and nature of the world are under the influence of exposure to many newly introduced noxious substances. These exposures are nowadays pushing the borders to be considered as the causative or exacerbating factors for many chronic disorders including allergic, autoimmune/inflammatory, and metabolic diseases. The epithelial linings serve as the outermost body's primary physical, chemical, and immunological barriers against external stimuli. The "epithelial barrier theory" hypothesizes that these diseases are aggravated by an ongoing periepithelial inflammation triggered by exposure to a wide range of epithelial barrier–damaging insults that lead to "epithelitis" and the release of alarmins. A leaky epithelial barrier enables the microbiome's translocation from the periphery to interepithelial and even deeper subepithelial areas together with allergens, toxins, and pollutants. Thereafter, microbial dysbiosis, characterized by colonization of opportunistic pathogen bacteria and loss of the number and biodiversity of commensal bacteria take place. Local inflammation, impaired tissue regeneration, and remodeling characterize the disease. The infiltration of inflammatory cells to affected tissues shows an effort to expulse the tissue invading bacteria, allergens, toxins, and pollutants away from the deep tissues to the surface, representing the "expulsion response." Cells that migrate to other organs from the inflammatory foci may play roles in the exacerbation of various inflammatory diseases in distant organs. The purpose of this review is to highlight and appraise recent opinions and findings on epithelial physiology and its role in the pathogenesis of chronic diseases in view of the epithelial barrier theory.

Keywords: Allergy; asthma; autoimmune diseases; barrier dysfunction; epithelial barrier theory; epithelitis; microbiota; tight junctions

1. Introduction

The prevalence of allergic diseases has been rising since 1960s [1, 2]. Around the same time, a set of autoimmune/inflammatory disorders was reported to be breaking out. Together with genetic background and environmental influences, epithelial barrier defect was highlighted to underlie the etiology of these disorders [3–5]. The discovery of the activated T-lymphocyte-mediated keratinocyte apoptosis in atopic dermatitis (AD) was the initial evidence to focus the research on epithelial barrier [4, 6], which was consequently followed by demonstration of the epithelial barrier disruption in asthma, chronic rhinosinusitis (CRS), and inflammatory bowel disease (IBD) [7–9]. The mucosal barrier's "keep away, wash away and suppress" functions are delicately facilitated by the immune system and encompass tissue and cell-related mechanisms. By forming a physical barrier against external stimuli with a dense lamina reticularis and secreted antimicrobial peptides and IgA antibodies, the "keep away" function prevents the entrance of external milieu including microbes and allergens. The "wash away" function of the epithelium uses mediators, cells, and cytokines present in the inflammation site. Excessive mucus production, ciliary movement, and also the opening of epithelial barriers eradicate mediators and the inflammatory cells from the inflammation site [10]. The allergic inflammation is strictly regulated by means of immune cells with regulatory capacities such as T regulatory cells and B regulatory cells, suppressive cell surface molecules such as CTLA-4 and PD-1, and regulatory cytokines such as interleukin 10 (IL-10), TGF-β, and IL-35 [11].

The epithelial barrier theory defines the impact of urbanization, industrialization, and Westernized lifestyle on skin, airways, and gut mucosa [1, 12], integrating the previous notions; the "Hygiene," "Biodiversity," and "Old Friends" hypotheses [13]. After barrier damage, opportunistic pathogenic bacteria colonize the affected organs and skew the microbial burden toward a more proinflammatory state [14]. A series of mutual events lead to persistent barrier leakiness and periepithelial

[1]Aziz Sancar Institute of Experimental Medicine, Department of Immunology, Istanbul University, Istanbul, Turkey, [2]Institute of Child Health, Department of Pediatric Basic Sciences, Istanbul University, Istanbul, Turkey, [3]Istanbul Faculty of Medicine, Department of Pediatrics, Division of Pediatric Allergy and Immunology, Istanbul University, Istanbul, Turkey, [4]Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland, [5]Research Center for Translational Medicine (KUTTAM), Koç University School of Medicine, Istanbul, Turkey, [6]Department of Environmental Studies, Harvard T.H. Chan School of Public Health, Cambridge, MA, USA,

*Correspondence to Cezmi A. Akdis Swiss Institute of Allergy and Asthma Research Herman-Burchard Strasse 9, CH-7265 Davos Wolfgang, Switzerland.

Tel: +41-81-410-0848

Fax: +41-81-410-0840

Email: akdisac@siaf.uzh.ch

†Umut Can Kucuksezer and Cevdet Ozdemir contributed equally to this article as co-first authors.

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inflammation. Translocation of pathogens, pollutants, and allergens to inter- and subepithelial spaces elicits an inflammatory response termed as "epithelitis" followed by an "expulsion response" that both underlie the pathogenesis of many immune-related diseases. This review aims to summarize novel findings on skin and mucosal barrier dysfunction and their possible contribution in chronic inflammatory diseases.

2. Risk factors of epithelial barrier dysfunction

2.1. Genetic predisposition

The epithelial barrier is the first line of defense to external milieu, whose dysfunction is closely linked with inflammatory disorders. Mutations in the genes of vital epithelial barrier proteins are associated with allergic disorders [15, 16]. The polymorphisms in the genes of type 2 cytokines (IL-4 and IL-13), alarmins (IL-33 and thymic stromal lymphopoietin [TSLP]), inflammation-related proteins (ADAM33 and HLA), and also vitamin D receptor could either reduce or increase the risk and severity of asthma [16, 17]. In addition, *CCL20*, *IL6*, *IRF4*, *MUC5AC*, *TBX21*, *FADS2*, and *RUNX1* were reported as asthma-associated genes [18]. Food allergies and AD have T helper type 2 (Th2) inflammation and itch-scratch further impairs skin barrier function, which could further facilitate the entry of toxins and microbes, leading to skin barrier damage [15].

The possible role of epigenetic alternations in epithelial integrity was covered by several studies, revealing the contribution of silent information regulator genes, histone deacetylases, and CpG methylation on tight junction (TJ) barrier integrity in the asthmatic epithelium [19]. The inhibition of histone deacetylases improved epithelial barrier integrity by increased synthesis of TJ molecules. Next-generation sequencing of asthma candidate genes revealed 2 single-nucleotide polymorphisms in the filaggrin (*FLG*) gene that were suggested to contribute to asthma pathogenesis [20].

2.2. Microbiota changes underlying epithelial functions

The host's metabolism, epithelial barrier integrity and functions, and immune homeostasis show vital links with microbiota [21]. Close relation between microbial dysbiosis and epithelial barrier dysfunction is also connected with several noncommunicable inflammatory disorders such as allergic, cardiovascular, metabolic, and autoimmune diseases [1, 13, 22, 23]. Local inflammation and progressive damage to epithelial barriers are persuaded by the translocation of the microbes to subepithelial tissues together with environmental agents, and induction of a type 2 expulsion response [1, 24–27]. Besides, microbiota prevents the colonization of the pathogenic microorganisms, regulates, and improves epithelial barrier functions [28]. In barrier defective tissues, type 2 immune responses are initiated against commensal microbes as well as facultative pathogens [29]. *Staphylococcus aureus* (*S. aureus*) is the most abundant bacterium colonizing damaged tissues of the respiratory system and the skin. Asthma exacerbations and severity are closely linked with antibody levels against *S. aureus* [30]. *Staphylococcus epidermidis* supports the skin barrier by increasing ceramide production in the stratum corneum by sphingomyelinase activity [31]. Beneficial microbiota provides the preservation and healing of the epithelial barrier [32]. On the contrary, resident microbiota could contribute to the strength of the epithelial barrier by mechanisms including the production of metabolites, such as short-chain fatty acids (SCFAs) [33–35]. Restoration of the microbial diversity could be a potential therapeutic approach to sustain the barrier integrity and avoid the onset of inflammatory-driven diseases. Fecal microbiota transplantation represents a promising tool for microbial diversity restoration and prevention of many inflammatory diseases [36]. Additionally, fungal communities known as mycobiota could contribute to the protection of the healthy state [37, 38].

The development of atopic diseases has links to gut dysbiosis. The abundance or low expression of certain bacteria may project about the risk for disease development or protection. *Acinetobacter* presence on the skin was attributed as "protective" against allergen sensitization [39]. Relatively low abundance of *Bacteriodetes* have been reported in food-allergic children [40]. The metabolomics research identified microbial metabolites and provided insight into host–microbiota interactions and disease onset [34, 41].

2.3. Environmental influence and pathogenic drivers

More than 350,000 new substances have been introduced to human lives with almost no control on their health effects after 1960s. Many of them ended up as pollutants [42]. Changes in environmental exposure particularly after 1960s have been proposed to be directly linked with development of autoimmune, allergic, and metabolic diseases [1, 26, 27]. TJs and epithelial barrier integrity could be damaged following encounter upon climate alternations, detergents, surfactants, household cleaners, food additives, particulate matter (PM), diesel exhaust particles, tobacco smoke, microplastics, ozone, and toothpaste, all of which account for the environmental insults (**Fig. 1**) [1, 12, 13, 26, 27, 43–47].

Climate change is a global problem. As a result of deforestation and the greenhouse effect, the Earth's CO_2 elimination capacity is crippled, which leads to climate change with harmful effects on human health along with animals, plants, agriculture, wildlife, forests, and oceans [12, 48, 49]. Pollutants including PM, CO_2, CO, NO, ozone, and volatile organic compounds are among the main driving forces of allergic diseases [50]. The hazardous levels of environmental ozone, PM, and nanomaterials could impair epithelial barrier functions [51]. Wildfires and toxic fumes are hazardous to human health. Wildfire smoke induces oxidative damage and lung inflammation and asthma exacerbations [52]. Animal studies revealed that air pollution has detrimental effects on epithelia, immune cells, and immune responses [53]. Cigarette smoke upregulates inflammatory dendritic cells in the lungs and disrupts the epithelial barrier function by suppressing proinflammatory cytokine and chemokine responses (**Fig. 1**) [54].

Detergents and their surfactants sodium lauryl sulphate and sodium benzene sulphanate, which were introduced to our lifes in 1960 with a similar formulation as of today, are regarded as important epithelial barrier disruptors. Public daily exposure to detergents was enhanced as detergent usage was increased, together with additive surfactants and proteolytic enzymes [55]. A direct link between asthma and AD development and detergent exposure, household cleaners and disinfectants has been repeatedly reported [56–58]. Laundry detergent exposure disrupts the epithelial barrier function of skin and bronchial epithelial cells, even at very high dilutions [59, 60]. Professional dishwashing became the state of the art worldwide for common food consuming areas, such as hospitals, armies, and schools after 2000 and their rinse aid containing alcohol ethoxylates show epithelial barrier opening, proinflammatory and cell toxic effects on gut epithelia in very low concentrations [61].

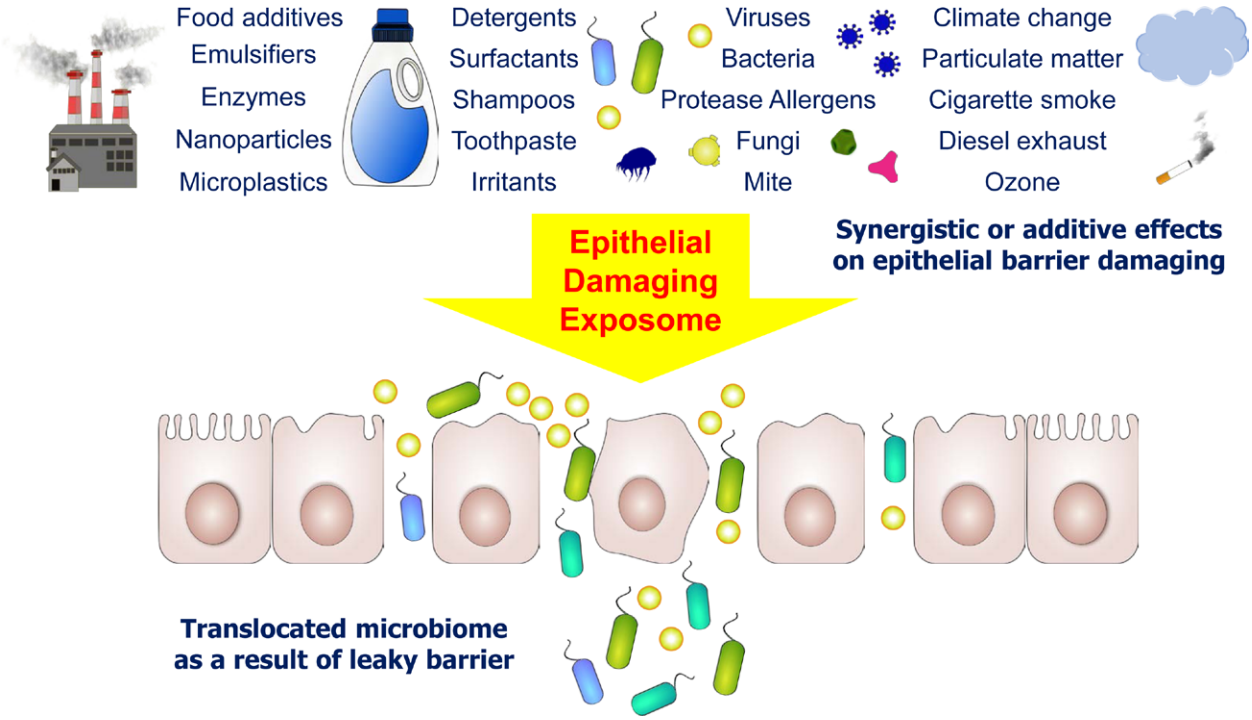

Figure 1. Epithelial barrier–damaging agents. A defective epithelial barrier is underlying a number of inflammatory disorders including allergy and autoimmune diseases. Epithelial barriers of the skin, respiratory, or gastrointestinal systems are disrupted upon synergistic or additive effects of a number of agents or factors. These include detergents, shampoos, toothpaste, diesel particles, cigarette smoke, food additives, allergens with protease activity, viruses, ozone, and also alterations in climate. Translocation of the microbiota occurs as the result of leaky epithelial barrier formation.

Production and usage of plastics have increased markedly to the levels of 8 billion tons per year. Approximately 1 billion tons of micro- and nanoplastics have been produced each year that contaminate food and water and may trigger inflammation on epithelial cells, leading to microbiota dysbiosis and causing barrier dysfunction in the digestive tract [62, 63]. Again, during the last 20 years, the consumption of processed food has substantially increased and jointly ingestion of emulsifiers may apparently contribute to the development of diseases. Even low concentrations of food emulsifiers may increase intestinal permeability and lead to mucosal damage [64].

2.4. Allergens

The synergistic and additive effect of epithelial barrier–damaging substances is still under investigation; however, it is clear that all of the pollutants are coexposed together with perennial allergens and depending on the time with seasonal allergens. For example, early in the year, birch pollen allergen exposure is always overlapping with air pollutants in March in the Northern Hemisphere [65]. Proteases released by several aeroallergens target transmembrane adhesion proteins such as E-cadherin and transmembrane receptors, damage barrier permeability, facilitate allergen absorption and sensitization, and initiate inflammatory responses (**Table 1**) [78, 79]. Protease inhibitors could maintain lung homeostasis to stabilize the action of allergens and control apoptosis. Allergen exposure could lead to differential expression of protease inhibitors, which could occur both in the presence or absence of Th2 cytokines, and could damage the lung epithelium [80]. Environmental factors such as climate change and thunderstorms could influence the severity and duration of allergic respiratory diseases directly and indirectly

Table 1.
Allergens with protease activity

Allergen type	Allergen source	Allergen name	References
Cockroaches	*Periplaneta americana*	*Per a 10*	[66]
Fruits	*Actinidia deliciosa*	*Act d 1*	[67]
	Ananas comonus	*Ana c 2*	
	Carica papaya	*Papain*	
Fungi	*Aspergillus fumigatus*	*Asp f 13*	[68–71]
	Aspergillus flavus	*Asp fl 13*	
	Flavus oryzae	*Asp o 13*	
	Penicillium chrysogenum	*Pen ch 13*	
	Penicillium citrinum	*Pen c 13*	
House dust mites	*Dermatophagoides pteronyssinus*	*Der p 1*	[72–77]
		Der p 3	
		Der p 9	
	Dermatophagoides farineae	*Der f 1*	
		Der f 3	

[80, 81]. Increased atmospheric CO_2 levels enhance photosynthesis, which leads to prolonged pollination periods. As a result, allergic individuals are exposed to higher pollen concentrations for longer durations. Elevated CO_2 concentrations also increase the allergenicity of ragweed pollen and could induce stronger inflammatory responses [82].

2.5. Cellular and molecular mechanisms of epithelial barrier impairment

Understanding the molecular mechanisms supporting barrier integrity under physiological circumstances is of great importance. The complex interplay between immunity and TJs is vital for immune homeostasis (**Fig. 2**). Most epithelial cell lineages express toll-like receptors, and they contribute to epithelial barrier integrity and regulation of the immune responses. Mucus and antimicrobial peptides could avoid damage to epithelial cells and may strengthen the barrier [83]. The barrier integrity is mainly maintained by the regulation of epithelial TJs and their expression levels could be used as a biomarker to evaluate barrier permeability [84]. Air pollutants are important environmental contributors to the epithelial barrier impairment [1]. Wildfire exposure upregulated CRP and IL-1β as inflammation markers [85]. Additionally, the inhalation of chorine-containing disinfectants revealed a stronger immune response and increased frequencies of Th2 cells and eosinophils, in an ovalbumin-induced mouse model [86].

The first step after the injury of epithelial cells is the release of alarmins that were secreted in response to pollutants. IL-33, IL-25, and TSLP secretion have been reported in exposure to epithelial barrier–damaging agents such as PM, ozone, detergents, and dishwasher rinse aid. This step is called epithelitis (**Fig. 2**). The second step is the dysbiosis in the microbiome with colonizing opportunistic pathogens and decreased numbers and biodiversity of commensal bacteria. An immune response develops to opportunistic pathogens as observed for *S. aureus* [87, 88].

The third step is the development of an expulsion response (**Fig. 3**). IL-13, eosinophils, Th2 cells, and group 2 innate lymphoid cells are the main players of epithelial barrier leakiness. This is very similar to eosinophilic expulsion response of parasites such as the lung stage of the larvae of ascaris, schistosoma, and hookworms. Expulsion of every single one of the larvae prevents that an adult does not develop in the lungs and occludes the bronchial tree. In addition, skin parasites such as *Sarcoptes scabiei* (the itch mite) is expulsed by a type 2 immune response-related eosinophilic dermatitis that initiates an itch-scratch axis. Opening of the epithelial barriers is an essential part of this type 2 immune response.

All of these mechanisms are followed up with a continuum of epigenetic regulation. The epithelial stem cells that are isolated from barrier leaky areas cannot make strong TJ barriers, which can be corrected by histone deacetylase inhibition [89]. In addition, histone acetylase activation has been reported in asthmatic bronchial epithelial cells [19]. Epigenetic regulation of epithelial

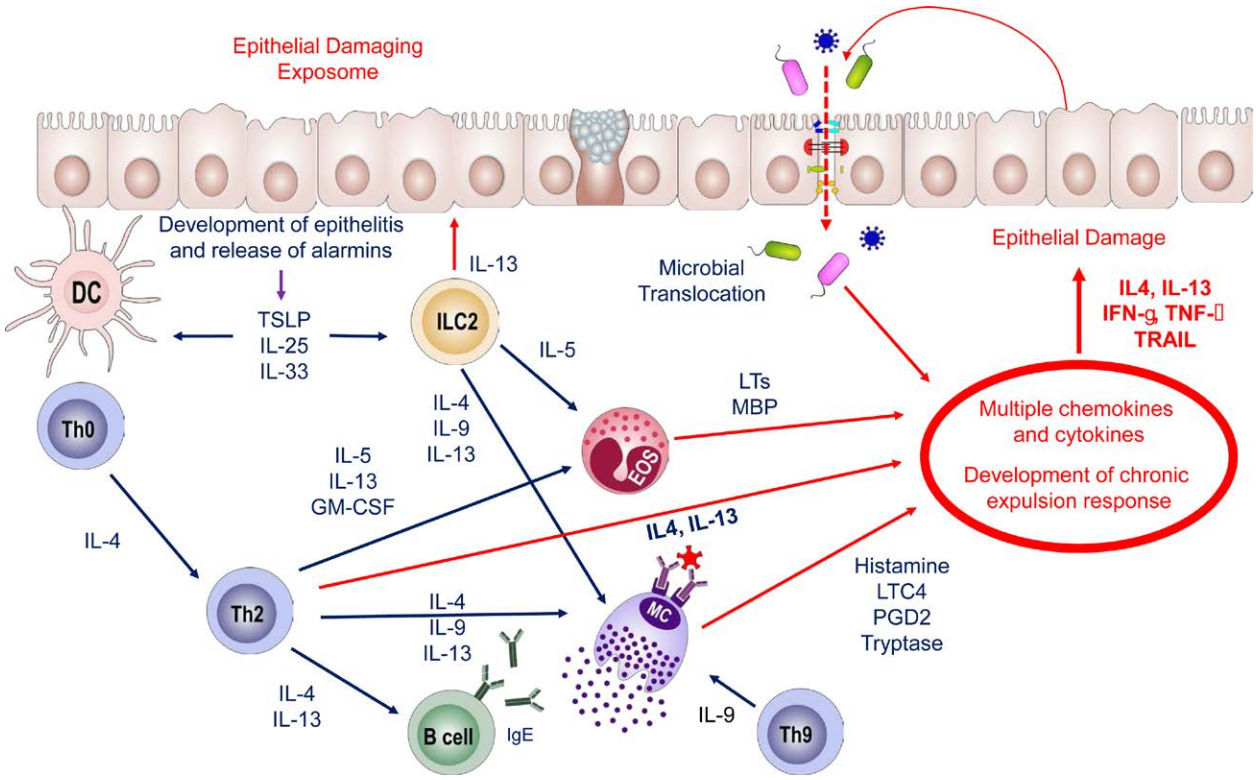

Figure 2. Immune mechanisms underlying epithelial barrier disruption. The epithelial barrier–damaging exposome disrupts epithelial barrier integrity, which is followed by development of epithelitis and release of alarmins. TSLP, IL-25, and IL-33 are secreted from the epithelial cells, and immune responses are triggered. At the same time, because of disruption of the epithelial barrier, microbial translocation is initiated. Following the differentiation of Th2 cells, type 2 cytokines including IL-4, IL-5, IL-13, and GM-CSF are produced, and B cells isotype-switch to IgE. Eosinophils and mast cells bind IgE, become potentiated thanks to the rich cytokine milieu and start producing their mediators such as LTs, MBP, and histamine, LTC4, PGD2, and tryptase, respectively. Th9 cells produce IL-9, which further potentiates the activity of mast cells. ILC2s produce type 2 cytokines and contribute to the cytokine milieu. The cytokines and mediators collectively initiate the development of a chronic expulsion response including IL-4, IL-13, IFN-γ, TNF-α, and TRAIL, and leads to further epithelial damage. DC, dendritic cell; EOS, eosinophil; GM-CSF, granulocyte colony-stimulating factor; IL, interleukin; ILC, innate lymphoid cell; LTs, leukotrienes; MBP, major basic protein; MC, mast cell; PGD, prostaglandin; TRAIL, TNF-related apoptosis inducing ligand; TSLP, thymic stromal lymphopoietin.

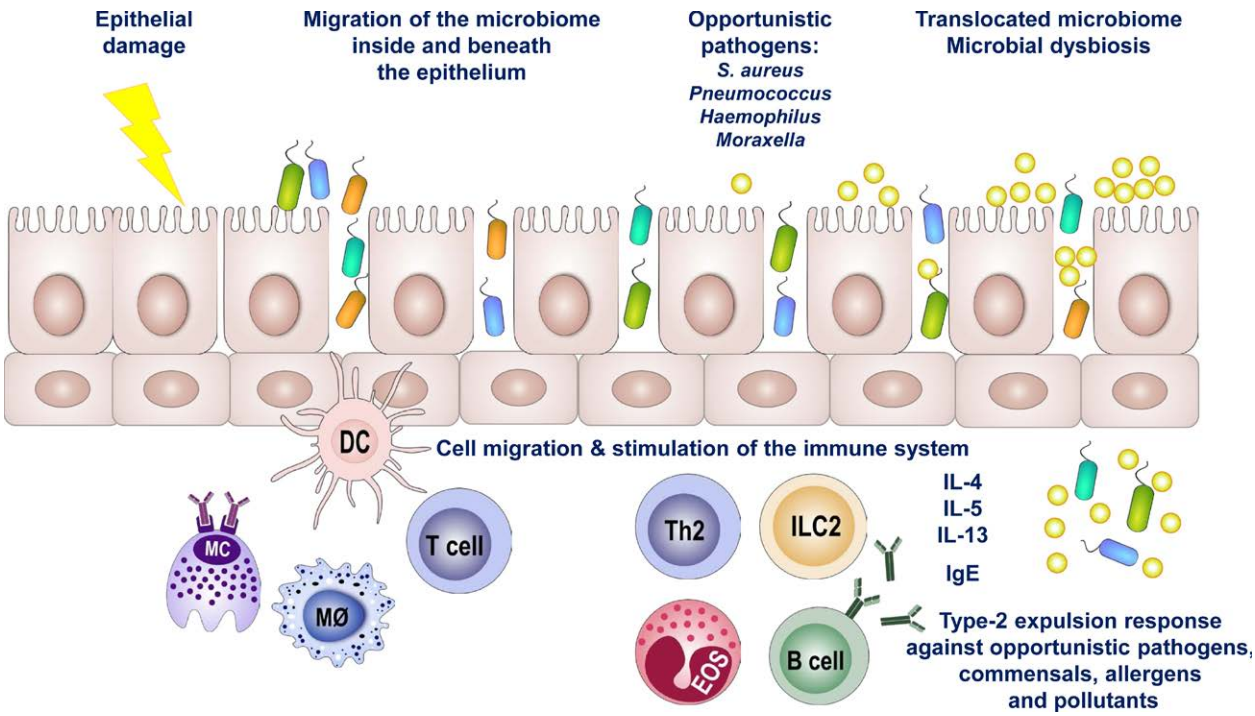

Figure 3. The expulsion response against microbiome and opportunistic pathogens. Following epithelial damage, microbiome migrates inside and beneath the epithelium, which consequently triggers cell migration and stimulation of the immune system. Activated immune cells including macrophages, DCs, mast cells, T and B cells, and ILCs migrate to the area and initiate a type 2 expulsion response with Th2 cells, IgE-producing B cells, ILC2, IL-4, IL-5, and IL-13 against opportunistic pathogens, commensals, allergens, and pollutants. The opportunistic pathogens include *Staphylococcus aureus, Pneumococcus, Haemophilus*, and *Moraxella*. The inflammatory response together with translocated microbiome and microbial dysbiosis leads to defects in epithelium repair, and misclosure of the barrier, which instigate a vicious cycle of leaky barriers and chronic inflammatory responses as well as microbial dysbiosis. DC, dendritic cell; EOS, eosinophil, IL, interleukin; ILC, innate lymphoid cell; MØ, macrophage; MC, mast cell.

barriers is the reason for chronicity and continuous epithelial barrier defects (**Fig. 4**).

3. Diseases related to barrier dysfunction

3.1. Allergic diseases

Allergic diseases have established links with epithelial barrier dysfunction [1, 12, 13, 26, 89–92]. Epithelial barrier integrity is important in sensitization to nonprotease allergens. The complex interaction between the skin epithelial barrier, the exposome, and immune cells is vital for understanding the AD pathogenesis [26, 27, 93, 94]. AD pathogenesis is related to TSLP activation of epithelium, dendritic cells, and macrophages that mainly induces Th2 cell differentiation. TSLP impairs epidermal barrier integrity by induced formation of nuclear IL-33/phosphorylated STAT3 complex in human keratinocytes [95]. RNA sequencing of tape-stripped skin samples from patients with AD demonstrated type 2 skewing and the downregulation of proteins related to barrier function, lipid biosynthesis, and metabolism [96]. Blocking IL-4 and IL-13 could be effective therapeutics for AD [97]. Following IL-4Rα blockade, barrier molecules were upregulated [98].

In asthma, defective epithelial barrier eases the entry of environmental toxins and aggravates exacerbations. Several studies demonstrate the role of exposure to environmental agents and the involvement of the immune system, and, therefore, the exposome paradigm can deliver a more ample risk profile in comparison with single predictors [1, 26, 27, 56, 82, 99]. Epithelial damage-initiated tissue environmental exposure leads to the production of IL-33; an alarmin of asthma [100]. IL-5 is an indispensable cytokine of allergic inflammation, whose receptor (IL-5R) expression was recently demonstrated on human airway epithelial cells [101]. IL-5 pathway-interfering biologicals could support barrier integrity by downregulation of eosinophils and their related epithelial barrier–damaging effects [102]. IL-13, a potent biomarker and key cytokine in the pathogenesis of asthma and CRS, alters claudin (CLDN) expression and induces TJ protein aggregation, leading to barrier leakiness [19, 92, 103–105].

Specific gut microbial taxa were shown to be correlated with asthma development [106, 107]. A lower abundance of anti-inflammatory metabolite-producing bacteria together with increased abundance of specific fungi could induce a type 2 immune response [106]. Certain pathogen-associated molecular patterns like lipopolysaccharide could protect against allergic diseases [108]. SCFA byproducts of bacterial fiber fermentation could weaken inflammatory responses. As an example, a mouse model revealed that vancomycin administration during pregnancy was related to the severity of asthma in offspring, which underlines the importance of SCFA in immune homeostasis [109]. On the contrary, respiratory syncytial virus infection can weaken the epithelial barrier integrity by alleviation of epithelial cell proliferation and wound-healing capacity [110, 111].

Functional disruption of the epithelial barrier was also found responsible in the pathogenesis of both allergic rhinitis (AR) and CRS [112]. Occludin, ZO-1, and several CLDNs were downregulated in patients with AR. Environmental and endogenous factors disrupt the integrity of TJs [113]. In addition, corticosteroid therapy upregulated expression of TJ proteins and improved barrier function in AR patients [114]. Inhibition of inflammatory cytokines reestablishes TJ protein expression, which has the capacity as therapeutic approaches. Mucin-1 deficiency leads to

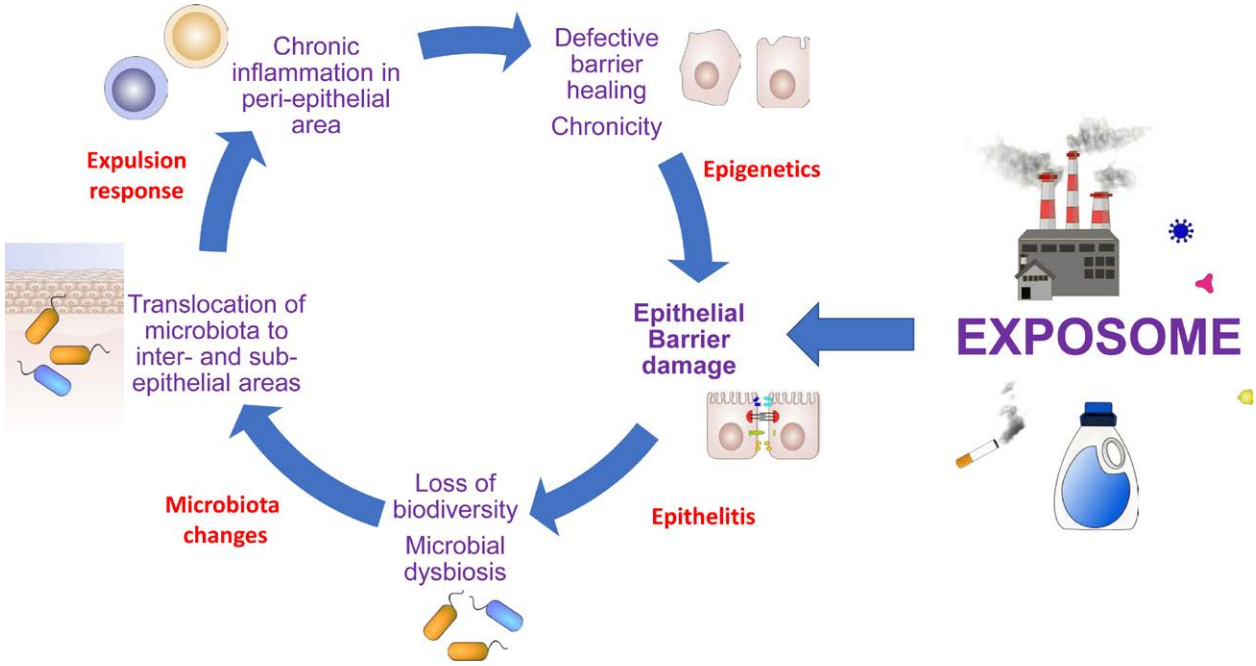

Figure 4. The vicious circle of chronic epithelial barrier dysfunction. Disruption of epithelial barriers are induced by exposome and damaging agents, which is facilitated by genetic defects in barrier-related molecules. Chronic inflammation in the periepithelial area leads to chronic, defective epithelial barrier healing and aggravates the damage. Epigenetics play role in defective barrier healing capacity, which in turn leads to epithelial barrier damage, and is termed as epithelitis. Then, loss of biodiversity and microbial dysbiosis end up with translocation of microbiota to inter- and subepithelial areas. An expulsion response is initiated, leading to chronic inflammation in the periepithelial area.

a decrease in CLDN-1 via RBFOX3 shortage, which acts to regulate the CLDN1 ubiquitin degradation. Nasal treatment with the inhibitor of ubiquitin-proteasome in mice limited the AR symptoms and restored nasal epithelial barrier function [115]. On the contrary, *Pseudomonas aeruginosa* exoproteins exerted damage to mucosal barriers in CRS and comorbid asthma patients [116]. The role of the local microbiome–host interactions in the pathogenesis of CRS still requires more investigation to be covered.

Food allergy results from interaction of environmental factors, epithelium, and host-immune responses [117]. Abnormal immune system maturation is associated with intensive hygiene, increased antibiotic use, c-section births, and reduced outdoor encounters. As a consequence, dysbiosis in skin and gut is promoted, all of which contribute to the development of atopy [118–120]. Food allergy could be initiated through the skin [118]. Viral infections, diet, vitamin supplementation, environment, and microbiome together with a damaged epithelial barrier all take part in both the development and prevention of the food allergies [121, 122]. A strong gut mucosal immunity requires diversification of the gut microbiome in early childhood and could protect against food allergy [123]. Butyrate, a SCFA in breast milk, acts as an anti-inflammatory metabolite. It is shown to prevent asthma development in mouse models and its increase can mitigate the childhood food allergy development risk [124–126]. In contrast, diminished levels of butyric acid-producing bacteria were reported in children with egg allergies [127]. Eosinophilic esophagitis (EoE) has a complicated pathology driven by genetic and intrinsic factors, environment, and antigen stimulation. Genes encoding the desmosome-associated proteins and periplakin control cell motility and barrier integrity and could lead to epithelial cell degradation in EoE [128]. IL-13 induces TJ dysfunction in EoE, leading to loss of barrier function [129].

3.2. Autoimmune and metabolic diseases

Compromised barrier integrity was also observed in other inflammatory disorders (**Table 2**). Autoimmune and metabolic diseases have epithelial barrier damage, which is followed by microbial dysbiosis and consequently affects many organs. In recent years, the gastrointestinal track is facing many harmful agents such as nanoparticles, emulsifiers, enzymes, nanoplastics, and many more, all of which account for intestinal barrier defects and an increase in intestinal permeability. Following intestinal barrier disruption, commensal bacteria infiltrate into tissues and stimulate the immunity. The leaky gut-induced dysbiosis triggers inflammation affecting the entire body and damages the intestinal mucosa [1, 26, 59–64].

TJ protein expressions such as occludin and CLDN in intestinal epithelium were downregulated in rheumatoid arthritis patients, while zonulin family peptide levels were significantly increased [141]. These features are complemented by a leaky intestinal barrier, inflammation, and dysbiosis. Gut barrier leakiness associated with rheumatoid arthritis could facilitate the inflammatory cell migration from the gut to the joints [141].

In celiac disease, diminished levels of sealing CLDNs, ZO-1, and occludin displacement in the cell membrane, together with small intestine structural defects, were observed [142]. Patients with celiac disease have a compromised oral epithelial barrier [143]. TJ integrity could be modulated by several microbial products. Butyrate enhances the TJ barrier by the hypoxia response, can diminish TNF-α, and increase TJ-related proteins [144].

Many studies aimed to illuminate the underlying mechanism of IBD with a focus on epithelial barrier dysfunction. Decreased ZO-1 expression has been reported in biopsy samples of patients with IBD [145]. In colitis, metformin as a therapeutic agent improved intestinal mucosal epithelial damage by decreasing the apoptosis of intestinal epithelial cells and increasing TJ proteins

Table 2.

Diseases in which epithelial barrier disruption has been linked to pathogenesis

Disease related to epithelial barrier disruption	References
Obesity	[130]
Nonalcoholic steatohepatitis	[131]
Liver cirrhosis	[87]
Multiple sclerosis	[132]
Systemic lupus erythematosus	[133]
Ankylosing spondylitis	[134]
Type 1 diabetes	[135]
Autism spectrum disorders	[136]
Parkinson disease	[137]
Alzheimer disease	[138]
Stress-related psychiatric disorders	[139]
Chronic depression	[140]

[146]. Investigation of quaking (QKI), an RNA-binding protein, in IBD and also in a mouse model of induced colitis revealed the binding of QKI to *keap1* mRNA under physiological conditions, and deficiency of QKI was reported to result in diminished antioxidative capacity, and together with increased reactive oxygen species production, this may end up with damage in intestinal epithelial barrier [147]. In relation to cytokine-induced changes in barrier permeability, the JAK-STAT signaling pathway has a vital role in IBD since JAK-STAT signaling pathways regulate the expression and localization of TJ proteins [148].

An important pathogenetic event in autoimmune diseases is the migration of inflammatory cells from barrier defective gut to distant organs [131–135]. Multiple sclerosis has been linked to air pollution in many studies [149]. In a recent study, it was reported in Stockholm that air pollution activates the immune cells in the lungs and that exacerbates multiple sclerosis, namely the brain migrating CCR6 expressing dendritic cells. In rheumatoid arthritis, a link to gut barrier defect has been shown very clearly [141].

There is also a growing body of evidence proposing that epithelial barrier dysfunction and permeability contribute to the pathogenesis of several chronic neurological and psychiatric disorders including Parkinson disease, Alzheimer disease, chronic depression, stress-related psychiatric disorders, and autism spectrum disorders [1]. As an example, a transgenic mouse model of Parkinson disease evaluated the influence of α-synuclein accumulation on the intestinal epithelial barrier in bowel inflammation. Increased caspase-1 activity and increased inflammatory markers were noted. These findings all together revealed increased intestinal barrier permeability and dysbiosis [150].

3.3. COVID-19 and the epithelial barrier theory

Epithelial barriers are vital in defense against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and solidification of this protection could be an important immunomodulatory strategy to prevent lung injury, systemic spread of the virus, and severe COVID-19 [151]. Epithelial cells express various SARS-CoV-2 receptors and related molecules, such as ACE2 [152]. SARS-CoV-2 infection compromises the barrier function of the nasal epithelium [153]. The barrier disruption in COVID-19 was attributed to the interaction between SARS-CoV-2 protein E and human ZO-1 protein [154]. Allergic diseases do not pose a predisposition to COVID-19 and could enhance the antiviral response, as lower number of severe cases were witnessed in atopic patients, with T lymphocytes less affected by SARS-CoV-2 [155, 156].

As a part of the epithelial barrier theory, air pollution, causing respiratory epithelial barrier dysfunction, may contribute to local chronic inflammation, microbiome dysbiosis, and impaired antiviral immune response against SARS-CoV-2, all of which contribute to the high incidence and excess mortality from COVID-19. This was observed at the beginning of the pandemic in Northern Italy. In addition, air pollution and epithelial barrier dysfunction contribute also to the higher prevalence of several comorbidities of COVID-19, such as diabetes, chronic obstructive pulmonary disease, and obesity, which can be identified as risk factors for severe diseases and mortality [157, 158].

4. Conclusions

Diseases related to the epithelial barrier theory have 5 common criteria: (1) they show increased prevalence in the last decades, which is not affected with the improved method of diagnosis; (2) they show epithelial barrier defect and epithelitis, which is characterized by the release of alarmins; (3) microbial dysbiosis with the loss of numbers and diversity of commensal bacteria and colonization of opportunistic pathogens is a common feature; (4) different and practically irrelevant diseases that fulfill these criteria appear in multimorbidities; and (5) they show increased inflammatory biomarkers in the circulation (circulating microinflammation).

Novel strategies for the prevention and treatment of allergic, autoimmune, and metabolic diseases require a thorough understanding of the underlying processes involved in epithelial barrier damage. Multiple immune regulatory mechanisms become dominant in leaky barrier areas to reduce the level of inflammation and avoid extensive tissue injury. Accordingly, the barrier hypothesis brings together several hypotheses that were proposed to explain the origins of allergic diseases. The biodiversity, hygiene, and old friends hypotheses are all associated with immune regulatory mechanisms, loss of biodiversity, and epithelial barrier leakiness.

The barrier hypothesis suggests a need for avoidance of the environmental cues and warrants further studies on safe levels of exposure to potentially harmful substances discussed here, such as inhaled and ingested detergents, ingestion of processed foods containing emulsifiers, exposure to PM, diesel exhaust, microplastics, and certain nanoparticles.

A comprehensive understanding of the barrier hypothesis is essential for the prevention, early intervention, and development of novel therapeutic approaches. Indeed, many treatment plans target protecting or repairing the epithelial barrier, such as avoidance of barrier-disrupting substances, development of safer products, identification of leaky barrier biomarkers, innovative treatments for reestablishing tissue-specific barrier elements, suppressing the colonization of opportunistic pathogens, dietary interventions, and microbiome-based therapies.

Conflicts of interest

CAA has received research grants from the Swiss National Science Foundation, European Union (EU CURE, EU Syn-Air-G), Novartis Research Institutes, (Basel, Switzerland), Stanford University (Redwood City, CA), Seed Health (Boston, USA) and SciBase (Stockholm, Sweden); is the Co-Chair for EAACI Guidelines on Environmental Science in Allergic Diseases and Asthma; Chair of the EAACI Epithelial Cell Biology Working Group; is on the Advisory Boards of Sanofi/Regeneron (Bern, Switzerland; New York, USA), Stanford University Sean

Parker Asthma Allergy Center (CA, USA), Novartis (Basel, Switzerland), Glaxo Smith Kline (Zurich, Switzerland), Bristol-Myers Squibb (New York, USA), Seed Health (Boston, USA), and SciBase (Stockholm, Sweden); and is the Editor-in-Chief of Allergy. MA has received research grants from Swiss National Science Foundation, Bern; research grant from the Stanford University; Leading House for the Latin American Region, Seed Money Grant. She is in the Scientific Advisory Board member of Stanford University Sean Parker Asthma Allergy Center (CA, USA); Advisory Board member of LEO Foundation Skin Immunology Research Center (Kopenhagen, Denmark); and Scientific Co-Chair of World Allergy Congress (WAC) Istanbul, 2022, Scientific Programme Committee Chair, EAACI. KN is the Director of the World Allergy Organization Center of Excellence for Stanford, Advisor at Cour Pharma, Consultant for Excellergy, Red tree ventures, Eli Lilly, and Phylaxis, Co-founder of Before Brands, Alladapt, Latitude, and IgGenix; and National Scientific Committee member at Immune Tolerance Network (ITN), and National Institutes of Health (NIH) clinical research centers, outside the submitted work; patents include "Mixed allergen composition and methods for using the same," "Granulocyte-based methods for detecting and monitoring immune system disorders," and "Methods and Assays for Detecting and Quantifying Pure Subpopulations of White Blood Cells in Immune System Disorders." The remaining authors declare no conflicts of interest.

Author contributions

Conceptualization: Umut Can Kucuksezer, Cevdet Ozdemir, Cezmi A. Akdis.
Formal analysis: Umut Can Kucuksezer, Cevdet Ozdemir, Cezmi A. Akdis.
Investigation: Duygu Yazici, Yagiz Pat, Yasutaka Mitamura, Manru Li, Na Sun, Paolo D'Avino, Xiangting Bu, Xueyi Zhu, Ismail Ogulur.
Project administration: Umut Can Kucuksezer, Cevdet Ozdemir, Cezmi A. Akdis.
Writing - original draft: Umut Can Kucuksezer, Cevdet Ozdemir, Cezmi A. Akdis, Ismail Ogulur.
Writing - review & editing: Umut Can Kucuksezer, Cevdet Ozdemir, Duygu Yazici, Yagiz Pat, Yasutaka Mitamura, Manru Li, Na Sun, Paolo D'Avino, Xiangting Bu, Xueyi Zhu, Mubeccel Akdis, Kari Nadeau, İsmail Ogulur, Cezmi A. Akdis.

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