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Involvement and therapeutic implications of airway epithelial barrier dysfunction in type 2 inflammation of asthma

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Abstract

Type 2 inflammation is a complex immune response and primary mechanism for several common allergic diseases including allergic rhinitis, allergic asthma, atopic dermatitis, and chronic rhinosinusitis with nasal polyps. It is the predominant type of immune response against helminths to prevent their tissue infiltration and induce their expulsion. Recent studies suggest that epithelial barrier dysfunction contributes to the development of type 2 inflammation in asthma, which may partly explain the increasing prevalence of asthma in China and around the globe. The epithelial barrier hypothesis has recently been proposed and has received great interest from the scientific community. The development of leaky epithelial barriers leads to microbial dysbiosis and the translocation of bacteria to inter- and sub-epithelial areas and the development of epithelial tissue inflammation. Accordingly, preventing the impairment and promoting the restoration of a deteriorated airway epithelial barrier represents a promising strategy for the treatment of asthma. This review introduces the interaction between type 2 inflammation and the airway epithelial barrier in asthma, the structure and molecular composition of the airway epithelial barrier, and the assessment of epithelial barrier integrity. The role of airway epithelial barrier disruption in the pathogenesis of asthma will be discussed. In addition, the possible mechanisms underlying the airway epithelial barrier dysfunction induced by allergens and environmental pollutants, and current treatments to restore the airway epithelial barrier are reviewed.

Keywords: Airway epithelial barrier; Type 2 inflammation; Asthma; Allergen; Environmental pollutants

Type 2 Inflammation and Its Role in Asthma

Asthma is a common chronic inflammatory airway disease affecting all ages with an estimate of more than 300 million cases all around the world, varying widely between different countries.[1] In China, the prevalence of asthma in individuals older than 20 years was 4.2%, according to a recently published nationwide survey.[2] Noticeably, the ongoing increase in the prevalence of allergic asthma contributes to the growing number of asthma patients.[3]

Type 2 inflammation has been described as the underlying immune responses driving allergic asthma.[4] Type 1 immunity is mainly regulated by $CD4^+$ T helper 1 cells (Th1), which secrete interleukin (IL)-2, interferon-γ and lymphotoxin-α. Th1 cells stimulate a type 1 immune response which is characterized by prominent phagocytotic activity. Type 2 inflammation originated as a response by the mucosal immunity against parasitic helminth infection that represents a very dedicated immune response to ameliorate the helminth burden in the tissues.[5] This type 2 cell-mediated immunity causes helminth expulsion or elimination, whilst simultaneously limits tissue injury, maintains tissue homeostasis, and contributes to regeneration and fibrosis.[6-8] Particularly, the expulsion response against helminth larvae represents all features of a full-blown type 2 immune response. An exciting series of molecular events to ensure the co-survival of the worm and the host are taking place. Löffler's pneumonia represents the basis for a type 2 immune response that was initially directed against *Ascaris*, hookworms, Toxocara and Schistosoma.[9,10] The life cycle of *Ascaris* infection is depicted in Figure 1. Similarly, an expulsion-like pathophysiology also occurs as an immune response to skin parasites, such as in scabies.[11]

Type 2 immunity is associated with a wide range of allergic diseases such as allergic rhinitis (AR), allergic asthma, and atopic dermatitis (AD).[5] In asthma, airway type 2

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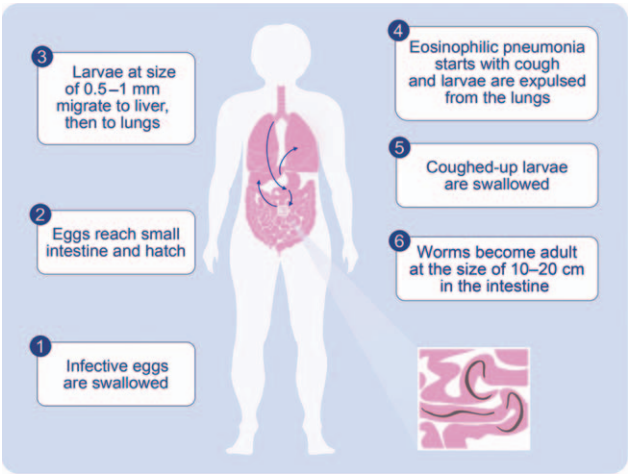

Figure 1: Life circle of *Ascaris* in human body and Löffler's pneumonia. *Ascaris* infection occurs when their fertilized eggs are ingested. The eggs hatch in the intestine, and the larvae migrate to portal veins and then pass through the vena cava inferior, right heart, pulmonary artery, and enter the lungs. The size of the larvae ranges between 0.5 and 1 mm. The growing larvae of the worms cause an eosinophilic pneumonia with cough, as initially described by Löffler. As an essential mechanism of survival of the host, every single larva should be expulsed from the lungs, before they become adults. Because in the case of *Ascaris*, an adult is 15–20 cm long, and there is no space in the lungs for the adult worms to accommodate their substantially large size, which becomes a big threat to the survival of both the host and parasite. Accordingly, the larvae are fully expulsed from the lungs and swallowed, where they find sufficient space in the guts to become adults.

inflammation is mediated by eosinophils, mast cells (MCs), basophils, $CD4^+$ T helper 2 cells (Th2), group 2 innate lymphoid cells (ILC2) and immunoglobulin E (IgE)-expressing memory B cells.[4] Type 2 immunity is mainly regulated by Th2 cells secreting IL-4, IL-5, and IL-13 and stimulating antibody production and eosinophilia.[4] Type 2 cytokines promote hallmark features of asthma with a type 2-high signature, such as eosinophilia, mucus hypersecretion, bronchial hyperresponsiveness (BHR), IgE production, and susceptibility to exacerbations.[12] Clinically, biological agents that target type 2 inflammation showed remarkable clinical efficacy in moderate to severe asthma.[13] Currently, five monoclonal antibodies against IgE (omalizumab), IL-5 (mepolizumab and reslizumab), IL-5 receptor α (benralizumab), and IL-4 receptor α (dupilumab) have been approved for the treatment of severe or refractory asthma, and function by blocking the type 2 inflammatory pathways.[14] Some potentially effective biologicals targeting upstream proinflammatory mediators, such as thymic stromal lymphopoietin (TSLP) and IL-33, are also under clinical trials.[15,16]

Epithelial Barrier Dysfunction and Allergic Diseases

Epithelial barrier dysfunction has been demonstrated to participate in the development of allergic diseases.[17] Structural and functional disruption of the airway epithelial barrier was found in inflammatory and allergic respiratory diseases, i.e., asthma, AR, and chronic rhinosinusitis.[18] Studies showed that epithelial damage in allergic asthma was associated with tight junction (TJ) defects and decrease of adherence junctions.[19-21] The expression of TJ molecules, such as occludin and zonula occludens (ZO)-1, decreased in AR patients compared with healthy controls, which was associated with disease severity.[22] It is well-known that skin barrier dysfunction is a fundamental feature in AD. Filaggrin (*FLG*) loss-of-function gene mutations are the strongest known genetic risk factor for AD.[23] FLG deficiency is associated with impairment of keratinocyte differentiation, reduced inflammatory thresholds to irritants and haptens, and enhanced percutaneous microbial and allergen penetration.[24-26] In addition to FLG mutations, TJ barrier dysfunction has also been reported in AD.[27] Skin barrier dysfunction and AD is associated with an increased risk of food allergy and allergic asthma, and transcutaneous exposure of food or airborne allergens increases the risk of sensitization.[28-30] Moreover, skin barrier injury can induce intestinal MC expansion through skin-to-gut axis mediated by IL-33, IL-25, and ILCs.[31] Subsequently, degranulation of MCs causes increased intestinal permeability and leads to enhanced sensitization to food allergens in the intestinal tract.[31] Therefore, the dysfunction of the epithelial barrier in the airway, skin, and gut is closely associated with allergic diseases.

The "Epithelial Barrier Hypothesis" proposes that increased exposure to epithelial barrier damaging agents linked to industrialization, urbanization, and modern life underlies the rise in allergic, autoimmune, and other chronic conditions.[17,32] It discusses whether the immune responses to dysbiotic microbiota that cross the damaged barrier are involved in the development of these diseases.[33] Almost two billion patients are affected with diseases which can be initiated or exacerbated with the exposure to epithelial barrier damaging agents.[34] The development of leaky epithelial barriers then leads to microbial dysbiosis and the translocation of bacteria to interepithelial and subepithelial areas and the development of tissue microinflammation [Figure 2]. Studies on the epithelial barrier suggest that these processes underlie not only the development of allergy and autoimmune conditions in barrier-damaged tissues but also a wide range of diseases in which an immune response to commensal bacteria and opportunistic pathogens occurs[17] [Figure 3].

Cellular and Molecular Components of the Airway Epithelial Barrier

The airway epithelium is a pseudostratified columnar structure composed of different types of cells. The predominant airway epithelial cells are ciliated epithelial cells, mucous-secreting goblet cells, airway basal cells, and club/clara cells;[35] and another three rare but specialized epithelial cells are neuroendocrine cells, solitary chemosensory cells, and ionocytes.[36,37] Airway basal cells are stem-cell-like progenitor cells that can differentiate to ciliated cells, mucus-secreting goblet cells, or other specialized epithelial cells.[38] Basal cells anchor the epithelium to the basal membrane via hemidesmosomes.[39] Ciliated epithelial cells originate from basal cells and/or club cells and contain abundant cilia that are necessary for the mucociliary clearance.[35] Mucus-secreting goblet cells are secretory cells that contain vesicles with tightly packed mucin granules and surfactant proteins.[40]

Club cells, also called clara cells, are nonciliated secretory cells differentiated from basal cells in small airways, which can secrete a specific protein belonging to the secretoglobin family (secretoglobin family 1A member 1, SCGB1A1).[41] When the epithelium is injured, club cells are able to differentiate into ciliated and mucus-secreting goblet cells driven by the intercellular junctional protein E-cadherin.[42] Neuroendocrine cells are located at airway branch points with allergens and other harmful substances accumulating, contain dense granules of various neuropeptides, amines, and neurotransmitters regulated by the sympathetic and parasympathetic nervous system and serve as airway chemoreceptors.[43,44] Solitary chemosensory cells contain an apical microvilli tuft, and the function and signal pathways of these cells are similar to intestinal tuft cells, which can regulate type 2 immunity and produce epithelial IL-25.[45,46] The recently identified ionocytes account for only 1% of airway epithelial cells and lie in multiple levels of the respiratory tract. These cells originate from basal cells and highly express the cystic fibrosis transmembrane conductance regulator (CFTR).[36] The inhibition of CFTR has been found to reduce ZO-1 expression and epithelial differentiation, which implies that ionocytes play a role in regulating TJ assembly and epithelial barrier function.[47]

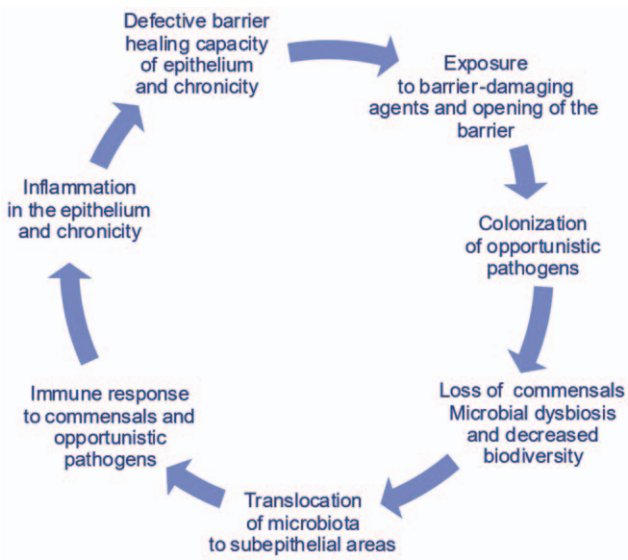

Figure 2: Fact circle of epithelial barrier hypothesis.

The chemical and physical barriers form the airway epithelial barrier function. Most exogenous substances are trapped in the mucus layer and cleared away by ciliary movements. The production and maintenance of the airway mucus is precisely regulated. It has been found that the balance between Muc5AC and Muc5B, major mucins secreted by goblet cells, can influence mucus viscosity, the ciliary beating and subsequently the likelihood of environmental molecules coming into contact with the airway epithelial cells.[48] On the other hand, the coordinated interaction between neighboring epithelial cells via cell-cell adhesion complexes is of great importance for the physical barrier function, including TJ, adherence junction, desmosome and hemidesmosome[49] [Figure 4]. These junctional structures not only build a physical barrier, but also play an important role in the regulation of epithelial permeability, cell proliferation and differentiation.[50]

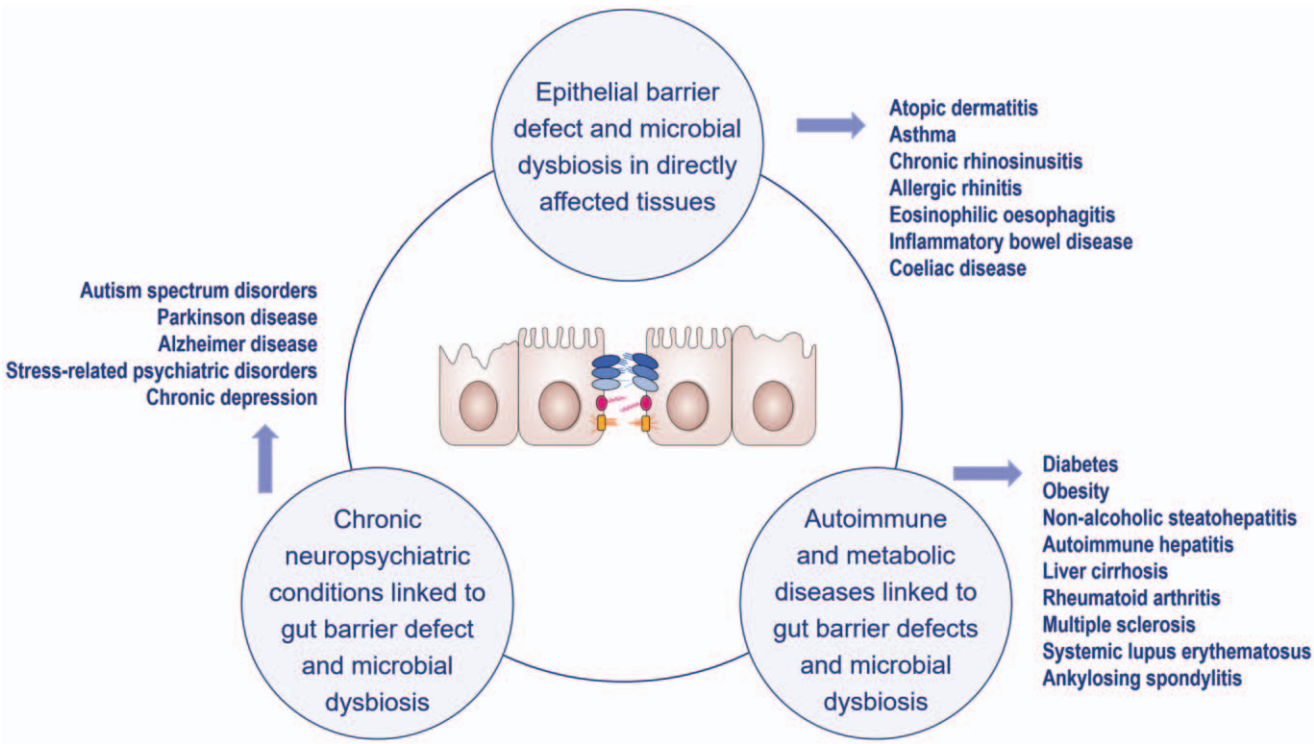

Figure 3: Conditions in which the pathogenesis is associated with epithelial barrier disruption.

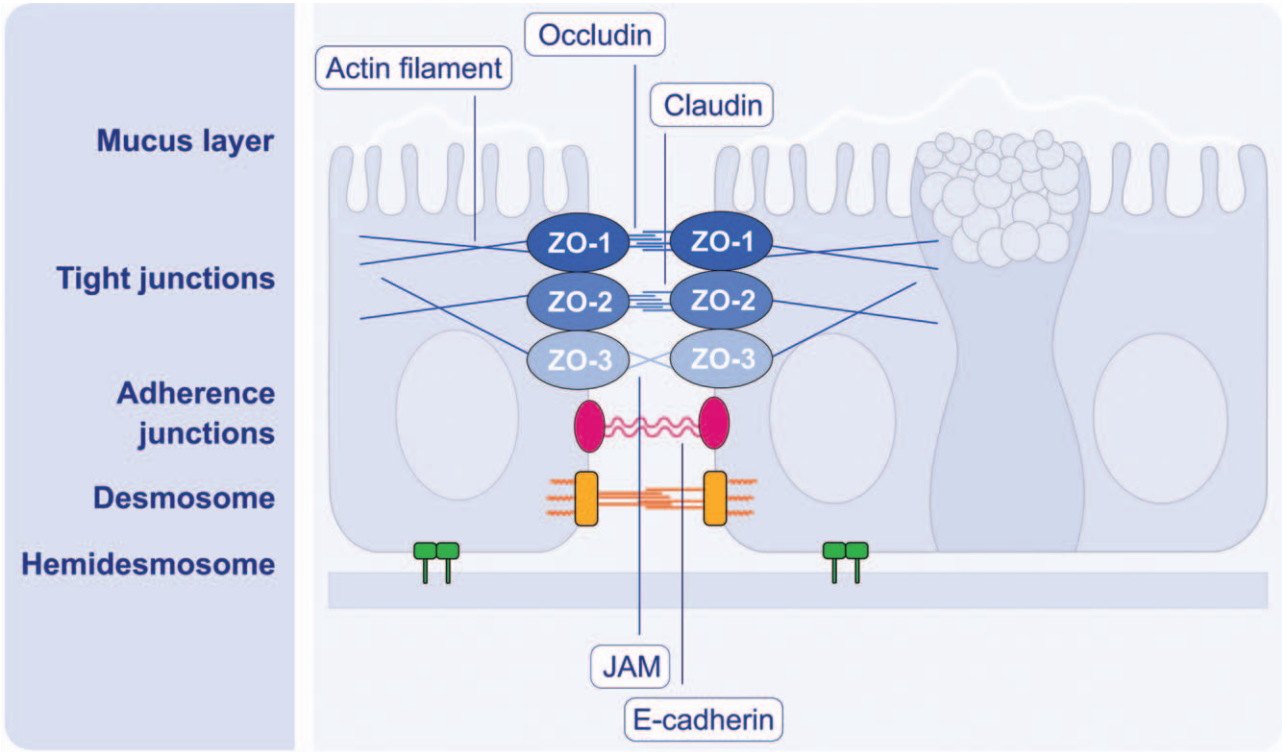

Figure 4: Schematic diagram of structure and molecular components of airway epithelial barrier. The mucus secreted by goblet cells forms the superficial mucus layer. The junctional structures between epithelial cells from the surface to base are tight junction (TJ), adherence junction (AJ), and desmosomes. TJs, located nearest to the epithelial surface, are key regulators of paracellular permeability depending on the size and ionize of molecules. TJs are constituted of transmembrane proteins including the claudin family (24 claudins), occludin, tricellulin, and junctional adhesion molecules, and the major TJ-associated cytoplasmic proteins are ZO-1, ZO-2, and ZO-3. AJs are located directly below TJs and composed of cadherin-catenin complexes. AJs provide intercellular adhesion to maintain epithelial integrity and perform multiple functions, such as initiation and stabilization of TJs, regulation of the actin cytoskeleton, intracellular signaling, and transcriptional regulation. Desmosomes are located around the midpoint of epithelial cells and contribute to the mechanical stability of airway epithelium due to their strong contact with the intermediate filaments. Hemidesmosomes make the epithelial layer attached to the basal membrane. JAM: Junction adhesion molecule; ZO: Zonula occludens.

Table 1: Methods to assess airway permeability and reflect epithelial barrier function.

Method	Sample-taking	Examination
Histology and/or cytology	Airway mucosal biopsy Bronchial brushing	Specific analysis of junctional structure and proteins
Permeability assay *in vivo*	Serum	Tracking the metabolism of radioisotopes (e.g., iodine 125 and technetium 99) or mannitol to reflect the permeability of airway epithelium
Biomarkers	Serum	Testing *in vitro* the levels of CC16, zonulin
Electrical impedance spectroscopy	None	Direct assessment *in vivo* of epidermal barrier function in previous studies, implying a potential method to examine the airway epithelial barrier

CC16: Club cell secretory protein-16.

Assessment of Epithelial Barrier Function

One of the direct implications of epithelial barrier damage is the increase in epithelial permeability leading to transepidermal water loss, which can be used as a measurable parameter for the assessment of epithelial barrier function. Although not available in routine clinical practice, some techniques can be used in research to evaluate epithelial permeability [Table 1]. For example, histological examination via airway mucosal tissue biopsy and/or cytological examination of epithelial cells can provide specific analysis of junctional structure and proteins, albeit it is an invasive method.[49] In addition, early studies have reported that compounds with traceable radioisotopes, e.g. iodine-125 and technetium-99, can be used to assess the permeability of the airway epithelium.[51,52] Mannitol, rarely metabolized and without radioactivity, was used in animal studies to evaluate the airway epithelial permeability.[53] However, a recent study showed no difference in serum mannitol levels between subjects with mild asthma and healthy controls after inhalation of mannitol.[54] Biomarkers for evaluating the epithelial barrier function are gaining research interest.

One such potential biomarker of airway epithelial damage is club cell secretory protein-16 (CC16).[55] Studies have demonstrated that the levels of CC16 in serum and bronchoalveolar lavage fluid were elevated in subjects exposed to asbestos and ozone.[56,57] Recently, zonulin, identified as pre-haptoglobin-2 (pre-HP2), was shown to modulate intercellular TJs and reversibly regulate epithelial permeability in the intestine.[58,59] Studies in mice also indicated the involvement of zonulin in respiratory tract epithelial barrier damage. Rittirsch *et al*[60] reported that zonulin facilitated the development of acute lung injury (ALI) by enhancing albumin leak and complement activation. In addition, zonulin inhibitor was found to exhibit protective effects on influenza infection and mitigate pulmonary edema in ALI,[61] and might be a potential therapy for coronavirus disease 2019 according to a recent *in silico* analytic study.[62] It has to be noted here that by using electrical impedance spectroscopy, skin barrier integrity can be detected within 8 seconds in a robust and reliable manner.[63,64] There is a current need for similar devices for the assessment of mucosal epithelia.

Common Allergens and Environmental Factors that Induce Airway Epithelial Barrier Dysfunction

Many different exogeneous factors can open the skin and mucosal epithelial barriers. It must be emphasized that the substances mentioned in this review may cooperate in opening the barriers in a synergistic way together with epithelial inflammation. Airway epithelial barrier damage can be caused by a number of allergens, microbes, and environmental substances [Figure 5]. Common aeroallergens, such as dust mites, pollens, and fungi, can disrupt the airway epithelium barrier. The cysteine proteinase allergen Der p1 from house dust mite (HDM), *Dermatophagoides pteronyssinus*, can directly cleave the TJ adhesion protein occludin. The disruption of intercellular TJs subsequently increases the permeability of the epithelial barrier and induces an immune response.[65] Saito *et al*[66] recently found that the amount of peroxisome proliferator-activated receptor γ coactivator-1 alpha (PGC-1α) and E-cadherin decreased significantly in HDM-stimulated cells. The HDM allergen disrupted the airway epithelial barrier function through the protease-activated receptor 2 (PAR2)/Toll-like receptor 4/PGC-1α pathway. Similarly, pollens often contain proteases, for example, serine proteases and metalloproteinases, which act on transmembrane adhesion proteins E-cadherin, claudin-1, and occludin, as well as the cytosolic complex ZO-1, and then damage intercellular TJs, the anchorage of columnar epithelial cells and the integrity of epithelial barrier.[67,68] Proteases of *Alternaria alternata* can also induce the disruption of the airway epithelial barrier.[69]

Importantly, increasing evidence indicates that exogenous noxious substances in the environment are risk factors for the airway epithelial barrier injury and leakiness, including cigarette smoke,[70,71] diesel exhaust,[72] ozone,[73] particulate matter,[74,75] nanoparticles,[76] microplastics,[77] detergents, surfactants, and proteolytic enzymes used in cleaning agents,[78-80] as well as emulsifiers in processed food.[81,82]

The skin epithelium is overwhelmingly exposed to toxic substances present in detergents and household cleaning products.[17] Increased use of detergents in general and the addition of surfactants to commercial detergents has significantly increased the daily exposure to tissue

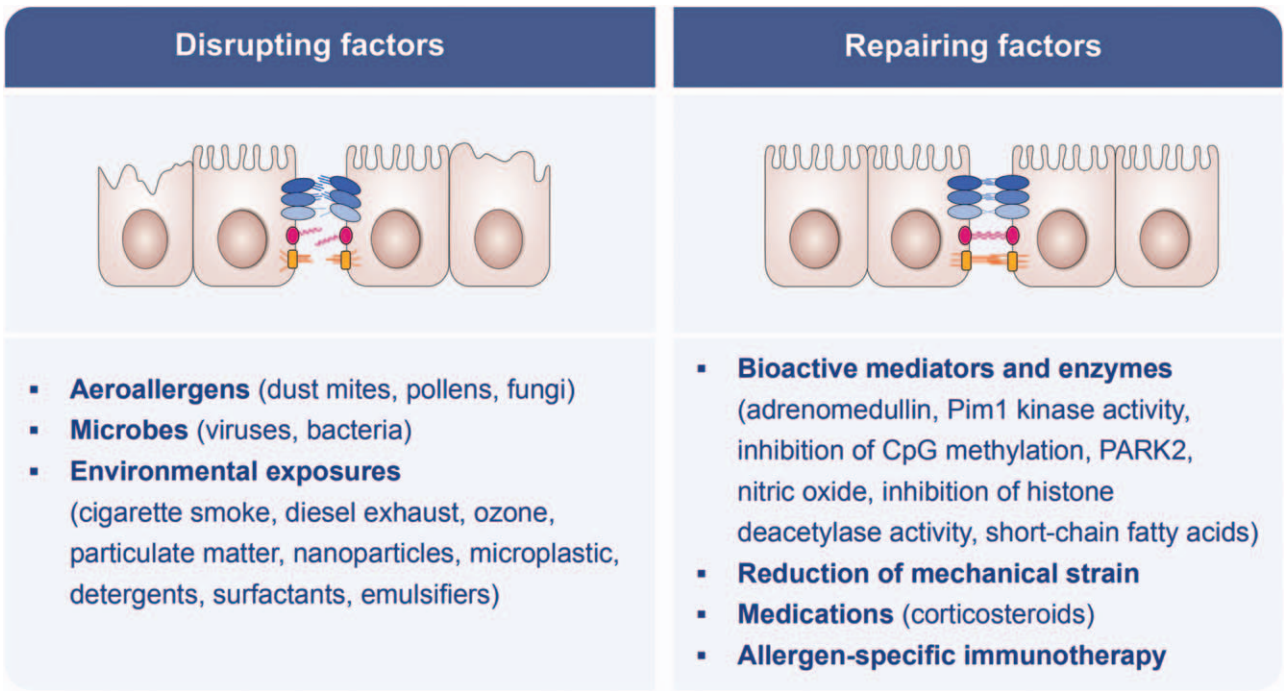

Figure 5: Disrupting and repairing factors for airway epithelial barrier. CpG: Repeated cytosine and guanine nucleotides linked with phosphate; PARK2: A Parkinson's disease-associated gene; Pim-1: Pim-1 proto-oncogene, serine/threonine kinase.

barrier-damaging substances.[83] An additional burden to the epithelial barrier was the introduction of proteolytic enzymes in washing powders in the mid-1960s to improve their cleaning efficiency.[84] Proteolytic enzymes derived from *Bacillus subtilis* have a direct disruptive effect on the airway epithelial barrier as observed in the development of asthma and rhinitis in employees of a detergent factory.[85,86] On the other hand, certain strains of *Bacillus subtilis* can serve as probiotics, regulating TJ proteins (ZO-1) and reducing death of intestinal epithelial cells.[87] A systematic review of epidemiological studies showed an association between exposure to cleaning products and asthma in four cross-sectional, longitudinal, and case-control studies.[88] Occupational allergies and asthma in the detergent industry have significantly decreased by adopting extensive measures and development of best practice guidelines focusing on exposure control in production facilities.[89] There has been extensive research on replacing nonbiodegradable products with more environmentally friendly and safer alternatives.[90] However, daily exposure to tissue barrier damaging doses of detergents and household cleaners continues today with the addition of household and professional dishwashers.

Viruses, such as rhinoviruses[91] and coronaviruses,[92,93] can disrupt TJs and epithelial barrier function, increasing epithelial permeability and viral invasion, and facilitating inflammatory reactions. A typical feature of chronic mucosal inflammation is the development of an immune response toward microbiome components or newly colonizing facultative pathogens, such as *Staphylococcus aureus* (*S. aureus*), moraxella, pneumococcus, hemophilus and *Pseudomonas aeruginosa*.[17,94] *S. aureus* is the most abundant bacteria that colonize barrier damaged tissues in the skin and respiratory mucosa. Increased colonization of *S. aureus* in the nose of asthma patients and increased serum levels of IgE against *S. aureus* enterotoxins have been repeatedly reported.[95-99] Prevalence of antibodies against *S. aureus* components has been linked to asthma severity and exacerbations.[97] *S. aureus* can enhance the TJ barrier integrity in nasal tissue in healthy individuals but not in nasal polyps.[100] *S. aureus* has also been shown to be dominant in skin microbiome of patients with AD, suggesting a role of this pathogen in skin barrier dysfunction.[101]

Role of Airway Epithelial Barrier Dysfunction in Type 2 Inflammation of Asthma

The development of asthma and respiratory allergies is a complex interaction between genes, immune system, and the environment whereby the airway epithelial barrier function plays a key role.[18,102] Airway epithelial damage leads to the loss of physical protection, facilitates the penetration of exogenous stimulants and allergens[103] and acts as an interface of innate and adaptive immunity.[104] Airway epithelial cells express pattern recognition receptors and detect environmental stimuli such as pathogens and allergens.[105] Epithelial barrier disruption has been the focus in understanding the pathogenesis of asthma with type 2 inflammation.[17]

Aeroallergens, virus, bacteria, and environmental toxins can impair the epithelial barrier and promote airway epithelial cells to release alarmins IL-25, IL-33, and TSLP, as well as chemokines C-C motif chemokine ligand 2 (CCL2) and CCL20.[105] The alarmins can induce the differentiation of ILC2, which then releases type 2 cytokines IL-5 and IL-13. CCL2 and CCL20 can recruit immature dendritic cells (DCs) and monocytes, the precursors of DCs, to the lungs.[106,107] Epithelial cytokines IL-25, IL-33, and TSLP favor the development of a proallergic DC phenotype.[108] Activated DCs act as antigen presenting cells and migrate to the draining lymph node where they induce the differentiation of naïve T cells to Th2 cells. The interactions between the airway epithelial cells, DCs and the regional lymph node provide a cytokine milieu for Th2 cell differentiation.[108] IL-4 produced by basophils, together with IL-4 and IL-21 produced by follicular helper T cells, promotes immunoglobulin class switch to IgE in B cells. Effector cells including MC, basophils, and eosinophils are activated, degranulate, and release inflammatory mediators upon being re-exposed to allergens. IL-4 and IL-13 are cardinal type 2 cytokines and central to many aspects of airway changes in asthma, e.g., directly participating in type 2 inflammation, disrupting the epithelial barrier function, acting on basement membrane, and promoting airway remodeling. Therefore, a vicious cycle composed of IL-4, IL-13, epithelial barrier impairment, and type 2 inflammation has been suggested in asthma.[106] In addition, airway epithelial barrier damage will also enhance permeability to foreign substances including allergens,[109] which are uptaken, processed, and presented by DCs and initiate adaptive immune responses.[110] A recent study showed that allergen-induced degranulation of MCs was only observed in those with injured nasal epithelia, and epithelial barrier dysfunction promoted transepithelial allergen passage, sensitization, and MC degranulation even in the absence of an inflammatory condition.[111] In return, MC mediators could rapidly increase epithelial permeability, which facilitated allergen penetration again.[112] Moreover, airway epithelial barrier function can maintain the balance of immunomodulation. Restoring the epithelial barrier integrity reduced inflammation in models of Th2-mediated respiratory inflammation.[113] In a mouse model, the activation of MCs was elevated when the epithelial barrier was disrupted.[50] It is speculated that nasal epithelial barrier dysfunction is one of the crucial risk factors in the inflammatory progression from upper to lower airways.[114] Thus, airway epithelial barrier dysfunction may represent a cardinal pathophysiological mechanism of type 2 immunity. The physical barrier injury, allergic sensitization, and immunological dysregulation resulted from airway epithelial barrier disruption and dysfunction participate in the pathogenesis of asthma and respiratory inflammatory diseases [Figure 6].

Molecular Mechanisms Underlying the Disruption of Airway Epithelial Barriers

Currently, the precise underlying mechanisms leading to airway epithelial barrier disruption in asthma are under extensive research. Different mechanisms may be involved for the various damaging factors of the epithelial barrier, such as allergens, bacteria, virus, particulate matter, and other environmental pollutants.[34,115] Many allergens possess protease activity, which acts on protease-activated receptors (PARs) and induces airway epithelial barrier impairment. HDM allergens were reported to induce

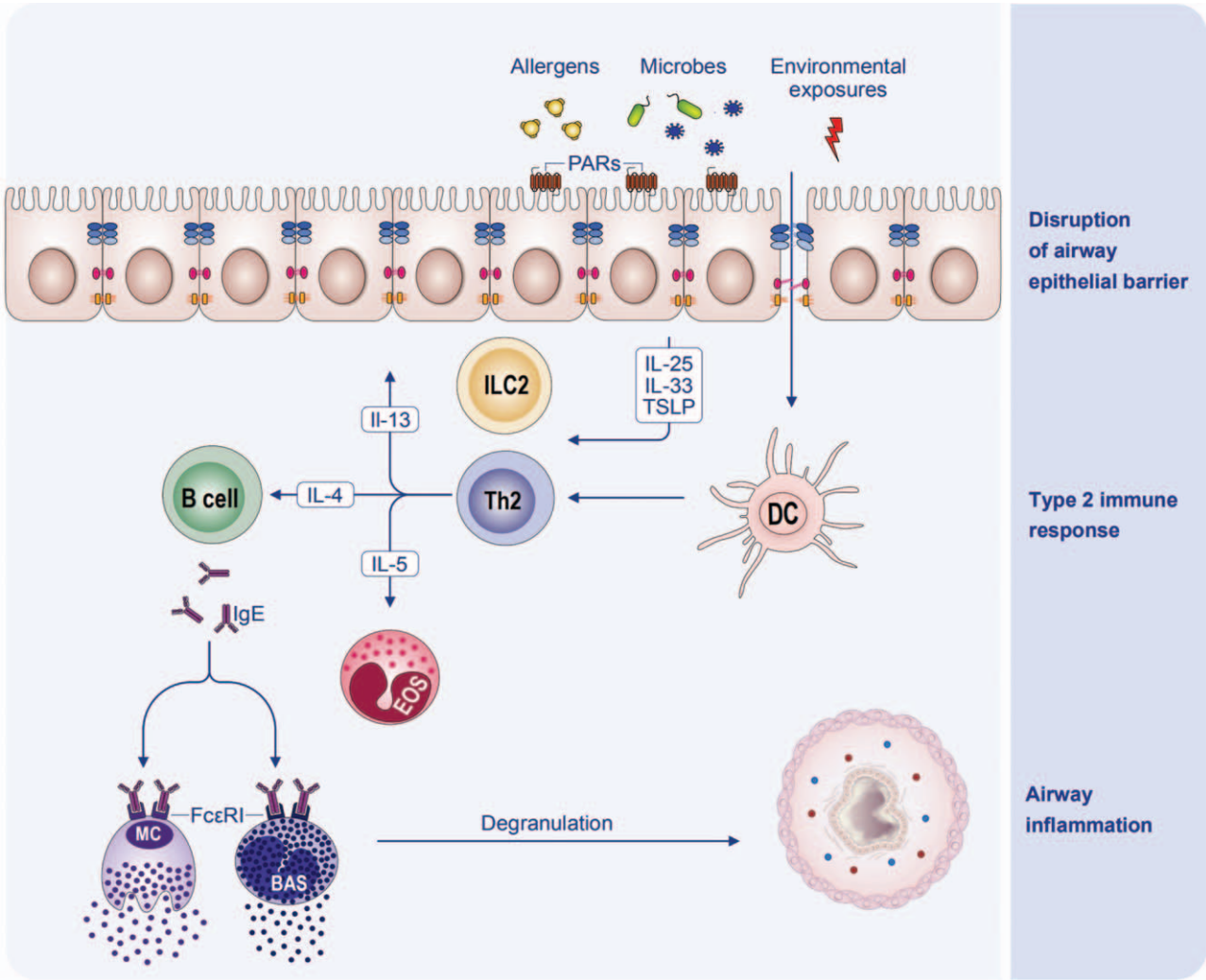

Figure 6: Schematic diagram of the interaction of type 2 inflammation and airway epithelial barrier in asthma. BAS: Basophil; DC: Dendritic cell; EOS: Eosinophils; FcεRI: High-affinity receptor for IgE; IgE: Immunoglobulin E; IL: Interleukin; ILC2: Group 2 innate lymphoid cell; MC: Mast cell; PARs: Protease-activated receptors; Th2: T helper 2 cell; TSLP: Thymic stromal lymphopoietin.

airway epithelial barrier dysfunction via proteolytic activity.[65] However, another report showed that HDM-induced airway inflammation and hypersensitivity was dependent on allergen sensitization but not to serine/cysteine protease activity, since HDM extract with the lowest serine protease activity still induced the most pronounced dysfunction of the epithelial barrier and CCL20 release *in vitro*.[116] Another study also demonstrated that inhalation of HDM allergens did not induce impairment of the airway epithelial barrier.[117] As non-allergic individuals mostly tolerate allergen exposure without or only with mild symptoms, mechanisms other than allergen-specific MC degranulation may have a relatively minor effect. It is suggested that HDM-induced PAR activation and epithelial barrier disruption depended on epidermal growth factor receptor (EGFR) signaling since EGFR inhibition reduced the HDM-triggered decrease in epithelial resistance and improved restoration of epithelial junctions.[118] Mitochondrial biogenesis and heat shock protein 90α have also been demonstrated to participate in HDM-induced airway epithelial barrier dysfunction with distinct signaling pathways.[66,119] Allergenic fungus *A. alternata* possesses serine protease activity and induces barrier disruption of airway epithelium in severe asthma patients.[69] German cockroach induced Ca^{2+} release from intracellular Ca^{2+} store by acting on PAR2 in the airway epithelium.[120] In addition, cockroach and HDM extracts also activated store-operated Ca^{2+} entry and thus sustained intracellular Ca^{2+} elevation in the airway epithelium,[121] which triggers proinflammatory cytokines release and airway epithelial barrier dysfunction.[122] Tumor necrosis factor (TNF)-α was shown to induce bronchial epithelial barrier dysfunction by activating Src-family kinase in severe asthma.[123]

The impact of type 2 cytokine IL-13 on epithelial barrier dysfunction has been well-established in air-liquid interface (ALI) cultures of bronchial epithelial cells and mouse models of lung inflammation.[124,125] IL-13, released both by ILC2 and Th2 cells, was shown to induce airway epithelial barrier disruption by targeting TJs in asthmatic patients.[124,125] By contrast, another study demonstrated that IL-13 plays an important role in restoration of airway epithelial barrier via IL-13 receptor α2.[126]

In addition to directly affecting TJ molecules in the epithelia, several programmed cell death processes have been suggested to contribute to airway epithelial barrier dysfunction. Both pyroptosis[127,128] and apoptosis[129] have been demonstrated to play a possible role in the airway epithelial barrier dysfunction and airway inflammation.[130,131] Similarly, ferroptosis and autophagy,[132] and their interactions[133] have also been suggested to contribute to airway epithelial barrier dysfunction in asthma. Particulate matter and respiratory syncytial virus-induced necroptosis of airway epithelial cells contribute to airway inflammation.[134,135] However, the role of necroptosis in airway epithelial barrier impairment needs to be clarified further.

Restoration of the Airway Epithelial Barrier

Epithelial barrier impairment is central to the pathogenesis of airway inflammation and may also be linked with severity and control of asthma, therefore, restoration of the barrier integrity may be a useful strategy in the treatment of asthma [Figure 5]. Deoxyribonucleic acid containing repeated cytosine and guanine nucleotides linked with phosphate (CpG DNA) treatment exhibited a barrier healing capacity *in vitro*.[136] Reduced adrenomedullin expression in airway epithelial cells was observed in asthma patients, and supplementation with adrenomedullin could promote airway epithelial wound repair.[137] It is reported that Pim1 kinase activity is essential to maintaining airway epithelial integrity and protects against HDM-induced proinflammatory cytokine secretion from airway epithelium.[138] Inhibition of CpG methylation was found to improve the integrity of the bronchial epithelial barrier in asthma.[139] Parkinson's disease-associated gene could also protect against HDM-induced airway epithelial barrier impairment by attenuating epithelial cell pyroptosis.[127] Nitric oxide promoted airway epithelial wound repair through increasing the activity of matrix metalloproteinases 9.[140] As also shown *in vitro* in bronchial epithelial cells,[125] inhibition of histone deacetylase activity could restore nasal epithelial integrity and prevent the development of allergic airway inflammation in patients with AR.[141] Therefore, further studies are warranted to provide evidence of the potential use of histone deacetylase activity inhibitors to restore the bronchial epithelial integrity in asthma patients. Mechanical strain inhibited airway epithelial repair as demonstrated in *in vitro* cultured epithelial cells,[142] thus maintaining well-control of asthma may reduce mechanical strain induced by hyperinflation secondary to airflow limitation.

As to the currently available treatments for asthma, corticosteroid dexamethasone was able to restore the expression of E-cadherin and beta- and gamma-catenin that was inhibited by TNF-α, as demonstrated in primary human bronchial epithelial cells.[143] A few studies demonstrated a protective effect of long-acting beta-agonists (LABA) on the airway epithelial barrier.[144,145] Montelukast could suppress cysteinyl leukotriene-induced disruption of TJs and adherence junctions (AJs) in human airway epithelial cells.[146] Allergen-specific immunotherapy (AIT) was also able to restore airway epithelial integrity that was damaged in mice exposed to HDM component Der f through inhibition of IL-25 expression and endoplasmic reticulum stress.[147] The effect of biologicals, such as anti-IgE, anti-IL-5/R, and anti-IL-4Rα monoclonal antibodies on airway epithelial barrier dysfunction in asthma patients, is not fully understood. Short-chain fatty acids propionate and butyrate were also capable of restoring HDM-induced bronchial epithelial barrier dysfunction and have been suggested for the potential treatment of asthma.[148] Even though there is limited evidence on the potential of probiotics in restoring the airway epithelial barrier integrity, a study showed a decrease in airway epithelial permeability in both animal models and *in vitro* cultured bronchial epithelial cells.[149]

Prospects

It should be noted that the airway epithelial barrier integrity is dynamically regulated by disrupting and repairing factors, both of which may coexist simultaneously. To date, most studies focus only on disruption or restoration of the barrier. Studies aiming to elucidate the imbalance between disruption and repair under different exposomes and its impacts on type 2 inflammation with state-of-the-art techniques will be of great importance to the development of new diagnostic and therapeutic strategies for asthma. A better understanding of the epithelial barrier hypothesis is needed for the prevention, early intervention, and development of novel therapeutic approaches.[17] Possible strategies to reduce diseases associated with a disrupted epithelial barrier include: avoidance and dose control of all of the above-mentioned noxious substances; development of safer, less-toxic products; discovery of biomarkers for the identification of barrier leaky subjects; development of novel therapeutic approaches for restoration of the expression of tissue-specific barrier molecules; strengthening other components of the mucosal barrier; blocking bacterial translocation; avoiding the colonization of opportunistic pathogens; interventions through diet and microbiome, and many more novel approaches. In addition, an international network has been initiated together with the development of the European Academy of Allergy and Clinical Immunology guidelines on environmental health, and a working group to target epithelial barrier related research, education, and communication to outreach regulatory authorities has been recently taken off[150] [Table 2].

In summary, future studies are warranted to understand: (1) the imbalance between impairment and repair of the airway epithelial barrier; (2) the molecular components of different aeroallergens responsible for the induction of airway epithelial barrier damage; (3) exposomes including virus, bacteria, fungi, particulate matter, microplastics, and their interactions and contributions to airway epithelial barrier damage; (4) biomarkers of airway barrier dysfunction in asthma; (5) novel strategies to repair the airway epithelial barrier. Researches focusing on the interactions of airway epithelial barrier dysfunction and type 2 inflammation in the context of asthma will be helpful to find novel therapeutic targets for asthma. Adoption of state-of-art techniques such as single-cell sequencing, proteomics, airway organoids, Visium spatial

Table 2: The aims of EAACI working group targeting epithelial barrier related research, education and communication.

Items	Contents
A	Coordination of research and education on the **avoidance and dose control of all of the toxic substances**
B	Coordination of research and education for the **development of safer, less-toxic products**
C	Coordination of research and education on the **discovery of biomarkers for the identification of individuals with a leaky epithelial barrier**
D	Coordination of research and education on the development of **novel therapeutic approaches for strengthening the tissue-specific barriers**
E	Coordination of research and education on understanding the **changes in microbiome on epithelial barrier leaky areas, bacterial translocation, decreased biodiversity, colonization of opportunistic pathogens**
F	Coordination of research and education on **treatments and interventions through diet and the microbiome**
G	Development of educational content on **epithelial cell biology**
H	Development of **Schools and Focused Meetings** on Epithelial Cells and Microbiome
I	**Collaborative work with research groups from** Immunology, Asthma, Pediatrics, Dermatology and ENT and **Interest Groups** of Aerobiology, Biologicals
J	**Lobbying in throughout the whole world** to have international projects and in the area

EAACI: European Academy of Allergy and Clinical Immunology; ENT: Ear, nose and throat.

imaging together with immunology and animal models will facilitate these studies.

Conclusions

The epithelial barriers of the skin, upper and lower airways, and gut mucosa have been severely impacted by the rapid change in the environment caused by industrialization, urbanization, and westernized lifestyle. The development of leaky epithelial barriers leads to the dysbiosis and translocation of microbiota to inter- and subepithelial areas, and the development of tissue micro-inflammation. Epithelial barrier dysfunction contributes to the development of type 2 inflammation in asthma, which then in turn aggravates barrier dysfunction. Allergens, bacteria, viruses, and environmental pollutants could cause epithelial barrier dysfunction by different mechanisms, such as proteases, Ca^{2+} signaling and programmed death of airway epithelial cells. Most currently available treatments for asthma, such as corticosteroids, LABA, montelukast, and AIT, are able to restore airway epithelial integrity. The interplay between the epithelial barrier and type 2 inflammation in asthma, as well as therapies aimed at regulating this balance is a promising field to be further explored.

Conflicts of interests

None.

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