

# The Role of Defective Epithelial Barriers in Allergic Lung Disease and Asthma Development

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**Abstract:** The respiratory epithelium constitutes the physical barrier between the human body and the environment, thus providing functional and immunological protection. It is often exposed to allergens, microbial substances, pathogens, pollutants, and environmental toxins, which lead to dysregulation of the epithelial barrier and result in the chronic inflammation seen in allergic diseases and asthma. This epithelial barrier dysfunction results from the disturbed tight junction formation, which are multi-protein subunits that promote cell-cell adhesion and barrier integrity. The increasing interest and evidence of the role of impaired epithelial barrier function in allergy and asthma highlight the need for innovative approaches that can provide new knowledge in this area. Here, we review and discuss the current role and mechanism of epithelial barrier dysfunction in developing allergic diseases and the effect of current allergy therapies on epithelial barrier restoration.

**Keywords:** bronchial epithelial cells, asthma, allergy, tight junction, inflammation

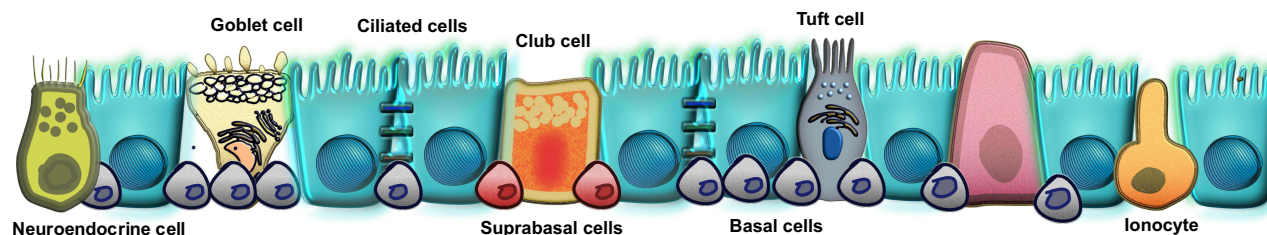
## Introduction

The human respiratory system consists of the nasal cavity, trachea, respiratory bronchioles, and distal alveoli, and it is linked together with the cardiovascular system to accomplish gas exchange.<sup>1,2</sup> The integral component in maintaining this process is a continuous layer of epithelial cells, which has a central role in defending the lungs against inhaled environmental factors. Airway epithelial cells are continuously exposed to several environmental factors and allergens, which are then cleared by the immune system. Mucociliary clearance is mediated by the actions of diverse conducting airway and secretory cells, such as goblet cells, and the mucous and serous cells in the submucosal glands. They secrete fluids, electrolytes, antimicrobial and anti-inflammatory proteins, and mucus onto airway surfaces and therefore play a critical role in protecting the lungs during an acute injury.<sup>3</sup> The continuous exposure of bronchial epithelium to external and internal factors causes structural, protein and genetic changes, which contribute to the development of allergy and asthma. Several treatments for asthma and allergy symptoms are currently available for patients but there are also novel possible therapies and studies, that are aimed at improving the impaired epithelial barrier.

## Structure of Bronchial Epithelial Cells

The airway epithelium is pseudostratified in the large airways and becomes columnar and cuboidal in the small airways. It consists of the predominant ciliated epithelial cells, mucous-secreting goblet cells, club cells, airway basal, suprabasal cells and rare cell types such as neuroendocrine cells, ionocytes, Hillock cells, and tuft cells (Figure 1, Table 1).<sup>4-6</sup> Epithelial cells form a barrier between neighboring cells via junctional complexes which consist of apical tight junctions (TJs), adherens junctions (AJs), and desmosomes (Figure 2).<sup>7,8</sup> TJs form a border between the apical and basolateral plasma-membrane domains, which controls cell polarization, transcription, growth, and differentiation. They are critical regulators of paracellular permeability and limit the transport of macromolecules.<sup>9-11</sup> Approximately 40 different proteins have been identified as TJ components, and these include the main transmembrane proteins belonging to the

### Epithelial cells repertoire



**Figure 1** Bronchial epithelial cells repertoire. Common cell types: basal cells, suprabasal cells, goblet cells, club cells (Clara cells) and ciliated cells. Rare cell types: neuroendocrine cells, ionocytes, Hillock cells and Tuft cells (brush cells). Created with [affinity.serif.com](https://affinity.serif.com).

claudin family (26 members in humans and 27 in mice) and the three junctional MARVEL (MAL and related proteins for vesicle trafficking and membrane link) domain proteins: occludin, tricellulin and MARVELD3 that regulate the recruitment of signaling complex proteins to TJs.<sup>8,12–14</sup> Other transmembrane TJs include junctional adhesion molecules (JAMs), coxsackievirus and adenovirus receptor and angulins (also known as lipolysis-stimulated lipoprotein receptors).<sup>8,15,16</sup> The zonula occludens (ZO)-1, ZO-2, and ZO-3 cytoplasmic molecules bind directly to occludin and claudin on one end while also linking to actin fibers on the other end, which is essential for the epithelial barrier function. Several other proteins are located in the cytoplasm, such as multi-PDZ domain protein-1 (MUPP1), cell polarity molecules ASIP/PAR-3, PAR-6, PALS-1, and PALS-1-associated tight junction (PATJ); and non-PDZ proteins, cingulin, symplekin, ZONAB, GEF-H1, aPKC, PP2A, Rab3b, Rab13, PTEN, and 7H6.<sup>17,18</sup> Multiple protein interactions couple the extra- and intracellular signaling that allows the complexity and plasticity of TJ function.<sup>13,19</sup>

AJs are cadherin-catenin adhesion complexes located below TJs and have an important role in tissue homeostasis, stabilization, and transcriptional and intracellular signaling.<sup>20</sup> Cadherin adhesion molecules are core AJ components.<sup>21</sup> The cytoplasmic tail of classic cadherin binds to the catenins, which allows for links to cytoskeletal networks as well as to the exocytotic and endocytic machinery. Crosstalk between cadherin–catenin clusters and actin regulators controls AJ assembly from initial cell–cell contacts.<sup>20</sup> Gap junction proteins (GJs), connexins, which are expressed in different types of cells in the lung tissue, coordinate ciliary beat frequency, enable the direct flow of signaling molecules and metabolites between cells, and regulate inflammation.<sup>22</sup> Desmosomes are specialized adhesive protein complexes responsible for maintaining the mechanical integrity of tissues.<sup>24</sup> They may also act as signaling centers, regulating the availability of signaling molecules and participating in fundamental processes such as cell proliferation, differentiation, and morphogenesis.<sup>25</sup> Desmosome composition and size vary depending on tissue-specific expression and differentiation state. Their constituent proteins are highly regulated by post-translational modifications that control their function in the desmosome itself and regulate many desmosome-independent functions.<sup>26</sup>

All these components of airway epithelium, besides their specific functions, closely interact with each other to form and maintain the epithelial cells' polarity from the apical and basolateral sides.<sup>19</sup> It was shown that TJs proteins like ZO-1, which are distributed in AJs and GJs, interact with their proteins like E-cadherin (AJs) and certain connexins (GJs). Such interactions are important for transmitting signals between intracellular junctions and inner cells.<sup>19,27–29</sup> Furthermore, the association between a cadherin and plakoglobin, the only known component of desmosomes and AJs, is essential for desmosomes formations.<sup>30</sup> The flexibility of cadherin molecules was shown to have an impact on desmosomes plasticity on strong calcium-independent hyper adhesion in adult tissues and on weaker calcium-dependent adhesion in wounds.<sup>31</sup> The proper function and homeostasis of airway epithelial cells works through the cooperation of junctional complex molecules.

## What Causes Epithelial Barrier Damage?

Airway epithelial cells are an essential part of the innate immune system in the lung. They are susceptible to damage due to exposure to allergens with complex proteolytic activity like house dust mite (HDM) (Der p 1, Der p 3, Der p 6, Der p 9), pollen (Ragweed pollen, Amb a, Birch pollen, Bet v), fungi (*Aspergillus fumigatus* and *Aspergillus oryzae*, Asp f 5, Asp f 6, Asp f 11), cockroaches (Bla g) and also animal dander and pathogens.<sup>32–34</sup> Allergens with a protease activity

**Table I** Types of Bronchial Epithelial Cells

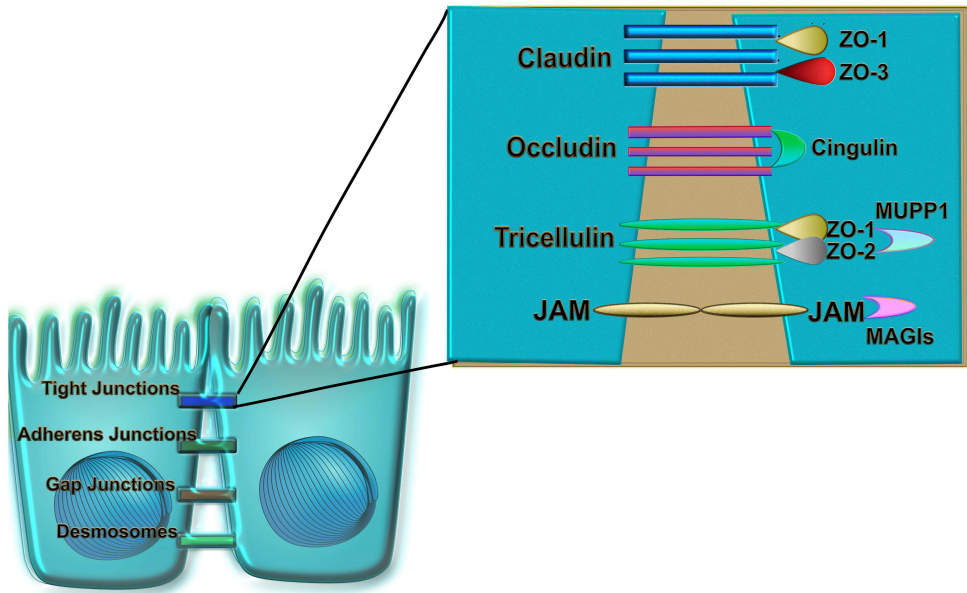
Cell Type	Localization	Function	Reference
<b>Basal cells</b>	Exist as a separate layer of cells covering most of the airway basal lamina.	Progenitor cells in regeneration and repair. Attachment of columnar epithelium with the basement membrane. Basal cells are more susceptible to RV infection than suprabasal cells	Evans et al <sup>188</sup> Hewitt and Lloyd <sup>189</sup> Yang et al <sup>190</sup> Morrissey <sup>191</sup> Jakiela et al <sup>192</sup>
<b>Suprabasal cells</b>	Intermediate between basal and club cells.	Connected to the tight junctions to form an impermeable barrier. Adhesion is mediated by E-cadherin.	Hewitt and Lloyd <sup>189</sup> Bukowy-Bieryllo <sup>193</sup>
<b>Goblet cells</b>	Line multiple mucosal surfaces, tightly packed mucin granules and surfactant proteins.	Secretion of mucus, antimicrobial proteins, chemokines and cytokines.	Knoop and Newberry <sup>194</sup> Rogers <sup>195,196</sup> Jackson <sup>197</sup> Yang et al <sup>198</sup>
<b>Club cells (Clara cells)</b>	Cells of the small airways, differentiated from basal cells in Notch-dependent manner.	Secretion of KL-6 protein, glycoproteins, and lipids. Chemical and physical protection. Able to self-renew and generate ciliated cells after injury thus, repopulating damaged airway tissue.	Rokicki et al <sup>199</sup> Broeckaert et al <sup>200</sup> Wang et al <sup>201</sup> Pilon <sup>202</sup> Tata et al <sup>203</sup>
<b>Ciliated cells</b>	Major cell type within the airways. Terminally differentiated and originate from club cells and/or airway basal cells regulated by Notch signaling.	Clearance of mucus and cleansing the airways of inhaled particles and pathogens. Ciliary dysfunction and ultrastructural abnormalities are closely related to asthma severity.	Hellings and Steelant <sup>5</sup> Morimoto et al <sup>204</sup> Guseh et al <sup>205</sup> Whitsett <sup>3</sup> Thomas et al <sup>206</sup> Tilley et al <sup>207</sup>
<b>Rare cell types</b>			
<b>Neuroendocrine cells</b>	Occur either as isolated cells or are organized in small clusters called neuroendocrine bodies, distributed throughout the conducting airways.	Sense airborne allergens and relay signals to stimulate immune cells and induce tissue/organ-wide responses. Increased secretory products in the regenerating airway epithelium may contribute to the development of the pathologic alterations in lung structure seen in bronchopulmonary dysplasia. Amplify allergic asthma responses.	Van Lommel et al <sup>208</sup> Noguchi et al <sup>209</sup> Kobayashi and Tata <sup>210</sup> Johnson and Gergieff <sup>211</sup> Sui et al <sup>212</sup>
<b>Ionocytes</b>	Tracheal epithelial cells.	Ion transport, fluid and pH regulation. Contains a C-terminal interaction domain that regulates TJ assembly and epithelial differentiation. Suggested role in pathology of cystic fibrosis by enrichment of the proton-secreting V-ATPases, important in regulating luminal pH and mucus viscosity.	Hewitt and Lloyd <sup>189</sup> Goldfarbmuren et al <sup>213</sup> Montoro et al <sup>214</sup> Plasschaert et al <sup>215</sup> Ruan et al <sup>216</sup> Shah et al <sup>217</sup>

(Continued)

**Table 1** (Continued).

Cell Type	Localization	Function	Reference
<b>Hillock cells</b>	Intermediate population between basal stem cells and differentiated luminal secretory cells. Do not contain luminal ciliated cells.	Play role in squamous barrier function and immunomodulation. Contain a particularly high number of cycling cells and expressed markers of cellular adhesion and epithelial differentiation as well as genes associated with barrier function and immunomodulation.	Montoro et al <sup>214</sup> Plasschaert et al <sup>215</sup> Vieira Braga et al <sup>218</sup> Deprez et al <sup>219</sup> Hewitt and Lloyd <sup>189</sup>
<b>Tuft cells (brush cells)</b>	Chemosensory epithelial cells, bottle shaped with apical microvilli, and are expressed in a range of organs, including the gut and airway as well as in the nose, trachea and proximal airways and exist in close contact with nerve fibers.	Coordinate interactions with the external environment. Mediate communication between neuronal and immune pathways. scRNAseq has now identified two terminally differentiated Trpm5+ tuft cell populations; one is positive for Gng13 and is likely to be responsible for “taste” sensing, and the other is positive for Alox5ap, suggesting that it contributes to leukotriene synthesis. Source of IL-25 in patients with chronic rhinosinusitis with nasal polyps.	Hewitt and Lloyd <sup>189</sup> Schneider et al <sup>220</sup> Plasschaert et al <sup>215</sup> Montoro et al <sup>214</sup> Krasteva et al <sup>221</sup> O’Leary et al <sup>222</sup> Kohanski et al <sup>223</sup> Patel et al <sup>224</sup>

were shown to injure the airway epithelial cells and help with initiation of allergen uptake by mucosal dendritic cells (DC) and antigen presentation with major histocompatibility class II to naïve T cells.<sup>33,35</sup> In mice, the intraepithelial DC expressing TJs claudin-1, claudin-7 and ZO-2, and the interaction with E-cadherin expressed by epithelial cells is used to uptake allergens by dendritic extensions between epithelial cells.<sup>32,35</sup> Infection of human bronchial epithelial cells (HBECs) with human rhinovirus increased their permeability and altered their TJs expression.<sup>36</sup> Whereas, respiratory



**Figure 2** The junctional complex of bronchial epithelial cells. Tight junctions, adherens junction, gap junctions and desmosomes are intracellular junctions which regulate the transport of ions, water and macromolecules between tissue and lumen. TJs consist of claudins, occludin, tricellulin, and JAMs, located directly between neighboring bronchial epithelial cells. They directly interact with cytoplasmic TJs such as cingulin, MUPP1, MAGIs, non-PDZ proteins, and ZO-1, ZO-2, ZO-3 which bind directly to occludin and claudin on one end while also linking to actin fibers on the other end. Created with [affinity.serif.com](https://affinity.serif.com).

syncytial virus infection in mice was seen only in lung parenchyma with decreased mRNA expression of claudin-1 and occludin observed in whole lungs. This observation was not seen in asthmatic HBECs.<sup>37</sup>

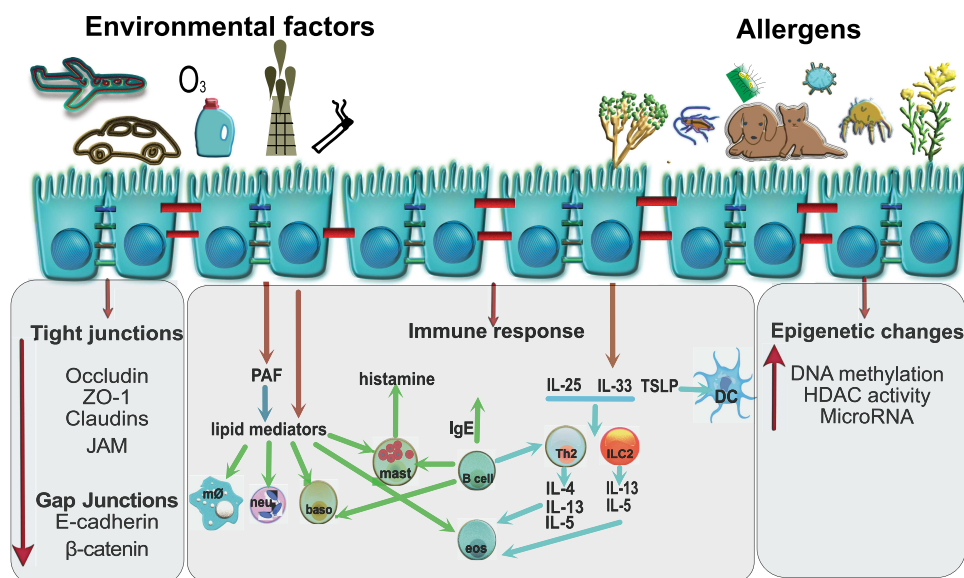
Increasing numbers of diseases with epithelial barrier damage are caused by lifestyle changes due to urbanization and modernization, and as a result more environmental toxins such as air pollutants, cigarette smoke and ozone are released, which affect more than one billion people worldwide.<sup>38–45</sup> The cadmium present in air pollutants and cigarette smoke disrupts epithelial integrity in *in vitro* human air-liquid interface (ALI) cultures through both occludin hyperphosphorylation via kinase activation and by direct disruption of the junction-interacting complex.<sup>46</sup> Recent studies have also revealed that nanoparticles, macroparticles, and toxins contained in laundry, dishwashing, and household cleaning agents can cause epithelial barrier disturbance in human keratinocytes and human bronchial epithelial cells.<sup>47–50</sup> Disturbance to the homeostatic balance in the epithelium including loss of differentiation, impairment of junctional complexes or insufficient innate immune response define the epithelial barrier dysfunction.<sup>51</sup> The disruption of the basic functions of the epithelium manifested in inability to rebuild causes the penetration of inflammatory cells.<sup>5</sup> This leads to chronic inflammatory airway diseases like asthma and chronic rhinosinusitis, which are heterogeneous diseases with complex etiology.<sup>52</sup> It was shown that the airway epithelium in asthmatic patients and *in vitro* ALI cultures is less differentiated, has elevated numbers of basal cells, and has increased phosphorylation of p38 mitogen-activated protein kinase.<sup>53</sup> The epithelial permeability was higher in asthma, specifically severe asthma, compared to mild asthma, and in biopsy specimens from patients with chronic rhinosinusitis with nasal polyps.<sup>53–57</sup> This decreased integrity of epithelial barrier was associated with decreased expression of the TJs molecules occludin and ZO-1. In *in vitro* study of asthma and HDM-induced allergic rhinitis, claudin-18 was shown in epithelial brushings in asthma patients and healthy controls. AJ like E-cadherin and  $\beta$ -catenin in patients with atopic asthma, were also shown to contribute to the disease development.<sup>56,58–61</sup> E-cadherin plays an important role in the epithelial-to-mesenchymal transition, a cellular process where epithelial cells acquire mesenchymal phenotypes and behavior following the downregulation of epithelial features. The epithelial cells lose their cell polarity and cell–cell adhesion, then display fibroblast-like morphology and cytoarchitecture, and gain migratory and invasive properties.<sup>62,63</sup> The Wnt/ $\beta$ -catenin pathway was shown to be involved in the remodeling process of fibrosis and allergic inflammation in a genetically modified mouse model.<sup>64</sup> Blocking of  $\beta$ -catenin pathway could be a promising therapeutic target in asthma because it can reduce allergic airway inflammation in mouse models.<sup>65,66</sup>

Disruption of the complex lung epithelium structure by the external components of the environment initiates the immune response, which could enhance the disease development and lead to a chronic stage.

## Epithelial Cell Response to Danger

The response of bronchial epithelium to danger is manifested by elevated serum IgE, increased smooth muscle mass, subepithelial fibrosis, epithelial desquamation, eosinophilic airway inflammation, and goblet cell hyperplasia.<sup>67</sup> The airway epithelium acts as a chemical barrier against environmental insults by secreting, for example, antimicrobial peptides, anti-proteases, and antioxidants.<sup>52</sup> The epithelial cells recognize pathogen-associated molecular patterns on inhaled microbes, parasites, and allergens as well as alarmins/damage-associated molecular patterns released from dying or damaged cells by expressing pattern recognition receptors like toll-like receptors, retinoic acid-inducible gene like receptors, nucleotide-binding oligomerization domain like receptors, C-type lectin receptors, protease activated receptor 2 and purinergic receptors.<sup>68,69</sup> Upon activation, epithelial cells produce and release chemokines, growth factors, lipid mediators, pro-inflammatory cytokines such as interleukin (IL)-6, IL-8, IL-25, IL-33, CCL20, CCL17, thymic stromal lymphopoietin (TSLP), and granulocyte-macrophage colony-stimulating factor (GM-CSF) which then attract and activate cells from the innate and adaptive immune system (Figure 3).<sup>70,71</sup> It has been shown that epithelial expression of the neutrophil chemoattractant IL-8 and macrophage inflammatory protein 1 alpha is increased in the biopsies from severe asthma patients. Their presence correlates with increased epidermal growth factor receptor (EGFR) expression as a marker of epithelial damage.<sup>72</sup> Human and mouse studies have revealed another molecule secreted by the respiratory epithelial cells which is nitric oxide that plays a role in ion transport, modulation of inflammation, and wound repair processes after injury.<sup>73–75</sup> Impairment of epithelial barrier induces deposition of extracellular matrix components and release of vascular endothelial growth factor (VEGF), which cause an increase in the size of airway wall vessels and





**Figure 3** Mechanisms involved in a bronchial epithelial cell response to environmental factors and allergens. Airway epithelial cells are susceptible to damage as a result of exposure to allergens (house dust mite, pollen, and animal dander), pathogens (viruses, bacteria), and environmental toxins (air pollutants, cigarette smoke, ozone, detergents). Disruption of bronchial epithelium, indicated by red cell junctions, decreases the barrier integrity as evidenced by lower expression of TJs (occludin, ZO-1, E-cadherin,  $\beta$ -catenin, JAM and EGFR). Consequently, epithelial cells respond by secretion of cytokines IL-25, IL-33, and TSLP, which then attract other inflammatory cells like Th2 (IL-4, IL-5, IL-13), ILC2 (IL-13, IL-5), B cells, and dendritic cells (DC). Additional manifestations of respiratory disease occur in response to lipid mediators. Epithelial cells can also produce PAF and eicosanoids which have been shown to be chemotactic for neutrophils (neu), basophils (baso) and macrophages (m $\phi$ ), activate eosinophils (eos) and macrophages, and alter vascular and epithelial permeability. Chronic inflammation also causes epigenetic changes in the bronchial epithelial cells by increasing DNA methylation and activating HDACs. Created with [affinity.serif.com](https://affinity.serif.com/).

promotes angiogenesis.<sup>76,77</sup> The airway epithelium maintains an active physical and functional barrier, and responds to the danger with secretion of cytokines, chemokines and mediators therefore activating innate and adaptive immune cells.

## The Influence of Cytokines on Epithelial Barrier Disorders

The main players driving the allergic disease pathology are T helper 2 (Th2) cells and their cytokines IL-4, IL-5 and IL-13.<sup>78</sup> During allergic airway inflammation, Wu et al observed elevated levels of IL-5 in mice in bronchial epithelial cells, which can impact the microenvironment of the lung by modifying pathologic and protective immune responses in the airways.<sup>79</sup> We have shown that Th2 cell numbers and the level of their cytokines, IL-4 and IL-13, decreased barrier integrity in ALI cultures of HBECs from control subjects. The HBECs from asthmatic patients had an initial low trans-epithelial resistance and reduced expression of ZO-1 and occludin, and the treatment with Th2 cells and cytokines IL-4 and IL-13 did not show any further changes. These cytokines induced a physical separation of the TJs of adjacent cells as seen in the immunofluorescence staining of the TJ molecules occludin and ZO-1.<sup>55</sup> Th2 cells and their cytokines (IL-4, IL-5, IL-13, IL-9) are necessary to initiate and propagate the inflammation associated with allergy. They induce class switching of B-cells to produce allergen-specific IgE, recruit mast cells (IL-9) and eosinophils (IL-5) to sites of allergic inflammation and induce goblet cell metaplasia (IL-4, IL-13).<sup>80,81</sup> Type 2 innate lymphoid cells (ILC2) through IL-13 were also linked to asthma pathogenesis by reducing human and mice epithelial barrier integrity.<sup>82</sup> Similar results were observed in the analysis of TJs in bronchial biopsies from asthmatic subjects and in vitro cultures.<sup>56</sup> Mouse studies demonstrated decreased expression of ZO-1, ZO-2, occludin, and claudin-5-8-18 and -23 in three chronic HDM models of eosinophilic, neutrophilic and mixed granulocyte asthma.<sup>83</sup> In addition, prolonged interferon (IFN) production impairs lung epithelial regeneration during influenza recovery in mice.<sup>84</sup> IFN $\gamma$  and tumor necrosis factor alpha (TNF $\alpha$ ) synergistically or singly disrupt barrier function in ALI cultures associated with reduced ZO-1 and JAM expression.<sup>54,85,86</sup> Zabner et al showed that histamine, which is a crucial agonist released during the immediate response to an inhaled allergen, increases paracellular airway permeability and increases the susceptibility of airway epithelial cells to infection by adenovirus by interrupting E-cadherin adhesion (Figure 3).<sup>87,88</sup> During the acute inflammatory response to pathogens or tissue injury, respiratory epithelium produces and releases eicosanoids together

with cytokines and chemokines, and mediators such as histamine (Figure 3).<sup>89</sup> They induce the recruitment of neutrophils and other immune cells into the tissue to engulf and kill invading pathogens. The two classes of eicosanoids, leukotrienes and prostaglandins, were shown to be increased in the airways of asthmatic patients and could be involved in asthma pathogenesis.<sup>90</sup> They are metabolites of the cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) pathways. Several studies have reported increased levels of COX pathway products, prostaglandin D (PGD<sub>2</sub>), prostaglandin F<sub>2</sub> alpha and thromboxane B<sub>2</sub> in the bronchoalveolar lavage fluid of allergic asthmatic.<sup>91,92</sup> Specifically, PGD<sub>2</sub> activities might contribute to asthma pathogenesis by vasodilation, increased capillary permeability, mucus production by lung epithelial cells, bronchoconstriction, and eosinophil recruitment.<sup>93</sup> PGD<sub>2</sub> has also been implicated in the trafficking of T cells in allergic inflammation.<sup>94</sup> In addition, leukotriene B<sub>4</sub> (LTB<sub>4</sub>) and the cysteinyl leukotrienes (Cys-LTs), products of the 5-LOX pathway, have been shown to be higher in exhaled breath condensate from asthmatic patients.<sup>95</sup> Cys-LTs were also reported to be higher in the induced sputum of asthmatic patients and their level correlated with disease severity.<sup>96</sup> LTB<sub>4</sub> has also been shown to induce chemotaxis of effector T cells to the airways of mice immediately after exposure to an allergen.<sup>97,98</sup> In addition to eicosanoids, platelet-activating factor (PAF), a phospholipid mediator, is prevalent in asthmatic airways. It is produced by various cells, including neutrophils, eosinophils, mast cells, fibroblasts, epithelial cells, and endothelial cells.<sup>99</sup> In the airways, PAF acts as a potent chemoattractant for neutrophils and eosinophils, promotes vascular permeability and edema and causes bronchoconstriction via acting on airway smooth muscle.<sup>100</sup>

During the resolution phase in the lungs, specialized pro-resolving mediators (SPMs) are produced by leukocytes, platelets, bronchial epithelial cells, alveolar epithelial type II cells as well as alveolar macrophages.<sup>101</sup> Their actions include participation in epithelial cell restoring, inhibition neutrophils' influx and activation, efferocytosis and phagocytosis of microorganisms, allergens and debris by macrophages as well as lymphocyte differentiation to effector cells that produce healing cytokines such as TGFβ.<sup>102,103</sup>

Severe asthma is resistant to current therapies and is marked by decreased lipoxin production in the airways due to the aberrant metabolism of AA.<sup>104–106</sup> Reduced levels of lipoxins, specifically lipoxin A<sub>4</sub> (LXA<sub>4</sub>), have been linked to more severe airway inflammation and a higher degree of airway obstruction.<sup>106</sup> In contrast, LXA<sub>4</sub> inhalation by asthmatic patients has been shown to affect airway response by attenuating the leukotriene C<sub>4</sub>-triggered airway obstruction and improved lung function in asthmatic children.<sup>107,108</sup> Infiltrating eosinophils during asthma pathogenesis are producing not only pro-inflammatory cytokines like IFNγ<sup>109</sup> but also LXA<sub>4</sub> which has been shown to suppress chemotaxis towards chemoattractants and inhibit the GM-CSF triggered secretion of IL-13 and eotaxin in vitro.<sup>110</sup> Eosinophils from severe asthmatic patients expressed lower levels of ALX the receptor for LXA<sub>4</sub>, compared to healthy humans.<sup>111</sup> Activation of ALX by LXA<sub>4</sub> has protective benefits in the lung airway by promoting the proliferation and wound repair of human airway epithelial cells.<sup>112</sup> The activation of this receptor on natural killer cells from asthma patients also increased their triggered apoptosis of eosinophils.<sup>113</sup> Various studies reported the beneficial and pro-resolution effects of resolvin E<sub>1</sub> in murine models of allergic airway inflammation, where it was shown to decrease eosinophil influx, airway hyperresponsiveness, and the secretion of IL-23, IL-17 and IL-6 in the lung while also increasing the production of LXA<sub>4</sub>.<sup>114,115</sup> Resolvin D<sub>1</sub> has also been shown to decrease allergic lung inflammation by stimulating the macrophages clearance of allergens.<sup>116</sup> Protectin D<sub>1</sub> treatment after an allergen challenge in mouse lungs was associated with a faster resolution of airway inflammation.<sup>117</sup> Classically regarded as a pro-inflammatory mediator, PGE<sub>2</sub> (prostaglandin E<sub>2</sub>) can promote resolution.<sup>118</sup> PGE<sub>2</sub> by inhibiting the proliferation, activation, and secretion of cytokines by ILC2.<sup>119</sup> Studies in asthmatic patients reported an inverse correlation between the sputum levels of PGE<sub>2</sub> and eosinophil numbers, thus suggesting it can play a role in reducing airway eosinophilia.<sup>96,120</sup> Additionally, inhaled PGE<sub>2</sub> was shown to have antiallergic effects by reducing the early and late bronchoconstrictor response to an allergen in asthmatic individuals.<sup>121</sup> PGI<sub>2</sub> (prostacyclin) has been mostly studied in mice models of asthma where it was involved in decreasing allergic inflammation by signaling through its receptor IP, as well as reducing lung fibrosis and remodelling.<sup>122–124</sup>

Systemic inflammation coordinated by a large number of factors such as cytokines, chemokines and mediators produced by immune cells, interact with each other and consequently cause changes in the bronchial epithelium. Long-term changes in the TJs protein expression, which are important for the maintenance and proper function of epithelial cells, can have an impact on the chronic stage of diseases.

## Genetic and Epigenetic Changes in Bronchial Epithelium

Under the influence of external factors and immune cell responses, bronchial epithelial cells undergo many changes in their DNA structure and post-translational genetic modifications. Several epithelial-derived genes have been identified in genome-wide association studies, such as metalloprotease 33 (*ADAM33*)<sup>125</sup> and protocadherin-1 (*PCDH1*),<sup>126,127</sup> which are associated with epithelial barrier function, differentiation, and homeostasis. Cadherin-related family member 3 (*CDHR3*) as a receptor for rhinovirus C was associated with childhood asthma with severe exacerbations.<sup>128,129</sup>  $\beta$ 2-adrenergic receptor haplotype pair (2/4) was shown to be associated with severe asthma,<sup>130</sup> while serine peptidase inhibitor, Kazal type 5 (*SPINK5*), and *TSLP* were associated with childhood asthma.<sup>131</sup> A large study involving more than a hundred centers worldwide identified genes associated with asthma on chromosomes 2 (*IL1RL1/IL18R1*), 6 (*HLA-DQ*), 9 (*IL33*), 15 (*SMAD3*), 17 (*ORMDL3/GSDMB*), and 22 (*IL2RB*).<sup>132</sup> *IL1RL1* encodes the ST2 receptor (ST2L) for IL-33, which promotes type 2 inflammation in some asthma patients. Soluble isoform, IL-1RL1-a or sST2, acts as a decoy receptor by sequestering IL-33, thereby inhibiting IL1RL1-b/IL-33 signaling, which could be used as a biomarker or target for pharmacological intervention.<sup>133,134</sup> Orosomucoid-like 3 (*ORMDL3*), was shown to play an important role in regulating epithelial barrier function in allergic asthma,<sup>135–137</sup> rhinovirus infection<sup>138,139</sup> and by inducing the p-ERK/MMP-9 pathway to promote pathological airway remodeling in patients with asthma.<sup>140</sup> *SMAD3* is an essential signal transducer in TGF- $\beta$  signaling, which is elevated in airway epithelial cells of some asthmatics<sup>141,142</sup> and is involved in the response of bronchial epithelial cells to viral infection.<sup>143,144</sup> Deletion of *P2Y13* in human airway epithelial cells and in a mouse model protects against asthma exacerbations.<sup>145</sup> A study in Der f 1 stimulated peripheral blood mononuclear cells from dust mite sensitized patients showed upregulation of *IL9*, *IL5*, and proteoglycan 2 (*PRG2*) expression with evidence for an interaction of *IL9* polymorphisms with dust mite in childhood asthma.<sup>146</sup>

Changes in bronchial epithelial cells also lead to epigenetic changes like DNA methylation, histone modification, and microRNA modifications, defined as heritable changes in gene activity without an alteration in the DNA sequence.<sup>147–149</sup> Recent studies in epigenome-wide association studies have shown an association between epigenetic signatures and allergic diseases, including pediatric asthma.<sup>150–152</sup> We showed a higher methylation level in bronchial epithelial cells from asthma donors following the changes in genes associated with cell growth, ion transport, and cytoskeletal remodeling. Additionally, higher methylation was observed in genes involved in the regulation of bronchial barrier integrity, eg, TJ family members: *AMOTL1*, *CLDN11*, *CLDN18*, *MAGI1*, *TJP2*, *JAM3*, actin protein: *ACTB*, a component of the cytoskeleton: *TUBA1C*, *ROCK2*, *LLGL1*. Interestingly ten-eleven translocation enzyme (*TET1*), which can reverse CpG methylation, was methylated in asthmatic HBEC.<sup>153</sup> Vermeulen et al reported differentially methylated regions between persistent asthma, remission, and healthy controls associated with ciliated epithelium genes.<sup>154</sup> Also, short-term exposure of bronchial epithelial cells to diesel exhaust, a significant contributor to air pollution, alters DNA methylation and could be implicated in pulmonary pathologies.<sup>155</sup> DNA-methyltransferases (Dnmts) play a crucial role in the methylation process. Qin et al showed that the bronchial epithelial Dnmt3b impairs the host defense during *Pseudomonas*-induced pneumonia, at least in part, by dampening the mucosal responses to flagellin.<sup>156</sup> Additionally, Dnmt1 deficiency disrupts epithelial-mesenchymal crosstalk and leads to an early-branching defect. It also causes a loss of epithelial polarity and proximal endodermal cell differentiation.<sup>157</sup> We showed that the inhibition of Dnmts restores leakiness in the bronchial epithelium in asthma.<sup>153</sup> Bronchial epithelium can also be influenced by histone acetyltransferases (HATs) and histone deacetylases (HDACs), that antagonistically control the overall balance of post-translational modification of DNA core histone proteins (Figure 3). They play a crucial role in cell signaling, cell cycle control, and epigenetic gene transcription regulation. HDAC inhibitors can inhibit these enzymes, resulting in the increased acetylation of histones, thereby affecting gene expression.<sup>158</sup> The HDAC family consists of 11 members of HDACs and 7 silent information regulator genes. We have shown that human bronchial epithelial cells from asthma patients showed higher HDAC activity with higher expression of HDAC1 and HDAC9. Most HDACs were significantly upregulated in control subjects and asthmatic patients upon IL-4 and IL-13 stimulation.<sup>55</sup> Similarly, Steelant et al<sup>159</sup> observed increased HDACs activity in allergic rhinitis patients with high expression of HDAC5 and HDAC11 and decreased HDAC2 was reported in patients with chronic obstructive pulmonary disease.<sup>160</sup> In a mouse model of ovalbumin (OVA)-induced asthma, HDAC4 was upregulated in the lung tissue.<sup>161</sup> We and others have also shown that inhibition of endogenous HDAC activity reconstitutes the defective barrier by increasing TJ expression.<sup>55,159,161–163</sup>



Genetic and epigenetic changes in the bronchial epithelial cells are an important part of the complex changes observed upon epithelium injury and therefore could be a possible approach to improving the epithelial barrier.

## The Effect of Treatment of Asthma and Allergy on Epithelial Barrier and Airway Remodeling

Epithelial barrier disruption, as a feature of airway remodeling which represents structural changes in bronchial wall encompassing wall thickening, basal membrane thickening, overgrowth of smooth muscle cell layer and enhanced angiogenesis, is observed in asthma patients. The effect of long-term asthma treatment on epithelial barrier and airway remodeling has been intensively studied (Table 2). Inhaled corticosteroids and  $\beta$ 2-adrenoreceptor agonists are the first-line medications used in asthma treatment and are effective in most patients. Several data indicate that glucocorticoids (GCs) inhalation therapy, including budesonide, can improve epithelial barrier integrity and might contribute to the therapeutic effects of GCs for treating asthma<sup>164,165</sup> or chronic rhinosinusitis with nasal polyps.<sup>166</sup> Similarly, other GCs, including mometasone and fluticasone, were shown to be effective in restoring nasal epithelial barrier dysfunction in allergic rhinitis.<sup>167</sup> In animal models, budesonide was also proved to inhibit airway remodeling in the early stage of allergen-induced airway hyperresponsiveness (AHR), however it did not reverse established AHR.<sup>168,169</sup> Interestingly, neither formoterol nor Montelukast, were shown to promote barrier integrity,<sup>165</sup> suggesting that  $\beta$ 2-adrenoreceptor agonists and anti-leukotrienes themselves might not have any positive effect on epithelial barrier restoration. In severe asthma patients, the long-term oral corticosteroid (CS) therapy is associated with serious side effects.<sup>170</sup> Therefore, currently, several biologicals are used in severe asthma treatment as an alternative for systemic CS. Currently, they encompass omalizumab (anti-IgE), mepolizumab (anti-IL-5), benralizumab (anti-IL5R), dupilumab (anti-IL4/13R) and reslizumab (anti-IL-5) approved by the Food and Drug Administration.<sup>171</sup> The question is posed whether they may affect epithelial barrier disruption and related bronchial remodeling in asthma patients. As omalizumab has been used for more than 15 years, there are some data indicating that it may decrease unfavorable structural airway changes in allergic asthmatics, with respect to the fibronectin deposit, the increased thickness of the basal lamina and the bronchial wall thickness.<sup>172–174</sup> Treatment with mepolizumab significantly reduced the expression of three extracellular matrix proteins: tenascin, lumican and procollagen III in the reticular basement membrane.<sup>171</sup> Benralizumab caused the consequent 29% relative reduction of airways smooth muscle mass and number of tissues myofibroblasts.<sup>175</sup> As IL-13 and IL-4 partly share the same receptor and signaling pathways and both are deeply involved in mucus secretion and airways remodeling dupilumab might exert a positive effect on airway remodelling.<sup>176</sup> Additionally, Anti-VEGF and TNF inhibition therapy was shown to be an effective treatment for remodeling in asthma with the significant restoration of the epithelial barrier.<sup>177</sup>

Allergen-specific immunotherapy (AIT) represents the only curative treatment in which an allergic patient is incrementally exposed to increasing quantities of a specific antigen, such as pollen, fungi, HDM, or food allergens.<sup>152</sup> Successful AIT induces the reinstatement of tolerance toward allergens and represents a disease-modifying treatment.<sup>178</sup> Long-term efficacy with allergen immunotherapy is associated with decreases in IgE-dependent activation of mast cells, tissue eosinophilia, regulatory T cells induction and local and systemic IgG, IgG<sub>4</sub>, and IgA antibodies.<sup>179,180</sup> In the mouse model of allergen specific immunotherapy (SIT), the restoration of the airway epithelial integrity was observed. Additionally, the use of 4-PBA, an inhibitor of endoplasmic reticulum (ER) stress, suppressed IL-25 induced airway epithelial ER stress and apoptosis triggered by *Dermatophagoides farinae* (*Der f*).<sup>181</sup> SIT has also been shown to affect HDM-induced activation of lung structural cells including airway epithelium.<sup>182</sup> Sublingual Immunotherapy was also shown to have a beneficial impact on airway wall thickness and remodeling in allergic asthma.<sup>183</sup>

Novel anti-inflammatory mediator, secretoglobulin1A1, was shown as a long-term allergen-specific therapeutic intervention that can suppress pro-inflammatory epithelial gene expression.<sup>184</sup> Several recent studies have studied novel molecules which could be used as a new potential treatment for allergy and asthma. We have shown that the oral gavage of polyamines spermine or spermidine can modulate HDM-induced cell infiltration, cytokine secretion, and epithelial cell tight junction expression in murine models.<sup>185</sup> Additionally, a redox-sensitive transcription factor Nuclear erythroid 2-related factor 2 (*Nrf2*), a key regulator of oxidative and environmental stress, enhanced epithelial barrier function and

**Table 2** Summary of Current and Novel Biological Therapies to Treat Asthma and Allergic Diseases

Class	Drug	Target/Mechanism	Publications
<b>Current drugs for asthma and allergy</b>			
Inhaled glucocorticoids	Budesonide	Anti-inflammatory actions	Sekiyama et al <sup>164</sup> Rimmer et al <sup>165</sup> Ma et al <sup>166</sup>
	Mometasone		Doulaptsi et al <sup>167</sup>
	Fluticasone		Doulaptsi et al <sup>167</sup>
	Beclometasone		
	Ciclesonide		
Monoclonal antibodies	Omalizumab	Anti-IgE	Kardas et al <sup>171</sup> Riccio et al <sup>172</sup> Zastrzezyńska et al <sup>173</sup> Hoshino et al <sup>174</sup>
	Mepolizumab	Anti-IL-5	Kardas et al <sup>171</sup>
	Benralizumab	Anti-IL5R, ADCC (Antibody-dependant cytotoxicity)	Kardas et al <sup>171</sup> Laviolette et al <sup>175</sup>
	Dupilumab	Anti-IL4/13R	Kardas et al <sup>171</sup> Bagnasco et al <sup>176</sup>
	Reslizumab	Anti-IL-5	Kardas et al <sup>171</sup>
Allergen-specific immunotherapy (AIT)	Allergen/antigen	Immune tolerance: decreases IgE-dependent activation of mast cells, tissue eosinophilia, regulatory T cells induction and local and systemic IgG, IgG4, and IgA antibodies	Globinska et al <sup>178</sup> Shamji et al <sup>179</sup> Akdis et al <sup>180</sup> Yuan et al <sup>181</sup> Hesse et al <sup>182</sup> Hoshino et al <sup>183</sup> Zissler et al <sup>184</sup>
<b>Other strategies tested as treatment for asthma and allergy</b>			
Receptor blocker	Etanercept	Anti-TNF- $\alpha$	Turkeli et al <sup>177</sup>
Monoclonal antibody	Bevacizumab	Anti-VEGF	Turkeli et al <sup>177</sup>
Polyamines	Spermine or spermidine	Anti-inflammatory actions	Wawrzyniak et al <sup>185</sup>
HDAC inhibitors	JNJ-26481585; sodium butyrate; siRNAs, tubastatin A HCl; PCI-34051; givinostat	Blocking histone deacetylases activity	Wawrzyniak et al <sup>55</sup> Steelant et al <sup>159</sup> Ren et al <sup>162</sup> Wang et al <sup>163</sup> Sekiyama et al <sup>164</sup>
DNMT inhibitor	SGI-1027	Blocking CpG methylation	Wawrzyniak et al <sup>153</sup>
Cannabinoids	WIN55212-2	CBI agonist; anti-inflammatory actions	Angelina et al <sup>187</sup>

**Abbreviations:** AJs, adherens junctions; ALI, air-liquid interface; AIT, allergen specific immunotherapy; COX, cyclooxygenase; DC, dendritic cells; DNMTs, DNA-methyltransferases; ER, endoplasmic reticulum; EGFR, epidermal growth factor receptor; GCs, glucocorticoids; GJs, gap junctions; GM-CSF, granulocyte-macrophage colony-stimulating factor; HATs, histone acetyltransferases; HDACs, histone deacetylases; HDM, house dust mite; HBECs, human bronchial epithelial cells; IFN, interferon; IL, interleukin; JAMs, junctional adhesion molecules; LXA4, lipoxin A4; ALX, lipoxin A4 receptor; MARVEL, MAL and related proteins for vesicle trafficking and membrane link; ADAM33, metalloprotease 33; MUPPI, multi-PDZ domain protein-1; NRF2, nuclear erythroid 2-related factor 2; OVA, ovalbumin; PATJ, PALS-1-associated tight junction; PTEN, phosphatase and tensin homolog; PGE2, prostaglandin E2; PGI2, prostacyclin; PKC, protein kinase C; PP2A, protein phosphatase 2; PRG2, proteoglycan 2 expression; PCDH1, protocadherin-1; SIT, allergen specific immunotherapy; SPINK5, serine protease inhibitor Kazal-type 5; SPMs, specialized pro-resolving mediators; Th2, T helper 2; TET1, ten-eleven translocation enzyme; TSLP, thymic stromal lymphopoietin; TJs, tight junctions; TGF- $\beta$ , transforming growth factor beta; TNF $\alpha$ , tumour necrosis factor alpha; ILC2, type 2 innate lymphoid cells; VEGF, vascular endothelial growth factor; ZO, zonula occludens.

increased localization of ZO-1 to the cell surface.<sup>186</sup> Furthermore, a study using the cannabinoid WIN55212-2 illustrated an essential role of this chemical in restoring airway epithelial barrier during rhinovirus infection and in suppressing T cell-mediated inflammation in human tonsil cells.<sup>187</sup>

## Conclusion

The influence of external factors and immune cell responses, cytokines and mediators associated with allergic airway inflammation can disrupt the epithelial barrier by interfering with junctional complex assembly. Understanding all the changes occurring in the bronchial epithelium during injury is very important for developing future possible treatments for asthma and allergy diseases. It is still unclear whether, the increased airway epithelial permeability that enables transport of allergens, pathogens and other damaging factors is constant and predisposes to disease development. However, the changes in structure and function in bronchial epithelium asthma and allergic diseases are well documented and there are important indications that restoring the epithelial barrier could be a potential target for new treatments. Nevertheless, data on the effects of particular biological therapies on epithelial barrier and airway remodeling in allergy and asthma are currently incomplete and thus require further studies.

## Disclosure

The authors report no conflicts of interest in this work.

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