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Invited review article

Role of airway epithelial barrier dysfunction in pathogenesis of asthma

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AJC, apical junctional complex; ALI, air–liquid interface; CDHR3, cadherin-related family member 3; EGF, epithelial growth factor; GSK-3β, glycogen synthase kinase 3; KIF3A, kinesin family member 3A; MyD88, myeloid differentiation primary response gene 88; Nrf2, NF-E2-related factor 2; PAR2, protease-activated receptor-2; PCDH1, protocadherin 1; START, steroid-acute regulatory protein-related lipid transport; Stard, START domain; ST2, suppression of tumorigenicity 2; TRIF, TIR-domain-containing adapter-inducing interferon-β; TSLP, thymic stromal lymphopoietin; STAT5, signal transducer and activator of transcription 5

ABSTRACT

Bronchial asthma is characterized by persistent cough, increased sputum, and repeated wheezing. The pathophysiology underlying these symptoms is the hyper-responsiveness of the airway along with chronic airway inflammation. Repeated injury, repair, and regeneration of the airway epithelium following exposure to environmental factors and inflammation results in histological changes and functional abnormalities in the airway mucosal epithelium; such changes are believed to have a significant association with the pathophysiology of asthma. Damage to the barrier functions of the airway epithelium enhances mucosal permeability of foreign substances in the airway epithelium of patients with asthma. Thus, epithelial barrier fragility is closely involved in releasing epithelial cytokines (e.g., TSLP, IL-25, and IL-33) because of the activation of airway epithelial cells, dendritic cells, and innate group 2 innate lymphoid cells (ILC2). Functional abnormalities of the airway epithelial cells along with the activation of dendritic cells, Th2 cells, and ILC2 form a single immunopathological unit that is considered to cause allergic airway inflammation. Here we use the latest published literature to discuss the potential pathological mechanisms regarding the onset and progressive severity of asthma with regard to the disruption of the airway epithelial function.

Introduction

The airway epithelium is located at the interface between the internal and external environment and has long been an area of interest as it possibly plays an important role in the onset mechanism of asthma. Airway epithelial cells play an important role in innate immune functions in the lungs. Airway epithelial cells also exhibit the characteristics of mucociliary cells and physically remove pathogens via a process known as the mucociliary escalator, which involves the trapping of pathogens in the mucus produced in airways under inflammatory conditions and removing the mucus via the movement of cilia present on epithelial cells. Moreover, the production of chemokines and cytokines mobilizes inflammatory cells, and their activation aids in removing microbes.[1–3] However, excessive induction of this protective mechanism that is used to prevent infection may trigger the onset of chronic airway inflammation associated with asthma. It has recently become clear that epithelium-derived cytokines that promote the Th2 immune response and that are released because of injured and activated airway epithelial cells play a role in allergic

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inflammation, and the importance of the activation of airway epithelial cells in the pathophysiology of asthma has also been emphasized.[4]

Airway epithelial cells, which form a physical barrier against the external environment, comprise the apical junctional complex (AJC), formed in the junction between adjacent cells. AJC comprises tight junctions and adherens junctions, which form cellular junctions between similar and dissimilar cells.[5–7] The tight junction is an intercellular junction between the apexes of cells, whereas the adherens junction functions as a barrier that regulates the passage of water-soluble substances and ions by creating a tight bond between the cell membranes of adjacent cells. In addition to their role as an intercellular binding mechanism, epithelial tight junctions and adherens junctions play an important role in establishing cell polarity.[4–6] AJC dysfunction of the airway epithelia has been recently identified in patients with asthma, suggesting that AJC is important in the pathophysiology of asthma. This type of damage to the epithelial barrier allows inhaled allergens to infiltrate the submucosa of the airway and prevents the complete repair of epithelial cells and excessively activates the epithelial cell signal transduction cascade, which is considered to activate immune cells present in the submucosa.[7,8] Therefore, disrupting the regulatory function of the airway epithelial barrier has recently been used as an important checkpoint for immunostimulation associated with asthma. Here we discuss the mechanism by which airway barrier function is disrupted in association with allergic airway inflammation and provide an overview of the disruption of the epithelial barrier and the resulting exacerbation of airway inflammation.

Disruption of the epithelial barrier owing to airway inflammation

Various environmental factors reportedly affect the tight junction barrier. Wan *et al.*[9–11] reported that *Der p1*, a mite allergen closely associated with the onset of allergic inflammation, disrupts the tight junction directly through protease activation and indirectly through protease-activated receptor-2 (PAR2). These effects accelerate epithelial permeability, making it easy for allergens to infiltrate the airway submucosa. It was subsequently discovered that in addition to *Der p1*, protease activation caused by other mite and pollen allergens also disrupt the epithelial barrier.[11] Tryptase released from degranulated mast cells in response to allergen stimulation disrupts epithelial tight junctions by activating PAR2, which accelerates epithelial permeability.[10,12–14] Moreover, multiple studies have found that cigarette smoke accelerates epithelial permeability by inducing reactive oxygen species.[15–18] Among the factors associated with the onset and exacerbation of bronchial asthma, the presence of the respiratory syncytial virus or rhinovirus in the airway and infection of the airway epithelial cells by these viruses is known to disrupt tight junctions and promote airway epithelium permeability.[19–24]

Cytokines reportedly alter tight junction functions. The proinflammatory cytokines, TNF-α and IFN-γ, disrupt the airway epithelial barrier,[25–27] and the same results were obtained for the Th2 cytokines, IL-4 and IL-13.[28,29] A study of the tight junction proteins in airway epithelial cells obtained via brushings from 67 patients with asthma and 42 healthy individuals reported that claudin-18 expressions were decreased in patients with asthma.[30] Claudin proteins determine the permeability of tight junctions. There are several dozen proteins in the claudin family, and their expression patterns differ according to the type of epithelial cell.[4,5] Claudin-18 is highly expressed in the airway epithelium; however, stimulation in response to IL-13 decreases claudin-18 expressions in the airway epithelium.[30] In addition, claudin-18-deficient mice with asthma exhibit an increased susceptibility to airway hypersensitivity, suggesting an association with the pathophysiology of asthma.[30]

A substantial number of factors, the so-called asthma-aggravating factors, can disrupt the barrier functions of the airway epithelium. Therefore, the involvement of airway inflammation in disrupting the epithelial barrier function and asthma is a topic of great interest (Fig. 1).

Disruption of the latent airway epithelial barrier in patients with asthma

Decreased epithelial barrier function associated with asthma is considered to occur because of the direct action of inflammatory substances and allergens on the epithelial barrier, as described in detail above. However, there have been several recent studies that have reported the possibility of latent barrier function abnormalities in airway epithelial cells of patients with asthma. Xiao *et al.*[31] cultivated airway epithelial cells obtained from patients with asthma and healthy individuals using the air-liquid interface (ALI) method and observed changes in the epithelial barrier function of differentiated airway epithelial cells. These findings indicated that the disruption of the epithelial barrier function decreased with asthma severity. Furthermore, cultivation of airway epithelial cells using the ALI method under the same cultivation conditions induces the differentiation of airway epithelial precursor cells into airway epithelial cells with cilia after 28 days of cultivation. Thus, Xiao *et al.*[31] suggested that the fragility of the epithelial barrier of patients with asthma was not because of inflammation only but could also involve pathological features already present in the airway epithelia of patients with asthma. This reduced barrier function can be improved to the same level as healthy individuals by addition of epithelial growth factor (EGF) into the medium, suggesting the potential involvement of EGFR signaling.

Basal cells are airway epithelium precursor cells. The basal cell layer is located below the ciliated columnar epithelium and is positive for cytokeratin 5, cytokeratin 14, and p63. Moreover, basal cells exhibit high EGFR expression levels, which decrease when basal cells differentiate into ciliated epithelium and goblet cells. A study of airway mucosa biopsies obtained from pediatric patients with asthma confirmed that cytokeratin 5-, cytokeratin 14-, and p63-positive basal cell-like epithelial cells proliferated in the airway epithelium.[32] Previous studies have reported that EGFR expression levels increased in the airway epithelia of patients with asthma, suggesting abnormal epithelium differentiation.[33–35] EGF acts on airway epithelial cells, promotes epithelial barrier functions, and suppresses the disruption of the epithelial barrier caused by cigarette smoke exposure.[31,36] Disruption of the epithelial barrier function caused by HDM allergen, TGF-β, and cigarette smoke exposure can be suppressed using an EGFR inhibitor, suggesting that excessive activation of EGFR is a factor that contributes to a reduced epithelial barrier function.[37] Proteins in the Erb family [e.g., EGFR (erb1), Erb2, and Erb3] form homo- and heteroreceptors. Moreover, a knockdown of Erb3 receptors in airway epithelial cells suppresses the reinforcing effect of heregulin on the epithelial barrier.[38] Because Erb3 receptors are a death-kinase variant, they are believed to be associated with the formation of the epithelial barrier via the formation of heteroreceptors with other Erb receptors.[38,39] These differences in Erb receptor signaling could be related to the different formative and disruptive effects of EGFR on the epithelial barrier (Fig. 1).

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