Airway epithelial dysfunction contributes to the pathogenesis of asthma

Keywords: epithelial cells, cytokines, interleukins, airway remodeling, tezepelumab, immunogenetics

Abbreviations: Th2, T helper cells; ILC2, innate lymphoid cells group 2; DCs, dendritic cells; ECM, extracellular matrix; EGF, epidermal growth factor; EMTU, epithelial-mesenchymal transition unit; EGFR, epidermal growth factor; PDGF, platelet-derived growth factor; FGF-β, fibroblast growth factor; VEGF, vascular endothelial growth factor; FDA, food and drug administration; FeNO, fractional exhaled nitric oxide; PRRs, pattern recognition receptors; Rig, retinoic acid-inducible gene; NOD, nucleotide-binding oligomerization domain; PAR, protease activated receptors; PAMPs, pathogen associated molecular patterns; DAMPS, danger-associated molecular patterns; WGS, whole genome sequencing; DPP, dipeptidyl peptidase; AHR, airway hyperresponsiveness; SNPs, single-nucleotide polymorphisms; AERD, aspirin exacerbated respiratory disease

Asthma is a significant public health problem, affecting more than 358 million individuals globally, and it is the most common chronic inflammatory respiratory disease in children. There are several distinct immunopathological pathways, and many immune and structural cells in the airways involved in the pathophysiology of asthma. The roles of type 2 T helper cells (Th2), innate lymphoid cells group 2 (ILC2), dendritic cells, mast cells, and eosinophils are well established in the pathogenesis of asthma. However, the part played by structural cell such as the epithelial “sentinel” cells is not fully understood.

Airway epithelium constitutes the first line of defense against allergens, bacteria, viruses, and pollutants in the atmospheric environment. The protective barrier of the airway epithelium in patients with asthma is often disrupted with loss of cell-to-cell connections, such as zonula occludens, zonula adherens, desimomes, and hemidesmosomes due to reduced expression of adhesion molecule E-cadherin. Airway dysfunction plays a central role in sensitization to allergens and pathogenesis of asthma. Epithelial damage occur in all phenotypes of asthma, and in childhood asthma, suggesting that epithelial dysfunction occurs early in the pathogenesis of the disease. Impaired epithelial barrier function renders the airway vulnerable to early life virus infections, which prime immature dendritic cells (DCs) toward directing Th2 responses, and local allergen sensitization. Dysfunctional airway epithelium is susceptible to environmental insults, such as increased permeability to allergen proteins, viral infections, chemical irritants, and pollutants. It exhibits impaired repair responses which contribute to persistent asthma. Continued airway injury and repair lead to increase in deposition of extracellular matrix (ECM) proteins, such as collagens, laminin, lumican, fibronectin, and tenasin in the epithelial lamina reticularis. This promotes subepithelial fibrosis, thickening and non-compliant airway wall, and fixed airflow obstruction. Furthermore, defective epithelial repair is characterized by overexpression of epidermal growth factor (EGF) with receptor activation, which correlates with disease severity. The extent of epithelial expression of EGF receptors correlates with immunoreactive CXCL8 (IL-8), a very potent chemoattractant for neutrophils, which is critical in the pathogenesis of neutrophilic asthma.

There is clear evidence suggesting that epithelial cells play an active role in inducing structural changes in the airways, also termed as airway remodeling. Airway remodeling is due to complex interaction between the airway epithelium and the underlying mesenchyme, resulting from reactivation of the developmental epithelial-mesenchymal transition unit (EMTU), which is responsible for lung morphogenesis during fetal life. The structural changes in the airways can be detected by bronchial biopsy histopathology, and non-invasively by computed tomography (CT) as thickening of the airway wall, increase in wall area (WA), and WA%, and is accompanied by greater centrilobular air trapping compared with health controls. The lung structural changes contribute to the severity of asthma, and correlates with lung function abnormalities.

Airways remodeling is due to immune responses orchestrated by pro-fibrotic cytokines, such as interleukin-13 (IL-13), IL-25, IL-33, and TSLP secreted by Th2 cells, ILC2, eosinophils, basophils, mast cells, and also by epithelial cells. Epithelial injury in asthmatic patients promotes increased release of growth factors secreted by immune and structural cells, such as TGF-β1, which plays an important role in airway remodeling. Other growth factors which contribute to airway remodeling include endothelin-1 (ET-1), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF-β), which activates fibroblasts and myofibroblasts. There is also increased release of vascular endothelial growth factor (VEGF), angiopoietin, and angiogenin in the airways, which promote neovascularization, expansion of the airway vascular bed, oedema, and airway narrowing. These changes are inevitably associated with thickening and shedding of the airway epithelium in both atopic and non-atopic asthmatic patients. Additionally, there is goblet cell, and submucous gland hyperplasia resulting in mucus hypersecretion. This is accompanied by hyperplasia and hypertrophy of ASM cells, which acquire a highly proliferative, secretory, and contractile phenotype. These structural changes are associated with more severe fixed airflow obstruction, which may be unresponsive to high dose inhaled corticosteroids (ICS), and to...
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Some of the interleukin antagonists, such as mepolizumab, reslizumab (anti-IL-5), benralizumab (anti-IL-5R), dupilumab (anti-IL-4Rα), and tezepelumab (anti-TSLP).  

Epithelial cells play a key role in the regulation of tissue homeostasis by producing and secreting numerous proteins, such as antioxidants, cytokines, chemokines, growth factors, and lipid mediators. Moreover, damaged and mechanically stressed epithelium produce large quantities of cytokines and growth factors that interact with the underlying mesenchymal cells, including fibroblasts and myofibroblasts to promote airway remodeling, and persistent airway obstruction.

Damaged allergic epithelium in response to allergens, pollutants, and viral respiratory infections release three cytokines cognomen “alarmins”, including IL-25, IL-33, and TSLP. The trio, although they belong to different cytokine families, play synergistic roles in the pathophysiology of severe asthma. They stimulate Th2 cells, ILCs, mast cells, basophils, and eosinophils to secret a variety of cytokine, chemokines, lipid mediators, and enzymes. TSLP, IL-25, and IL-33 are favourable targets for the development of new biologics for the treatment and prophylaxis of asthma, particularly asthma exacerbations due to respiratory viral infections.

There are no anti-IL-25, and anti-IL-33 biologics approved for the treatment of severe uncontrolled asthma. Currently, only tezepelumab a first-in-class fully human IgG42 monoclonal antibody (mAb) that blocks the action of TSLP is approved by the US Food and Drug Administration (FDA) for the treatment of severe asthma without an eosinophilic phenotype in patients 18 years and older. Tezepelumab has been shown to significantly reduce exacerbation rates, and biomarkers of inflammation, such as blood eosinophil count, and fractional exhaled nitric oxide (FeNO). It also significantly reduced the levels of the instigator interleukins responsible for the pathophysiology of eosinophilic asthma, such as IL-4, IL-5, and IL-13. Tezepelumab is effective in most asthma phenotypes, irrespective of eosinophil counts, and FeNO levels, the classic biomarkers of eosinophilic asthma. It is safe and well tolerated by most patients with severe uncontrolled asthma.

Most recently, CSJ117 a potent neutralizing antibody fragment directed against TSLP, formulated as PulmoSol engineered powder in hard capsule for delivery to the lung via a dry powder inhaler, met the endpoints in the latest clinical trial. CSJ117 significantly attenuated the early and late asthmatic responses, and reduced biomarkers of eosinophilic asthma (blood eosinophil count, and FeNO). It may possibly be the first inhaler biologic for the add-on treatment of patients with severe asthma. Monoclonal antibodies targeting alarmin cytokines, e.g. tezepelumab are more likely to be effective in several phenotypes of asthma, including eosinophilic, neutrophilic, mixed granulocytic, and paucigranulocytic phenotypes.

Noteworthy, airway epithelial cells express a broad array of protective receptors, such as pattern recognition receptors (PRRs), retinoic acid-inducible gene (RIG)-1-like receptors (RLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), protease activated receptors (PAR)-2, and purinergic receptors. These receptors detect environmental stimuli, in response to pathogen associated molecular patterns (PAMPs) present on microbes and parasites, or to danger-associated molecular patterns (DAMPs) released after tissue damage, cell necrosis, or cellular stress. Activation of PRRs on epithelial cells stimulates downstream signaling that promote the release of pro-inflammatory cytokines, such as IL-6, IL-8, IL-25, IL-33, and TSLP; chemokine, including CXCL8/IL-8, CCL17, and CCL20; and growth factors, namely GM-CSF, EGF, and FGF-β. TSLP, IL-25, and IL-33 secreted by epithelial cells alert and activate the immune system of the impending threat, which immunopathologically results in activation of Th2 cells, ILC2, eosinophils, and mast cells to produce large quantities of IL-4, IL-5, IL-13, IL-25, IL-33, and TSLP. The roles of cytokines which are released consequently to activation of epithelial cell dysfunction, are well established in the pathogenesis of Th2-driven eosinophilic asthma.

Genetic and environmental factors play an important role in the pathogenesis of asthma. Environmental factors, such as allergens, microbacteria and viruses, irritant chemicals, pollutants, and environmental tobacco smoke interact with genes through epigenetic mechanisms that influence gene expression. Epigenetic factors are regulators of gene transcription, that do not influence gene sequence. Epigenetic mechanisms include DNA methylation, histone modifications, and regulation of non-coding RNA, especially microRNAs (miRNAs). The interaction between the airway epithelium and the underlying mesenchyme plays a central role in the pathophysiology of airway remodeling and pathogenesis of different phenotypes of asthma.

There are several genes associated with asthma susceptibility expressed in the airway epithelium and the underlying mesenchyme. This indicates that responses at airway epithelial surface, and lung may play an important role in the pathogenesis of the disease.

Linkage designs and candidate gene associated studies, genome-wide association studies (GWA), and whole genome sequencing (WGS) have shown that there are several genes in epithelial cells and mesenchymal cells linked to asthma susceptibility. The identified genes in epithelial cells include interleukin 1 receptor-like 1 (IL1RL1), IL-18 receptor 1 (IL18R1), HLA-DQ, HLA-G, SMAD3, IRAKM, ESE1 and 3, DPP10, PCDH1, CH13L1, ORM1-like 3 (ORMDL3), gasdermin B (GSDMB), CDHR3, CST1, OPN3, IL-33, and TSLP (Table 1). In the mesenchyme, they are disintegrin and metalloprotease (ADAM)33, KCNMB1, MYLK, and C/EBPα.

| Table 1 Immunogenetics and epigenetics landmarks of asthma |
|-----------------------------------------------------------|
| **Epithelial derived genes**                              |
| HLA-DQ                                                   | ORM1-like 3 (ORMDL3) |
| HLA-G                                                    | Gasdermin B (GSDMB) |
| SMAD3                                                    | CDHR3               |
| IRAKM                                                    | OPN3                |
| ESE1 and 3                                               | IL-18 receptor 1 (IL18R1) |
| DPP10                                                    | Interleukin 1 receptor-like 1 (IL1RL1) |
| PCDH1                                                    | IL-33               |
| CH13L1                                                   | TSLP                |
| **Mesenchyma genes**                                     |
| Disintegrin                                              | miR-146b            |
| Metalloprotease (ADAM)33                                  | miR-148a            |
| KCNMB1                                                   | miR-52              |
| MYLK                                                     | C/EBPα              |
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Dipeptidyl peptidase (DPP) 10, disintegrin and ADAM33 are newly identified genes strongly associated with asthma and are preferentially expressed in airway epithelium and mesenchyme, respectively. DPP10 is located on chromosome 2q14-32, and encodes dipeptidyl peptidase 10 which is preferentially expressed in the epithelium of asthmatic patients. It is associated with airway hyperresponsiveness (AHR) in the Chinese population. ADMA33 on chromosome 20p13 is mainly expressed in mesenchymal cells, and is associated with impaired lung function in infants, increased susceptibility to respiratory syncytial virus induced bronchiolitis, and a later development of AHR through epithelial-mesenchymal trophic unit. It is also associated with AHR and accelerated decline in lung function over time point, and is strongly involved in the proliferation of biosynthetically active fibroblasts, myofibroblasts, and smooth muscle cells.

PCDH1 is located on chromosome 5q31-p33 and encodes the protocadherin-1 protein. It is associated with asthma through epithelial structural defects leading to AHR.

HLA-G on chromosome 6p21 is expressed highly in bronchial epithelial cells of asthmatics and is associated with AHR. Three miRNAs; miR-148a, miR-146b, and miR-52 have been reported to affect HLA-G expression in epithelial cells, suggesting that miRNA mediated mechanisms may contribute to the impact of HLA-G on asthma risk. GPRA, also known as Neuropeptide S Receptor 1 is located on chromosome 1p5-p14, it plays an important role in the pathogenesis of asthma. ORMDL3 and GSDMB at chromosome 17q21, are associated with childhood asthma. SMAD3 located on chromosome 15, is another susceptibility gene for asthma. SMAD3 is critical for TGF-β signaling which is elevated in airway epithelial cells, and plays an important role in airway remodeling in asthma.

Notably, a few epithelial genes are shared among asthmatics, such as IL-33, and TSLP, indicating that alarmin cytokines play a central role in the pathogenesis of asthma. Furthermore, the expression of IL-33 and TSLP are both elevated in the airways of patients with severe refractory asthma. IL1RL1 (also known as T1, ST2, DER4) is located on chromosome 2, belongs to the IL-1 superfamily, and is a receptor for the alarmin cytokine IL33. IL-33 is located on chromosome 9, and is associated with atopic asthma.

The human TSLP gene is located on chromosome 5q22.1, next to other IL-2 family member’s clusters, including IL-4, IL-5, IL-7, and IL-13. Several genome-wide associated studies have shown association between asthma and single-nucleotide polymorphisms (SNPs) in the TSLP gene. The likely causal polymorphism for allergy, asthma, and nasal allergy is rs1837253, which also directly regulates TSLP secretion. TSLP gene polymorphism is associated with the development of AHR, different phenotypes of asthma, aspirin exacerbated respiratory disease (AERD), and allergic rhinitis.

Several genes and genetic loci in the airway epithelial cells and mesenchymal cells are associated with susceptibility to different phenotypes of severe asthma. The airway epithelium is the first cell layer of contact with environmental insults, such as allergens, microbes, viruses, chemical irritants, and pollutants. Dysfunctional airway epithelium orchestrate the inflammatory responses, and remodeling in patient with asthma. The epithelium is a suitable therapeutic target for discovery and development of new biologics, and therapeutic interventions for the treatment of severe uncontrolled asthma. Furthermore, injured and dysfunctional airway epithelial secrete alarmin cytokines, such as IL-25, IL-33, and TSLP. TSLP and its fragments seem to be attractive to target because they are involved in the pathophysiology of most phenotypes of asthma. Tezepelumab is an efficacious, safe and well tolerated biologic, which is available as add-on treatment for patients 18 years and above with severe uncontrolled eosinophilic, and non-eosinophilic phenotypes. The usual dosages which have been used in clinical trials are 70 mg every 4 weeks (Q4W), 210 mg Q4W, and 280 mg Q4W subcutaneously or intravenously, but the 210 mg Q4W dosage is preferable in routine clinical practice.

Conflicts of Interest
The author declares that the research was conducted in the absence of any financial relationship that could be construed as a potential conflict of interest.

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