REVIEW

Role of airway epithelial cells in development of asthma and allergic rhinitis

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Summary
Asthma and allergic rhinitis frequently coexist in the same patient. There is a similarity and variation as well as potential relationship between asthma and allergic rhinitis. There is an increasing evidence to suggest a major involvement of airway epithelial cells in the pathogenesis of asthma and allergic rhinitis. The present review describes the importance of the airway epithelial cell in the development of allergic airway diseases, its role as the primary airway defense against exposure of the airway and lung to inflammatory stimuli and antigens and as an important player through activation of epithelial Toll-like receptors (TLRs) to provide an important link between innate immunity and allergic disease. Additionally, airway epithelial cells can act as inflammatory promotores capable of directing dendritic cells (DCs) towards a T helper 2 (Th2) response, and as active producers of several inflammatory/anti-inflammatory mediators. It is hypothesized that airway epithelial cells may play as both inflammatory initiator and immuno-pathological feedback regulation between allergic rhinitis and asthma via release of systemic inflammatory mediators. Thus, airway epithelial cells may be valuable therapeutic targets for discovery and development of new drugs and/or new therapeutic strategies to treat asthma and allergic rhinitis.

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Introduction

Asthma is a chronic, inflammatory condition of the lower airways characterized by largely reversible airflow obstruction, airway hyper-responsiveness, and episodic respiratory symptoms. Allergic rhinitis (AR) is a disorder of the upper airways resulting from IgE-mediated inflammation of the nose upon contact of the nasal mucosa with allergens. AR is a common ailment, affecting 10–25% of the world’s population and has an impact on asthma as a public health initiative of the World Health Organization based on the concept of “one airway, one disease”. Asthma and AR frequently coexist in the same patient and are thought to share common predisposing genetic factors which interact with environmental influences, increasing in prevalence over recent decades.

The links between the upper and lower airways were clinically noted and first envisaged in the early 1800s and then gradually elucidated and confirmed as the pathogenic unity of the upper and lower respiratory tract in allergy. The relationship between asthma and AR is also supported by epidemiological studies, by histological, physiological, and immunopathological characteristics, and by the positive effect of various therapies on asthma symptoms in patients with rhinitis.

Airway epithelial cells are the first line of defense against exposure of the airway and lung to inflammatory stimuli and antigens, and epithelial activation is one of characteristics of asthma and AR, significantly associated with allergic sensitization. The association between two diseases is believed to be primarily due to a common allergic trigger. Thymic stromal lymphopoietin (TSLP) is a cytokine produced by airway epithelium, orientating dendritic cells (DCs) towards a T helper 2 (Th2) response and acting as an essential link between epithelial cell activation and allergic inflammation. The present review describes current evidence that airway epithelial cells are involved in the pathogenesis of asthma and AR, by reviewing the importance and central role of airway epithelial cells in the development of diseases. The potential role of nasal epithelial cells in the pathogenesis of rhinitis is also explored separately, although the number of works on nasal epithelial pathophysiology is limited. It should also be kept in mind that the results from bronchial epithelial studies cannot be extrapolated into nasal epithelia, even though there is a similarity between two.

Role in viral infections

Upper airway viral infections (URI), caused by different types of the virus, are associated with the development of airway inflammation. In particular, human rhinovirus (HRV) infections could increase numbers of neutrophils and lymphocytes in the upper airways, and induce neutrophil recruitment to the lower airways in subjects with asthma. Cold, dry air (CDA) can cause symptoms of rhinitis and obstructive airway responses. Epithelial cell shedding mostly accompanies with clinical responses to CDA in the nose. Although the pathophysiology of these reactions is not fully understood, it is possible that the respiratory mucosa of individuals with CDA hypersensitivity cannot compensate for the loss of water that occurs on exposure to the stimulus, leading to epithelial damage. In addition to allergen and air pollutants, the asthmatic airway is particularly susceptible to respiratory virus infection, which can contribute to 40–80% of asthma exacerbations in both children and adults. Of particular significance is the finding in asthma that viruses usually caused only upper respiratory tract symptoms also cause exacerbations in patients, especially in certain seasons.

The mechanisms by which viral infections can enhance upper and lower airway inflammation are not fully defined, but the growing evidence supports the concept that viral modulation of epithelial function may initiate the inflammatory response (Figure 1). Infection of epithelial cells by HRV has been shown to provoke the generation of a wide variety of proinflammatory chemokines and cytokines, including interleukin (IL)-8(CXCL8), ENA-78(CXCL5), IP-10(CXCL10), RANTES (CCL5), IL-1, IL-6 and IL-11. Once viral infection of the epithelium initiates a proinflammatory process, subsequent production of other mediators may further contribute to the inflammation of the airway.

Role in innate immune responses

The lung is the largest surface in the body contacting with the outside environment, and presents an estimated area of 100 m² that comes into contact with approximately 10,000 L of inhaled air each day. The airway epithelium is the direct interface with inhaled air and others and forms the initial defense barrier against inhaled exogenous substances. Epithelial cells play important roles in host defense, inflammation, and regulation of immune responses. A role for epithelial roles in innate immunity has been described by the fact that lysozyme and other mucosal substances could prevent the growth of bacteria and other microorganisms in the lung and airways.

Airway epithelium is emerging as a regulator of innate immune responses to a variety of insults. The maintenance of mucosal barrier function integrity is another important component of the epithelial
armamentarium in innate immunity. Epithelial cells are involved in killing or neutralizing microorganisms through the production of several families of molecules, including enzymes, permeabilizing peptides, collectins, protease inhibitors, and others. The production of these substances is initiated by pathogen-recognition receptors, such as Toll-like receptors (TLRs).

In order to explore the effects of antigens in TLR expression and activation, we studied the density of antigen with a human bronchial epithelial cell line for 24h, and found that antigen increased TLR4 expression and nuclear factor-kappa B (NF-κB) and ErK1/2 activation, and further increased IL-8 release and chemotactic activity toward neutrophils. Accumulation of neutrophils within the airways in response to antigen appeared to increase the expression of TLR4 and preferentially orients TLR4 activation toward subsequent activation of ERK and IL-8 production.

Role in adaptive immune responses

Epithelial cells act as an initiator, mediator, and regulator in innate and adaptive immune responses, as well as the transition from innate immunity to adaptive immunity. DCs and airway macrophages collaborate as sentinels against foreign particulate antigens by building a transepithelial interacting cellular network. During inflammatory and immune responses, epithelial cells express pattern-recognition receptors to trigger a host defense response, interact with DC to regulate antigen sensitization, and release cytokines to recruit effector cells. Epithelial cells also regulate adaptive immune cells by expression of soluble and cell-surface molecules that alter the function of DCs, T and B cells in the airways.

Role in allergic reactions

Although asthma is an inflammatory disorder of the conducting airways involving Th2-type T cells, the epithelium also plays an important role in orchestrating the inflammatory response by interacting with multiple environmental factors to produce a chronic wound scenario involving tissue injury and aberrant repair. Part of this is a primary disruption of epithelial tight junctions that allows inhaled substances to pass more easily into the airway wall to interact with immune and inflammatory cells. Aberrant communication between the damaged and stressed epithelia leads to the generation of growth factors that interact with the underlying mesenchyme to promote airway remodeling responses and a more chronic and persistent inflammatory phenotype. Disordered epithelial function with reduced antioxidant defense and impaired capacity to produce primary interferon-gamma may also account for asthmatic susceptibility to air pollution and respiratory virus infection, respectively.

AR is characterized by an initial sensitization phase where allergen exposure results in IgE formation as well as induction of the humoral response, and subsequent clinical disease after repeated antigen exposure. Mucosal epithelial cells may play critical roles in initiating and/or maintaining local inflammation. It is accepted that mast cells involve the early phase inflammatory response within minutes of allergen exposure by the release of mediators, but the...
question is that how can the mast cells contact and communicate with the antigens without the involvement of epithelial cells and whether epithelial cells pass the message or signal to other cells. Cytokine secretion is a major feature of the inflammatory process in AR, playing an important role in cellular adhesion, e.g., intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin on the vascular endothelium. It would be important to understand the role of epithelial cells in the recruitment of leukocytes from the circulation to the mucosa.

Role in airway hyper-responsiveness (AHR)

AHR is considered to be related to chronic airway inflammation, including leukocyte infiltration, hypersecretion of mucus, bronchial smooth muscle spasm, and airway wall remodeling, one of the main clinical features in asthma. Non-asthmatic subjects with AR can present with AHR when exposed to an allergen to which they are sensitized. It has been proposed that the nasal mucosa may process allergens into a form more capable of inducing nasal and bronchial reactions. AHR often occurs in patients with AR, even if they have no asthma symptoms, associated with an increased risk for developing asthma. About 40% of patients with AR were found to have AHR, with a potential to develop asthma over the subsequent 4–5 years. Among patients with exacerbation of asthma symptoms and the onset of seasonal AR, nasal allergen challenge resulted in an increased nonspecific bronchial responsiveness. Segmental bronchial provocation in patients with AR rather than asthma results in allergic inflammatory changes in the nose.

Epithelial cell barrier dysfunction has recently been considered to be an important mechanism in the development of AHR. Current theories concerning its pathogenesis, apart from the classic allergic theory, include the neurogenic airway inflammation hypothesis and epithelial defect hypothesis. Bronchial epithelial cells play a critical role in maintenance of homeostasis in the airway microenvironment through a wide range of biological functions including anti-oxidative activity, exocrine/endocrine secretion, mucus production, and antigen presentation. It is reasonable to hypothesize that disruption of these functional processes or defects in airway epithelial integrity may be an initial step leading to AHR. TLR stimulation could induce AHR, by JNK and NF-κB signaling pathways, supported by the finding that LPS and poly-I-C-induced translocation of NF-κB p65 to the nucleus and up-regulation of kinase B(1) and B(2) receptor mRNA and TLRs were expressed in the tracheal smooth muscle. It is also possible that hypertrophy and hyperplasia of goblet cells may also contribute to the formation of AHR.

Role in mucus overproduction

Mucus overproduction is a prominent pathological change in the exacerbation of asthma and AR. Epithelial cells are downstream targets of molecules that activate IL-13R and epidermal growth factor receptor (EGFR) and are responsible for mucus production in both protective immune responses and allergic airway inflammatory diseases. Multiple stimuli induce mucin production in airway epithelium via effects of EGFR activation (Figure 2). Autocrine activation of EGFR in response to stimuli appears to be an important mechanism of EGFR activation. EGFR expression and activation induce goblet cell hyperplasia and metaplasia and increase mucin production, resulting in epithelial proliferation, differentiation, migration, and wound repair. On the other hand, IL-4 affects differentiation of epithelial cells towards a phenotype that releases more IL-8 and expresses more mucins.

The γ-aminobutyric acid (GABA) system, aquaporin (AQPs) water channels and LPS-induced over-expression of MUC5AC seem to play a major role in over-production of mucus. Mucin over-production can be induced via a GABA system in airway epithelium, and IL-13 appears as a critical role in regulating airway epithelial GABA signaling. GABAergic blockade could prevent antigen-induced airway goblet cell hyperplasia and mucus over-production. The AQPs, a family of homologous water channels expressed in many epithelial

Figure 2 Mucus overproduction is prominent pathological change in the exacerbation of asthma and allergic rhinitis. Multiple stimuli induce mucin production in airway epithelium via the effects of epidermal growth factor (EGFR) activation. The direction of the inflammatory reaction in mainly from stimulus to EGFR, as indicated by arrows.
cells, may regulate airway mucin secretion and transmembrane water transport. Although LPS-induced over-expression of MUC5AC in the airway might be the activation of the TLR-4 pathway and mediated by the release of tumor necrosis factor (TNF)-α, IL-1β, and IL-8, evidenced by the fact that the inhibition of TLR-4 expression could prevent mucus hypersecretion and AHR.

Role in allergic cascade

Th2-type inflammation has a prominent role in epithelial disorders during asthma and AR. TSLP is capable of directing DCs towards a Th2 response, providing an essential link between epithelial cell activation and allergic-type inflammation and between epithelial injury and generation of an allergic-type inflammatory response. In addition, TSLP can interact directly with mast cells to initiate Th2 cytokine production, providing a non-T cell addition, TSLP can interact directly with mast cells to initiate Th2 cytokine production, providing a non-T cell

TLR-involved mediators

The pattern recognition receptors, including TLRs in the epithelium and on DCs, are important in the origins of allergy. Their differential activation is associated with the prevalence of allergic diseases. The activation of TLRs in the airways and nose by viral, bacterial, and fungal ligands has revealed a profound effect in shaping the subsequent adaptive immune response in favor of Th1, Th2, or Treg cells. TSLP production can be induced in airway epithelial cells by ligands that activate TLR2 and TLR3 to release TSLP protein, and TLR8 and TLR9 to stimulate TLSP gene transcription through NF-κB activation. Ligands capable of activating these TLRs include bacterial lipoteichoic acid and peptidoglycans from bacteria (TLR2), single-stranded (TLR8) and double-stranded (TLR3) viral RNA, and CpG DNA motifs in both viruses and bacteria (TLR9). The proinflammatory cytokines e.g. TNFα, IL-1β, IL-4 and IL-13 can also induce TSLP production to drive TSLP-dependent maturation of blood CD11c+ dendritic cells. TLR activation can also be initiated by other factors, such as viruses, dusts, and chemicals.

Role in airway remodeling

Airway remodeling is a major contributing factor to the pathogenesis of asthma, especially the development of airflow obstruction and the progressive decline in lung function associated with the duration and severity. Airway epithelial cells play an important role in development of both airway inflammation and remodeling in asthma. The remodeling with epithelial shedding, collagen deposition basement membrane thickening, smooth muscle hyperplasia is a distinctive feature of bronchial asthma.

Th2 cytokines not only affect airway inflammation and innate immunity in the lung, but also epithelial differentiation and airway remodeling. Oxidative stress is capable of increasing production of Tn and Ln β2 chain by bronchial epithelial cells, contributing to remodeling in chronic inflammatory airway diseases. Remodeling of the airway wall is considered as a direct result of the inflammatory environment present in the asthmatic airway, but in many cases the epithelium is the primary target of mechanical forces in the lung due to the high loads and deformations. Mechanical activation of the epithelium can lead to profound changes in signaling and gene expression, and alter epithelial release of cytokines, nucleotides, and growth factors. The mechanical forces developed during constriction of intact airways could lead to EGFR signaling in cultured cells. These data raise important questions about the biochemical links between mechanical transduction and downstream biochemical activation in airway epithelial cells. Specific immunotherapy has been suggested to affect the natural course of allergic disease and be effective in the treatment of asthma and AR.
in several double-blind randomized clinical studies. It is possible that epithelial cells are involved in the efficacy as message carriers.

**Epithelial feedback regulation via systemic inflammation**

Recent studies have suggested that other pathways may be involved in asthma. Epithelial cells in different organs/tissues have similarities and variations dependent upon the organ, function, location, and challenge, and can communicate with each other and play a central role in systemic reactions and multiple organ dysfunction. Airway epithelial cells act not only as a defensive line against inflammatory stimuli and antigens, but also may be initiators of secondary inflammatory responses and systemic reactions. It is suggested that “feedback regulation” between the upper and lower airway takes place at initiation of the inflammatory process, possibly through a systemic pathway, or via cytokine release of airway cells, which are abundantly present throughout the respiratory mucosa. Possible mechanisms for the influence of AR on lower airways include systemic propagation of nasal inflammation to the bronchial mucosa via effects of mediators and inflammatory cells on bone marrow.

In conclusion, there is a clear indication that epithelial cells are involved in the pathogenesis of asthma and AR, as the first line of defense facing local and primary challenges. Airway epithelial cells are important players in the development of airway inflammation and remodeling, which act as an inflammatory promoter for initiating both local and systemic inflammation. Structural and functional abnormalities of the epithelium can be both primer and promoter of airway and distant organ dysfunction. Airway epithelial cells may be a valuable therapeutic target for discovering and developing new drugs and/or new therapeutic strategies for the treatment of allergic diseases.

**Conflict of interest statement**

None of the authors have a conflict of interest to declare in relation to this work.

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