Published in final edited form as:

J Allergy Clin Immunol. 2011 December ; 128(6): 1225–1226. doi:10.1016/j.jaci.2011.10.006.

PLASTICITY OF AIRWAY EPITHELIAL CELLS

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Keywords

Airway epithelial cell; plasticity; transdifferentiation

EDITORIAL

The pseudostratified ciliated epithelium of airways provides a mucociliary barrier and participates in immune responses to protect the host against airborne threats. Airborne threats such as microbes and environmental noxious stimuli trigger airway epithelial innate immune response aimed at defending the host against the threat and at engaging adaptive immune response. After the threat is controlled, the epithelium is able to repair itself. In this issue, two articles show alterations in airway epithelial mucociliary barrier in the setting of innate antiviral immune response and chronic inflammation (adaptive immune response).

In one article, Rezaee F et al.¹ stimulated differentiated bronchial epithelial cells with the synthetic double stranded RNA (dsRNA) polyinosinic:polycytidylic acid (polyI:C), a mimic of viral replication. The majority of respiratory viruses have single stranded RNA genomes and produce dsRNA during replication, which stimulates host intracellular dsRNA sensors such as Toll-like receptor 3 (TLR-3), protein kinase dsRNA dependent (PKR), and the helicases retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated gene 5 (MDA5) and LPS glycosyltransferase 2 (LPG2). These sensors trigger epithelial antiviral innate response, including interferon response. Rezaee F et al. showed that polyI:C stimulation results in disruption of the epithelial intercellular apical adhesion complex. This complex comprises of 3 zonulae: *zonula occludens* (or tight junctions), *zonula adherens* (or intermediate junction) and the *macula adherens* (or desmosome). PolyI:C, but not other TLR ligands, disassembled tight junction proteins (occludin and ZO-1) and intermediate junction proteins (E-cadherin, beta-catenin), resulting in disruption of intercellular adhesion, disruption of apical intracellular actin cytoskeleton, increased epithelial permeability, and loss of epithelial electrical resistance. This disruption in epithelial barrier was mediated by PKC μ and did not cause cell death. Although this phenomenon was not confirmed with a virus infection in combination with assessment of permeability to allergens, it may play a role in the pathogenesis of the observed association among early life lower respiratory viral infections, allergic sensitization and later development of childhood asthma².

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In another article in this issue, Lai et al.³ investigated in the upper airways of patients with chronic rhinosinusitis the role of centrosomal protein 110 (Cp110), a protein that prevents terminal formation and elongation of cilia. They observed that Cp110 was increased and cilia coverage decreased in ethmoid sinus mucosa of patients with chronic rhinosinusitis (CRS) with and without nasal polyps compared with similar mucosal samples from normal control patients. *Ex vivo* cultures of differentiated ethmoidal epithelial cells showed a persistently elevated Cp110 in cells from patients with nasal polyps compared with cells from normal controls. In differentiated epithelial cultures from normal controls, cilia coverage decreased and Cp110 increased upon *ex vivo* treatment with tumor necrosis factor alpha and interleukins (IL-) 6, 8, and 13. The combination of IL-6 with IL-13 induced the greatest changes, and both cytokines are increased in nasal polyps^{4, 5}. The authors speculate that this mechanism may contribute to mucus stasis, biofilms formation on mucosa, and recurrent infections which are common in patients with CRS.

These two articles indicate that innate and adaptive immune responses in the airway mucosa alter morphology and function of the epithelium. This alteration does not involve death of epithelial cells exposed to the stimuli (polyI:C or cytokines), neither does it seem to induce proliferation of basal epithelial cells generating a defective epithelium. Instead, the resident epithelial cells change their morphology and physiology as they respond to airborne threats and inflammation. Such changes may be beneficial or harmful. On one hand, increased permeability of epithelial barrier may facilitate luminal influx of immune cells, and increased mucus production can augment secretion of antimicrobials into the lumen. On the other hand, these changes may lead to mucus stasis and airway obstruction. An example of plasticity - the ability of cells to change morphology and function - of epithelial cells involves the process of transdifferentiation. In transdifferentiation, one type of differentiated cell transforms into another type of differentiated cell, which is distinct from the usual differentiation process in which undifferentiated progenitor cells (e.g. stem cells, basal epithelial cells) give rise to differentiated cells (e.g. ciliated cells, goblet cells, Clara cells). It is now known that ciliated epithelial cells can transdifferentiate into mucous (goblet) cells upon stimulation with IL-13^{6, 7}, and back to ciliated cells after cessation of IL-13 stimulation⁸. Transition cells with a combined "ciliated mucous cell" morphology are observed during this transdifferentiation process⁸. Secretory (Clara) cells can also transdifferentiate into goblet cells and into ciliated cells⁹. Therefore, the inflammatory milieu can induce transdifferentiation of the respiratory epithelium, resulting in a predominance of ciliated or mucous cells. It is possible that the persistence of Cp110 in IL-13-treated epithelial cells observed by Lai et al.³ was part of transdifferentiation of ciliated cells into mucous cells.

Another example of the plasticity of airway epithelial cells is the epithelial-mesenchymal transition (EMT) process. Undifferentiated bronchial epithelial cells exposed to transforming growth factor beta 1 (TGF-beta1) for 72 hours start losing epithelial cell markers such as E-cadherin, and begin to express markers of myofibroblasts such as alpha smooth muscle actin (alpha-SMA) and vimentin¹⁰. In addition, epithelial cells undergo dramatic alteration in the organization of their filamentous actin (F-actin) cytoskeleton, changing morphology from the epithelial ovoid shape to the spindle shape of myofibroblasts. Myofibroblasts can migrate to subepithelial regions and secrete collagen, fibronectin, and extracellular matrix material, which could contribute to the subepithelial fibrosis observed in asthma¹¹. IL-13, present in airway Th2 inflammation of asthmatic patients, can stimulate and activate TGF-beta1 in the airways¹². In addition, inflammatory cytokines produced in acute response to respiratory viral infections such as tumor necrosis factor alpha (TNF-alpha) and interleukin 1 beta (IL-1beta) can enhance the TGF-beta1-induced EMT process^{13, 14}. It is therefore conceivable that the EMT process may contribute to the pathogenesis of airway remodeling in patients with asthma¹⁵.

In summary, plastic changes can occur in undifferentiated and differentiated epithelial cells in response to airborne threats and to chronic airway inflammation. Such plastic changes may play important roles in causing airway epithelial pathological and physiological changes observed both during acute injury such as respiratory viral infections, as well as in chronic airway epithelial remodeling of patients with asthma, COPD and cystic fibrosis. Understanding the molecular mechanism of epithelial cell plasticity will unveil new targets that may lead to the development of treatments to improve epithelial barrier, enhance mucociliary clearance, decrease mucus production, and possibly prevent or reverse subepithelial fibrosis.

Acknowledgments

Support: Ernest S. Bazley Grant to Northwestern University, AI072570, AI082984.

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