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REVIEW

Airway epithelial regulation of pulmonary immune homeostasis and inflammation

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Abstract Recent genetic, structural and functional studies have identified the airway and lung epithelium as a key orchestrator of the immune response. Further, there is now strong evidence that epithelium dysfunction is involved in the development of inflammatory disorders of the lung. Here we review the characteristic immune responses that are orchestrated by the epithelium in response to diverse triggers such as pollutants, cigarette smoke, bacterial peptides, and viruses. We focus in part on the role of epithelium-derived interleukin (IL)-25, IL-33 and thymic stromal lymphopoietin (TSLP), as well as CC family chemokines as critical regulators of the immune response. We cite examples of the function of the epithelium in host defense and the role of epithelium dysfunction in the development of inflammatory diseases.

Abbreviations: AAM, alternatively activated macrophage; AEC, airway epithelial cell; AHR, airway hyperresponsiveness; AJ, adherens junction; CARD, caspase recruitment and activation domain; CPA3, carboxypeptidase A3; DAMP, damage associated molecular pattern(s); DC, dendritic cell; EMCV, encephalomyocarditis virus; HNP, human neutrophil defensin; FLG, filaggrin; HDM, house dust mite; ICAM-1, intercellular adhesion molecule 1; IFN, interferon; IL, interleukin; JAM, junction adhesion molecule; KLRG1, killer cell lectin-like receptor G1; MAPK, mitogen activated protein kinase; LDL, low density lipoprotein(s); MC, mast cell; MDA5, melanoma differentiation-associated protein 5; MID1, midline 1; NK, natural killer; NLR, NOD-like receptor; PAMP, pathogen-associated molecular pattern(s); PAR, protease-activated receptors; PRR, pattern-recognition receptor(s); RIG-I, retinoic acid-inducible gene 1; RLR, RIG-I-like receptor; RORA, retinoic acid-related orphan receptor α; RSV, respiratory syncytial virus; RV, rhinovirus; SP-C, surfactant protein C; STAT, signal transducer and activator of transcription; TJ, tight junction; TLR, Toll-like receptor; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin; TSLPR, TSLP receptor; ZO, zonular occluden.

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Contents

1. Introduction

The regulation of immune homeostasis in the lung has long focused on leukocytes as the key orchestrators of the immune system; however, genetic, structural, and functional studies indicate that the epithelium is required for normal immune homeostasis and that epithelial dysfunction is involved in the development of inflammatory disorders of the airways and lung. The airway epithelium functions an essential barrier that responds to environmental stimuli as a critical immune regulator through the secretion of cytokines, chemokines, growth factors, antimicrobial peptides, and the recruitment of leukocytes. This epithelial centered view of disease pathogenesis provides a better understanding of the reasons why diverse stimuli such as inhaled allergens and non-allergic triggers such as pollutants, cigarette smoke, bacterial peptides, and viruses can all drive characteristic immune responses through their interactions with the epithelium. The epithelium is ideally situated to orchestrate and influence the adaptive immune response, and in this capacity acts as an interface between innate and adaptive immune regulation. In this regard, epithelial production of interleukin (IL)-25, IL-33 and thymic stromal lymphopoietin (TSLP), as well as CC family chemokines have emerged as critical epithelial factors that can initiate and amplify airway inflammation. These newly identified epithelial-specific cytokines are produced prior to the release of more commonly recognized Th2 type mediators of allergic inflammation including IL-4, IL-5 and IL-13. The objective of this article is to review the recent findings about the molecular and cellular mechanisms by which the epithelium regulates airway inflammation, host defense and immunity. We focus on the impact of inhaled environmental stimuli and pathogens on epithelial cell function and the role of these cells in immune regulation.

1.1. The epithelial barrier

The airway epithelium forms a continuous, highly regulated physical barrier that lines the airway lumen, separating the underlying tissue from inhaled environmental antigens. Intercellular epithelial junctions form the structural adhesive forces that maintain the airway epithelial barrier, and are comprised of tight junctions (TJs), adherens junctions (AJs) and desmosomes (Fig. 1). Tight junctions are the main regulators of paracellular permeability and movement of ions and solutes between cells. Transmembrane proteins such as junction-adhesion-molecule (JAMs), occludin, and claudins that anchor to the cytoskeleton to zonular occluden (ZO)-1, -2, and -3 and cingulin form these tight junctions. Adherens junctions mechanically connect the adjacent cells and initiate proliferation and differentiation through homotypic transmembrane E-cadherin adhesions that are anchored to the actin cytoskeleton and microtubule network by p120 catenin, β-catenin, and α-catenin. E-cadherin provides the architectural support required to form other junctional complexes, as delocalization of the TJ proteins ZO-1, occludin and claudins occurs following distorted AJ architecture [1,2]. Desmosomes consist of non-classical cadherins that form adhesive bonds between the filamentous cytoskeleton of epithelial cells and the lamina propria. In addition to its role in AJs, E-cadherin is also a ligand for the cognate receptor CD103 ($\alpha_E\beta_7$ integrin) expressed on innate and adaptive immune cells, including $CD8^+$ T cells, and a significant fraction of effector $CD4^+$ T cells and regulatory $CD4^+CD25^+Foxp3^+$ T cells (Tregs) [3]. CD103 also identifies a novel subset of dendritic cells (DCs) that also express E-cadherin, TJ proteins and langerin [4] that are involved in the induction of tolerance following inhaled allergen [5], and are critical for the clearance of several respiratory viral infections [4–7]. E-cadherin also binds to killer cell lectin-like receptor G1 (KLRG1), an inhibitory receptor expressed on a subset of activated natural killer (NK) cells, effector/memory T cells and $Foxp3^+$ Tregs. Engagement of KLRG1 inhibits secretion of inflammatory cytokines by DCs, thereby exerting immunosuppressive effects [8]. Thus, it is tempting to speculate that the interaction of innate and adaptive immune cells with E-cadherin on intact epithelium may play a role in the inhibition of DC and T cell activation.

Exposure of airway epithelial cells (AEC) *in vitro* to proteolytically active allergens such as Der p1 derived from house dust mite (HDM) [9,10], or Ragweed, White Birch, Kentucky Blue Grass, and Easter Lily pollen [11] can lead to the proteolytic degradation of airway epithelial intercellular