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The Pulmonary Epithelium in Health and Disease
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Edited by

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Preface

The past two decades have seen extraordinary advances in our understanding of the role of the pulmonary epithelium in airway health and disease. The traditional view of the epithelium as predominantly a physical barrier that also plays a role in ion and water transport has been supplanted by one in which the epithelium is now also considered to be a central regulator of airway inflammation, structure and function. In light of the dramatic changes in our awareness of the complexity of epithelial cell functions, it seemed particularly timely to produce a book to comprehensively address our current understanding of epithelial cell biology. In particular, I wished to focus not only on the epithelium as a regulator of normal airway function, but also to highlight the important roles of the epithelium in host defense, and the contributions of aberrant epithelial biology to the pathogenesis of inflammatory airway diseases.

The first two chapters of this volume are designed to provide an update on the basic structure of the epithelium, including information on the cell types that comprise the epithelium at different levels of the airway, and on the capacity of specific cell types to serve as progenitor cells for new growth. In addition, the remarkable recent increases in our understanding of the molecular components of the structures that are critical for the cell-cell, and cell-matrix, adhesion necessary to maintain epithelial structure are discussed, along with the complex roles of epithelial adhesion molecules in regulating not only epithelial function but also the interactions of the epithelium with other cell types and pathogens. The subsequent two chapters focus on the role of the epithelium as a target for damage by a variety of agents, and on the process of epithelial repair. Fragility of the epithelium is a hallmark of asthma, and there is growing recognition that a chronic damage/repair cycle may play a role in the pathogenesis of this disease. Although ion transport has long been recognized as a major function of the epithelium, our understanding of the complexity and regulation of epithelial ion transport, and of the consequences of dysregulation of these events, has improved considerably in recent years, and our current knowledge is detailed in Chapter 5.

Perhaps no facet of our awareness of epithelial cell function has grown as rapidly as our understanding of the role of the epithelium in host defense, the focus of the next block of chapters. As may be expected from its location at the airway surface, the epithelium plays a critical role in protection of the host from inspired pathogens and irritants. In the larger airways, the tightly regulated process of mucociliary clearance provides the initial defense to prevent pathogens from contacting the epithelial surface, and defects in ciliary beat, or abnormal mucus composition, underlie several airway diseases that are characterized by increased susceptibility to repeated infection. In the distal airways, where mucociliary clearance is absent, surfactant plays a critical role in reducing surface tension at the airway surface. Of equal importance, however, is the role of surfactant in host defense. Not only
does it coat particulates and microbes, facilitating clearance via cough, but it is now clear that several of the protein components of surfactant have broad ranging direct antimicrobial actions. If microbes can evade these initial defenses and come into contact with the epithelium, they are detected by a range of recognition molecules. These include specific receptors as well as broad-ranging “pattern recognition molecules”. Depending upon the specific nature of the ligand to be recognized, these molecules can be intracellular or expressed on the cell surface. Once microbial pattern recognition or specific receptor engagement occurs, epithelial cells respond by generating a wide range of defense molecules. These include direct antimicrobials, as well as molecules that serve to recruit and activate inflammatory cells that contribute to host defense. Finally, in this section, a major area of new investigation is the ability of the epithelium to play a major role in immunoregulation, in particular to provide an important link between innate and specific immunity.

The past decade or so also has seen marked improvements in our understanding both of the interactions of specific inhaled stimuli with the epithelium, and of the consequences of such interactions on airway function. The next set of chapters, therefore, deal with the interaction of four major classes of inhaled stimuli that affect epithelial function. Respiratory viruses not only cause upper airway diseases but also play a major role in triggering exacerbations of asthma and chronic obstructive pulmonary disease (COPD). Such effects are initiated via interactions with the epithelium. Similarly, epithelial responses to bacteria play a major pathogenic role in diseases from pneumonia, to cystic fibrosis to COPD. In our modern environment, pollutants are major exacerbarators of a range of airway diseases. Finally, while the interactions of allergens with cells such as mast cells, basophils and lymphocytes obviously play a major role in allergic diseases, a growing body of literature demonstrates that interactions of allergens, particularly those with endogenous proteolytic activity, with the epithelium not only contribute to direct inflammatory effects but also play a critical role in permitting access of allergens to target cells in the underlying airway tissue.

There is now no doubt that the epithelial cell plays a major role in regulating the inflammatory and structural status of the airway. The epithelium has wide ranging synthetic and metabolic capacities. It can maintain normal airway status via its ability to inhibit or degrade a range of proinflammatory molecules but, upon repeated exposure to stimuli, can also generate a wide range of mediators that can contribute to, and exacerbate, chronic airway inflammation. Recurrent epithelial damage and repair can also cause repeated interactions between the epithelium and other structural cells, such as fibroblasts/myofibroblasts, leading to chronic reactivation of the so-called “epithelial mesenchymal trophic unit”. This can lead to marked structural changes in the airway, such as the hallmark changes in asthma collectively referred to as airway remodeling.

The final set of chapters deals with the interactions of inhaled medications with the epithelium. Given the wide ranging properties discussed above, and the alterations of epithelial function in airway diseases, several of the beneficial actions of inhaled medications, including glucocorticoids, β2-adrenergic agonists and muscarinic receptor antagonists, in diseases such as asthma and COPD may well be mediated via alterations of epithelial cell function. Last, but not least, there is growing interest in inhaled delivery of drugs, not only as a means to exert local effects in the lung, but also as a means of systemic delivery for drugs, particularly those that cannot survive oral delivery. Preserving the molecular integrity of a formulation and delivering it to the appropriate target in the lung are critical for effective therapy, and some of the recent advances in this regard are discussed in the final chapter.
Each of the chapters in this text were written by leaders in their field. Production of a text of this comprehensive nature would not have been possible without their commitment. I would like to take this opportunity to extend my sincere thanks to all of the contributors for devoting their valuable time and expertise to this volume.

David Proud