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Review Series

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Take a deep breath: pulmonary research inspires

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The lung is one of only three organs (along with the skin and gastrointestinal tract) that are in constant contact with the surrounding environment. Interactions with the environment pose unique challenges to host defense, and the lung has evolved adaptive mechanisms for coping with exogenous insults, including infections and ambient exposure to allergens and irritants that result from our industrial society and changes in atmospheric constituents. Additional manmade insults, such as tobacco smoke, challenge the lung in potentially devastating ways. Pulmonary diseases such as asthma, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), and pulmonary fibrosis are important causes of morbidity and mortality worldwide.

Although there are numerous resident cell types in the lung and upper airways, from the nasal mucosa to the distal alveoli, there are common responses to injury that generate distinct pathologies based on the location of the injury. From the study of the interactions that take place between the epithelial lining of the lung and resident immune cells after insult, we can discern the processes that regulate the expansion of resident mesenchymal cells and recruitment of nonresident populations that influence the fate of the host. The goal of this Review Series is to concisely review of some of the most prevalent pulmonary diseases and to elucidate how new insights into the mechanisms that underlie these might lead to pathways for identifying novel and efficacious treatments. By framing mechanistic studies in a clinical context, we hope that these reviews will be of interest to both practicing clinicians and pulmonary scientists.

Begin at the beginning

In order to understand the functional basis of the pathobiology of lung disease, it is essential to outline the determinants of the specialized epithelium that lines the lung from proximal to distal regions. Here, Rackley and Stripp review the origins of lung epithelium and progenitor cells in distinct regions that contribute to lung repair (1). They further explain that understanding the complex cell signaling pathways and developmental patterning sequences required for the establishment of normal lung physiology is crucial to understanding disease, in part because pathological changes are often related to disruptions in the relationship between the epithelium and the underlying stroma.

Conflict of interest: P.W. Noble serves or has served as a consultant for Intermune, Boehringer-Ingelheim, Bristol-Meyers-Squibb, Celgene, Anthera, Stromedix, Glaxo-SmithKline, Actelion, Gilead, Regeneron, Moerae Matrix, and Takeda in the development of therapeutics for idiopathic pulmonary fibrosis.

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Barrier breakdown

As mentioned above, one of the key roles of the pulmonary epithelium is to act as a barrier between environmental insults and the internal milieu. ARDS occurs when these epithelial and endothelial barriers begin to break down, resulting in edema that can lead to acute respiratory failure that is often associated with multiple organ failure. The mortality rate for patients with ARDS has improved dramatically over the last three decades (2), in large part because of the success of networks of clinical researchers that have applied basic concepts of lung injury to clinical trial design. The review by Matthay, Ware, and Zimmerman discusses evolving concepts in the pathogenesis, treatment, and development of biomarkers for ARDS (3).

Worlds colliding: immunology in the lung

Despite the development of effective therapies that improve the symptoms of patients with asthma, significant unmet medical needs persist. The enormous heterogeneity of asthma remains unexplained, in large part because of deficient understanding of the complex immunology contributing to disease pathogenesis. Holtzman reviews evolving concepts in the relationship between innate and adaptive immunity that have the potential to identify novel therapeutic approaches to this important lung disease (4). Importantly, the author highlights the paradox of asthma as both a chronic immune condition and one driven by acute innate responses to infection, suggesting innovative ways that these characteristics might be targeted therapeutically.

COPD research has witnessed a resurgence over the last several years with the identification of novel concepts of pathogenesis. In particular, the recognition of mechanisms that perpetuate emphysema, even in the absence of exposure to tobacco smoke, have generated great enthusiasm that novel therapies can be identified. Indeed, as in asthma, COPD may be triggered or exacerbated by the immune responses to acute infection, and thus insight into the molecular mechanisms that drive these responses in the lung will be critical. Here, Tudor and Petrache review the novel developments in our understanding of the pathogenesis of COPD (5).

The end products

Pulmonary fibrosis in many ways represents one of the largest unmet medical needs in pulmonary medicine. However, the last decade has seen the successful execution of randomized clinical trials in idiopathic pulmonary fibrosis (6, 7), and although success to date has been limited, a consensus is emerging that pathways for identifying safe and effective therapies are being defined. In the final piece in this series, Barkauskas, Jiang, and I delineate the importance of discerning among different forms of pulmonary



fibrosis and describe exciting discoveries that are leading to novel therapeutic approaches in this severe pulmonary problem (8).

Although progress has been made in ameliorating symptoms in patients with a number of pulmonary diseases, morbidity and mortality due to progressive loss of lung function continues to be of major concern. Research needs to focus on identifying fundamental pathways that lead to loss of lung function, whether due to airway disease (asthma), parenchymal disease (pulmonary fibrosis and ARDS), or both (emphysema). As indicated in this series,

common themes can be identified whereby dysregulated cellular communications can lead to loss of organ function. The challenge is to translate these themes into efficacious therapies for patients with pulmonary diseases.

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