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Editorial Comment

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Immune Modulation in Chronic Respiratory Diseases: The Path to Precision Medicine

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In the last 50 years, there have been major advances in the understanding of the pathophysiology and, more recently, the pathobiology of chronic respiratory diseases. A deeper understanding of the immune system has significantly advanced our understanding of the pathogenesis of chronic respiratory conditions and the pivotal role that "chronic inflammation" plays in disease pathogenesis and disease progression. Indeed, there is accumulating evidence that dysregulations of the immune system play a central role not only in chronic airway diseases, such as asthma or chronic obstructive pulmonary disease (COPD), but also in various interstitial lung diseases (ILDs) and in the origin and growth of pulmonary neoplasms. This has led to new insights into the immunopathology of respiratory diseases, fueled further research in dysregulation of the immune response to injury resulting in novel highly targeted and more effective therapeutic options for a variety of respiratory conditions. This thematic review series focused on four common chronic respiratory conditions, the impact of chronic inflammation and immune dysregulation, and potential for immune modulation as a therapeutic option.

The advances in molecular network analyses (such as genomics, proteomics, or metabolomics) allow the exploration of the molecular complexity of a particular disease condition, the identification of specific disease pathways, and the exploration of molecular associations and differences between distinct clinical disease phenotypes. These network analyses have the potential to identify novel genetic or epigenetic changes that either cause or are associated with specific disease phenotypes. This could ultimately lead to the discovery of downstream changes in protein expression and metabolism, which have biological importance for phenotypic disease expressions. These analyses are key for identifying novel drug targets and biomarkers for a complex disease, such as COPD, asthma, bronchiectasis, and interstitial fibrosis, and the initiation and propagation of pulmonary malignancies. The unifying characteristic of all these conditions is a "chronic inflammatory response." Altering this chronic inflammatory response to be less destructive and more reparative in nature is the broad aim of immune modulation therapy. The advances in the field of "omics" complemented by network analyses have identified potential targets for immune-modulatory interventions. These network analyses have also allowed us to refine phenotyping and endotyping of these conditions, identifying both overlapping and unique immune inflammatory pathways that we can apply using our current therapies in a more personalized manner. Furthermore, the development of reliable biomarkers to identify unique disease phenotypes and to follow their progress are pivotal elements for future advancement in immune-modulatory therapies in chronic respiratory conditions. These tools will allow physicians to personalize therapeutic interventions for each patient.

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Chronic obstructive airways disease encompasses a broad range of very common inflammatory respiratory conditions, such as asthma, COPD, bronchiectasis, and other obstructive bronchial processes. These processes can overlap in both clinical presentation, pathogenesis, and pathophysiology and, therefore, have similar treatable traits (such as airways obstruction or eosinophilia) and treatment goals (such as bronchodilation or anti-inflammation) [1]. Although it seems to be clinically useful to lump these chronic airway inflammatory conditions together, it can hamper our efforts to better understand the underlying pathogenesis and pathobiology of these conditions and hamper the discovery and design of new therapeutic interventions. For example, current treatment options for asthma are a very good example of the success of immune-modulatory interventions and the concept of precision medicine. The approval of highly targeted biologics with minimal adverse effects, the advances in allergen immunotherapy, and a better understanding of the beneficial effects and limitations of inhaled corticosteroids have fundamentally changed the management and the outcomes of asthma. The review by Lommatzsch on immune modulation in asthma does not only discuss advances in asthma treatment but also sheds light on new immune-modulatory strategies which could enter clinical practice in the future. In contrast to asthma, there are currently few immune-modulatory interventions available for the treatment of COPD. Van Eeden and Hogg reviewed the advances in our understanding of the cellular and molecular mechanisms underlying the pathogenesis of COPD. Immune dysregulation is a unifying characteristic of this disease and is thought to be largely responsible for the progressive nature of COPD. The critical importance for disease phenotyping and endotyping in the quest for the development of targeted immune modulation interventions and the opportunities and challenges in developing immune-modulatory drugs for this complex and heterogeneous disease are discussed.

ILDs are a spectrum of diseases that originate with an insult/injury to the lung that elicits an inflammatory response that persists and results in fibrosis and/or a combination of inflammation and fibrosis [2]. While the fibrotic process is targeted with anti-fibrotic therapy, immune modulation is a logical target for specific therapeutic interventions in those ILDs where inflammation is a major component of the disease. Seeliger and Prasse review current immune modulation in ILDs associated with systemic inflammatory conditions, predominantly connective tissue diseases. The current treatment concepts are still dominated by the use of nonspecific conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). The role of targeted synthetic DMARDs (tsDMARDS) or biologic DMARDS (boDMARDS or bsDMARDS) is currently explored in various promising clinical trials. Although some of the latter drugs will probably enter clinical ILD practice in the near future, there are still significant challenges due to the diversity of the associated connective tissue diseases. Because the development of ILD is an important prognostic indicator in subjects with connective tissue diseases, this review focused on current evidence of specific immune interventions in ILDs associated with systemic inflammatory diseases.

In the 20th century, the treatment of metastatic lung cancer was dominated by rather nonspecific chemotherapies, which were associated with often severe life-threatening side effects and with poor outcomes. The advent of highly effective immune checkpoint inhibitors has changed the clinical management of lung cancer dramatically [3]. This has also underlined the importance of an assessment of molecular markers to guide treatment. Christopoulos and Gossamer review current concepts in the diagnosis and management of pulmonary malignancies with the focus on immune-modulatory strategies and options in lung cancer. They explore the complex interactions of the tumor with the immune system that will pave the way for future targeted therapeutic interventions. As with all new therapies, the use of these novel immune-modulating agents can have complex immune-mediated side effects. The review provides fascinating insights into the large landscape of potential future immune interventions in pulmo-oncology.

Because most chronic respiratory conditions are characterized by an underlying chronic inflammatory process, immune modulation has become a cornerstone for novel therapeutic options and will shape the future of pulmonary medicine. We hope that these four reviews of immune modulation in common respiratory conditions will inspire researchers and clinicians to explore immune modulation as a promising option for future therapeutic interventions in respiratory diseases.

Conflict of Interest Statement

M.L. reports no conflicts of interest regarding this Editorial.

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