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Allergy and hypersensitivity – airway inflammation and remodeling

Editorial overview

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Although asthma is a clinical diagnosis based on episodic symptoms, it is pathologically characterized by various types and degrees of chronic inflammation and structural changes in the airways. The structural changes, termed as ‘airway remodeling’, include epithelial denudation, goblet cell metaplasia, subepithelial thickening, airway smooth muscle hypertrophy, increased angiogenesis, and others [1]. Airway remodeling has been generally considered as a consequence of inflammation persisting for many years. However, recent accumulated evidences suggest that airway remodeling often continues even after successful treatment for airway inflammation by the state-of-the-art therapies such as inhaled corticosteroids. This section of Current Opinion in Immunology is devoted to reviews discussing recent advances in the field of allergy and hypersensitivity by focusing on airway inflammation and remodeling.

Doherty and Broide have reviewed in this issue the recent advances in the role of cytokines and growth factors in airway remodeling in asthma [2]. They noticed an important role for transforming growth factor (TGF)- β , vascular endothelial growth factor (VEGF), interleukin (IL)-5, IL-9, IL-13, and epithelial-derived NF- κ B-regulated chemokines such as eotaxin-1 in both human asthmatics and murine asthma model. TGF- β has been known to induce peribronchial fibrosis for a long time. What the most striking observation in the recent years is considered to be the discovery of the role of TGF- β in airway smooth muscle cell proliferation [2,3]. Thus, TGF- β may be a key cytokine for thickening subepithelial and smooth muscle layers and causing irreversible airway narrowing. Regulatory T cell-derived IL-9 is known to play a crucial role in allograft tolerance in a mouse model via mast-cell proliferation and activation [4]. In murine model of airway inflammation, however, IL-9 is shown to induce goblet cell hyperplasia in bronchial epithelial cells in association with accumulation of mast cells [2].

Thus, mast cells are recognized to be important for airway remodeling. **Okayama *et al.*** have reviewed the recent reports regarding the role of mast cells in airway remodeling [5]. The increase in airway smooth muscle mass is recognized as one of the most important factors related to airway hypersensitivity and to the severity of asthma. The infiltration of airway smooth muscle by mast cells is associated with the disordered airway function [6]. The mediators such as tryptase and cytokines from mast cells can modulate airway smooth muscle cell function and induce goblet cell hyperplasia. Thus, mast cells play an important role not only in immediate hypersensitivity and late phase inflammation but also in tissue remodeling in the airway.

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Eosinophils have been confirmed as an important source of TGF- β as well as other important cytokines that can lead to the direct activation of epithelium and mesenchymal cells that are considered to drive airway remodeling. The current studies that support a role for eosinophils in airway remodeling are reviewed by Kariyawasam and Robinson [7]. An eosinophil depletion study in human by the same author [8] has demonstrated that several aspects of remodeling are attenuated, suggesting that some elements of remodeling are more or less eosinophil dependent.

There is a spectrum of reversibility of airway remodeling changes in asthma which may affect various aspects of lung function differentially. Certainly it has been reported that hypersensitivity of airway muscle cells derived from asthmatic patients persists beyond cell division and proliferation compared to control patients, suggesting the presence of epigenetic changes [9]. Adcock *et al.* [10] have summarized the role of epigenetic regulation in airway inflammation and remodeling by focusing on histone modifications. As these changes are due to enzymatic activity, it raises the possibility of reversing these epigenetic effects and preventing further disease progression.

The lung contains many subsets of dendritic cells that are distributed in various anatomical compartments. Kool and Lambrecht have summarized [11] the roles of various dendritic cell subsets in the lung. Among these subsets, mature inflammatory CD11b⁺ dendritic cells play a pivotal role in the initiation and maintenance phase of airway inflammation seen in asthma and chronic obstructive pulmonary disease. Especially when exposed to thymic stromal lymphopoietin (TSLP) derived from bronchial epithelial cells, these cells produce a large amount of inflammatory chemokine, CCL17. Then, CCL17 attracts many Th2 cells into the lung.

The presence of virus in nasal secretions and indications of allergy (eosinophilic inflammation or positive RAST testing) synergistically increased the odds ratio for wheezing at 25-fold [12]. Kato and Schleimer have introduced their recent work demonstrating that double strand RNA and IL-4 synergistically induce the production of TSLP by bronchial epithelial cells [13]. They have reviewed also the role of newly found epithelial cell-derived cytokines, TSLP, IL-33, and B cell-activating factor of the TNF family (BAFF) in shaping the local accumulation and activation of Th2 responses and B cell immunoglobulin production. They have speculated that, in asthmatic airways, these epithelial cytokines may also contribute to

local production of IgE [13]. Thus, improved understanding of epithelial immune and inflammatory responses will hopefully suggest new strategies for therapeutic intervention.

Although airway remodeling is now thought to be the most important concept in asthma, it was termed only based on pathological findings which may cause irreversible airway narrowing. It involves different types of structural changes in various cell types. Most of the molecular mechanisms therefore remain unidentified. As suggested by Kato and Schleimer [13], even local immunoglobulin production may occur. This issue provides update knowledge on several important aspects of airway inflammation, remodeling and immunity, and I wish to thank all authors for their wonderful contributions.

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