Editorial

Airway remodeling in asthma

Carolyn Damilola Ekpruke^, Patricia Silveyra^

Department of Environmental and Occupational Health, Indiana University Bloomington, School of Public Health, Bloomington, IN, USA

Correspondence to: Patricia Silveyra. Department of Environmental and Occupational Health, Indiana University Bloomington, School of Public Health, Bloomington, IN 47405, USA. Email: psilveyr@iu.edu.

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Asthma is a heterogeneous lung disease affecting approximately 300 million patients worldwide. Asthma is generally characterized by anatomical alterations of the airway. Such alterations are collectively referred to as airway remodeling. In airway remodeling, both small and large airways are affected (1). Airway remodeling comprises the thickening of airway smooth muscle layers due to increased cell proliferation and inflammation (1). In allergic asthma, pattern recognition receptors in epithelial cells help secrete chemokines and cytokines to recruit dendritic cells; the reason why epithelial cells are referred to as airway remodeling initiators (2). Immune cells release interleukin-13, platelet-derived growth factor, and transforming growth factor-β which help in the amplification of the airway remodeling magnitude in asthma (3). These cells are also referred to as airway remodeling mediators through the activation of fibroblasts in the submucosa (4).

Several scientists have reported the pathological features of airway remodeling, including thickening of the airway wall and subepithelial reticular basement membrane, damage to epithelial cells, alterations in airway smooth muscle cells, mucus gland hyperplasia and hypertrophy, and angiogenesis and vascular remodeling. In this issue of the journal, Huang and Qiu reviewed the most recent research advances in airway remodeling in asthma, from the literature available between 2001–2022. The authors addressed this topic by discussing the various pathological features of airway remodeling, including the interaction of different cell types within the airway smooth muscle layer and the submucosa (5). They indicated that airway remodeling can be either pathological or physiological and either prevent or contribute to bronchoconstriction. For example, bronchoconstriction in asthma can result from the degradation of the cartilage thereby contributing to the stiffness of the airway (6). Similarly, goblet cell hyperplasia causes an increase in the production of sputum, consequently leading to the narrowing and thickening of the airway walls (5). However, some studies suggest that the thickening of the airway walls in airway remodeling may also prevent bronchoconstriction (6). During airway remodeling, the deposition of the matrix to the subepithelial layer can make the airway stiff and therefore prevent its narrowing (7). Similarly, the migration and increased contractility of the airway smooth muscle cells may help prevent obstruction of airflow in the airway (8).

The study by Huang and Qiu looked at the various ways of evaluating airway remodeling either by directly or indirectly assessing the airway tissues using invasive or non-invasive tools. The authors, clearly discuss the direct methods and stated the limitations of these methods as reported by the American Thoracic Society guidelines. Direct methods of evaluating airway remodeling include carrying out endobronchial biopsy (9), transbronchial biopsy, and trans-endobronchial cryobiopsy (9), though these methods have limitations. Indirectly, airway remodeling has been evaluated by collecting and analyzing the bronchoalveolar lavage fluid (BALF). While BALF is a well-recognized method for quantifying the number of cells released during the asthma allergic cascade, the dilution factor used by different investigators is usually inconsistent, which makes the method less accurate. Other relatively non-invasive, indirect methods used to assess airway remodeling are sputum analysis (10), exhaled breath condensate,

^ ORCID: Carolyn Damilola Ekpruke, 0000-0002-9045-4457; Patricia Silveyra, 0000-0001-7083-8915.

and blood and urine analysis (11). These methods are easier than the direct methods, but their accuracy remain controversial. Alternative tools use to assess air remodeling in asthma include computed tomography (12), optical coherence tomography (13), endobronchial ultrasound (14), position emission tomography (15), hyperpolarized magnetic resonance imaging and Birefringence microscopy. These methods are very efficient but also costly. Similarly, high resolution non-linear optical microscopy has replaced the normal tissue staining method by scientists evaluating airway remodeling in asthma (16). The ratio of forced expiratory volume in one second and forced vital capacity values obtained during lung function testing can also be used to characterize this major asthma component (17).

The authors also discussed different ways of treating airway remodeling in asthma. These methods include the use of glucocorticoids, anti-IgE, anti-TNF antibodies and vitamin D therapies. They also made mention of a non-pharmacological, safe, and efficient method, bronchial thermoplasty and the development of individualized treatment protocols. Some researchers reported that glucocorticoid drugs may not be effective for the treatment of airway remodeling as they observed that it can only partially reduce lung function and airway thickness (18), while others reported that the use of these sets of drugs induced epithelial cell apoptosis and hindered their migration (19). The effectiveness of monoclonal antibodies, include varieties of anti-IL-5, IL-4/IL-13 and IL-33 in the treatment of airway remodeling that occurs in asthma has also been investigated (20). Recently, the use of bronchial thermoplasty was reported as a new therapy for the treatment of severe refractory asthma (21). This procedure consists of the introduction of radiofrequency into the airway wall through bronchoscopy and has proven to reduce airway remodeling. All these methods and their limitations are described in the review.

This study has several limitations. First, it concentrates on clinical evidence and did not discuss information from experimental models used to understand mechanisms of airway remodeling in the past few years. Such models range from *in vitro* to *in vivo* and have been specifically developed to study the pathogenesis of asthma and airway remodeling. Examples of models that were recently used for this purpose include the epithelial-mesenchymal trophic unit model of the bronchial mucosa (22), and porcine airway smooth muscle strips to assess airway contractility (23). Second, sex differences in airway remodeling and asthma treatment were not discussed. There is well-established evidence that sex differences occur in asthma across the life span, and many researchers are advocating for a sex-specific treatment of the disease. Finally, the authors do not mention potential ways of improving the present methods of treating asthma to make them affordable and accessible to more patients. Recently, some researchers have studied the role of nutrition in the prevention and treatment of asthma (24) as there is a general belief that nutrition or diet possesses immunomodulatory effect. This may help to complement the existing methods for treatment lung disease.

In short, this review summarizes the different pathological features of airway remodeling and the existing different ways of treating asthma. The summary provided by the authors might help provide information leading to development of better strategies for evaluating airway remodeling mechanisms both in animal models and clinical studies. For instance, sex-differences in airway remodeling that occur in asthma need to be investigated, and sex-specific responses to treatment reviewed. Future review studies should focus on integrating evidence of airway remodeling in both clinical and animal studies and providing therapeutic options that account for sex differences in disease pathogenesis and presentation, as well as consideration of more affordable therapeutic options such as nutritional interventions.

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