Recent Advances in Mechanisms and Treatments of Airway Remodeling in Asthma: A Message from the Bench Side to the Clinic

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Airway remodeling in asthma is a result of persistent inflammation and epithelial damage in response to repetitive injury. Recent studies have identified several important mediators associated with airway remodeling in asthma, including transforming growth factor-β, interleukin (IL)-5, basic fibroblast growth factor, vascular endothelial growth factor, LIGHT, tumor necrosis factor (TNF)-α, thymic stromal lymphopoietin, IL-33, and IL-25. In addition, the epithelium mesenchymal transformation (EMT) induced by environmental factors may play an important role in initiating this process. Diagnostic methods using sputum and blood biomarkers as well as radiological interventions have been developed to distinguish between asthma sub-phenotypes. Human clinical trials have been conducted to evaluate biological therapies that target individual inflammatory cells or mediators including anti IgE, anti IL-5, and anti TNF-α. Furthermore, new drugs such as c-kit/platelet-derived growth factor receptor kinase inhibitors, endothelin-1 receptor antagonists, calcium channel inhibitors, and HMG-CoA reductase inhibitors have been developed to treat asthma-related symptoms. In addition to targeting specific inflammatory cells or mediators, preventing the initiation of EMT may be important for targeted treatment. Interestingly, bronchial thermoplasty reduces smooth muscle mass in patients with severe asthma and improves asthma-specific quality of life, particularly by reducing severe exacerbation and healthcare use. A wide range of different therapeutic approaches has been developed to address the immunological processes of asthma and to treat this complex chronic illness. An important future direction may be to investigate the role of mediators involved in the development of airway remodeling to enhance asthma therapy.

Keywords: Transforming growth factor beta; Fibroblast growth factor; Vascular endothelial growth factor; Thymic stromal lymphopoietin; Biologic therapy

INTRODUCTION

Asthma is a chronic inflammatory disease of the airway that is characterized by the presence of inflammatory cells and structural changes that are referred to as “airway remodeling.” Classically, airway remodeling in patients with asthma constitutes subepithelial fibrosis, increased deposition of extracellular matrix protein, goblet cell hyperplasia and mucus gland hypertrophy, smooth muscle hypertrophy and hyperplasia, and epithelial damage [1-3]. Candidate cells involved in airway remodeling are eosinophils, T-lymphocytes, mast cells, epithelia, macrophages, airway smooth muscle (ASM) cells, and fibroblasts. Immune cells provide mediators that are involved in the process of airway remodeling [4-6]. Several mediators such as transforming growth factor-β (TGF-β), vascular...
endothelial growth factor (VEGF), ADAM metallopeptidase domain 33 (ADAM-33), matrix metalloproteinase-9 (MMP-9), and Th2 cytokines (interleukin [IL]-5, IL-13, IL-4, and IL-9) are linked to remodeling [4-6]. Additional mediators have recently been identified including LIGHT (TNFSF14), tumor necrosis factor (TNF)-α, and basic fibroblast growth factor (bFGF) [7-10]. Epithelial cells are also important in the initiation of allergic inflammation. Epithelial injury results in the persistent activation of epithelial mesenchymal transforming unit (EMTU), which promotes airway remodeling, leading to persistent asthma [10,11]. Epithelial injury increases the expression of thymic stromal lymphopoietin (TSLP), IL-33, and IL-25, which induce Th2 memory cell expansion and cytokine secretion [12]. Clinicians seek additional options other than the currently available conventional treatments to improve the condition of patients with severe asthma and to spare systemic corticosteroid administration. This review presents recent advances in the mechanism, diagnosis, and treatment of asthma, focusing on the use of mediators for airway remodeling therapy, as well as procedures that assess asthma severity. Animal research and human studies have enabled clinicians to better evaluate the extent of airway remodeling and to design specific treatment strategies appropriate for each patient.

MECHANISMS OF AIRWAY REMODELING: A LINK BETWEEN CELLS AND MEDIATORS

Animal studies using models of airway remodeling and human studies both support the finding that immune or inflammatory cells and mediators are important in the pathogenesis of airway remodeling (Fig. 1). For example, recent studies have demonstrated that environmental factors cause a defect in the epithelia, inducing an innate immune response by activating dendritic cells and Th2 memory cells to release mediators linked to remodeling [13]. In addition, eosinophils are immune cells that express TGF-β, which acts as a key mediator during airway remodeling. Studies using anti IL-5 antibody to deplete eosinophils have reported a link between eosinophilic depletion and decreased TGF-β expression. Other cell types such as bronchial epithelial cells and macrophages may also express TGF-β in the lung. It is essential to understand the link between cells and mediators during remodeling to enhance current biological therapies for asthma.

Eosinophil related cytokines: IL-5, CCR-3, Siglec-8(F)

Allergen-induced murine models of airway remodeling have highlighted the importance of eosinophils during airway remodeling. IL-5 transgenic mice exhibit an increase in eosinophils in the lung, accumulation of peribronchial eosinophils, goblet cell hyperplasia, epithelial hypertrophy, and focal collagen deposition. They also show airway hyper-responsiveness (AHR) to methacholine in the absence of an aerosolized antigen challenge [4]. IL-5, chemokine receptor (CCR)-3, and siglec-8(F) are critical molecules associated with eosinophilic trafficking in target organs.

IL-5

IL-5 is a key cytokine that regulates the proliferation and differentiation of eosinophils, as well as the trafficking of eosinophils from the bone marrow to the lung [14,15]. A remarkable reduction in TGF-β-expressing eosinophils occurs in the remodeled airways of IL-5-deficient mice. Anti IL-5 treatment significantly reduces levels of bronchoalveolar lavage (BAL) eosinophils and remodeling, as assessed by reduced deposition of the extracellular matrix-associated remodeling proteins procollagen and tenascin [16]. Furthermore, the anti IL-5 antibody mepolizumab decreases airway thickness and wall area in patients with refractory asthma [17]. Several anti IL-5 antibodies including mepolizumab, reslizumab, and enralizumab (MEDI563) are now in clinical trials. However, blocking IL-5 alone only reduces 50–60% of tissue eosinophils; therefore, additional blocking of eosinophil trafficking may be required to completely block eosinophils.

CCR-3

CCR-3 is a chemokine receptor expressed by eosinophils that mediates chemotaxis in response to chemokines including eotaxin and RANTES. CCR-3-deficient mice and eotaxin-deficient mice show decreased levels of airway eosinophilia and mucus production [6]. Reduced subepithelial fibrosis and goblet cell hyperplasia are observed in a mouse model of airway remodeling subjected to low-molecular-weight CCR-3 antagonists [18]. A recent study administered a CCR-3 receptor antagonist (Ki19003) to an ovalbumin (OVA)-induced asthma model and found that