Editorial
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Angiogenic Factors Play a Significant Role in Nasal Airway Remodeling in Allergic Rhinitis

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The definition of remodeling is "model again or differently, reconstruct." In the airway, reaction to chronic inflammatory conditions can lead to changes in the structural components of the airway wall, known as airway remodeling. Airway remodeling in response to allergens is a well-known key feature of pathogenesis in asthma, a representative allergic disease of the lower airway.[1-3] The structural changes in airway remodeling comprise epithelial disruption, smooth muscle hypertrophy, goblet cell hyperplasia, subepithelial fibrosis, inflammatory cell infiltration, and vascular remodeling such as neovascularization.[4] The nasal and bronchial mucosa present similarities, and epidemiologic studies have revealed that allergic rhinitis and asthma are closely related with each other.[5] Therefore, once regarded as two separate disease entities, they are now considered to be a common disease with different clinical manifestations. Thus, airway remodeling is presumed to occur in allergic rhinitis.[6] Many previous studies have shown that airway remodeling exists in allergic rhinitis, although it seems to be less extensive than that in asthma.[7-11]

Several studies have been performed to elucidate the epithelial changes in the nasal mucosa of patients with allergic rhinitis. An electron microscopic study has revealed that damaged epithelium and tight junctions of the epithelial cells were found in the nasal mucosa of patients with allergic rhinitis.[12] Allergic patients also present a marked goblet cell hyperplasia, and have a thicker epithelium than normal persons.[8,13] However, there was a contradictory result that patients with perennial rhinitis have an epithelium thickness comparable with that of normal persons.[14] In addition, the epithelial damage is less extensive in the nose than in the bronchi of the same asthmatic patients.[15] Also, there is pseudo-thickening of the reticular basement membrane caused by collagen deposition in allergic rhinitis, although the extent was less severe than in asthma.[9] Furthermore, matrix metalloproteinases (MMPs), major proteolytic enzymes that are involved in extracellular matrix turnover, is increased in the nasal mucosa 10 hours after nasal allergen challenge.[16] Expression of tissue inhibitors of matrix metalloproteinases (TIMPs) mRNA was also increased in the nasal mucosa of patients with perennial allergic rhinitis.[7]

In terms of vascular remodeling, only few studies have been conducted to evaluate the association between angiogenesis and nasal airway remodeling until now. Mori et al.[17] have reported that the hypervascularity and overexpression of the platelet-derived endothelial cell growth factor, a potent angiogenic factor, were observed in the nasal mucosa of allergic rhinitis. However, the mechanism and exact process of remodeling, especially regarding angiogenesis, is still poorly understood in allergic rhinitis.

In the present issue of *Allergy, Asthma & Immunology Research*, Moon et al.[18] addressed this topic that angiogenic factors can be associated with nasal airway remodeling. The authors assessed the role of representative angiogenic factors, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), in the development of nasal airway remodeling in response to chronic allergic inflammation. Though the interpretation of the data is complicated, the results provide interesting information. After repetitive intranasal challenge with ovalbumin for 3 months in experimental mice, significant nasal airway remodeling, such as increases in eosinophil infiltration, subepithelial fibrosis, goblet cell count, and MMP-9/TIMP-1 expression, was developed as compared with

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control mice challenged with PBS. Of particularly interest, these abnormal responses were inhibited following systemic administration of SU1498, a VEGF receptor inhibitor, and/or AG1296, a PDGF receptor inhibitor. As far as we know, this is the first attempt to clarify the association between inhibitors of potent angiogenic factors and nasal airway remodeling in allergic rhinitis, and the result is noteworthy.

This result provides indirect evidence that angiogenic factors may play some role in nasal airway remodeling. Increased eosinophil infiltration was consistently inhibited by blocking the function of angiogenic factors in this study. It is well known that eosinophils are the main effector cells of allergic inflammation and an important source of VEGF along with other inflammatory and structural cells in inflamed tissue.[19] Eosinophils are a source of several molecules, such as fibroblast growth factor-2, MMP-9, and TIMP-1 that are implicated in tissue remodeling processes.[20] In addition, PDGF is a physiologically important activator of eosinophils in pulmonary inflammation associated with asthma.[21] Furthermore, the authors found that subepithelial fibrosis along with MMP-9/TIMP-1 expression were also influenced by the inhibitors of angiogenic factors. This is in accordance of the previous report that there is a significant correlation between VEGF and MMP-9 levels in asthmatic patients.[22] Also, VEGF receptor inhibitors were effective in reducing MMP-9 expression and reversing all pathophysiologic signs in an asthma murine model. Therefore, Moon et al.[18] hypothesized that increased vascular permeability caused by angiogenic factors after chronic allergen challenges can lead to leakage of inflammatory cells, such as eosinophils. Subsequent augmented eosinophilic inflammation may influence MMP-9/TIMP-1 and subepithelial fibrosis.

In the study, the authors only confirmed that inhibition of angiogenic factors can reduce the nasal airway remodeling. However, the authors did not provide an evidence of increased neovascularization in the nasal mucosa. This may be a limitation of the study, and further studies are necessary to confirm the exact relationship between angiogenesis and nasal airway remodeling.

Recently, scientific concern with regard to the nasal airway remodeling in allergic rhinitis has grown. Clarifying responsible mechanism for nasal airway remodeling is necessary in allergic rhinitis in order to better understand the underlying pathophysiology and develop new treatment strategy. In addition, elucidating the role of angiogenic factors in nasal airway remodeling in the study may develop new treatment strategies in patients with allergic rhinitis in the future. In a clinical aspect, however, further studies regarding demonstrating dose-response relationship between anti-angiogenic agents and airway remodeling and comparing treatment efficacy of airway remodeling among well-known anti-inflammatory drugs (steroid) and anti-angiogenic agents are needed to investigate the clinical applicability of these anti-angiogenic agents.

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