Fibronectin and matrix metalloproteinases are involved in airway smooth muscle cell migration for the process of airway remodeling

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Abstract

The asthma patients have led to airway narrowing as a result of tissue structural change called airway remodeling. Remodeling is one of the pathological condition in which tissue components such as epithelial cells, fibroblasts, smooth muscle cells (SMCs), and microvascular endothelial cells are involved in the repair process after airway injury. The primary histopathological feature of airway remodeling is smooth muscle thickening. We proposed the hypothesis that "autocrine" migration and proliferation of SMCs may play a crucial role in the smooth muscle thickening of bronchi, and paid our attention to the mechanism of the chemotactic migration of the bronchial SMCs (bSMCs) into the connective tissue in the airway mucosal tissue.

We found that chemoattractants for bSMCs were produced in bSMC-conditioned medium using the modified Boyden chamber assay. Extracellular matrix (ECM) components such as laminin, fibronectin and type I collagen were examined as candidates of chemoattractants for bSMCs. However, fibronectin only was determined as a chemoattractant in bSMC-conditioned medium by Western blotting analysis using these ECM antibodies. The proof that fibronectin is the chemoattractant in bSMC-conditioned medium was confirmed by the fact that the migration of bSMC to bSMC-conditioned medium was inhibited by addition of anti-fibronectin antibody. In addition, we found by Gelatin Zymography that metalloproteinases (MMPs) were secreted in bSMC-conditioned medium and elucidated by Western blotting analysis that MMP-2 was one of the MMPs.

These findings suggest that bSMCs produced MMPs containing MMP-2 to degrade connective tissue and migrate into the degraded connective tissue by producing fibronectin as a chemoattractant, indicating that "autocrine" migration of bSMCs into connective tissue may be an important process for smooth muscle thickening in airway remodeling of asthma.

Future finding is to identify receptor on the membrane of bSMCs that recognizes fibronectin. It has been reported by Cyman, et al. [1] that β1 and β3 integrins play important roles in the migration of vascular smooth muscle cell to fibronectin. We also found that the migration of bSMC to fibronectin and bSMC-conditioned medium was inhibited by addition of anti-β1 and β3 integrin antibodies. Further studies on identification of receptor and signaling pathway are under way.