**A25** Targeted deletion or pharmacological inhibition of MMP-2 prevents cardiac rupture after myocardial infarction in mice

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**Objectives** Matrix metalloproteinase (MMPs) are implicated in left ventricular (LV) remodeling after acute myocardial infarction (MI). In the present study, we investigated the influence of either a targeted deletion of the MMP-2 gene or its selective inhibition on LV remodeling after inducing MI in mice, and examined the implication of extracellular matrix (ECM) degradation in cardiac rupture and the role of ECM degradation products in macrophage migration.

**Methods** MI was created by either ligating the left coronary artery of MMP-2 knockout mice and wild-type mice or the latter group were administered orally an MMP-2 selective inhibitor (TISAM).

**Results** The survival rate was considerably higher in MMP-2 knockout and TISAM-treated mice than in control wild-type mice. The main cause of mortality in control wild-type mice was cardiac rupture, which was not observed in MMP-2 knockout or TISAM-treated mice. Control wild-type mice, but not MMP-2 knockout or TISAM-treated mice, showed proMMP-2 activation, strong gelatinolytic activity and degradation of ECM components including laminin and fibronectin in the infarcted myocardium. Although infarcted cardiomyocytes in control wild-type mice were rapidly removed by macrophages, the removal was suppressed in MMP-2 knockout and TISAM-treated mice. Macrophage migration was induced by the infarcted myocardium from control wild-type mice and was inhibited by treatment of macrophages with laminin or fibronectin peptides prior to migration assay.

**Conclusion** These data suggest that inhibition of MMP-2 activity improves the survival rate of acute MI by preventing cardiac rupture and delays post-MI remodeling through a reduction in macrophage infiltration.

MMP-2の遺伝子欠損と薬物的阻害はマウスの心筋梗塞後の心破壊を抑制する

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**A26** 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.


気道組織の異常形成機序：気道平滑筋細胞の異常組織へのフィブロネクチン及びマトリックスメタロプロテアーゼの関与

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