

ROLE OF THROMBIN IN VASCULAR REMODELING IN CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

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Objective: Chronic thromboembolic pulmonary hypertension (CTEPH) has been increasingly recognized as a cause of pulmonary hypertension. However, it remains unclear why and how pulmonary vascular remodeling occurs in CTEPH. We have previously reported that platelet-derived growth factor (PDGF) plays an important role in progression of pulmonary vascular remodeling in CTEPH. Thrombin is a part of the common coagulation cascade and another participant in thrombosis. Thrombin also has direct cellular effects through interaction with the family of protease activated receptors. The current study is designed to determine the significance of thrombin in vascular remodeling and further evaluate whether inhibition of thrombin could be therapeutic target in CTEPH.

Methods: The endarterectomized tissues were obtained from patients with CTEPH and used to isolate pulmonary vascular cells (CTEPH cells). Control lungs were obtained from subjects who underwent lung lobectomy. Immunohistochemical studies were performed using formalin-fixed paraffin-embedded sections. Cell proliferation was assessed by ³H-thymidine incorporation assay and tetrazolium salt assay. Intracellular Ca²⁺ imaging system was used to measure changes in cytosolic Ca²⁺ with fura-2.

Results: In normal lung tissues, thrombin receptor was expressed in endothelial cells. In contrast, in the endarterectomized tissues from CTEPH patients, thrombin receptor was expressed not only in endothelial cell layers but also in smooth muscle actin-positive layers. Thrombin treatment was associated with a rise in cytosolic Ca²⁺ and enhanced store-operated calcium entry (SOCE). Inhibition of thrombin could significantly reduce thrombin- and PDGF- induced augmentation of SOCE. In cell proliferation assays, thrombin- and PDGF- induced excessive cell proliferation were also significantly reduced by thrombin inhibition.

Conclusions: Thrombin has direct effects on increasing SOCE and cell proliferation of CTEPH cells. Inhibition of thrombin was effective in attenuating SOCE and cell proliferation induced by PDGF as well as by thrombin. Inhibiting thrombin signaling may potentially be a therapeutic target in CTEPH.