Abstract

Increased expression of plasminogen activator inhibitor type 1 (PAI-1) contributes to vascular remodeling and pulmonary arterial hypertension (PAH). However, the cellular and molecular mechanism of PAI-1 in regulating PAH pathogenesis has not been fully understood. Proliferation of pulmonary artery smooth muscle cells (PASMC) is critical for vascular remodeling. We have recently generated smooth muscle specifc-PAI-1 transgenic mice and demonstrated that increased PAI-1 in VSMC promotes proliferation and inhibits apoptosis. Thus, increased PAI-1 may regulate vascular remodeling by increasing PASMC proliferation and decreasing apoptosis. Antagonists of endothelin-1 are widely used clinical therapies for PAH. Endothelin-1 induces PAI-1 in a variety of cells; and endoithelin-1 inhibits apoptosis and induce proliferation of VSMC. Accordingly, PAI-1 may mediate the effect of endothelin-1 in PAH. We hypothesize that **elevation of PAI-1 promotes PASMC proliferation, thus regulating vascular remodeling and progression of pulmonary hypertension.** Two specific aims are proposed to test the hypothesis:

Specific Aim 1 Characterize the role of PAI-1 in hypoxia-induced PAH *in vivo*
Part A Effect of PAI-1 deficiency on hypoxia-induced PAH in mice
Part B Role of PAI-1 in mediating the effect of ET-1 in hypoxia-induced PAH

Specific Aim 2 Characterize the role of PAI-1 in hypoxia-induced PASMC proliferation *in vitro*
Part A Effect of hypoxia on the expression of PAI-1 and ET-1 by PASMC
Part B Role of PAI-1 in mediating the effect of hypoxia on proliferation of PASMC

Results from the proposed studies will facilitate the identification of potential therapeutical strategies and targets to prevent or retard PAH.