Endothelial Senescence Mediates Hypoxia-induced Vascular Remodeling in the Lung

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Introduction: Pulmonary hypertension (PH) is a fatal pulmonary vascular disease characterized by a sustained elevation of pulmonary arterial (PA) pressure. The major characteristic of PH is uncontrolled accumulation of PA smooth muscle cells (SMCs) to normally non-muscularized distal PAs. Disrupted PA endothelial cell (EC) signaling stimulates PASMC proliferation and accumulation to distal PAs. Cellular senescence contributes to aging and lung diseases associated with PH. Although senescent cells are unable to replicate, they secrete senescence-associated secretory phenotype (SASP) factors, allowing the cells to be metabolically active and control behaviors of neighboring cells. The mechanistic role of EC senescence in pathogenesis of PH has not been fully understood. The Hippo pathway signaling transducer, Yes-associated protein (YAP1) stimulates angiogenesis and controls cell proliferation and survival.

Methods: We utilize PH patient-derived PAECs to examine YAP1, PDGFB, and EC senescence activity. We also use hypoxia-induced PH model to investigate PA remodeling as well as measure right ventricular (RV) systolic pressure and RV hypertrophy to study the effects of EC senescence.

Results: YAP1 activity is upregulated in idiopathic pulmonary arterial hypertension (IPAH) patient-derived PAECs. The levels of senescence markers are higher in ECs isolated from PH patients compared to those from healthy individuals. The levels of PDGFB upregulated in PH patient-derived ECs are inhibited by knocking down $p16^{INK4A}$ expression. $p16^{INK4A}$ knockdown decreases YAP1 expression, which suppresses PDGFB expression in IPAH patient PAECs. Accumulation of □-smooth muscle actin (αSMA)-positive cells to the PAs in a hypoxia-induced mouse PH model is attenuated in *$p16^{INK4afl/fl}$-Cdh5(PAC)-Cre^{ERT2}* mice, in which $p16^{INK4a}$ expression is knocked down in ECs after tamoxifen induction. Hypoxia-induced PA remodeling is reversed when mice are reoxygenated after 21 days of hypoxia.

Conclusions:
These results suggest that increases in EC senescence mediate vascular remodeling in PH through endothelial YAP1-PDGFB signaling.