Endothelial senescence mediates hypoxia-induced vascular remodeling in the lung through TWIST1 signaling

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Introduction: Pulmonary hypertension (PH) is a fatal pulmonary vascular disease characterized by a sustained elevation of pulmonary arterial (PA) pressure. One of the major characteristics of PH is uncontrolled accumulation of PA smooth muscle cells (SMCs) to normally non-muscularized distal PAs. Cellular senescence contributes to aging and lung diseases associated with PH. We have reported that a transcription factor, TWIST1, in endothelial cells (ECs) mediates hypoxia-induced accumulation of PASMCs to PAs by increasing platelet-derived growth factor (PDGFB) expression. The aim of this study is to examine whether cellular senescence controls vascular remodeling in PH through TWIST1. **Methods:** We utilize PAECs derived from healthy individuals and PH patients to examine EC senescence. We also use a *p16$^{INK4Afl/fl}$-Cdh5(PAC)-Cre^{ERT2}* mouse model to determine the effects of EC senescence on vascular remodeling in a hypoxia-induced PH model. **Results:** The levels of senescence markers are higher in ECs isolated from PH patients compared to those from healthy individuals. Publicly available microarray data of PH patient lungs reveal the alteration of senescence-related gene expression and their interaction with TWIST1. The levels of PDGFB upregulated in PH patient-derived ECs are inhibited by knocking down p16^{INK4A} expression or treatment with senolytic reagent ABT-263. Hypoxia-induced accumulation of α-smooth muscle actin (αSMA)-positive cells to the PAs and TWIST1 expression are attenuated in *p16$^{INK4Afl/fl}$-Cdh5(PAC)-Cre^{ERT2}* mice after tamoxifen induction. Exosomes derived from hypoxia-treated mouse lung ECs stimulate DNA synthesis and migration of PASMCs, while those derived from *p16$^{INK4Afl/fl}$-Cdh5(PAC)-Cre^{ERT2}* mouse lung ECs inhibit these effects. These results suggest that EC senescence mediates vascular remodeling in PH through TWIST1 signaling.