

Lymphatic YAP1 in hypoxia-induced vascular remodeling

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Pulmonary hypertension (PH) is a life-threatening pulmonary vascular disease characterized by sustained elevation of pulmonary arterial (PA) pressure. Remodeling of distal pulmonary arterioles (PAs) is a key feature of PH and involves accumulation of PA smooth muscle cells (PASMCs) to PAs. Lymphatic endothelial cells (LECs) contribute to cardiovascular and lung diseases associated with PH. The role of lymphatics in PH pathology has not been examined before. Depletion of lymphatics accelerates hypoxia-induced PA remodeling and right ventricular (RV) hypertrophy. Expression of Hippo signaling transducer, Yes associated protein (YAP1) increases in hypoxia-treated mouse lung LECs. Hypoxia induced PA remodeling and RV hypertrophy are enhanced in the *Prox1-Cre^{ERT2}-Yap1^{fl/fl}* mouse lungs, in which expression of APLN that inhibits PA remodeling in LECs decreases. Conditioned medium collected from hypoxia-treated LECs or LECs treated with YAP activator suppresses DNA synthesis of SMCs; in contrast, an APLN receptor inhibitor inhibits the effects. These results suggest that lymphatic YAP1 signaling is necessary for suppressing hypoxia-induced distal PA remodeling.