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Inhibin Beta-A is a novel gene involved in the development of pulmonary arterial hypertension through inhibiting BMPRII-signaling in endothelial cells

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Introduction: Pulmonary Arterial Hypertension (PAH) is marked by vascular remodeling process that eventually causes pressure increase. Endothelial cells (EC) dysfunction is known to be a major cause for pulmonary vascular remodeling; however, the molecular mechanism remains to be elucidated.

Purpose: This study aims to identify novel genes and mechanisms involved in PAH development.

Methods: We performed DNA microarray analysis using RNA samples isolated from human ECs of various vascular beds (including lung microvessels) and organs (including lung). We subsequently searched for genes highly and specifically expressed in lung microvessels since these genes are likely involved in pulmonary circulation homeostasis maintenance. Once found, we confirmed its expressional changes during hypoxia in ECs and lung tissues. We next analyzed its role in EC functions using human pulmonary artery ECs (hPAECs) by in vitro angiogenesis assay, using both candidate gene overexpression via retrovirus transfection and treatment with its active form using appropriate recombinant protein. To explore the role of candidate gene in PAH development in vivo, we generated EC-specific knockout mice and transgenic mice in which the candidate gene is genetically deleted and activated in ECs, respectively. PAH was induced by chronic hypoxia exposure (10% O2 for 3 weeks). Lastly, to explore the underlying mechanisms, we analyzed expressional alterations in possible signaling pathways in ECs that could relate with the effect of the candidate gene.

Results: From microarray analysis, we identified inhibin Beta-A (INHBA) as a candidate gene that was highly and specifically expressed in human lung microvascular ECs. INHBA homo-dimerization is known to produce activin A (ActA), a TGF-beta superfamily member. Hypoxia exposure caused significant decrease of INHBA mRNA expression in ECs and mouse lung tissues. Both INHBA overexpression and ActA-treatment in hPAECs caused dramatic reduction of their angiogenic capacities (reduced migration and tube formation capability with increased apoptosis). In vivo, EC-specific INHBA overexpressing mice (VEcad-INHBA-TG) showed exacerbated hypoxia-induced PAH, assessed by higher right ventricular systolic pressure (RVSP) and more severely remodeled pulmonary arteries. By contrast, EC-specific INHBA knockout mice (INHBA-floxed/VEcad-Cre-TG) showed significant amelioration of PAH, shown by reduced RVSP and vascular remodeling. Furthermore, we found that INHBA overexpression and ActA-treatment induced a marked reduction of BMPRII, known to play pivotal roles in PAH, in hPAECs by accelerating its lysosomal degradation.

Conclusion: We identified a novel gene that is crucially involved in PAH development. INHBA and/or ActA negatively regulates EC functions potentially through its BMPRII-altering capability. Gain- and loss-of-function studies in mice revealed that INHBA pathways are promising therapeutic targets for the treatment of PAH.