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Pulmonary Hypertension and Venous Thrombo-embolic Disease

IMPACT OF ENDOTHELIAL FIBROBLAST GROWTH FACTORS ON PULMONARY HYPERTENSION

Poster Contributions
Poster Hall, Hall C
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Session Title: Understanding Pulmonary Vascular Disease: From Bench to Bedside
Abstract Category: 35. Pulmonary Hypertension and Pulmonary Thrombo-embolic Disease
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Background: Pulmonary hypertension is a debilitating disease where 1 in 4 patients will die within five years of diagnosis. Pathologic changes of endothelial cell function, together with smooth muscle and adventitial hyperplasia increase pulmonary vascular resistance. Consequent elevation in right ventricular pressure ultimately causes right heart failure.

Methods: Expression of Fibroblast Growth Factor Receptors (FGFRs), FGFR1 and FGFR2, are elevated in lung samples from pulmonary hypertension patients; however, the impact of these receptors on endothelial cell function, and endothelial to smooth muscle interaction is poorly understood.

We hypothesize that activation of endothelial FGFR1 and FGFR2 promotes endothelial cell survival, elaborating signals that protect against pulmonary hypertension via inhibition of smooth muscle cell recruitment.

Results: We used the *Tie2-Cre* transgene to conditionally inactivate *Fgfr1* and *Fgfr2* in endothelial cells. Experimental mice with genotype *Tie2-Cre; Fgfr1f/f; Fgfr2f/f* (DCKO) and control *Fgfr1f/f; Fgfr2f/f* (DFF) were challenged with 10% hypoxia for 15 days. At the end, right ventricular pressure (RVp) was measured by cardiac catheterization. Compared to mice in normoxia, control littermates in hypoxia demonstrated significant increases in RVp and RV to left ventricle + septum (LV+S) weight ratio, consistent with development of PH. DCKO mice demonstrate further elevation in RVp and an increase in the RV to LV+S weight ratio, demonstrating worsening pulmonary hypertension. Although the FGF ligands that mediate this endothelial response to hypoxia are not known, preliminary studies show that FGF10 expression was decreased in hypoxia-challenged DCKO mice as compared to both DCKO littermates on room air, and to hypoxia challenged DFF control mice.

Conclusion: These data suggest that endothelial FGFR1 and FGFR2 activation may protect against pulmonary hypertension. Further studies are underway to elucidate the role of FGF10 and its mechanism in the pathogenesis of pulmonary hypertension as well as other FGF ligands and associated signaling mechanisms that could regulate endothelial to smooth muscle interactions.