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Insight into Right Ventricular Defenses to Pulmonary Arterial Hypertension: Potential Role of TRF2, A Telomeric Protein

INTRODUCTION:

Pulmonary hypertension (PH) is a debilitating disease characterized by pathologic changes of endothelial cell (EC) function, leading to increased pulmonary vascular resistance. Group 3 PH, caused by lung disease and/or hypoxia, including bronchopulmonary dysplasia (BPD) and chronic obstructive lung disease (COPD), is the second largest cause of mortality in PH patients. PH further increases the morbidity and mortality in both COPD and BPD patients. There is an unmet medical need to understand the mechanisms of pulmonary vascular remodeling in group 3 PH and to identify novel therapeutic targets.

BACKGROUND:

Fibroblast growth factor (FGF) 2 and FGF receptor 1 (FGFR1) are elevated in the lung tissue of PH patients. We have developed a physiologically relevant hypoxia mouse model that mimics group 3 PH. We showed that the inactivation of FGFRs in ECs worsens PH, while the expression of a constitutively active FGFR1 (caFGFR1) in ECs protects against hypoxia-induced PH. These data suggest that FGF activity plays a vital role, signaling in part via endothelial FGFR1, to protect against group 3 PH.

HYPOTHESIS AND OBJECTIVES:

We hypothesize that direct activation of FGF signaling or FGFR-regulated signaling pathways in ECs will protect against PH. In this proposal, we will identify targets of EC-FGFR1 signaling involved in the protection of hypoxia-induced PH, and we will develop a viral vector to therapeutically activate FGF signaling in ECs.

SPECIFIC AIMS:

To achieve these goals, we will identify associated FGF signaling pathways activated in hypoxia-challenged EC cultures, and we will use translating ribosome affinity purification technology to identify and characterize FGFR-regulated transcripts in ECs in vivo. We will develop an in vivo adenovirus (Ad) system to deliver activated FGFR1 to pulmonary ECs. We will use an engineered adenovirus (Ad5.MBP) with tropism for ECs to construct an Ad5.MBP.caFGFR1 delivery package and test its efficacy in preventing or reversing the pulmonary vascular remodeling in hypoxia-induced PH. This project will advance our understanding of PH and explore a potential therapeutic approach that could prevent or even reverse the effects of hypoxia on PH.