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PDE9A in right ventricular and pulmonary vascular remodeling

Introduction:

Augmentation of cyclic guanosine monophosphate (cGMP) signaling via phosphodiesterase (PDE) inhibition is a cornerstone of therapy in PAH. Available PDE inhibitors require endogenous nitric oxide (NO), which has limited bioavailability in PAH. This application aims to elucidate the role of an NO-independent PDE (PDE9A) in a murine PH model.

Background:

The intracellular second messenger cGMP is critical for endothelial, vascular smooth muscle, and cardiac myocyte function. In the RV and pulmonary circulation, NO and natriuretic peptides are the two primary endogenous activators of cGMP. PDE activity promotes cGMP catabolism, and PH promotes PDE5 expression (and cGMP inhibition) in the RV and pulmonary vasculature. PDE5 inhibitors (sildenafil, tadalafil) have vasodilatory and anti-proliferative effects in the lung and inotropic effects in the RV. However, reduced NO bioavailability may limit efficacy in some patients. We have intriguing new preliminary data that an alternative, NO-independent PDE (PDE9A) is up-regulated in the RV during myocardial remodeling in a murine PH model (chronic hypoxic PH; CH-PH). Our coinvestigator, Dr. David Kass, recently demonstrated that PDE9A is up-regulated in the left ventricle during hypertrophy and failure. Furthermore, PDE9A specifically inhibited natriuretic peptide-cGMP signaling (not NO-cGMP) in cardiac myocytes, and PDE9A inhibition prevented pressure-overload induced left ventricular remodeling independent of NO. The role of PDE9A in RV and pulmonary vascular remodeling has not been explored. Given the critical role of cGMP-dependent signaling in myocyte and pulmonary vascular homeostasis, we believe the elucidation of an NO-independent regulatory pathway may yield significant therapeutic promise.

Hypothesis and Objectives:

We hypothesize that PDE9A regulates RV and pulmonary vascular remodeling via cGMP signaling in the CH-PH model. This proposal aims to use advanced molecular, morphological, and physiological methods to elucidate the role of PDE9A activity on CH-PH induced cGMP signaling, RV and pulmonary vascular remodeling.

Specific Aim 1:

To determine whether PDE9A regulates RV and lung cGMP signaling during CH-PH. We will expose PDE9A-/-mice and wild-type littermates to CH-PH for 1 and 3 weeks. We will measure and compare PDE9A expression and activity, cGMP, and protein kinase G activity (PKG-1; downstream effector kinase) in RV and lung samples.

Specific Aim 2:

To measure the effects of PDE9A deficiency on CH-PH induced RV and pulmonary vascular remodeling. Through a combination of stereological morphometry and RV pressure-volume loops, we will compare pulmonary vascular and RV remodeling between PDE9A-/-mice and wild-type littermates after 1 and 3 weeks of CH-PH.