2012 Abstracts

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The Role of Sirtuins and Lysine Acetylation in Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a progressive, incurable, and fatal disease of the lung vasculature characterized by increasing pulmonary vascular resistance (PVR) that ultimately leads to right ventricular failure and death. Although the gene responsible for the majority of cases of heritable PAH – bone morphogenetic protein receptor type 2 (BMPR2) – was identified over a decade ago, and despite creation of a robust transgenic mouse model, the precise molecular etiologies of PAH remain unclear. Increasingly, disrupted metabolic processes have been implicated as being key pathologic processes leading to PAH. Decreased insulin sensitivity, impaired glucose homeostasis, and increased aerobic glycolysis have all been demonstrated in PAH in cell culture, in animal models, and in patients with disease. We have recently analyzed the entire metabolome of human pulmonary endothelial cells expressing disease-causing BMPR2 mutations and have shown that many interconnected metabolic pathways are disrupted in PAH. These widespread and interconnected changes suggest the possibility of one or more master regulators that coordinate the balance of cellular metabolic flux and that may be dysfunctional in PAH. Sirtuins are class III lysine deacetylases that have been shown to regulate inflammation, transcriptional activation, and cellular metabolism. Many of the specific pathways regulated by sirtuins align very closely with the metabolic changes we and others have observed in PAH. We thus hypothesize that

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lysine hyperacetylation resulting from decreased sirtuin function drives the metabolic defects underlying PAH. The proposed studies will demonstrate decreased sirtuin function in cell culture, in transgenic mouse models of PAH, and in cells and tissues from PAH patients. These studies will also use manipulation of sirtuin function (e.g., using knockout mice, caloric restriction, and nutrient excess) to show that sirtuins directly impact disease course in PAH. Demonstration of a causative role for decreased sirtuin function would allow for targeting sirtuins and the downstream metabolic defects to have a potentially disease-modifying effect.