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Osteopontin in Idiopathic Pulmonary Arterial Hypertension, a Biomarker and Therapeutic Target

Proliferation of smooth muscle cells (SMCs) and pulmonary arterial remodelling are key mechanisms in the pathogenesis of idiopathic pulmonary arterial hypertension (IPAH). Osteopontin (OPN) is a pleiotropic cytokine involved in the proliferation of vascular SMCs. We recently discovered that OPN is upregulated in the lungs of patients with pulmonary hypertension (PH) associated with pulmonary fibrosis (PF), suggesting that the lung tissue is a source of OPN. Genome-wide RNA expression profiling experiments demonstrated a significant elevation of OPN in lungs of rats with hypoxic PH. Circulating OPN levels are significantly higher in IPAH patients compared to healthy subjects, they independently predict survival and are associated with a higher NYHA class. *In vitro*, the OPN expression level is highly related to the proliferative state of arterial SMCs, promoting adhesion and chemotaxys of vascular cells. However, the expression level and the cellular sources of OPN in the lungs of IPAH are unknown. The correlation between OPN levels and hemodynamics has also never been studied. We hypothesize that there is a high expression of OPN in the lungs of IPAH patients, and that there is a significant correlation with circulating OPN and hemodynamic parameters. Ultimately we hope to provide further rationale for OPN as a biomarker and therapeutic target. To do this, we will compare the OPN gene expression (microarray analysis) in the lung tissue of patients with IPAH who underwent lung transplantation (LTx) with normal controls. To validate the microarray results, we will analyze the molecular expression level of OPN in the lung tissue with real-time RT-PCR,

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and measure OPN levels in the peripheral blood from the same patients. As heart catheterization is routinely performed immediately before starting LTx, we will study the relationship between OPN lung expression, circulating OPN and hemodynamic parameters. To investigate the cellular sources of OPN, we will perform OPN immunohistochemistry on the histological slides obtained from the native lungs of IPAH patients and normal controls.