**Hyaluronan and the development of Pulmonary Hypertension secondary to Lung Fibrosis**


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**Introduction:**

Pulmonary Hypertension (PH) is a fatal disorder characterized by increased vascular tone and remodeling of the lung vasculature. PH is diagnosed by heart catheterization (mPAP ≥ 25 mmHg), it affects between 20-84% of patients with Idiopathic Pulmonary Fibrosis (IPF) and drastically impacts survival. Currently, there are no effective treatments for PH in IPF, other than lung transplantation.

Increased levels of hyaluronan, a component of the lung extracellular matrix, have been observed in patients with IPF and idiopathic pulmonary arterial hypertension (IPAH), a form of PH where the lung parenchyma is not affected. Furthermore, overexpression of hyaluronan synthase 2 (HAS2), an enzyme responsible for the synthesis of hyaluronan, has been implicated in severe fibrosis.

These observations suggest a role for hyaluronan in the pathophysiology of PH in IPF. However, hyaluronan-mediated vascular remodeling and the mechanisms promoting increased hyaluronan synthesis in PH associated to IPF are not fully understood.

**Hypothesis:**

Increased hyaluronan deposition in the lungs promotes vascular remodeling in PH associated with IPF.

**Methods:**

**Human Studies:**
Flash frozen and FFPE lung tissues from patients diagnosed with IPF +/- PH were collected from patients at the time of transplant and processed for analysis of HAS2 transcript levels and immunohistochemistry for hyaluronan.

**Animal Studies:**
Two distinct models of lung fibrosis and PH: bleomycin (BLM)-induced and adenosine deaminase (ADA)-deficient mice were utilized. Mice were treated with the hyaluronan synthesis inhibitor, 4-Methylumbelliferone (4-MU) and markers of PH and lung fibrosis were determined.

**Funding:**

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**Results:**

The bleomycin model of Lung fibrosis and pulmonary hypertension

BLM-exposure to mice led to body weight loss, lower arterial oxygenation levels, fibrosis in the lungs and elevated markers of pulmonary hypertension, including right ventricle systolic pressures (RVSP), RV hypertrophy (Fulton index), and enhanced smooth muscle actin (alpha-smooth muscle actin), a marker of vascular remodeling observed histologically. Treatment with 4-MU was able to attenuate vascular remodeling, RVH and RVSP, however no changes in weight loss or fibrotic deposition were observed.

The Chronic Adenosine Deaminase Deficient model

Ado ^"^ mice treated weekly with decreasing doses of PEG-ADA presented with reduced arterial oxygenation levels and elevated Ashcroft scores, consistent with the development of lung fibrosis. In addition, these mice presented with increased RVSP, Fulton indices and vascular remodeling, observed histologically from osma-stained sections. Treatment with 4-MU for 4 weeks was able to attenuate lung fibrosis and markers of pulmonary hypertension including RVSP and vascular remodeling.

**Conclusions:**

Taken together, these data suggest that hyaluronan may be an important molecular trigger leading to excess vascular remodeling and pulmonary hypertension secondary to chronic lung injury. 4MU, a compound already used clinically, attenuates vascular remodeling secondary to chronic lung injury and may offer some therapeutic potential in patients at risk of developing PH secondary to chronic lung diseases.