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The Role of Hyaluronan in Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis (IPF)

Pulmonary hypertension (PH) is a disorder affecting the vasculature of the lung that is often associated with idiopathic pulmonary fibrosis (IPF). PH is characterized by increased vascular tone and remodeling of the vasculature, including increased vascular smooth muscle mass and neo-muscularization of vessels. If left untreated, patients die as a result of right ventricular hypertrophy leading to right-sided heart failure. Increased levels of hyaluronan, a component of the lung extracellular matrix, have been observed in patients with pulmonary arterial hypertension. Hyaluronan is produced by hyaluronan synthases (HAS) and can be broken down by hyalrurindases into fragments that promote inflammation, remodeling, and angiogenesis through its interaction with hyaluronan binding proteins. However, the involvement of hyaluronan signaling in PH in IPF is not fully understood. Our preliminary data demonstrate a strong correlation between HAS2 expression and mean pulmonary arterial pressure (mPAP) in patients with IPF with and without PH. In addition, increased presence of hyaluronan is observed in remodeled vessels of patients with IPF and PH. Based on these observations our hypothesis is that: Increased hyaluronan deposition in the lungs promotes vascular remodeling in PH associated with IPF. In order to test this hypothesis, we will perform critical proof-of-concept experiments on a unique set of lung tissue derived from lung explants from patients diagnosed with IPF where right-heart catheterization was performed and a diagnosis of PH is available. Human pulmonary artery smooth muscle cells will be used to determine the effect of hyaluronan fragments on cell proliferation and migration. Finally, an experimental model of lung fibrosis and pulmonary hypertension will be utilized to generate pre-clinical data supporting the role of HAS inhibition as a potential therapy to prevent the development of PH in patients with IPF. This proposal will provide key mechanistic and pre-clinical data aimed at enhancing our understanding of how the extracellular matrix is able to participate in vessel remodeling, with the view of developing novel therapies against PH secondary to lung fibrosis.