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Enriching Research in Pulmonary Vascular Medicine

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Hyaluronan Drives Pathologic Vascular Metabolism in Pulmonary Hypertension

INTRODUCTION AND BACKGROUND:

Pulmonary hypertension (PH) is a complex and incurable cardiovascular disorder that is both deadly and morbid. Contemporary treatment rests upon supportive care and maximal relief of pulmonary vasoconstriction. However, disease-modifying therapies that can halt or reverse vascular remodeling, a cardinal feature of PH, are lacking. Mounting evidence indicates that vascular remodeling in PH involves crosstalk between metabolically defective vascular wall cells and their abnormal extracellular matrices.

This basic and translational study examines the impact of hyaluronan (HA), the extracellular matrix glycan, on aberrant vascular metabolism and growth responses in pulmonary hypertension (PH). This project will confront a critical gap in knowledge about the interface between cellular and matrix metabolism in pulmonary vascular biology. The biochemical foundation for this proposal is found in the structure of HA, which is formed by the linear polymerization of aminosugars generated through the hexosamine biosynthetic pathway (HBP). The HBP directly connects to and orchestrates glucose, glutamine, fatty acid, and nucleotide metabolism. Derangements in these metabolite families have been implicated in the pathogenesis of PH.

HYPOTHESIS AND OBJECTIVES:

The proposed studies explore the hypothesis that excessive HA synthesis and HBP activation exacerbate metabolic reprogramming and proliferation of pulmonary artery smooth muscle cells to drive PH. Three main objectives test this hypothesis. The first objective will define the dynamics and key regulators of HA synthesis and HBP in human samples and rodent models of PH. The second objective will elucidate the impact of HA on cellular bioenergetics, and the third objective will test the therapeutic potential of a pharmacologic HA inhibitor in experimental PH.

SPECIFIC AIM 1:

Establish the contribution of the HA-HBP axis to PH pathogenesis and progression.

SPECIFIC AIM 2:

Define the impact of the HA-HBP axis on PASMC bioenergetics and phenotype.

SPECIFIC AIM 3:

Evaluate the therapeutic potential of HA blockade on experimental PH.