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Therapeutic Targeting of Gasdermin D in Pulmonary Arterial Hypertension

INTRODUCTION:

Pulmonary arterial hypertension (PAH) is characterized by inflammation-mediated pulmonary vasculature remodeling. The inflammasome pathway, terminating in lytic cell death termed pyroptosis, may contribute to PAH pathogenesis. The pyroptosis executioner, gasdermin D, has not been investigated as a therapeutic target in PAH, and is the focus of this proposal.

BACKGROUND:

Pyrotposis is initiated by the inflammasome, a multimeric cytosolic signaling platform, which culminates in the activation of the pore-forming protein gasdermin D. Active gasdermin D oligomerizes in the plasma membrane to serve as a conduit through which IL-1β is released from the cell. This large pore, however, also triggers pyroptosis, cell death mediated by plasma membrane disruption and the further release of pro-inflammatory intracellular molecules. To date, no published studies have demonstrated a specific role for gasdermin D in experimental or human pulmonary arterial hypertension. Yet, this prospect is substantiated by considerable indirect evidence: (1) Inflammasomes are activated by chronic hypoxia and their genetic or pharmacologic inhibition attenuates vascular remodeling and pulmonary hypertension development in mice and rats. (2) Inhibition of the pyroptosis-dependent cytokine IL-1β reduces pulmonary hypertension in rodent models. In humans with pulmonary arterial hypertension, serum IL-1β is elevated and correlates with clinical outcomes. (3) Our own work has shown that HMGB1, a danger associated molecular pattern released by pyroptosis, is increased in the lungs of patients with pulmonary arterial hypertension. In associated proof-of-concept studies using rat models of pulmonary hypertension, we found that HMGB1 inhibition prevents vascular remodeling, improves hemodynamics and right ventricular function, and confers a survival advantage. (4) Lastly, in preliminary studies, we have found that genetic deletion of gasdermin D is protective against chronic hypoxia-induced pulmonary hypertension in mice.

The discovery of gasdermin D as the common terminal machinery of pyroptosis positions it as a potentially important target for pulmonary arterial hypertension treatment.

HYPOTHESIS AND SPECIFIC AIMS:

We hypothesize that inflammasome activation leading to pyroptosis drives the development of pulmonary arterial hypertension, and blockade of pyroptosis through gasdermin D inhibition may represent a novel therapeutic strategy. Our overall objective is to thoroughly characterize the immunologic pathogenesis of pulmonary arterial hypertension to develop immune-based treatments.