



Enriching Research in Pulmonary Vascular Medicine

Embracing the Potential of

**YOUNG
INVESTIGATORS**

HAIYANG TANG, PHD

University of Arizona
Tucson, AZ

Differential role of mTORC1 and mTORC2 in hypoxic vasoconstriction and the development of pulmonary hypertension

INTRODUCTION:

The project for which we request funding will focus on the implication of PI3K/AKT/mTOR signaling pathway in the development of pulmonary hypertension (PH). We expect completion of the proposed studies will provide novel insights into the understanding of pathogenesis of PH, which may lead to novel therapeutic targets for PH.

BACKGROUND:

Pulmonary arterial hypertension (PAH) is a rare but progressive and deadly disease caused by functional and structural changes in the pulmonary vasculature, which lead to an increase in pulmonary vascular resistance (PVR). Pulmonary vascular remodeling or concentric vascular wall thickening of small pulmonary arteries and arterioles, due partially to enhanced proliferation and migration of pulmonary arterial smooth muscle cells (PASMCs), is a major cause for elevated PVR in patients with PAH and chronic hypoxia-induced pulmonary hypertension (HPH). Multiple cellular and molecular mechanisms have been demonstrated to contribute to the development and progression of pulmonary vascular remodeling; however, the specific sequence of events involved in the enhanced PASMCs proliferation in pulmonary hypertension remains unclear. The PI3K-Akt-mTOR pathway is one of the fundamental intracellular signaling cascades that communicate extracellular mitogenic signals to the nuclear transcriptional machinery that induces cell proliferation and protein synthesis. Our previous studies demonstrate that unique Akt isoforms have distinctive effects in the development of HPH and that Akt1 but not Akt2 is essential for pulmonary vascular remodeling. We have also shown the importance of the Akt1/mTOR pathway in which increased levels of PTEN, an upstream repressor, or specific KO of downstream mTOR in PASMC, can significantly attenuate the development and progression of HPH. The Akt/mTOR pathway will continue to be a focus of research aimed at determining factors that affect pulmonary vascular remodeling, and focusing on specific isoforms or targets of this pathway may lead to novel therapeutic targets for pulmonary hypertension.

HYPOTHESIS AND OBJECTIVES:

Since mTOR associates with different proteins (Raptor or Rictor) to form two functional macromolecular complexes (mTORC1 and mTORC2), we propose that mTORC1 and mTORC2 play differential roles in the development of hypoxia-induced pulmonary hypertension and dual inhibition of mTOR1/2 complexes attenuates hypoxic vasoconstriction and the development of pulmonary hypertension.

SPECIFIC AIM 1:

To determine the roles of mTORC1 and mTORC2 in the cell proliferation, migration, smooth muscle cells phenotypic switching under hypoxia conditions, and PAECs endothelial-mesenchymal transition using pharmacologic and genetic approaches.

SPECIFIC AIM 2:

To investigate whether mTORC1/2 complexes regulate hypoxic pulmonary vasoconstriction (HPV) and the development of vascular remodeling in HPH models using PASMC or PAEC conditional KO mice.

SPECIFIC AIM 3:

To determine whether dual inhibition of mTORC1/2 complexes prevent and reverse the development of HPH, using inhibitors targeting the Akt/mTORC1/2 signaling pathway.