Medical University of Graz

Altered ion channel conductance leads to pulmonary arterial stiffening

Summary

Experimental Anesthesiology, Department of Anesthesiology, Medical University of Graz Ludwig Boltzmann Institute for Lung Vascular Researcgh, Graz

Supervisors:	Prof. Dr. Andrea Olschewski Dr. Chandran Nagaraj
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 15, 2022 00:00 and March 28, 2022 23:59 (Europe/Zurich)

Description

Background:

Pulmonary arterial stiffening is a key component in the pathogenesis of vascular remodeling in the lung and can serve as an index of disease progression. Emerging evidence also supports the idea that stiffening can precede the development and promotes the remodeling of the small lung vessels leading to pulmonary hypertension (PH), a severe disease limiting survival (1). However, the exact role of vascular stiffening in the development and progression of PH has yet to be defined. Essential questions in this context are: i) what are the mechanosensitive pathways/factors that are activated, and ii) how can they regulate cellular proliferation, survival, and metabolism, particularly during the development and progression of PH. Ion channels have already been identified as important regulators of pulmonary vascular tone and vascular remodeling (2)(3). However, the mechanosensitive ion channels have been largely neglected so far.

Hypothesis and Objectives:

We hypothesis that the mechanosensitive ion channels in human pulmonary arterial smooth muscle cells (PASMCs) and endothelial cells (PAECs) are novel players in PH. We will characterize their expression and function in healthy and PH human lungs and explore the pathways leading to pulmonary vascular remodeling. Proof of concept studies will be performed in pre-clinical animal models of PH.

Methodology:

In this project the student will: (i) investigate mechanosensitive ion channels in PASMCs from explanted PH lungs and healthy donor samples; (ii) explore their role in downstream signaling in PH with a special focus on cellular ion homeostasis, cell proliferation, metabolism and vascular stiffening/vascular tone; (iii) prove the importance of selected ion channels in vivo models of PH incl. genetically modified mouse models. *Year 1:* The PhD student work on isolated primary PASMCs/PAECs from explanted human lungs. Ion channel expression, trafficking, localization and function will be examined by molecular biological techniques, confocal fluorescence microscopy/FRET, proximity ligation assay and by analysis of cell proliferation, survival and cellular metabolism. *Year 2:* The functional role of the channels will be investigated by wire-myograph, patch-clamping, gel contraction assay and live-cell calcium imaging. *Year 3-4:* The student will analyze the role of the pathways in well-established experimental models for PH.

References:

1. Liu F et al. Distal vessel stiffening is an early and pivotal mechanobiological regulator of vascular remodeling and pulmonary hypertension. JCI Insight 2016;1:e86987.
2. Humbert M, Guignabert C, … Olschewski AJ… Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. Eur Respir J. 2019 Jan 24;53(1):1801887. doi: 10.1183/13993003.01887-2018.
3. Nagaraj C, Tang B, … Olschewski A. Src tyrosine kinase is crucial for potassium channel function in human pulmonary arteries. Eur Respir J. 2013 Jan;41(1):85-95. doi: 10.1183/09031936.00211811.

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