Medical University of Graz

The chloride channel regulator CLCA1 and the calcium-activated chlorid channel TMEM16A in inflammatory lung diseases

Summary

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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 March 24, 2021 00:00 and May 05, 2021 23:59 (Europe/Zurich)

Description

Background:

Mediators released from inflammatory cells associated with chronic inflammatory lung diseases (ILD) such are known to elevate intracellular calcium in target cells or directly regulate ion channels (1). The TMEM family, particularly TMEM16A, is a critical component of Ca-activated chloride (Cl) channels in various physiological functions and they are widely expressed in lung epithelium. Several key signaling factors affect anion channel activity in inflammatory epithelia: a soluble chloride channel regulator (CLCA1) and TMEM16A. In addition, they support both cell proliferation and regulated cell death. Our recent data provide evidence that CLCA1/TMEM16A expression and function is dysregulated in other chronic lung diseases such as idiopathic pulmonary hypertension (IPAH) (2). However, the relationship between CLCA1, TMEM16A and signalling related to inflammatory mediators is still under investigation. In addition, the possible role of circulating CLCA1 and TMEM16A in ILD has not been elucidated yet.

Hypothesis and Objectives:

We hypothesis that the CLCA1/TMEM16A axis is a novel player in ILD. We will futher characterize the CLCA1/TMEM16A expression and function in healthy and ILD human lungs and their manipulation by inflammatory modulators leading to parenchymal remodeling. Proof of concept studies will be performed in pre-clinical animal models of ILD.

Methodology:

In this project the student will: (i) investigate soluble CLCA1 level in the bronchoalveolar lavage fluid (BALF) and lung homogenate samples from the explanted ILD lungs; (ii) investigate the role of TMEM16A on epithelial cells and its upstream and downstream signaling in ILD with special focus on inflammatory markers; (iii) prove the importance of TMEM16A in in vivo models of ILD. Year 1: The PhD student work on isolated primary epithelial cells from explanted human lungs. CLCA1/TMEM16A expression, localisation and function will be examined by qPCRandflow cytometry followed by confocal fluorescence microscopy. Circulating plasma CLCA1 levels will be measured by ELISA in human samples and in the animal model of ILD. Year 2: Functional role of CLCA1/TMEM16A manipulation of epithelial cells will be investigated by patch-clamping, live cell calcium imaging and its impact on cell proliferation and secreted inflammatory mediators. Year 3-4: The student will analyse the CLCA1/TMEM16A axis in well-established experimental mouse models for ILD. He/she will perform in vivo measurements such as lung function and morphological analysis. The in vivo findings will be futher validated on human tissue samples.

References:

1. Hamacher J et al. Cytokine-Ion Channel Interactions in Pulmonary Inflammation. *Front Immunol.* (2018) doi: 10.3389/fimmu.2017.01644.

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2. Papp R, Nagaraj C, … Olschewski A. Targeting TMEM16A to reverse vasoconstriction and remodelling in idiopathic pulmonary arterial hypertension. *Eur Respir J* (2019) 53(6):1800965. doi: 10.1183/13993003.00965-2018.