Medical University of Graz

Interplay between inflammatory cells and basement membrane components in the development of PH due to the lung fibrosis

Summary

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Supervisors:	PD Dr. Grazyna Kwapiszewska-Marsh Dr. Gabor Kovacs
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: Pulmonary fibrosis (PF) is a chronic and progressive lung disease that lead to a decrease in lung function. PF can be complicated by pulmonary hypertension (PH), which worsens patient survival. Remodelling of the small pulmonary arteries is the key pathologic hallmark of PH in PF [1, 2]. Basement membrane (BM) is integrative part of the vessel wall and is produced by endothelial (EC) as well as pulmonary arterial smooth muscle cells (PASMC). Disturbance of BM can lead to the influx of inflammatory cells. Previously we have shown that BM components are dysregulated in the vessel wall of patients suffering from idiopathic pulmonary arterial hypertension and that BM components actively influence the function of EC [3]. BM degradation products, matrikines, can lead to EC apoptosis and serve as prognostic markers. The major source of the enzymes such as MMPs and cathepsins leading to matrikine release are inflammatory cells. Additionally, matrikins can actively modulate the inflammatory landscape and further potentiate the disease development.

Hypothesis and objectives: Our recent data provide evidence that (1) BM expression is dysregulated in PH, (2) inflammatory cells could be a potential source of enzymes leading to release of matrikines, (3) PF possess distinct inflammatory profiles in remodelled vessels. Therefore, against this background we hypothesize that BM composition is disturbed in PH due to the lung fibrosis. We also hypothesize that certain inflammatory cell subpopulations are the source of enzymes liberating matrikines, which in turn modulate EC and SMC behaviour facilitating vascular remodelling in PH-PF. Thus, matrikines can actively lead to PH-PF development and progression.

Methodology: In this project the student will: (i) assess the expression and composition of BM in PH-PF (ii) determine the inflammatory cells being the source of enzymes releasing matrikines´ from BM, (iii) delineate the role of BM/matrikines on both EC and PASMC and its downstream signalling; (iv) investigate the role of matrikines on inflammatory cell recruitment, and (v) their role as possible biomarkers.

1st and 2nd year: BM and liberating enzymes: MMPs and cathepsins will be quantified by qPCR and localisation determined by multicolour-confocal fluorescence microscopy. The specific inflammatory cells will be isolated and co-culture with EC and PASMC as well as as spheroids to investigate the effects of matrikines. **3rd year:** Functional responses of BM/matrikines on EC and PASMC will be investigated by migration, proliferation and electric cell-substrate impedance sensing. Downstream signaling will be assessed by transcriptomic analysis and by RNA-seq and shot-gun proteomics to assess real-time activity in a single sample. **4th year**: The student will analyse the effects of matrikines on inflammatory landscape. Chemoattractant activities will be measured. The effects of matrikines on lung function, haemodynamics and morphological analysis will be analysed in in vivo models and their potential as biomarkers will be accessed in human plasma samples.

References:

[1]. Hoffmann J, Marsh LM, Pieper M, Stacher E, Ghanim B, Kovacs G, König P, Wilkens H, Haitchi HM, Hoefler G, Klepetko W, Olschewski H, Olschewski A, Kwapiszewska G. Compartment-specific expression of collagens and their processing enzymes in intrapulmonary arteries of IPAH patients. Am J Physiol Lung Cell Mol Physiol. 2015 May 15;308(10):L1002-13.

[2]. Hoffmann J, Wilhelm J, Marsh LM, Ghanim B, Klepetko W, Kovacs G, Olschewski H, Olschewski A, Kwapiszewska G. Distinct differences in gene expression patterns in pulmonary arteries of patients with chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis with pulmonary hypertension. Am J Respir Crit Care Med. 2014 Jul 1;190(1)

[3]. Jandl K, Marsh LM, Hoffmann J, Mutgan AC, Baum O, Bloch W, Thekkekara-Puthenparampil H, Kolb D, Sinn K, Klepetko W, Heinemann A, Olschewski A, Olschewski H, Kwapiszewska G. Basement Membrane Remodeling Controls Endothelial Function in Idiopathic Pulmonary Arterial. Hypertension.Am J Respir Cell Mol Biol. 2020 Jul;63(1):104-117.