Medical University of Graz

Intersection between basal membrane and immune system in the vascular wall of lung fibrosis

Summary

Otto Loewi Research Center (Physiology), Medical University of Graz

Supervisor:	PD Dr. Grazyna Kwapiszewska-Marsh
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 Hypertension (PH) can enhance progression of underlying chronic lung diseases such as pulmonary fibrosis (PF). One of the key hallmarks of PH connected with PF is the degradation of the basal membrane in small pulmonary arteries. As a consequence, degradation products such as matrikines are being produced which can be used as biomarkers of certain chronic lung diseases. Matrikines can actively shape endothelial cells and are able to modulate inflammatory processes. They can additionally enhance immune cell influx due to the disturbed barrier function of the endothelial cells and eventually exacerbate disease progression.

Hypothesis and Objectives:

Based on our previous work, we hypothesize that the specific composition of basement membrane and immune cells leads to the the development of lung fibrosis associated with PH. Furthermore, we suggest that specific inflammatory cell populations that migrate to the tissue due to chronic lung diseases, are the source of enzymes that liberate the matrikines, and thereby drive disease progression. During the PhD project, the candidate will characterize the basal membrane composition in different forms of lung fibrosis. Additionally, she/he will anlyze which specific immune cells essentially drive the release of matrikines and thereby lead to disease progression. To elaborate on the immune component the PhD candidate will be working in a close collaboration with other research groups within RESPImmun PhD Programme (e.g. Division of Immunology and Pathophysiology, Johannes Fessler).

Methodology:

In order to evaluate basal membrane compositions in PH due to lung fibrosis, the PhD candidate will perform expression analysis, as well as electron and multicolour fluorescence microscopy analysis. To establish which inflammatory cells are involved in the release of matrikines, cells will be studied in cell co-culture systems. We will also analyze the direct effects of certain enzymes on endothelial cells. To decipher downstream signaling transcriptomic analysis, chip-based technology, immunohistology stainings, multiplex ELISA, and flow cytometry, among others will be employed. The functional effects of liberating enzymes and matrikines on structural cells will be analyzed by chemotaxis analysis, CELIX and ECIS. The relevance of the investigated molecules will be further proven in the in vivo studies.

References:

1. 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):98-111. doi: 10.1164/rccm.201401-0037OC.
2. Jandl K, Mutgan AC, Eller K, Schaefer L, Kwapiszewska G. The basement membrane in the cross-roads between the lung and kidney. Matrix Biol. 2021 Nov 25:S0945-053X(21)00107-4. doi: 10.1016/j.matbio.2021.11.003
3. Marsh LM, Jandl K, Grünig G, Foris V, Bashir M, Ghanim B, Klepetko W, Olschewski H, Olschewski A, Kwapiszewska G. The inflammatory cell landscape in the lungs of patients with idiopathic pulmonary arterial hypertension. Eur Respir J. 2018 Jan 25;51(1):1701214. doi: 10.1183/13993003.01214-2017

4. 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. doi: 10.1165/rcmb.2019-0303OC.
5. Kwapiszewska G, Markart P, Dahal BK, Kojonazarov B, Marsh LM, Schermuly RT, Taube C, Meinhardt A, Ghofrani HA, Steinhoff M, Seeger W, Preissner KT, Olschewski A, Weissmann N, Wygrecka M. PAR-2 inhibition reverses experimental pulmonary hypertension. Circ Res. 2012 Apr 27;110(9):1179-91. doi: 10.1161/CIRCRESAHA.111.257568