Medical University of Graz

Immune cell crosstalk as driver of vascular remodelling

Summary

Leigh Marsh, LBI for Lung Vascular Research

Supervisor:	PD Dr. Leigh Marsh
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:

Cardiovascular diseases are one of the leading causes of adult mortality worldwide and associated with poor quality of life. A common theme underlying these diseases is inflammation and an altered immune response. In pulmonary hypertension (PH) immune cell infiltration is associated with degree of vascular remodelling. Previously, we have used advanced flow cytometry in combination with bioinformatical analysis to shown that the idiopathic form of PH presents with a distinct inflammatory cell landscape. Within this landscape, two previously uncharacterized populations potentially involved in disease pathogenesis were identified, namely, γδT-cells and plasmacytoid dendritic cells (pDC). Both cell types exist at the crossroads between innate and adaptive immunity and therefore may control the transistion to a chronic inflammatory environment found in PH.

Hypothesis and Objectives:

We hypothesise that γδT-cells and pDC potentiate vascular remodeling by altering the local inflammatory environment. We will investigate how the cellular crosstalk between these cells, other immune cells (e.g. macrophages and T cells), and structural cells alters vascular homeostasis and ultimately controls disease pathogenesis.

Methodology:

Flow cytometry will be used to identify pDC and γδT-cells and their activation states in both healthy and diseased lung tissue. Immune cell cross-talk will be investigated in vitro, using isolated (FACSsorting/MACS) pDC/γδT-cells to determine effect cell activation and polarisation (proliferation/cytokine production). Multicolour immunofluorescence will be applied to determine spatial localisation. To define how the immune cells control structural cell behaviour and visa versa, direct and indirect co-culture systems using primary human cells isolated from both healthy and diseased lung tissue will be used. Secreted factors will be identified by multiplex ELISA and functional blocking experiments (antibodies/small molecule inhibitors) will test their role in modulating structural cell behaviour. Downstream signalling and functionally relevant pathways will be investigated using bulk-sequencing, intra-cellular flow cytometry, CRISPR-Cas mediated deletions, and standard molecular and visualisation methodology (e.g. western blotting, immunofluorescence imaging).

References:

Bordag N, Biasin V, Schnoegl D, Valzano F, Jandl K, Nagy BM, Sharma N, Wygrecka M, Kwapiszewska G, Marsh LM. Machine Learning Analysis of the Bleomycin Mouse Model Reveals the Compartmental and Temporal Inflammatory Pulmonary Fingerprint. iScience. 2020 Nov 18;23(12):101819.

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)

Zabini D, Crnkovic S, Xu H, Tscherner M, Ghanim B, Klepetko W, Olschewski A, Kwapiszewska G, Marsh LM. High-mobility group box-1 induces vascular remodelling processes via c-Jun activation. J Cell Mol Med. 2015 May;19(5):1151-61

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.

Stacher E, Graham BB, Hunt JM, Gandjeva A, Groshong SD, McLaughlin VV, Jessup M, Grizzle WE, Aldred MA, Cool CD, Tuder RM. Modern age pathology of pulmonary arterial hypertension. Am J Respir Crit Care Med. 07 Jun 2012, 186(3):261-272