Medical University of Graz

Dissecting the role of vascular endothelial cells in the development of lung fibrosis

Summary

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Supervisor:	PD Dr. Grazyna Kwapiszewska-Marsh
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 10, 2020 00:00 and March 30, 2020 23:59 (Europe/Zurich)

Description

Background:

Vascular abnormalities are a common feature of chronic lung diseases such as idiopathic pulmonary fibrosis (IPF), or systemic sclerosis-associated pulmonary fibrosis (SSc-PF). These vascular abnormalities can manifest as remodeling and obliteration of pulmonary arteries, as seen in pulmonary hypertension (PH), or as changes of vascularity and vessel distributions as observed in PF. Current studies indicate that endothelial cell (EC) dysfunction, with increased endothelial cell apoptosis and hyperproliferation of remaining apoptosis-resistant cells is a key pathomechanisms in vascular remodeling. We have previously shown that pulmonary vascular remodeling occurs in PH as well as in PF, although to a different extent and that it is possibly caused by different molecular mechanisms (Hoffmann, 2014; Hoffmann, 2015). Further we extensively studied the role of the transcription factor fos-realted antigen-2 (Fra-2) in the development of pulmonary vascular and parenchymal remodeling (Birnhuber, 2019a, b).

Hypothesis and Objectives:

We hypothesize that aberrant expression and activation of Fra-2 leads to endothelial changes and dysfunction leading to vasculopathy and consequently to development of pulmonary fibrosis as seen in patients with SSc-PF. Using a wide array of methods and models, we aim to investigate the influence of Fra-2 on EC function and their crosstalk with surrounding cells in the development of pulmonary fibrosis.

Methodology:

A detailed assessment of vascular remodeling and EC proliferation/apoptosis will be acquired using standard histology techniques (immunohistochemistry/ immunofluorescence stainings) and semi-automated image analysis. Studies on human lung tissue will be complemented by a variety of *in vivo* and *in vitro* approaches: Primary endothelial cell cultures from healthy and diseased lung tissue (human and murine) will be performed for *in vitro* assays to assess endothelial cell function. Additionally, lineage tracing of endothelial cells (Crnkovic, 2018). will be performed in Fra-2 overexpressing mice, a model of SSc-PF. Ultrastructural changes of EC morphology will be investigated by electron microscopy.

References:

- 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.
- 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.

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- Birnhuber A, Crnkovic S, Biasin V, Marsh LM, Odler B, Sahu-Osen A, Stacher-Priehse E, Brcic L, Schneider F, Cikes N, Ghanim B, Klepetko W, Graninger W, Allanore Y, Eferl R, Olschewski A, Olschewski H, Kwapiszewska G. **IL-1 receptor blockade skews inflammation towards Th2 in a mouse model of systemic sclerosis.** Eur Respir J. 2019 Sep 29;54(3). pii: 1900154.
- Birnhuber A, Biasin V, Schnoegl D, Marsh LM, Kwapiszewska G. **Transcription factor Fra-2 and its emerging role in matrix deposition, proliferation and inflammation in chronic lung diseases.** Cell Signal. 2019 Dec;64:109408.
- Crnkovic S, Marsh LM, El Agha E, Voswinckel R, Ghanim B, Klepetko W, Stacher-Priehse E, Olschewski H, Bloch W, Bellusci S, Olschewski A, Kwapiszewska G. **Resident cell lineages are preserved in pulmonary vascular remodeling.** J Pathol. 2018 Apr;244(4):485-498.

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