The role of regulators of G-protein signaling (RGS) in lung fibrosis

Summary
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Description
Background
Signal transduction through G-protein–coupled receptors (GPCRs) is essential for the regulation of virtually all cellular functions including growth, contraction, cardiovascular function and vascular tone (1,2). Regulators of G-protein signaling (RGS proteins) belong to a diverse protein family accelerating signal termination in response to GPCR stimulation, thereby reducing the amplitude and duration of GPCR effects. Perturbations in GPCR signaling have pathophysiological consequences and are major contributors to different human disease. The RGS protein superfamily is divided into subfamilies, based on sequence homology within the RGS domain and the nature and identity of non-RGS domains that facilitate protein-protein interactions, target specificity, protein stability, and subcellular location. The expression pattern, regulation, and functional role of canonical RGS proteins are well characterized in e.g. the nervous system, inflammation and cancer, however in the healthy lung and in the diseased lung, as well as their potential as therapeutic drug targets are still largely unknown.

Goals
1. To characterize RGS expression pattern in the lung parenchyma of healthy human lungs and in human lungs obtained from patients with lung fibrosis as well as in the pulmonary arteries obtained from healthy human lungs and from patients with lung fibrosis.
2. To elucidate the regulation of RGS gene expression by pathways leading to lung fibrosis and lung vascular remodelling.
3. To investigate posttranslational modifications of RGS.
4. To prove functional consequences of RGS modifications in different animal models of lung fibrosis and pulmonary hypertension.

Methods
The major strength of this project is the use of human material combined with established animal modes of the disease. If applicable, knock-out or transgenic mouse line will be also included. The lab also has different inducible cell specific mouse lines which than can be combined with knock-out model(s) if necessary.
In vitro studies: Laser-captured microdissection (LCM) will be applied to investigate compartmental distribution of RGS in the lung (2). Expression pattern and changes in gene expression will be investigated by standard molecular biological methods. Consequences of these changes will be proved by siRNA or overexpression in vitro using adequate read-outs in primary human cells. In order to prove posttranslational modifications, epigenetic methods (with focus on histone modification of RGS) and functional testing e.g. life cell imaging will be applied as well as ex vivo models such as wire-myograph or the isolated perfused lung model.

In vivo studies: Animal studies will include histological analysis, lung function tests and hemodynamic measurements (4) such as right catheterization in mouse model(s) of the disease using genetically modified strains and/or specific inhibitors i.a.

References