Medical University of Graz

Compartment specific immunophenotyping in chronic obstructive pulmonary disease

Summary

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Supervisors:	PD Dr. Leigh Marsh Dr. Alexander Avian
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: Chronic obstructive pulmonary disease (COPD) is a highly heterologous disease with several know phenotypes, these can be distinguished by the pathology, degree of inflammation, or response to treatment. Similar to asthma, COPD is characterised by an upper airway obstruction and chronic inflammation, however, COPD patients also suffer from loss of the small conducting airways, and chronic destruction of the lung parenchyma resulting in emphysema. The presence of pulmonary hypertension (PH) in patients with COPD is associated with even worse survival. However, there is only limited knowledge how the compartment specific inflammatory profile overlaps in COPD and contributes to pathogenic remodelling.

Hypothesis and objectives: We hypothesize that the inflammatory cell profile exhibits a compartmental specific fingerprint and can discriminate between different COPD phenotypes. Here we will determine the compartmental inflammatory cell landscape in COPD and determine its relationship to local structural changes. Functionally characterize regulated inflammatory cell populations and determine their implications for remodeling.

Methodology: Years 1-2: The student will make extensive use of flow cytometry and computational analysis to characterize the inflammatory cell profile in COPD patients. Multivariate analysis including unbiased dimensionality reduction (e.g. PCA) and hierarchical clustering will identify different profiles. Multi-color confocal fluorescence microscopy will be used to determine the 3D localization of identified populations and their association with pathological lesions, including airway disease, emphysema and vascular remodeling. **Years 2-4:** For sub-type classification machine learning approaches with an emphasis on interpretable algorithms (e.g. Random Forest, k-nearest neighbours' algorithm) will be used. Advanced data modelling, including supervised regression models we will determine the relationships between the inflammatory profiles with clinical (mPAP; PVR, FEV1 etc.) and pathological data. Classification and supervised analysis will allow us to delineate differences in cell populations for deeper mechanistic insights. Additionally, microbiome analysis in the lung tissue will be performed and correlated with inflammatory profiles. **Years 3-4:** The student will determine how regulated inflammatory cell populations can promote aberrant remodelling; functional experiments will be performed using isolated primary cells in both direct and indirect co-culture systems. Readouts will include: proliferation, apoptosis and barrier function. Expression profiling and activated signalling cascades in the structural cells will identify disease relevant mechanisms.

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