Medical University of Graz

Characterization of the vascular phenotype in COPD. Are there gender differences?

Summary

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Supervisors:	Prof. Dr. Horst Olschewski Dr. Slaven Crnkovic
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 multifaceted disease with a high morbidity and mortality. Deeper clinical phenotyping has discovered that a subgroup of COPD patients develops an out-of-proportion increase in pulmonary arterial pressure, the so-called “pulmonary vascular phenotype”. Patients with this phenotype have worse outcome compared to other COPD patients and no currently available therapy option. Better identification of patients with a vascular phenotype and understanding the pathologic mechanisms might open new therapeutic options. Interestingly, many forms of pulmonary vascular disease affect predominantly females and currently females are increasing their likelihood for COPD, approaching the likelihood of men. We have recently investigated the expression of p22phox in explanted lungs of patients with end-stage COPD (1). P22phox codes for a critical component of NADPH oxidases, serving as oxygen sensors in pulmonary arteries. Additionally, free radical species from NADPH oxidase mediate cell signalling processes that elicit inflammatory responses. The p22phox expression was reduced in patients with predominant bronchial obstruction and well preserved in those with vascular obstruction and low DLCO. This suggests that a loss of p22phox in severe COPD prevents a vascular phenotype.

Hypothesis and Objectives: We hypothesize that i) in COPD, the pulmonary expression of p22phox is associated with pulmonary arterial pressure (PAP) ii) a clinically defined vascular phenotype is associated with the inflammatory cell composition in the bronchoalveolar lavage (BAL), biomarkers in the peripheral blood, and specific changes in the ECG, iii) the association between the clinically defined pulmonary vascular phenotype and biomarkers, inflammatory mediators, metabolites, and ECG is gender-related. The main aim of the project is to reveal whether gender-related differences in p22phox expression are associated with a potential gender-related predisposition for the vascular phenotype in COPD patients.

Methodology: The clinical work-up including right heart catheterization and bronchoscopy will be performed at the Clinical Division of Pulmonology (Med Uni Graz). Severe COPD patients will be characterized by a broad spectrum of clinical parameters and the vascular phenotype will be defined based on right heart catheterization (RHC). We will determine p22phox expression from lung biopsies and perform FACS analysis from BAL. In year 1-2, the PhD student will co-ordinate the clinical investigations, probe sampling and processing. She/he will perform FACS analysis from BAL probes and manage the biopsies and gene arrays and analyse the cellular landscape by clinical phenotypes. In year 2-3, the PhD student will perform analysis of all the results using artificial intelligence methods in order to recognize the vascular phenotype and to specify the relation between p22phox expression and that phenotype, taking care of gender as an important covariate. In year 3-4, the PhD student will finalize the analysis, prepare presentations for international conferences and at least one full paper as first author.

References: (1) Nagaraj C et al. Eur. Respir J. 2017 Jul 20;50(1):1601651