EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
J.H. YUN ET AL.

An interferon-inducible signature of airway disease from blood gene expression profiling

Jeong H. Yun [1,2,3], Sool Lee[1], Pooja Srinivasa[1], Jarrett Morrow[1,3], Robert Chase [1], Aadbida Saferali[1,3], Zhonghui Xu[1,3], Michael Cho [1,2,3], Peter Castaldi[1,3] and Craig P. Hersh[1,2,3]

[1]Channing Division of Network Medicine, Dept of Medicine, Brigham and Women's Hospital, Boston, MA, USA. [2]Division of Pulmonary and Critical Care Medicine, Dept of Medicine, Brigham and Women's Hospital, Boston, MA, USA. [3]Harvard Medical School, Boston, MA, USA.

Corresponding author: Craig P. Hersh (craig.hersh@channing.harvard.edu)

Shareable abstract (@ERSpublications)
Airway wall thickness in chronic obstructive pulmonary disease (COPD) is associated with type 1 interferon signalling from peripheral blood gene expression https://bit.ly/2WEjvFH

Cite this article as: Yun JH, Lee S, Srinivasa P, *et al*. An interferon-inducible signature of airway disease from blood gene expression profiling. *Eur Respir J* 2022; 59: 2100569 [DOI: 10.1183/13993003.00569-2021].

Received: 23 Feb 2021
Accepted: 24 Sept 2021

Abstract

Background The molecular basis of airway remodelling in chronic obstructive pulmonary disease (COPD) remains poorly understood. We identified gene expression signatures associated with chest computed tomography (CT) scan airway measures to understand molecular pathways associated with airway disease.

Methods In 2396 subjects in the COPDGene Study, we examined the relationship between quantitative CT airway phenotypes and blood transcriptomes to identify airway disease-specific genes and to define an airway wall thickness (AWT) gene set score. Multivariable regression analyses were performed to identify associations of the AWT score with clinical phenotypes, bronchial gene expression and genetic variants.

Results Type 1 interferon (IFN)-induced genes were consistently associated with AWT, square root wall area of a hypothetical airway with 10 mm internal perimeter (Pi10) and wall area percentage, with the strongest enrichment in AWT. A score derived from 18 genes whose expression was associated with AWT was associated with COPD-related phenotypes including reduced lung function (forced expiratory volume in 1 s percentage predicted $\beta = -3.4$; $p<0.05$) and increased exacerbations (incidence rate ratio 1.7; $p<0.05$). The AWT score was reproducibly associated with AWT in bronchial samples from 23 subjects ($\beta=3.22$; $p<0.05$). The blood AWT score was associated with genetic variant rs876039, an expression quantitative trait locus for *IKZF1*, a gene that regulates IFN signalling and is associated with inflammatory diseases.

Conclusions A gene expression signature with IFN-stimulated genes from peripheral blood and bronchial brushings is associated with CT AWT, lung function and exacerbations. Shared genes and genetic associations suggest viral responses and/or autoimmune dysregulation as potential underlying mechanisms of airway disease in COPD.