European Respiratory Society
Annual Congress 2012

Abstract Number: 898

Publication Number: P1438

Abstract Group: 3.2. Airway Cell Biology and Immunopathology

Keyword 1: Asthma - mechanism **Keyword 2:** COPD - mechanism **Keyword 3:** Airway smooth muscle

Title: Corticosteroid insensitivity in airway smooth muscle cells of severe asthma and COPD: Modulation by IFN-γ

Dr. Po-Jui 2943 Chang playchang5478@gmail.com MD [1,2], Ms. Josephine 2944 Baker josephine.baker@imperial.ac.uk [1], Dr. Pankaj K. 2945 Bhavsar p.bhavsar@imperial.ac.uk [1], Dr. Mark M. 2946 Perry m.perry@imperial.ac.uk [1] and Prof. Dr Kian Fan 11697 Chung f.chung@imperial.ac.uk MD [1]. [1] Experimental Studies Group, Airway Disease Section, National Heart and Lung Institute, Imperial College, London, United Kingdom, SW3 6LY and [2] Department of Thoracic Medicine, Chang Gung Memorial Hospital, Linkou, Taoyuan County, Taiwan, 333 .

Body: Background: Patients with severe asthma or COPD respond poorly to corticosteroids (CS). IFN-γ impairs CS response in airway smooth muscle cells (ASMCs) of healthy subjects. Aims and objectives: Compare cytokine-induced chemokines and CS response in ASMCs of severe asthma or COPD. Investigate the effect of IFN-γ on CS response. Methods: ASMCs of healthy subjects (12), non-severe (NSA; 10) and severe asthma (SA; 10), smokers (8) and COPD (8), were obtained via endobronchial biopsy. At passage 4-5, cells were pretreated with dexamethasone (Dex; 10^{-10}-10^{-6} M; 2 hr) and stimulated with TNF-α/IFN-γ (10 ng/mL each; 24 hr). CCL11 and CXCL8 release and mRNA were assessed by ELISA and qRT-PCR, p65 NF-κB promoter recruitment by ChIP, and p38 MAPK activity by Western Blot. Results: Baseline and TNFα-induced CCL11 release/mRNA were increased in NSA, and CXCL8 increased at baseline in smokers and COPD. Dex suppression of induced chemokines was impaired in SA, smokers and COPD. IFN-γ inhibited i) induced CCL11 and CXCL8; ii) p65 recruitment to chemokine promoters, and iii) Dex suppression of induced chemokines in the healthy. In SA, IFN-γ further reduced suppression of only CXCL8. Paradoxically, IFN-γ improved the suppressive effect of Dex on CXCL8 in smokers and COPD. p38 MAPK activity was raised in SA, and inhibition of p38 restored corticosteroid sensitivity. However, IFN-γ did not modulate induced p38 activity. Conclusions: ASMCs of SA, smokers and COPD display CS insensitivity. IFN-γ impairs the suppressive effect of Dex on CXCL8 in the healthy and asthmatics but improves it in smokers and COPD, suggesting differential mechanisms underlying CS insensitivity in SA and smokers/COPD.