Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol12Issue2abst0007P.pdf

Interleukin 33: A critical mediator that orchestrates innate immune responses to virus induced exacerbations of Chronic Obstructive Pulmonary Disease

J Kearley[1], J Silver[1], C Sanden[2], N White[1], C Ward[1], TH Pham[1], G Criner[3], N Marchetti[3], T Mustelin[1], R Kolbeck[1], J Erjefalt[2], AA Humbles[1]. [1]MedImmune, Gaithersburg, MD, USA, [2]Lund University, Lund, Sweden, [3]Temple University School of Medicine, Philadelpia, PA, USA

Rationale: The alarmin IL-33 is an IL-1 family member primarily released in response to tissue injury and necrosis. While suggested to be involved in a plethora of inflammatory diseases, in particular Asthma, its potential role in Chronic Obstructive Pulmonary Disease (COPD) is unknown. **Methods:** We have used patient samples and mouse models to investigate the expression and function of IL-33 in COPD. Unless otherwise stated, data are expressed as Mean±SEM, and p values were calculated using a Mann-Whitney U test. **Results:** Here we postulate a novel role for the IL-33/ST2 axis in COPD by showing significantly upregulated expression, specifically within the airway epithelium of COPD patients, correlating with disease severity as measured by decline in FEV_1 (Figure 1). Subsequent functional studies in mice revealed that cigarette smoke (CS) exposure significantly enhanced intracellular IL-33 levels and yielded a similar epithelial expression as to that seen in man (IL-33 positivity per total tissue area; Control:450±15 vs Smoke:551±21.1, n=8/group, $p<0.05$). Despite this increase, mice deficient in IL-33 or its cognate receptor, T1/ST2, were not protected from CS-induced inflammation or emphysema. However, further analyses suggested that this was due to lack of IL-33 release following smoke exposure. One of the key characteristics of COPD is debilitating pathogen-induced exacerbations and given the airway damage following viral infection, we examined the role of IL-33 in a CS-induced viral exacerbation model. Remarkably, deficiency in IL-33, its receptor or therapeutic IL-33 blockade conferred complete protection from exacerbated disease, i.e. these mice did not exhibit enhanced inflammation or exacerbated weight loss when compared to respective controls (Figure 2). IL-33 appeared to be an early mediator since we observed changes in cytokines associated with the innate immune response as early as 2 days post virus infection (significant changes in IFN-γ, IFN-α, TNF-α, IL-6, CXCL5 and IL-12p40 comparing wild type and ST2 deficient mice, n=8-16 mice/group, 1-2 experiments).

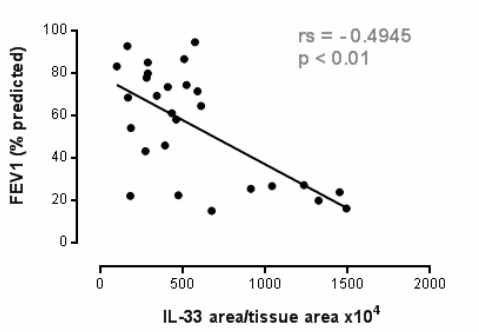

Figure 1 IL-33 expression correlates with disease severity in COPD

Spearman's rank correlation was performed, n=27.

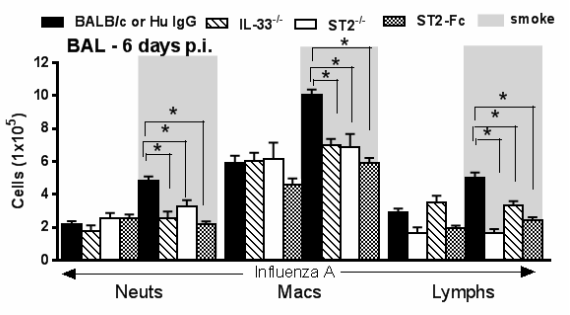

Figure 2 IL-33 is required for exacerbated viral inflammation due to prior smoke exposure

BAL cell data are expressed as Mean±SEM, n=8-16 mice/group, 1-2 experiments, *p<0.05

Conclusion: These data suggest that IL-33 is upregulated during COPD, released upon pathogen-induced damage and may be a key player in orchestrating acute exacerbations of COPD through its action on the innate immune system.