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PULMONARY TRANSCRIPTOME ANALYSES OF IL-33-MEDIATED RESPONSES IN A MURINE MODEL

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Background:
IL-33 induces airway-inflammation and hyperresponsiveness in respiratory diseases like asthma and Chronic Obstructive Pulmonary Disease (COPD), including in children. Despite being defined as a therapeutic target, there are limited studies that comprehensively define IL-33-mediated responses in the lungs *in vivo*.

Objective:
The aim of this study is to characterize IL-33-induced global transcriptome responses in the lungs using a murine model.

Methods:
IL-33 (1 mg) was intranasally administered to BALB/c mice for 5 days. Lung mechanics was monitored using a flexiVentÓventilator and cell differentials measured using modified Wright-Giemsa staining. Inflammatory mediators were measured using the Mesoscale platform. Transcriptomic profiling of lung tissues was performed using RNA-Seq and analyzed using DESeq2 package in R, with functional enrichment performed using the Ingenuity Pathway Analysis (IPA) tool and InnateDB.

Results:
IL-33 challenge increased leukocyte accumulation in the bronchoalveolar lavage, airway hyperresponsiveness (AHR) and goblet cell hyperplasia. RNA-Seq identified 2279 transcripts up-regulated and 1378 genes downregulated (^{3}2-fold, $p<0.01$) in IL-33-challenged mice. Bioinformatic interrogation of the RNA-Seq data identified an enrichment of Th2-skewed inflammation and leukocyte migration as top biological pathways, and airway inflammation in asthma as a top upregulated network while PU.1, E1AF, E2F family, TEL-2A and NRF2 were predicted to be activated transcription factors induced by IL-33. STAT4, a predicted upstream regulator of IL-33 responses based on IPA, was validated to be upregulated in response to IL-33 in the lungs. IL-33-challenge also increased the expression of cytokines including IL-4, IL-5, IL-6, IL-10, MIP1α and IP10, at both the transcript and protein level.

Conclusion:
This study comprehensively defines IL-33-induced lung transcriptome responses *in vivo,* demonstrating a major Th2-skewed inflammatory response. The specific IL-33-induced molecular targets and hubs defined in this study can be used to assess outcomes in a murine model, for example in studies examining novel interventions to target the downstream effects of IL-33.