Poster Number 63

Abstract 0240_0346_000061

Defining IL-33-induced responses and transcriptome in murine lungs

Dylan Lloyd, Manitoba Center for Proteomics and Systems Biology, University of Manitoba; **Hadeesha Piyadasa**, Manitoba Centre for Proteomics and Systems Biology; **Mahadevappa Hemshekhar**, Manitoba Center for Proteomics and Systems Biology; **Amy Yeung**, Center for Microbial Disease and Immunity, University of British Columbia; **Sujata Basu**, Children's Hospital Research Institute of Manitoba; **Robert Hancock**, Center for Microbial Disease and Immunity, University of British Columbia; **Andrew Halayko**, Children's Hospital Institute of Research Manitoba; **Neeloffer Mookherjee**, Manitoba Center for Proteomics and Systems Biology; Children's Hospital Research Institute of Manitoba

Background:

Environmental factors such as air pollution can exacerbate inflammatory airway inflammation in asthma. Inhaled allergens and particulates in air pollution significantly enhance pro-inflammatory cytokine IL-33 in the lungs. IL-33 plays a central role in inducing airway inflammation and contributes to steroid-refractory response. Moreover, IL-33 elevated in cord blood is associated with altered development of newborn immune system.

Objective:

To characterize global responses induced by IL-33 in the lungs *in-vivo*.

Methods:

Female BALB/c mice (n=5 per group) were challenged with recombinant murine IL-33 (1 mg) in saline intranasal (i.n) or saline alone (i.n) for 5 consecutive days. Mice were sacrificed 24 hours after the last challenge. Lung mechanics was monitored using a flexiVent© small animal ventilator, cell differentials performed in bronchoalveolar lavage fluid (BALF) using a modified Wright-Giemsa staining, and RNA isolated from the bottom left lobe of the lung was used for RNA-Seq (iLlumina sequencer). STAR© was used for sequence alignment, differential gene expression was analyzed through DESeq2 package in R, and Ingenuity Pathway Analysis tool was used for pathway analyses. Protein expressions of selected targets were validated using western blots and MesoScale Discovery Platform.

Results:

IL-33-challenged mice showed increased airway hyperresponsiveness, and enhanced leukocyte accumulation (eosinophils, neutrophils, macrophages and lymphocytes) in BALF, compared to naïve mice. 2520 transcripts were identified by RNA-seq to be >2-fold ($p < 0.01$) up-regulated in IL-33-challenged mice, compared to saline challenge. Bioinformatics analyses of differentially expressed genes predicted overrepresentation of networks that included HMGB1, STAT4, STAT6, EGR1 and CARM1. Transcript and protein abundance of cytokines namely IL13, IL5, IL17A, IL4, IL10, IL6, MIP1, and CXCL10 were all enhanced response to IL-33.

Conclusion:

This is the first study to define IL-33-induced global responses in the lungs *in vivo*. Results of this study will facilitate systematic interrogation of IL-33-mediated molecular mechanisms and targeted intervention strategies.