Abstract #35 (0346_0513_000044)

REGULATION OF AIRWAY INFLAMMATION: CATHELICIDIN LL-37 & CYTOKINE IL-17

Anthony Altieri, Department of Immunology; **Hadeesha Piyadasa**, Department of Immunology; **Hemshekhar Mahadevappa**, Manitoba Centre for Proteomics and Systems Biology; **Natasha Osawa**, Manitoba Centre for Proteomics and Systems Biology; **Breann Recksiedler**, Manitoba Centre for Proteomics and Systems Biology; **Victor Spicer**, Manitoba Centre for Proteomics and Systems Biology; **Neeloffer Mookherjee**, Department of Immunology, Manitoba Centre for Proteomics and Systems Biology, Department of Internal Medicine

Background:
Asthma is a heterogeneous disease reflecting different pathophysiology. Inhaled allergen-mediated disease can be Th2-driven or Th2-low/Th17-driven. The Th2-low/Th17-driven disease is predominantly neutrophilic inflammation and associated with non-responsiveness to inhaled corticosteroids. There are currently no effective therapies for the control of such steroid-refractory, severe asthma. This disease is characterized by increased production of IL-17 along with enhanced abundance of peptide LL-37 in the lungs.

Objective:
To characterize the interplay of IL-17 & LL-37 in airway inflammation and identify the molecular targets of IL-17 and LL-37. These targets may represent pivotal checkpoints in airway inflammation that can be exploited to develop new therapeutic strategies.

Methods:
Human Bronchial Epithelial Cells (HBECs) were stimulated with IL-17A/F (50 ng/mL) and/or TNF (20 ng/mL). Cell lysates (n=5) were probed using high content aptamer-based proteomic array. Differential analysis was performed on normalized log2 protein expression values, along with Welch's t-test ($p<0.05$) to identify differentially abundant proteins. Top molecular targets were independently validated using ELISA and western blots, with HBECs *in vitro*, in the presence/absence of physiological concentrations of LL-37.

Results:
IL-17 and/or TNF enhances proteins associated with pulmonary host defense and neutrophilic airway inflammation, such as antimicrobial peptides (AMP) Lipocalin-2 & Elafin, chemokines CXCL1 & CXCL8 and airway remodeling factor MMP13 (>2-fold) in HBECs. Inhibition of PI3K resulted in the suppression of AMP, Lipocalin-2 and Elafin. LL-37 disparately alters IL-17-mediated AMP production; suppressing Lipocalin-2 production and enhancing Elafin. Additionally, LL-37 enhanced IL-17-mediated production of neutrophil chemokines CXCL1 and CXCL8.

Conclusion:
LL-37 enhances IL-17-mediated production of neutrophil associated chemokines CXCL1 and CXCL8. Additionally, LL-37 enhances Elafin production, while decreasing Lipocalin-2 production. Overall, this study suggests that inflammatory cytokines alter the expression profile of antimicrobial peptides and proteins, and that physiological concentrations of LL-37 specifically alter IL-17 mediated airway inflammation.