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COMBINING LUNG PROTEOMIC PROFILES IDENTIFIES COMMON AND HIDDEN BIOLOGICAL INSIGHT IN A MOUSE MODEL OF ALLERGIC ASTHMA

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Background:

New therapeutic strategies for pediatric asthma rely on comprehensive understanding of pathobiological mechanisms. Our pre-clinical asthma model involves repeated inhalation challenge with house dust mite (HDM) to induce hallmark pathophysiological features of human disease. The lung proteome includes proteins from tissue and those secreted from airway epithelial and immune cells into the airways; each compartment providing insight into signaling processes within the lung. However, traditional proteomic analysis approaches only examine biological processes in isolation and *not the interactions between* the tissue and extracellular proteins.

Objective:

To define a combined lung proteome that can be partitioned to understand compartment-to-compartment interactions during response to allergen challenge in the lung.

Methods:

Eight-week old female BALB/c mice (n=3) were subjected to repeated intranasal challenge with HDM lysate (25µg) for two weeks. Bronchoalveolar lavage fluid (BALF) was processed to remove immune cells, and remaining lung tissue was collected. Allergen-naïve mice (n=3) were used as controls. Lung tissue and cell-free BALF was analyzed in parallel using 1D LC-MS/MS. Protein quantification was completed using X!Tandem. Biological pathway and statistical analysis was performed (partial least squared discriminate analysis, PLSDA).

Results:

We quantified 2695 proteins in HDM and allergen-naïve mice including 1486 and 332 unique proteins in the lung tissue and BALF, respectively. We created a pseudo-combined lung dataset to examine the BALF-tissue proteomic interactions. Our statistical analysis revealed that lung

tissue, BALF and the combined proteomes segregate as statistically different clusters (Figure 1). The combined dataset also highlighted inter-connected protein networks that differ from those in the lung tissue or BALF proteome, individually.

Conclusion:

Our analysis method provides researchers a precise tool to study the dysfunctional molecular signatures found in the allergen challenged lung. We found biological mechanisms that are absent from single dataset analysis. This work highlights the importance of big data integration across biological compartments to fully describe disease mechanisms.

Figure 1: The combined lung tissue-BALF proteome produces a dataset which is distinct from its individual contributions during HDM exposure. PLSDA multivariate statistical analysis identifies the lung tissue proteome, the BALF proteome and the combination of the two (BALF + lung tissue proteome) as completely individual and statistically distinct datasets. PLSDA (Partial least squares discriminant analysis).