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Proteomic Characterization of the Murine Model of Allergic-Asthma

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Background:

Our understanding of childhood asthma is only as good as our understanding of the strengths and weakness of how animal models can recapitulate the disease. Though our established pre-clinical model using house dust mite (HDM) allergen can partially recapitulate features of asthma, we lack a global molecular signature of the lung lavage (secretome).

Objective:

Our objective was to develop an unbiased proteomic approach to characterize the mouse secretome following HDM challenge to identify molecular pathways that define HDM exposure.

Methods:

Female, BALB/c mice (6-8 weeks, n=3) received intranasal HDM challenge for two weeks and compared to the age matched allergen naïve animals. Lung lavage from naïve and HDM challenged mice were cleared of cellular debris prior to analysis. We optimized an unbiased high-throughput proteomic approach which both concentrates low abundant proteins and trypsinizes them for HPLC-MS/MS analysis. Using X!Tandem we performed protein identification and quantification along with hypergeometric statistical analysis (to identify presence/absence proteins) and IPA (Ingenuity Pathway Analysis) for biological insight.

Results:

Parallel replicate analysis identified greater biological variation (r=0.80) than technical (r=0.90); negating repeated assessment of individual samples. X!Tandem analyses yielded ~585 proteins per mouse. We identified 121 proteins unique to HDM exposed mice and 12 unique to allergen-naïve mice. All 53 proteins detected in both groups were significantly up-regulated by HDM. Using IPA, we identified a prominent remodelling signature induced by HDM exposure through actin cytoskeleton ($p=3.39x10^{-10}$) and epithelial adherens junction signaling ($p=1.07x10^{-7}$). These pathways are concomitant to immune cell signaling through IGHA (Ig alpha chain C region) and PIGR (polymeric immunoglobulin receptor).

Conclusion:

We defined changes in the lung secretome upon HDM challenge that implicate proteins associated with acute inflammation, altered epithelial and cytoskeletal remodelling. Our characterized HDM model

provides lung researchers a precise tool to study the dysfunctional molecular signatures found in asthmatic lavage fluid.