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Exploring the impact of intranasal simvastatin on the lung transcriptome

Christopher Pascoe, University of Manitoba; **Aruni Jha**, University of Manitoba; **Sujata Basu**, University of Manitoba; **Thomas Mahood**, University of Manitoba; **Amy Lee**, University of British Columbia; **Reza Falsafi**, University of British Columbia; **Sam Hinshaw**, University of British Columbia; **Bob Hancock**, University of British Columbia; **Andrew Halayko**, University of Manitoba

Background:

Steroid refractoriness is a problem that affects 10% of people with asthma and is an enormous economic burden. Current alternatives for steroid refractory asthmatics are expensive, which creates a need for alternative therapies that are safe and cost-effective. Our work has shown that treating house dust mite (HDM) sensitized mice with low dose intranasal simvastatin (S_{IN}) can prevent and reverse airway inflammation and hyperresponsiveness. However, the mechanism by which simvastatin imparts these benefits is currently unknown.

Objective:

We hypothesize that S_{IN} treatment alters the lung transcriptome of HDM sensitized mice to promote resolution of airway inflammation.

Methods:

6-8 week old female BALB/c mice received intranasal HDM 5x per week for 2 weeks with or without concurrent S_{IN} (6µg/kg/day). 48 hours after the last HDM challenge, lung function was measured using the *flexi*Vent™. Immune cell infiltrate was measured in the lavage fluid. Lung tissue was subjected to RNA-Sequencing. Genes that were significantly altered by simvastatin treatment (adj-$p<0.05$) were used to construct minimally connected protein-protein interaction network on which pathway analysis was performed.

Results:

Concurrent S_{IN} treatment significantly altered the lung expression of 5419 genes relative to HDM sensitized mice. Key pathways involved in cell-cell connections and epidermal growth factor receptor (EGFR) signaling are enhanced by S_{IN} while antigen presentation and lymphocyte signaling pathways are decreased. There were 765 genes whose HDM induced changes were completely reversed by S_{IN} treatment (ie. increased abundance by HDM but decreased abundance by S_{IN}). These homeostatic genes included elevation of genes involved in α-linoleic acid metabolism and chaperone mediated protein folding and suppression of genes involved in B-cell receptor signaling and mitosis.

Conclusion:

The anti-asthma effects of S_{IN} are rooted in its ability to prevent immune cell signaling and its ability to promote maintenance of cell homeostasis and the production of inflammation resolving lipid mediators.