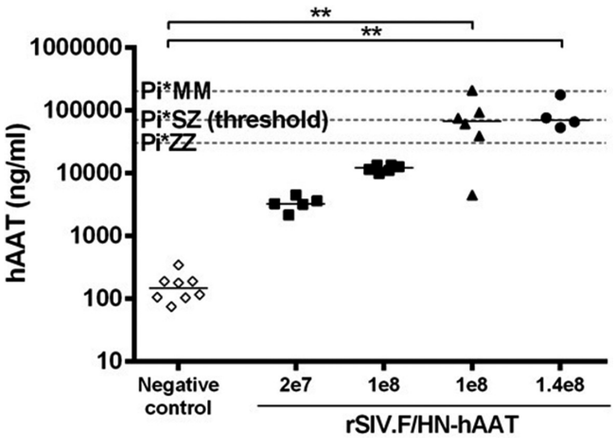
REFERENCE

1 Chapman KR, Burdon JG, Piitulainen E *et al*. Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;**386**:360–8



Abstract S127 Figure 1 Expression of hAAT in epithelial lining fluid following treatment with rSIV. F/HN-hAAT. Mice were given between 2e7 and 1.4e8 TU virus and sacrificed 7–10 days post-treatment

S128 SOLUBLE ADAM33 CAUSES AIRWAY REMODELLING TO PROMOTE ALLERGIC AIRWAY INFLAMMATION

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Introduction and objectives *ADAM33* is an asthma susceptibility gene associated with bronchial hyperresponsiveness (BHR). It encodes a membrane-anchored protein with metalloprotease (MP) activity whose ectodomain can be shed from the cell surface as a soluble protein (sADAM33-MP). sADAM33-MP levels are increased in asthmatic airways and inversely correlated with FEV1. We have previously generated a pulmonary epithelium-specific, doxycycline (DOX)-inducible double transgenic (dTg) mouse expressing human (h)sADAM33-MP and found that the transgene caused airway remodelling in the absence of inflammation or BHR. Therefore, as asthma involves gene-environment interactions, we postulated that there is a synergistic relationship between ADAM33-remodelled airways and responses to the common aeroallergen, house dust mite (HDM).

Methods DOX was administered to dTg mice to induce hsADAM33 expression and airway remodelling for up to 6 weeks; single transgenic (sTg) littermate controls were similarly treated. Mice were then sensitised to HDM and challenged with HDM or saline. Airway resistance was measured in response to increasing concentrations of methacholine using the forced oscillation technique in anesthetised mice. Inflammatory cell counts were performed on bronchoalveolar lavage fluid (BALF) and indices of inflammation measured by RTqPCR and Luminex ELISA.

Results We first performed a concentration-response experiment with HDM extract with a standard sensitisation protocol to determine the amount of HDM extract (6.25 μg), which elicited minimal BHR and eosinophilia. This low-dose allergen challenge protocol was then applied to dTg *Ccsp*/*ADAM33* and sTg control mice. Allergen challenge of dTg mice resulted in a significant increase in methacholine-induced airway resistance and eosinophilic airway inflammation compared to HDM-challenged sTg controls. The dTg mice also showed a significant increase in airway inflammatory mediators IL-5, IL-13 and eotaxin, in addition to markers of remodelling.

Conclusions This study demonstrates that hsADAM33-MP driven airway remodelling enhances susceptibility to HDM with increases in BHR and inflammation. These functional studies demonstrate, for the first time, a gene-environment interaction involving ADAM33 to cause remodelling and the disproportional inflammatory responses seen in the asthmatic airway. sADAM33 might be a potential target for novel disease-modifying therapies.

S129 A TWO SPECIES PROTEOMICS APPROACH TO DETERMINE MMP-12 SUBSTRATES IN COPD

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Background Genetic variability in MMP-12 is associated with COPD; the matrix Metalloproteinase (MMP)-12 knockout (KO) mouse is resistant to emphysema despite cigarette smoke exposure, strongly implicating MMP-12 in COPD pathogenesis. However, the complete MMP-12 substrate profile (degradome) in COPD remains unknown. Terminal amine isobaric labelling of substrates (TAILS) is a novel proteomic technique allowing identification of a protease degradome on an organism-wide scale. Identification of the MMP-12 degradome will lead to novel drugs, desperately needed in COPD.

Objectives To identify the MMP-12 degradome in COPD by comparing cigarette smoke exposed MMP-12 KO and wildtype (WT) controls by TAILS and validating these targets against the human COPD sputum proteome during exacerbations and stable disease.

Methods C57BL/6J MMP-12 KO and WT mice (n = 4) were exposed to cigarette smoke and airways sampled by bronchoalveolar lavage (BAL). BAL fluid was analysed by TAILS, high performance liquid chromatography (HPLC) and tandem mass spectrometry (MS/MS). Matched COPD exacerbation and stable disease sputum samples (n = 9) were analysed by TAILS, HPLC and MS/MS.

Results The following new MMP-12 targets in the COPD mouse model were identified: alpha-2-HS glycoprotein, anti-thrombin III, clusterin, complement C3, complement C4b, complement factor H-related protein-1, hemopexin, serotransferrin and serum albumin, alpha-2-macroglobulin, beta-1, 4-galactosyltransferase 2, transmembrane protease 7, DEP domain-containing mTOR-interacting protein, kininogen-1, tumour necrosis factor ligand superfamily member 11. Of these, alpha-2-HS-glycoprotein, anti-thrombin III, complement factors C3 and C4B, hemopexin and serum albumin were identified in both exacerbation and stable COPD human sputum. Furthermore, 1,116 peptides were identified in COPD exacerbation and stable disease sputum, grouped into the following categories: cell adhesion/migration, complement system, acute phase response, extracellular matrix structure/function, anti-microbicidal activity, cytoskeletal function/remodelling, carbohydrate metabolism, oxidoreductase activity, cell death regulation/DNA synthesis/repair, immune response, protease activity, protease inhibition and ATP synthesis/function.

Conclusion This study identifies the MMP-12 degradome in COPD and provides the most comprehensive analysis of the