SOLUBLE ADAM33 AUGMENTS THE PULMONARY IMMUNE RESPONSE PROMOTING ALLERGIC AIRWAY SENSITIVITY

1F Kelly, 1ER Davies, 2ST Holgate, 3X Xu, 1JA Whitsett, 4DE Davies, 4HM Hatchi, 5B Brooke Laboratories, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK; 2Institute for Life Sciences, University of Southampton, Southampton, UK; 3Division of Neurosciences, Perinatal and Pulmonary Biology, Cincinnati Children’s Hospital Medical Centre, Cincinnati, USA; 4NHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK
10.1136/thoraxjnl-2017-210983.95

Rational A disintegrin and metalloproteinase 33 (ADAM33) was discovered in 2002 as an asthma susceptibility gene. Genetic associations have been made between ADAM33 polymorphisms and asthma disease severity, bronchial hyperresponsiveness (BHR) and rate of lung function decline in both adults and children. A soluble, catalytically active form of the protein (sADAM33) has been identified in the bronchoalveolar lavage fluid of patients, levels of which correlate with disease severity (Lee JY et al, AJRCCM 2006). To study the role sADAM33, a lung specific, docosylcine (Dox) inducible, transgenic mouse, expressing the human pro and metalloprotease domains of the full-length protein was generated (Ccspr-TTA/Otet-ADAM33-Pro-MP). Induction of sADAM33, followed by house dust mite (HDM) sensitisation and challenge, resulted in increased BHR and airway inflammation (Davies ER et al, JCI-Insight 2016). The mechanisms by which ADAM33 promotes this susceptibility are unclear. The aim of this work is to identify pathways that are augmented by the induction of sADAM33, which promote increased sensitivity to allergen.

Methods RNA samples from whole lung of adult mice, where sADAM33 had been induced for 4 or 8 weeks, were analysed by next generation RNA sequencing. Identified genes were confirmed across experimental time points (72 hour, 7 day, 4 and 8 weeks on Dox) in wider sample cohorts of Ccspr-TTA/Otet-ADAM33-Pro-MP and control mice through RT-qPCR.

Results The predominant signal from the RNAseq output was for modulation of immune response genes at 4 weeks of sADAM33 expression (GO:0006955 Immune response: 31 genes, 58.49% coverage, FDR p value=7.09 E-22). Genes associated with an immune activation signature (Ccl5, Irgm1, Gm12250, Gzmb, Ncr1) were validated across experimental time points (72 hour, 7 day, 4 and 8 weeks on Dox) in wider sample cohorts of Ccspr-TTA/Otet-ADAM33-Pro-MP and control mice through RT-qPCR.

Conclusion Induction of sADAM33 in murine lungs, without allergic sensitisation, augmented underlying immune processes in this transgenic mouse model, which may contribute to increased susceptibility to allergic airway inflammation and BHR when challenged with allergen. Further work is required to delineate how sADAM33 affects immune cell populations and their behaviour in the lung.
investigate relationships of lung function in early childhood with growth patterns (here considered as change in weight) before the age of five years. We use flexible longitudinal modelling methods to describe early growth trajectories, and identify factors associated with suboptimal growth.

Methods Growth measurements from diagnosis to five years were extracted from two national CF registries: UK (n=2999, years 2007–2015) and Canada (n=2690, years 1990–2013). SITAR (super-imposition by translation and rotation) was used to model weight (kg) over the 5 years. Output parameters were average growth curve, summaries of growth velocity and overall weight. Associations of growth and growth velocity with sex, genotype and new born screening (NBS) were investigated.

Results Most children in the UK had been diagnosed early in life (median age of diagnosis 0.06 years; inter quartile range 0.03 to 0.1) by NBS. 52% were homozygous for deltaF508. Despite similar initial average weight in boys and girls, males were heavier than females over the first five years. Children homozygous for deltaF508 were lighter than other children. No tested factor was associated with velocity of weight gain. Only 10% of the Canadian children were diagnosed by NBS, and, overall, the age at diagnosis was later (median 0.17 years; inter quartile range 0.08 to 0.53). Over the first five years, Canadian CF children were lighter than those in the UK (figure 1). Associations of weight with sex and genotype were similar to those seen in the UK. In addition, we observed that those diagnosed by NBS were heavier than those who were not.

Conclusions In children with CF there are sex differences in weight during the first 5 years, despite similar initial weight. In Canada, NBS has a positive impact on early growth. SITAR allows exploration of growth patterns in CF patients, but time independent characteristics were not associated with velocity of growth. Statistical modelling incorporating time dependent factors (e.g., infections, treatments) are required to explain variability of growth trajectories.

![Abstract S91 Figure 1](https://doi.org/10.1136/thoraxjnl-2017-210983.97)