and KO (*Adam33*$^{-/-}$) offspring from the same litters were studied on embryonic day (ED)17.5 and 2 or 4 weeks *post partum (pp)*. Lung function was measured in response to increasing doses of methacholine and bronchoalveolar lavage fluid (BALF) was collected for differential cell counts. Lung tissue was obtained for RTqPCR, Western blot and immunohistochemistry.

Results At 4 weeks *pp*, WT offspring of HDM challenged mothers showed significantly enhanced AHR compared to WT offspring of control mothers. KO of *Adam33* protected against AHR in the offspring of allergic mothers. *Adam33* mRNA expression was significantly enhanced in WT lungs of HDM challenged mothers at ED17.5, but unchanged *pp*. Differential cell counts in the BALF and mRNA expression of inflammatory mediators indicated an absence of allergic airway inflammation in all of the offspring. Remodelling genes were not affected at any time point studied. In contrast, *Cholinergic Receptor Muscarinic 1 (Chrm1)* mRNA was increased at 4 weeks in all offspring of HDM challenged mothers.

Conclusions This study identifies an *in utero* gene-environment interaction involving *Adam33*. This interaction has implications for the subsequent development of AHR in early life. Further studies are needed to elucidate the precise mechanism(s) whereby ADAM33 mediates its effects. Our data suggest modulation of the contractility of the airways, possibly involving muscarinic receptors.

S29 THE EFFECT OF SOLUBLE ADAM33 ON ALLERGIC AIRWAY INFLAMMATION IN EARLY LIFE IS AGE DEPENDENT

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Introduction Most asthma has its origin in early life and probably involves gene-environment interactions. The asthma susceptibility gene *ADAM33* is associated with bronchial hyperresponsiveness (BHR) and reduced lung function in young children. It encodes a membrane-anchored metalloprotease, which is shed as a soluble protein (sADAM33) whose levels are increased in asthma. We have previously shown that sADAM33, promotes airway remodelling and augments allergic airway inflammation in juvenile mice (Davies ER *et al*, *JCI Insight* 2016). This might be initiated by *ADAM33* induced innate lymphocytes (Kelly JFC *et al*, *Thorax* 2017). The aim of this work was to evaluate the effect of sADAM33 on the allergic airway responses of neonates.

Methods Human sADAM33 was induced in lungs of double transgenic (*Ccsp*/*ADAM33*) (dTg) mice from *in utero* up to 4 weeks *post-partum*. dTg mice or single transgenic (sTg) controls were challenged with house dust mite extract (HDM) 3 times a week for 2 weeks from 3 or 14 days *post-partum*. BHR and inflammation were quantified. Lung tissue was analysed by RT-qPCR and immunohistochemistry (IHC).

Results After HDM challenge from day 3, Type 2-responsive genes *Il-5*, *Ccl11*/*Eotaxin* and *Muc5ac were* significantly increased. Whilst an increase in BHR was observed after HDM challenge, there was no significant difference between sADAM33-expressing and control mice. In contrast, when challenged from day 14, sADAM33-expressing mice had a more robust eosinophilic inflammatory response in the bronchoalveolar lavage fluid with increased *Il-5* and *Ccl11*/*Eotaxin* mRNA expression compared to littermate controls. This was also associated with increased *Acta2* mRNA expression and BHR.

Conclusion These data indicate that s*ADAM33* does not augment allergic responses in neonatal mice as robustly as in older mice. This suggests that the immune microenvironment in neonates is not sufficiently mature to respond to the pro-allergic effects of s*ADAM33* that may induce innate lymphocytes to make the airways more susceptible to allergic airway inflammation.

S30 CEACAM5 (CD66E) MUCOSAL IMMUNOREACTIVITY AND ITS RELATIONSHIP TO ASTHMA

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Introduction The CEACAM immunoglobulin superfamily receptors are involved in cell signalling, cell proliferation and cell repair responses and have relevance to the maintenance of the intact bronchial epithelium. A number of these family members recognise bacteria and, as such, are part of the host defence response. However, some CEACAM-binding bacterial pathogens, in particular *Haemophillus influenzae*, exploit the binding capacity to enhance their chances of colonizing the mucosal surface. As there is increased *Haemophillus* presence within the airways in severe asthma, linked to neutrophilic airway inflammation, we investigated the presence of CEACAM5 within endobronchial biopsies by immunohistochemistry in health and in asthma. CEACAM5 was selected is one of the main bacterial binding immunoglobulins of relevance.

Method Immunohistochemical staining for submucosal CEACAM5 expression was performed on GMA embedded endobronchial biopsies from healthy controls (n=16), mild asthmatics (n=12) and severe asthmatics (n=15). Epithelial immunoexpression (percentage epithelial area using KS400 software) and sub-mucosal positive cell count quantification was undertaken. Sequentially cut sections, stained with neutrophil elastase and CEACAM5, were analysed by the Camera Lucida system to identify the percentage of submucosal positive CEACAM5 cells that were neutrophils.

Results Epithelial immunoreactivity was significantly greater in severe asthma than in health (p=0.027). There was insufficient intact and orientated epithelium to derive quantitative measures in the mild asthmatics. Median CEACAM5 immunoreactive sub-mucosal cell count/mm^2 was significantly higher in severe asthma (37.1 cells), than in both health (15.5, p≤0.001) and mild asthma (23.6, p=0.037). There was no significant difference between health and mild asthma. The median percentage CEACAM5-neutrophil positive submucosal cells in severe asthmatics (n=5) was 52%, with the range being 50%–90.63%.

Conclusion CEACAM5 expression is higher in the epithelium and submucosa of severe asthmatics. This has potential relevance to the altered airway microbiome and biofilm formation in severe asthma. As such, CEACAM5 targeted therapies could be of benefit. Longitudinal studies to understand this relationship would be desirable.