proteome of COPD sputum at exacerbation and stable disease. It suggests a role for MMP-12 in complement regulation and haemostasis in COPD. Thus an important peptide library has been unravelled, providing an ideal tool in developing drugs and understanding COPD pathogenesis.

S130 AXL RECEPTOR TYROSINE KINASE ON AIRWAY MACROPHAGES HAS A KEY ROLE IN LUNG IMMUNE HOMEOSTASIS

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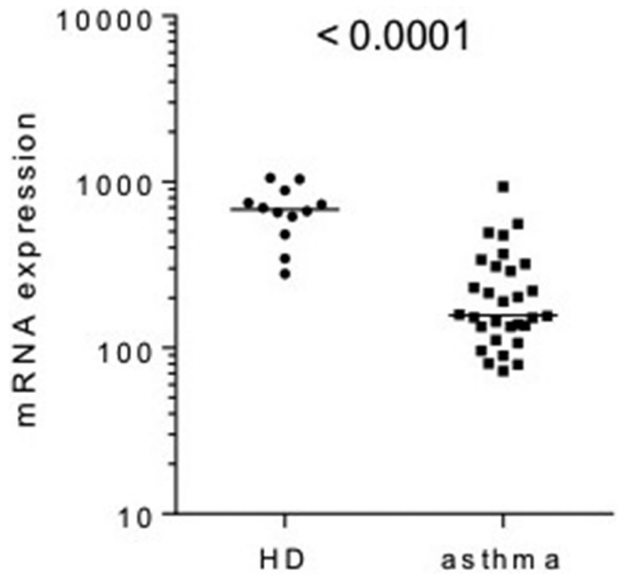
Rationale Apoptotic cell uptake (efferocytosis) by airway macrophages (AMs) is critical for lung immune homeostasis and is defective in chronic lung diseases, including asthma,[1] although the molecular mechanism behind this remains unknown. The TAM (Tyro3, Axl, MerTK) receptor tyrosine kinases are one of the main receptor classes that mediate efferocytosis but little is known about their regulation and function in inflammatory lung diseases.

Aim To investigate expression profile of TAM receptors and their ligand Gas6 in human AMs and analyse potential defects in TAM receptor expression in chronic lung inflammation.

Methods AMs from the sputum of patients with asthma (BTS step 3–5) (n = 30) or healthy donors (HD) (n = 12) were enriched by plastic adhesion. Monocytes were isolated from matched whole blood samples by CD14 positive selection and differentiated into monocyte-derived macrophages (MDMs). Total RNA was extracted from all purified cell populations and mRNA expression analysed by qPCR. HD MDMs were stimulated with Th2 cytokines *in vitro* and TAM receptor expression was analysed using qPCR and ELISA.



Abstract S130 Figure 1 mRNA expression of Axl in airway macrophages of healthy donors and patients with asthma

Main results Axl was the dominant TAM receptor expressed in HD AMs whereas monocytes and MDMs predominantly expressed MerTK. Axl expression was significantly reduced in AMs from patients with asthma compared to HD ($p < 0.0001$), while mRNA levels of MerTK and Gas6 was similar in both groups. We found no differences in Axl and MerTK expression in monocytes and MDMs from HD and patients with asthma, indicating that the observed differences were restricted to the site of inflammation. *In vitro*, MDM stimulation with IL-4 or IL-13 downregulated Axl mRNA and protein expression in a time-dependent manner.

Conclusions We have shown for the first time that Axl is the principal TAM receptor expressed in human AMs. Significant reduction of Axl expression in AMs from patients with asthma might be responsible for inefficient clearance of apoptotic cells from the inflamed airways and contribute to persistent airway inflammation. Strategies aimed at restoration of Axl expression or activity may represent a novel therapeutic strategy in asthma and other chronic lung diseases.

REFERENCE

1 Simpson JL, Gibson PG, Yang IA *et al*. Impaired macrophage phagocytosis in non-eosinophilic asthma. *Clin Exp Allergy*. 2013;**43**:29–35

S131 DEFICIENCY MUTATIONS OF α1-ANTITRYPSIN DIFFERENTIALLY AFFECT FOLDING, FUNCTION AND POLYMERISATION

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Misfolding, polymerisation and defective secretion of functional α_1-antitrypsin underlie the predispositions to severe liver and lung disease in α_1-antitrypsin deficiency. We have identified a novel (Ala336Pro, Baghdad) deficiency variant and characterised it relative to the wild-type (M) and common severe Z (Glu342Lys) variant. The index case is a homozygous individual of consangineous parentage. Absolute levels of circulating α_1-antitrypsin were in the moderate deficiency range but the biochemical phenotype could not be clearly classified by standard methods. Moreover the majority was polymerised, i.e. functionally inactive, and the purified monomer was only 37% active relative to the wild-type 'M' variant. Together these resulted in 85–95% loss-of-function, a similarly severe functional deficiency to that of ZZ homozygotes. Biochemical, biophysical and computational studies further defined the molecular basis of this functional deficiency. These demonstrated that native Ala336Pro α_1-antitrypsin could adopt the polymerogenic intermediate conformation and polymerised more readily not only than M α_1-antitrypsin but also the severe Z variant. Nevertheless folding was far less impaired in Ala336Pro α_1-antitrypsin than in the Z variant. The data therefore indicate partitions between the contribution of the 'breach' (site of Z mutation) and 'shutter' (Ala336Pro) regions of strand 5A to folding and to polymerisation mechanisms. Moreover the findings demonstrate that in these variants, folding efficiency does not correlate directly with the tendency to polymerise *in vitro* or *in vivo*. They therefore differentiate generalised misfolding from polymerisation tendencies in missense variants of α_1-antitrypsin. Clinically they further support the need to quantify loss-of-function in α_1-antitrypsin deficiency to individualise patient care.