COPD: from genetics to old age

S62 POLYCLONAL FREE LIGHT CHAINS: A POTENTIAL BIOMARKER FOR IMMUNE ACTIVATION IN ALPHA-1-ANTITRYPSIN DEFICIENCY (A1ATD) RELATED CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Introduction A1ATD is a hereditary condition associated with the premature onset of chronic obstructive pulmonary disease (COPD). In COPD, the immune response within the lung is known to involve cells of both the innate and adaptive immune systems. However, the antigenic stimulus to the adaptive immune response remains unknown. Bacterial colonisation of the lower airways is one potential factor. Alternatively this could reflect an autoimmune component. The production of antibodies by B-cells is a key element of the adaptive immune system. An excess of free light chains (FLCs) are produced as a by-product of antibody synthesis. The recent discovery of high polyclonal FLC levels in a number of autoimmune and inflammatory conditions has led to the assessment of their value as a biomarker of

adaptive immune activation. Our aim was to investigate the use of serum FLCs as a marker of immune activation, phenotypic variation and disease severity in COPD related to A1ATD.

Methods We measured FLC levels in 294 patients with A1ATD using the Freelite serum FLC assay. We then compared combined (? & ?) FLC levels (cFLC) in different subgroups defined by the presence of chronic bronchitis, CT findings, smoking status, subsequent mortality and colonisation status. In addition we determined any correlation with lung function parameters in a cross sectional analysis.

Results Significantly higher cFLC levels were found to be associated with, subsequent mortality ($p = 0.005$), the presence of chronic bronchitis ($p = 0.008$) and chronic colonisation of the lower respiratory tract ($p = 0.036$) (Table 1). FLC levels are known to increase with age and reducing renal function. A partial correlation controlling for these factors revealed no relationship between cFLC levels and the severity of lung function impairment.

Conclusions These results suggest that A1ATD patients with chronic bronchitis and chronically colonised airways have a greater adaptive immune response compared to those without. Whether this response is driven directly by microorganisms residing in the airways, or through an autoimmune phenomenon remains to be elucidated. Whether the use of FLCs in sub cohorts could have an impact on the clinical management of patients with COPD is yet to be determined.

Abstract S62 Table 1. Comparison of combined FLC (cFLC) concentrations in different sub groups (using Mann Whitney U test)

	Group 1	Group 2	P value
Mortality	Dead 11.2% median cFLC = 28.8 (IQR 16.2)	Alive 88.8% median cFLC = 25.2 (IQR 10.1)	0.005**
Emphysema	Yes 77.8% median cFLC = 25.2 (IQR 10.3)	No 22.2% median cFLC = 26.8 (IQR 11.2)	0.222
Bronchiectasis	Yes 31.9% median cFLC = 25.8 (IQR 10.4)	No 68.1% median cFLC = 26.4 (IQR 10.5)	0.446
Chronic bronchitis	Yes 33.7% median cFLC = 27.8 (IQR 14.3)	No 66.3% median cFLC = 25.0 (IQR 9.4)	0.008**
Current smokers	Yes 9.2% median cFLC = 25.4 (IQR 8.0)	No 90.8% median cFLC = 26.1 (IQR 10.5)	0.944
Culture positive (1 stable sputum PPM >10 ⁵ CFU/ml)	Yes n = 47 median cFLC = 29.9 (IQR 17.3)	No n = 24 median cFLC = 28.8 (IQR 15.3)	0.584
Chronically colonised ***	Yes n = 8 median cFLC = 38.9 (IQR 9.7)	No n = 13 median cFLC = 26.3 (IQR 17.1)	0.036*

* $p \leq 0.05$

** $p \leq 0.01$

PPM = potentially pathogenic organism, CFU = colony forming unit

***Only patients who had provided a minimum of 3 stable state sputum cultures included in analysis

S63 F ALPHA-1 ANTITRYPSIN POLYMERISES AND PROMOTES AN EXAGGERATED INFLAMMATORY RESPONSE

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Alpha-1 antitrypsin (AT) is the most important anti-elastase in the lung. Z-AT (342Glu>Lys) polymerises within the hepatocyte resulting in severe plasma deficiency and is the commonest genetic reason for the development of COPD. The F₁-anti-trypsin variant (223Arg>Cys) has been associated with mild plasma deficiency, and when found in association with the Z allele linked to emphysema and liver cirrhosis. We investigated the properties of F-AT in a cell-model.

Human F-AT cDNA was generated by site-directed mutagenesis and overexpressed into hepatocytes (HepG2 cells). Supernatants, lysates and inclusion bodies were assessed for total AT. F-AT cells were assessed for polymeric-AT, PERK, NF-kB, AP-1, TNF- α and IL-6 by ELISA, immunoblot or RT-PCR in comparison with normal (non-polymerising) M-AT and Z AT (polymerising control).

F-AT cells had no cell cytotoxicity or apoptosis upto 72h. At 24h (unless stated) F-AT secretion was slightly lower, but comparable to M-AT secretion (1479.3 ± 142 pg/ml vs. 1745.5 ± 102.3 pg/ml, $P = 0.413$) Secreted F-AT had significantly reduced elastase inhibitory capacity compared to M-AT (0.972 ± 0.069 (OD at 405nm) vs. 0.449 ± 0.085 , $P < 0.001$). F-AT formed insoluble aggregates of polymeric-AT (375 ± 32 pg/ml vs. undetectable), upregulated PERK mRNA (at 3h) and significantly increased NF- κ B (at 16h), AP-1, TNF- α (34.5 ± 5.3 pg/ml vs. 10.53 ± 3.2 , $P = 0.023$) and IL-6 (at 48h) (132.3 ± 20.8 pg/ml vs. 23.9 ± 16) ($P = 0.006$). All of which were inhibited by treatment with an inhibitor of polymerisation ($P < 0.001$ for all). In comparison to Z-AT, F-AT secretion was greater ($P < 0.001$) but had significantly reduced anti-elastase activity ($P = 0.032$) and