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

***p = ≤ 0.05**
****p = ≤ 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 F $_1$-antitrypsin 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- 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 ± 142pg/ml vs. 1745.5 ± 102.3pg/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 ± 32pg/ml vs. undetectable), upregulated PERK mRNA (at 3h) and significantly increased NF- B (at 16h), AP-1, TNF- (34.5 ± 5.3pg/ml vs. 10.53 ± 3.2, P = 0.023) and IL-6 (at 48h) (132.3 ± 20.8pg/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