European Respiratory Society
Annual Congress 2012

Abstract Number: 3649

Publication Number: P812

Abstract Group: 3.2. Airway Cell Biology and Immunopathology

Keyword 1: Asthma - mechanism **Keyword 2:** Airway smooth muscle **Keyword 3:** Cell biology

Title: Phenotypic plasticity of fibrocytes upon culture with airway smooth muscle

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Body: Asthma is a major cause of morbidity and mortality worldwide and its prevalence is increasing. Increased airway smooth muscle (ASM) mass is a hallmark of asthma, which increases with disease severity and is associated with decline in lung function. Fibrocytes (FCs) are elevated in the peripheral blood and ASM in asthma and ASM has the potential to mediate FC recruitment (Saunders et al, J Allergy Clin Immunol, 2009;123:376-84). We hypothesised that once recruited to the ASM FCs differentiate into a more ASM like phenotype under the influence of local factors. FCs were isolated from peripheral blood, ASM from bronchial biopsies and lung resection material. FCs were labelled with CFSE prior to culture with ASM cells for 7d, allowing identification by gating following flow cytometry. 24h after isolation from the peripheral blood cells are predominantly $CD14^{high}$/α-smooth muscle actin ($\alpha SMA)^{low}$. Subsequent monoculture yields $CD14^{low}$/αSMA^{high} cells, consistent with differentiation to fibrocytes. Coculture with ASM from both non-asthmatic (NA) and asthmatic (A) donors yields $CD14^{high}$ FCs, whereas ASM from NA donors yields αSMA^{low} FCs and ASM from A donors yields αSMA^{high} FCs (Table 1).

Table 1

	Cells (% positive)				
		ASM - NA		ASM - A	
	24h after isolation	FC	FC+ASM	FC	FC+ASM
CD14	78±5	12±8*	70±6§	22±3*	71±6§
αSMA	15±10	52±10*	14±3§	80±8*	74±5*#

$p<0.05$ compared to * - 24h after isolation, § - paired FC data, # - FC+ASM, t-tests, n=4-7.

Our results show that FCs have the capability to undergo phenotypic plasticity, depending on culture conditions. Further work is required to understand the factors affecting FC differentiation upon localisation to the ASM in asthma and the resultant contribution of FCs to ASM dysfunction.