asthmatic fibrocytes (1-EBIO-dependent current at +40 mV 969 ± 216 pA; $n=17$ cells) compared to healthy fibrocytes (1-EBIO-induced current 506 ± 94 pA; $n=30$ cells; $p=0.029$). $K_{Ca}3.1$ currents were blocked by the selective $K_{Ca}3.1$ blocker TRAM-34. The migration of differentiated fibrocytes induced by airway smooth muscle supernatant was inhibited by $71.1 \pm 6.9\%$ by TRAM-34 200 nM ($p<0.0001$). The CXCL12-dependent migration of fibrocyte progenitors within a freshly isolated PBMC population was reduced by $70.9 \pm 7.9\%$ by TRAM-34 ($p=0.003$).

Conclusions The K^+ channel $K_{Ca}3.1$ is expressed in human fibrocytes, and plays a key role in their migration. $K_{Ca}3.1$ blockers may therefore offer a novel approach to the treatment of airway wall remodelling in asthma, and parenchymal fibrosis in idiopathic pulmonary fibrosis.

S46 ACTIVATION OF TGF- β BY AIRWAY SMOOTH MUSCLE CELLS VIA THE $\alpha V\beta 5$ INTEGRIN IN ASTHMATIC AIRWAY REMODELLING

doi:10.1136/thx.2010.150912.46

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Airway remodelling is a common feature of severe asthma. Transforming growth factor- β (TGF- β) is a pro-fibrotic, pleiotropic cytokine implicated in airway remodelling. TGF- β is sequestered in the extracellular matrix as a latent complex and requires activation to function. Lysophosphatidic acid (LPA) causes TGF- β activation in airway epithelial cells. The study aims were to investigate the effect of LPA on TGF- β activation by ASM cells in asthma. TGF- β activation was assessed by a reporter cell co-culture assay, by determining expression of the TGF- β -inducible gene plasminogen activator inhibitor-1 (PAI1) and by detecting the nuclear translocation of Smad proteins. The effect of LPA on TGF- β activation in asthma was investigated by comparing the responses of ASM cells from non-asthmatic ($n=3$) and asthmatic ($n=3$) donors. TGF β activation was also assessed using a chronic ovalbumin model of airway remodelling in mice. LPA induced a time, and concentration, dependent increase in TGF- β activation by ASM cells that was abrogated by an integrin $\alpha V\beta 5$ antibody. An inhibitor of cytoskeletal reorganisation inhibited the effects of LPA. Furthermore, the $\beta 2$ -agonist formoterol inhibited LPA-induced PAI1 expression. Primary asthmatic ASM cells activated more TGF- β via $\alpha V\beta 5$ in response to LPA than control cells, however they did not express more $\alpha V\beta 5$ on the cell surface. Phosphorylation of Smad2 and expression of *pa11* in the lungs was increased in a chronic ovalbumin model of asthmatic airway remodelling in mice. Furthermore, $\alpha V\beta 5$ integrin staining and α -smooth muscle actin staining in the ASM layer around the airways is increased in this model. Collectively, these data show that ASM cells can activate TGF- β via the $\alpha V\beta 5$ integrin and highlight a novel pathway of TGF- β activation in ASM cells, which may be important in development of asthmatic airway remodelling.

Inflammation in lung injury: the key mediators

S47 RAGE-MEDIATED CYTOKINE RELEASE FROM LEUKOCYTES: IMPLICATIONS FOR SYSTEMIC INFLAMMATION

doi:10.1136/thx.2010.150912.47

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Introduction Systemic inflammatory response syndrome (SIRS) is the physiological and biochemical changes that result from an

Abstract S47 Figure 1a and b Graph a shows the pre (grey) and post-bypass (striped) effects of the stimuli S100B and LPS in releasing the pro-inflammatory cytokine IL-8. The graph shows in the presence of S100B and LPS, IL-8 release is significantly reduced in post-bypass ($p<0.01$), showing a reduced responsiveness to S100B and LPS. Graph b shows the pre and post-bypass effects of the stimuli S100B and LPS in releasing the IL-10. The graph shows that in the presence of S100B and LPS, all of the mean IL-10 release is significantly increased in post-bypass ($p<0.01$). The mean cytokine release was calculated from nine patients done in duplicates. $p<0.01$ shows a significant difference between groups joined by a bar. PBS=Phosphate Buffered Saline; LPS=lipopolysaccharide.