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±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±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 αVβ5 INTEGRIN IN ASTHMATIC AIRWAY REMODELLING

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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. TGFb 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 αVβ5 antibody. An inhibitor of cytoskeletal reorganisation inhibited the effects of LPA. Furthermore, the β2-agonist formoterol inhibited LPA-induced PAI1 expression. Primary asthmatic ASM cells activated more TGF-β via αVβ5 in response to LPA than control cells, however they did not express more αVβ5 on the cell surface. Phosphorylation of Smad2 and expression ofpai1 in the lungs was increased in a chronic ovalbumin model of asthmatic airway remodelling in mice. Furthermore, αVβ5 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 αVβ5 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

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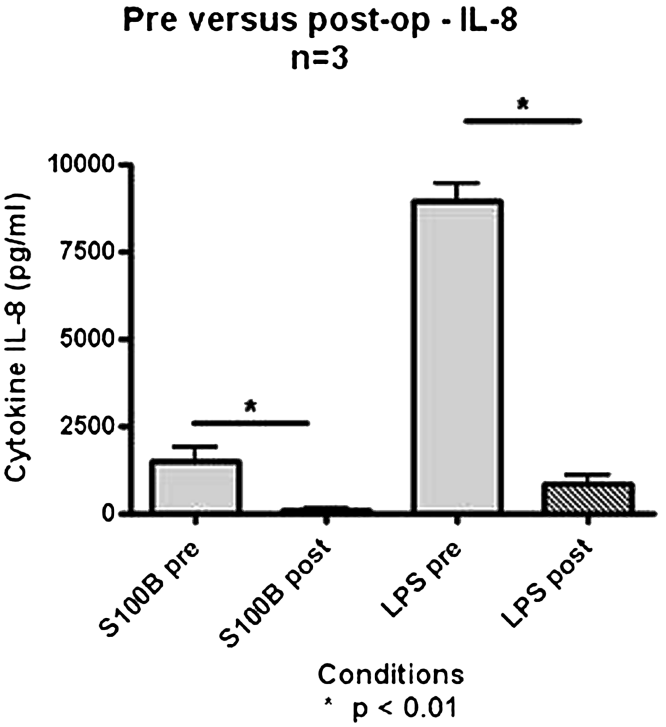
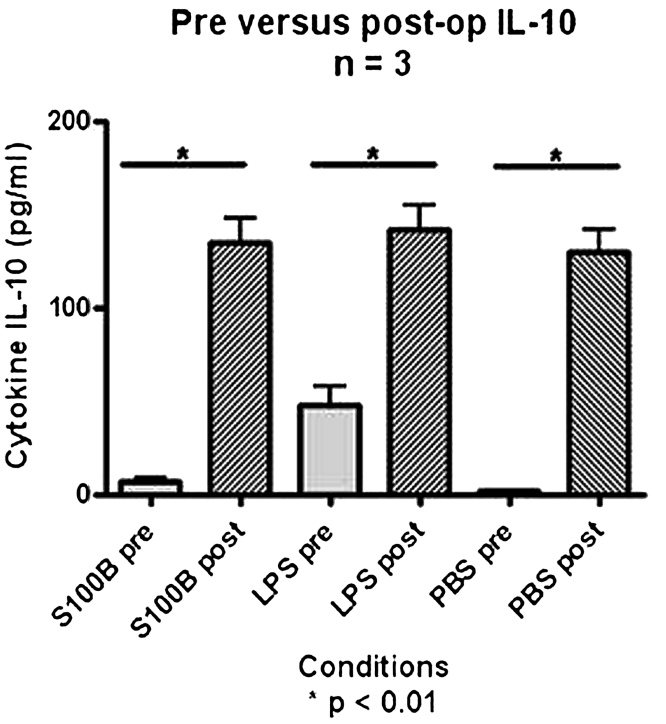
Introduction Systemic inflammatory response syndrome (SIRS) is the physiological and biochemical changes that result from an





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.