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Title: Inhibition of p38 mitogen-activated protein kinase has no effect on macrophage phagocytosis of bacteria in patients with COPD

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Body: Pulmonary inflammation and episodes of bacterial colonisation are central to the pathogenesis of COPD. COPD patients show insensitivity to glucocorticosteroids and alternative anti-inflammatory therapies including p38 mitogen activated protein kinase (MAPK) inhibitors are currently being investigated in clinical trials. However, concerns still exist about off-target effects. We investigated the effect of two p38 MAPK inhibitors, VX745 and SCIO469 on macrophage innate immune cell function. Monocyte-derived macrophages (MDM), or alveolar macrophages (AM) from bronchoalveolar lavage (BAL) and lung sections from healthy volunteers or COPD patients were challenged with either fluorescently-labelled heat-killed or non-labelled live serotype 14 Streptococcus pneumoniae (Spn). Phagocytosis of Spn was assessed at 4 hours fluorometrically or by measuring intracellular viable bacteria at 4 hours by gentamicin protection assay. Opsonisation of bacteria increased Spn internalisation in healthy and COPD MDM (Healthy:3.2+/-0.3 vs 4.2+/-0.19 $\log_{10}$CFU/ml, n=7 $p<0.01$. COPD:2.9+/-0.5 vs 3.8+/-0.3 $\log_{10}$CFU/ml, n=8, $p<0.01$) but only healthy AM (3.7+/-0.5 vs 4.7+/-0.6, n=4, $p<0.05$). MDM and AM from COPD patients exhibited lower levels of internalisation compared to healthy controls (3.7+/-0.5 healthy AM, n=5 vs 2.8+/-0.3 COPD AM $\log_{10}$CFU/ml, n=7 $p<0.01$). The presence of VX745 or SCIO469 had no effect on internalisation of opsonised or non-opsonised bacteria in either healthy or COPD MDM or AM. In conclusion, COPD reduced bacterial internalisation but was not altered by modulation of p38 MAPK. Importantly, p38 MAPK inhibitors had no detrimental effect on bacterial phagocytosis.