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Title: Defective macrophage phagocytosis in COPD is associated with reduced STAT1 phosphorylation

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Body: Macrophages are professional phagocytes that maintain sterility and remove invading pathogens. Chronic obstructive pulmonary disease (COPD) is associated with increased lung macrophages but the lower airways are colonised with bacteria such as Haemophilus influenzae and Streptococcus pneumoniae. This is associated with a decreased phagocytic response of COPD macrophages to these bacteria. IFNγ is increased in COPD airways and is associated with decreased phagocytosis. IFNγ activates the JAK/STAT pathway via phosphorylation of STAT1 to initiate signal transduction. We hypothesise that reduced phagocytosis in COPD is linked to STAT1 phosphorylation and JAK/STAT activation. Monocyte derived macrophages (MDM) from non-smoker, smoker and COPD donors and COPD lung tissue macrophages (n=3-4) were challenged with fluorescently labelled inert beads or heat killed bacteria (H. influenzae or S. pneumoniae). IFNγ stimulation (10ng/ml, 10min) was used as a positive control. STAT1 phosphorylation was assessed by Western blotting. STAT1 was phosphorylated in response to inert beads in both non-smoker and smoker MDM but not in those from COPD donors. In addition, none of the phagocytic prey initiated STAT1 phosphorylation in COPD lung tissue macrophages. However, IFNγ stimulation caused phosphorylation of STAT1 in all three donor groups. To conclude, COPD MDM and lung tissue macrophages are capable of STAT1 phosphorylation although not in response to phagocytic prey. This is in contrast to non-smoker and smoker cells that show JAK/STAT activation in response to inert beads. Further investigation of this signalling pathway in phagocytosis may lead to increased knowledge of COPD pathogenesis.