European Respiratory Society
Annual Congress 2013

Abstract Number: 1007

Publication Number: P3874

Abstract Group: 3.2. Airway Cell Biology and Immunopathology

Keyword 1: COPD - mechanism **Keyword 2:** Cell biology **Keyword 3:** Immunology

Title: Does tumour necrosis factor-alpha (TNF-α) induced by lipopolysaccharide have a positive feedback effect on the up-regulation of interleukin-8 (IL-8) messenger RNA by monocytes from COPD patients?

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Body: Background Monocytes are the principal source of the cytokine TNF-α and both play a role in COPD pathogenesis. There is a relative lack of data regarding the autocrine effects of TNF-α in this cell type. Objectives The study aimed to investigate the role of TNF-α in contributing to the up-regulation of the chemokine IL-8 by monocytes. We hypothesised that co-incubation with a monoclonal TNF-α antibody (Mab) would abrogate IL-8 message production caused by TNF-α. Methods Monocytes from 16 subjects with COPD were stimulated with 100ng/ml of Salmonella Enterica Lipopolysaccharide (LPS), 100ng/ml LPS in the presence of 10mcg/ml of TNF-α Mab or were un-stimulated. mRNA was extracted from cells at 5 time-points over 24 hours and reverse transcribed. The expression of TNF-α and IL-8 mRNA was quantified using real time PCR, normalised against the stably expressed glyceraldehyde 3-phosphate dehydrogenase (GAPDH) gene. Results LPS elicited statistically significant increases in TNF-α and IL-8 mRNA expression at each time-point (except 0.5 hours) over that by quiescent cells (p values <0.05). TNF-α mRNA at 6 hours correlated with IL8 mRNA expression at 6 hours (R=0.90, p<0.001) and at 24 hours (R=0.79, p<0.001). At 24 hours a 43.1% decrease in IL8 mRNA, from 21.1 to 12.0 (fold change relative to GAPDH), was seen in the cells co-incubated with LPS and TNF-α Mab compared to those cells stimulated with LPS alone (p=0.001). Conclusions LPS initiates an autocrine positive feedback loop whereby TNF-α signals to the monocyte to enhance IL8 mRNA production/persistence. This effect can be abrogated by TNF-α Mab.