

COPD and asthma: mechanisms of airways inflammation and treatment

P184 MACROPHAGE PHAGOCYTOSIS IN COPD PATIENTS AT EXACERBATION COMPARED TO STABLE STATE

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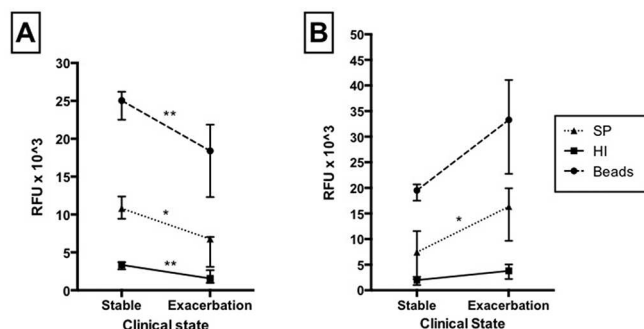
Introduction COPD exacerbations are clinically important events, commonly triggered by bacterial infection. Defective phagocytosis of potentially pathogenic microorganisms (PPMs) in stable COPD has been demonstrated in both alveolar and monocyte-derived macrophages (MDMs). We hypothesised that phagocytosis may be suppressed further during an acute COPD exacerbation and relate to bacterial aetiology of the exacerbation.

Methods Whole blood was collected from patients in the London COPD cohort at both stable state and at exacerbation, as defined by prospectively completed daily symptom diary cards (Seemungal *et al.*, 1998). Monocytes were isolated and cultured with GM-CSF (2ng/ml) for 12 days to generate MDMs. MDM phagocytosis of fluorescently-labelled polystyrene beads, *Haemophilus influenzae* (HI) and *Streptococcus pneumoniae* (SP) was measured by fluorimetry. Diary card data was used to determine prodromal symptoms, exacerbation duration and exacerbation symptom intensity. Sputa collected at exacerbation were cultured for PPMs.

Results MDMs were cultured from 13 COPD patients at paired stable and exacerbation states. 54% were male, mean age 72.8 years (SD 6.2), FEV₁ predicted 55.7% (20.5) and 38% current smokers. The median time between stable and exacerbation states was 147 days [IQR 75–212].

Two distinct patterns of change in phagocytic ability were seen between the stable and exacerbation state. Eight patients significantly decreased their phagocytic capacity compared to stable state for beads, HI and SP ($p = 0.004$, $p = 0.008$ and $p = 0.020$ respectively, Figure 1A). Five of these eight patients (63%) had a PPM isolated in their exacerbation sputum sample. Five of 13 patients increased phagocytosis at exacerbation (Figure 1B), but only SP reached statistical significance ($p = 0.031$). Only one of these five (20%) had a PPM in their exacerbation sputum sample.

There was no significant difference between the presence of prodromal symptoms, exacerbation duration or symptom intensity between the two patterns.



Abstract P184 Figure 1(A). Increased MDM Phagocytosis at exacerbation, $n = 8$; **(B)** Decreased MDM phagocytosis at exacerbation, $n = 5$.

Conclusion Phagocytosis of bacteria is suppressed further during some COPD exacerbations. This may contribute to bacterial aetiology of these exacerbations. Phagocytosis appears partially more effective in other exacerbations. Further work is needed to understand these apparently dichotomous changes and their impact on clinical outcomes.

P185 PULMONARY INFECTION IN PIZZ ANTITRYPSIN INDIVIDUALS IS ASSOCIATED WITH INCREASED OXIDATIVE AND NITROSATIVE STRESS

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Severe deficiency of the major anti-elastase α_1 -antitrypsin (AT) due to the Z (Glu342Lys) variant is associated with early-onset emphysema which can require lung transplantation. AT is mainly produced by the liver and a lesser proportion (around 10%) is produced in the lung. Therefore individuals with Z-AT post-lung transplantation remain severely deficient in AT. We studied patients with and without AT deficiency with infection (post lung transplantation) to examine the relationship between deficiency of AT and oxidative/nitrosative stress.

BALF was obtained at scheduled surveillance, and when clinically indicated to assess for infection, rejection and airway injury. 25 patients post-transplant were evaluated; 12/26 samples from 12 Z-AT patients had infective tracheobronchitis, and 7/29 samples from 13 M(normal)-AT had infective tracheobronchitis. The level of oxidative stress (F₂-Isoprostane), TNF- α , IL-1, IFN- γ was quantified using respective ELISA kits and for total glutathione (GSH) and oxidised GSH (GSSG) using OxiSelect™ Total Glutathione (GSSG/GSH) Assay Kit and nitrosative stress using Griess reagent.

BALF of Z-AT patients with infection had increased oxidative stress compared to infected M-AT patients; F₂-Isoprostane, $773 \text{ SEM} \pm 79.5 \text{ pg/ml}$ vs. 425.8 ± 53.2 , $P < 0.001$ respectively, oxidised glutathione ($0.112 \pm 0.1 \mu\text{M/ml}$ vs. 0.155 ± 0.1 , $P = 0.027$). However, total glutathione was unchanged ($0.885 \pm 13 \mu\text{M/ml}$ vs. 1.17 ± 0.141 , $P = 0.117$). There was increased nitrosative stress in Z-AT vs. M-AT patients (nitrite release as a measure of nitric oxide (NO) production ($261 \pm 47 \text{ pg/ml}$ vs. 117 ± 41.2 , $P < 0.001$), and increased levels of TNF- α ($91 \pm 16.3 \text{ pg/ml}$ vs. 59 ± 10.5 , $P = 0.002$), IL-1 ($121.2 \pm 17.4 \text{ pg/ml}$ vs. 69.6 ± 5.8 , $P = 0.047$) and IFN- γ ($481.3 \pm 74.8 \text{ pg/ml}$ vs. 201.2 ± 28.5 , $P = 0.025$). Infected Z-AT BALF had increased free HLE compared to infected M-AT patients ($167 \pm 16 \text{ ng/ml}$ vs. 42.7 ± 16 , $P < 0.001$).

In conclusion, Z-AT lungs had increased oxidative and nitrosative stress, and furthermore had increased levels of cytokines that are associated with induction of the inducible NO synthase (iNOS) gene. This suggests that excess production of iNOS-derived NO is likely to contribute to exaggerated inflammation in the PiZZ individuals lungs during episodes of infection which may contribute to progression of their lung disease.

P186 MAST CELL MEDIATORS STIMULATE HUMAN AIRWAY SMOOTH MUSCLE GROWTH, A FEATURE OF AIRWAY REMODELLING IN ASTHMA VIA MATRIX METALLOPROTEINASE (MMP-1) ACTIVITY

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