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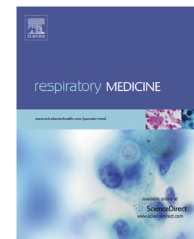

Bronchial platelet-activating factor receptor in chronic obstructive pulmonary disease

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Summary
Background: Bacteria expressing phosphorylcholine (ChoP) co-opt host-expressed platelet-activating factor receptor (PAFR) to adhere to lower airway cells. Cigarette smoke and rhinovirus (RV) infection upregulate PAFR-dependent bacterial adhesion to airway cells *in vitro*, and in healthy adults smoking increases the proportion of PAFR positive bronchial epithelial cells. To date the effect of chronic obstructive pulmonary disease (COPD) on smoke-induced PAFR is unknown. We therefore sought to test the hypothesis that bronchial PAFR mRNA expression is increased in smokers with chronic obstructive pulmonary disease (COPD), and further increases after RV infection.
Methods: Endobronchial biopsies were obtained by fibreoptic bronchoscopy from healthy non-smokers, smokers without airway obstruction, and smokers with COPD, before and after infection with rhinovirus (RV) serotype 16. Endobronchial PAFR mRNA expression was assessed by quantitative PCR and expressed as a ratio of glyceraldehyde-3-phosphate dehydrogenase. The distribution of PAFR was assessed by immunohistochemistry.
Results: Baseline PAFR mRNA expression was increased ($p < 0.05$) in smokers ($n = 16$), and smokers with COPD ($n = 14$) compared with non-smokers ($n = 18$). In RV16 infected subjects there was no increase in PAFR mRNA expression in either non-smokers ($n = 9$), smokers ($n = 8$), or smokers with COPD ($n = 7$). PAFR immunoreactivity in all 3 groups was predominately restricted to the bronchial epithelium and submucosal glands.

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Conclusions: Endobronchial PAFR mRNA is increased in both smokers without airway obstruction and smokers with COPD. We found preliminary evidence that RV16 infection does not increase PAFR mRNA expression in either smokers or smokers with COPD.
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Background

Exacerbations of chronic obstructive pulmonary disease (COPD) result from an interaction between external factors such as smoking and viral infection, and host innate immune responses [1]. Wilkinson et al. [2] for example, reported that 20% of COPD exacerbations are associated with a rhinovirus (RV) infection, and patients with both RV and bacterial infection (predominately *Haemophilus influenzae* and/or *Streptococcus pneumoniae*) have increased airway inflammation and poorer clinical outcomes [2,25]. Smoking not only causes COPD, but also increases vulnerability to airway bacterial infection and invasive pneumococcal disease in its own right [3,4]. A putative mechanism for increased vulnerability of the lower airway to bacterial infection is an increased capacity of airway cells to support bacterial adhesion. *In vitro* studies suggest that for phosphorycholine (ChoP)-expressing bacteria such as *S. pneumoniae* [5,6], and *H. influenzae* [6,7], adhesion is enhanced by increased expression of platelet-activating factor receptor (PAFR) on host cells. During the resulting interaction, bacterial ChoP is a molecular mimic of PAF. Thus ChoP-expressing bacteria have the capacity to both adhere to PAFR, and to move across the cell membrane as the receptor is internalised.

Wide range stimuli have been reported to increase PAFR-dependent adhesion of ChoP-expressing bacteria to airway epithelial cells. These include acid [8], interleukin 1α [5], RV infection [9], and cigarette smoke [10,14]. But to date, data on PAFR expression in the human lung are limited. In a recent pilot study, we found an increased proportion of PAFR-positive epithelial cells in bronchial biopsies from smokers with normal lung function compared with non-smokers [10]. By contrast, in the only other study using human lung tissue, Shirasaki et al. [11] reported decreased PAFR mRNA expression in peripheral lung biopsy specimens in 4 smokers compared with 8 controls and no PAFR mRNA expression on airway epithelial cells — the major site for clinically relevant bacterial adhesion. However in human turbinates, PAFR immunoreactivity has been reported in both the submucosal glands and epithelial cells [12].

To date, the effect of smoking on airway PAFR expression in COPD is unknown. We hypothesised that i) PAFR is increased in bronchial biopsies of current smokers with COPD compared with healthy controls, and ii) PAFR expression is increased by RV infection. In the present study, we sought to test this hypothesis using stored endobronchial biopsies from a study of healthy subjects, smokers with normal lung function, and smokers with COPD [13].

Methods

Subjects

Endobronchial biopsies were obtained from an experimental RV infection study that recruited human volunteers in London (UK). Data on bacterial infection, symptoms and antimicrobial peptides have been previously reported [13]. Three groups were studied; i) healthy non-smokers (controls), ii) smokers without airway obstruction, and iii) smokers with moderate COPD (Gold stage II). Bronchoscopy, endobronchial biopsy, bronchoalveolar lavage, and induced sputum were carried out at baseline before RV serotype 16 (RV16) inoculation as previously described [13]. Endobronchial biopsy was repeated on day 7 after RV inoculation. Informed consent was obtained from all subjects (Research Ethics Committee approval 07/H0712/138, and 11/LO/0400).

Rhinovirus inoculation and detection

Ten tissue culture infective doses 50% of RV16 were diluted in a total volume of 1 ml of 0.9% saline and inoculated in both nostrils using an atomizer (No. 286; DeVilbiss Co., Heston, UK). Rhinovirus infection was defined as; either a positive RV culture or qPCR, in nasal lavage/sputum/bronchoalveolar lavage, or RV seroconversion defined as a titre of serum neutralising antibodies to RV of at least 1:4 at 6 wk. Serology was performed at screening and 6 wk post-infection by microneutralisation test for neutralising antibody to rhinovirus. Infection with viruses other than RV was excluded by testing nasal lavage samples at baseline and at the peak of upper respiratory symptoms with PCR.

Endobronchial biopsy

Subjects were premedicated with nebulised salbutamol (2.5 mg) and intravenous midazolam (2—10 mg). Lignocaine gel and solutions (1—4%) were used for topical anesthesia. Bronchoscopy was performed using an Olympus BF 1T20 (Olympus Optical Co., Tokyo, Japan), and biopsies were taken from the lower lobe subcarinae and were snap frozen in liquid nitrogen and stored at −70 °C for analysis of PAFR mRNA.

PAFR mRNA

Endobronchial biopsy tissue was homogenised and the RNA extracted using the RNAeasy kit (Qiagen, Crawley, UK). First strand cDNA was synthesised using SuperScript VILO master mix according to manufacturer's instructions (Life

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