than from Ad-lacZ (5.4x10^5, P<0.05) or PBS mice (6.3x10^5, P<0.05). Median elafin level in the Ad-eflin group was 17ng/ml.

We conclude that elafin gene transfer protects lung epithelium against HNE-induced neutrophilic infiltration. Elafin’s role in defense may therefore be as an inducible antibiotic which can recruit neutrophils while protecting pulmonary parenchyma, potentially suggesting novel therapeutic strategies.

P4 THE EPITHELIAL–MENSECHYMAL TROPHIC UNIT IN ASTHMA

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Epithelial-mesenchymal interactions play important roles during lung development, repair and inflammation. These interactions appear to be locally regulated by a resident layer of myofibroblasts and fibroblasts in close proximity to the epithelium. The epithelial-mesenchymal trophic unit (Evans et al, Am J Respir Cell Mol Biol 1993;8:188–92). In asthma, there is an increase in number of subepithelial myofibroblasts and these are responsible for deposition of interstitial collagens and thickening of the subepithelial basement membrane (SBM) (Brewster et al, Am J Respir Cell Mol Biol 1993;8:507–14). We postulate that this increase in mesenchymal activity arises from altered communication with the bronchial epithelium, which is characteristically damaged in asthma.

Using increased epidermal growth factor receptor (EGFR) expression as a marker of injury, we found that the amount of EGFR detected in asthmatic bronchial epithelium increased in proportion with disease severity and correlated with SBM thickening (r=0.62, P<0.001). Although in vitro experiments confirmed the ability of EGF to promote LPS-induced neointimal hyperplasia, a model of bronchial epithelial cell monolayers, previous biopsy studies have failed to show increased epithelial proliferation in asthma (Demolloy et al, Am J Respir Crit Care Med 1994;150:214–7). As these observations suggested that mitogenic signalling from the EGFR might be blocked in asthmatic epithelium, we used our in vitro model to study the relationship between EGFR inhibition and the production of profibrogenic growth factors. The EGFR-selective inhibitor, tyrphostin AG1478, reduced EGFR-mediated wound closure and this resulted in a 4-fold increase in release of TGFβ, a potent stimulus for myofibroblast collagen gene expression.

These observations suggest that epithelial damage causes a functional disturbance of the epithelial-mesenchymal trophic unit and that this may underlie the remodelling responses characteristic of chronic asthma.

P5 THE TRANSCRIPTIONAL REGULATION OF INTERLEUKIN-8 (IL-8) FROM HYPXYOCIN HUMAN MACROPHAGES - A POTENTIAL ROLE IN THE ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

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Introduction. We have previously reported our finding of significantly elevated levels of IL-8 within the alveolar airspaces of patients at risk of developing ARDS (Lancet 1993; 341: 643-647). These high IL-8 levels were detected as early as 86 mins following the initiating event and the macrophage identified as a potent source. Retrospective analysis of data from trauma patients revealed a correlation between reduced PaO2/FIO2 ratio on presentation to casualty and raised bronchoalveolar lavage IL-8 levels. We postulated that acute hypoxia may upregulate IL-8 synthesis in human macrophages.

Methods. Macrophages cultured from peripheral blood mononuclear cells from healthy volunteers were exposed hypoxia (PaO2=50KPa) or normoxia (PaO2=20KPa) for up to 2 hrs. Secreted IL-8 protein was measured by ELISA and mRNA expression by northern blotting. Activation of the IL-8 promoter-binding transcription factors AP-1, C/EBP and NFκB was assessed by electromobility gel shift assay (EMSA). Finally the relative specificity for hypoxia on IL-8 upregulation was addressed by measuring mRNA levels by multiplex RT-PCR. Results. Data is expressed as mean±SEM. Hypoxia increases IL-8 protein secretion by 2 hrs compared to normoxic controls (0.94±0.28 vs 0.54±0.24 μg/ml, p<0.02). Hypoxia increases IL-8 mRNA levels by 104±38% (p<0.05) as early as 60 mins post-exposure compared to normoxic controls. EMSA revealed activation of AP-1 by 90±34%, (p<0.05) and C/EBP by 70±18% (p<0.02) within 30 mins of hypoxia compared to normoxia. NFκB was not activated at these early time points. Multi-probe RNase protection assay revealed that in contrast to the increase in IL-8, 2 hrs hypoxia significantly inhibited expression of the chemokines IP-10, MIP-1α, MIP-1β and MCP-1.

Conclusions. In human macrophages short periods of hypoxia can upregulate IL-8 protein and mRNA. The transcription factors AP-1 and C/EBP are implicated in this activation. This rapid hypoxic upregulation is relatively specific to IL-8 and is not seen with several other chemokines. These findings may be relevant to our observation of elevated lung IL-8 levels in hypoxic trauma patients who subsequently develop ARDS. NH and SCD are supported by the Wellcome Trust.