Pulmonary Vascular Disease

M Fitzgerald, DF McAuley, CM O’Kane. Queen’s University Belfast, Belfast, UK

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Background In the acute respiratory distress syndrome (ARDS) predominantly neutrophil mediated inflammation causes injury to the alveolar epithelial and capillary endothelial junction. Oncostatin M (OSM) is a pleiotropic IL-6 cytokine, upregulated in the lung in ARDS. We have shown that OSM synergizes with other cytokines to drive IL-8 secretion from alveolar epithelial cells, but its role in driving endothelial injury is unknown. CXCL5 is an OSM-dependent neutrophil chemokine that is implicated in driving endothelial cell-mediated neutrophil recruitment to the lung in animal models of pneumonia.

We hypothesised that OSM stimulates the production of neutrophilic chemokines and proteases by the alveolar endothelium in patients with ARDS.

Methods Immunocytochemistry and western blotting were performed respectively on fixed and lysed human pulmonary microvascular endothelial cells (HPMECs). The cells were stimulated with OSM ± TNF-α, and chemokine (CXCL5/8) and matrix metalloproteinase (MMP) production measured by ELISA. Conditioned media from LPS-stimulated human macrophages (CoMLPS), pre-incubated with inhibitory antibodies to OSM, was used to stimulate HPMECs, and the effect on endothelial protease and chemokine production measured.

Results
- The OSM receptor (OSMR) was detected in HPMECs at immunocytochemistry and western blot of cell lysates.
- Stimulation of HPMECs with recombinant OSM and TNF-α increased CXCL5 from 32 (5.6) to 739 (166) pg/ml, CXCL8 from 2.2(0.4) to 11.0 (2.9) ng/ml, and MMP-3 from 35.3 (1.8) to 57.6 (10.7) pg/ml. Concentrations of the endogenous inhibitors of MMPs, i.e. Tissue Inhibitors of Metalloproteinases (TIMPs)-2 were decreased from 25.2 (1.7) to 13.7 (3.2) ng/ml while concentrations of TIMP-1 were unchanged.
- CXCL5 levels were decreased from 13.2 (2.2) to 6.5 (1.1) ng/ml and levels of MMP-3 were decreased from 78.7 (16.6) to 41.4 (9.4) pg/ml from HPMEC stimulated with CoMLPS + inhibitory Ab to OSM. Interestingly, CXCL8 was not significantly abrogated by OSM neutralisation.
- CXCL5 was increased in BALF from 20.7 (1.9) to 392.5 (33.5) pg/ml from patients with ARDS (Figure 1).

Conclusions OSM drives induction of neutrophil chemokines, particularly CXCL5, and proteases by the alveolar endothelium. Targeted therapeutic inhibition of OSM may down-regulate neutrophil recruitment and MMP activity in ARDS, and will be further explored in an ex vivo human lung model.