European Respiratory Society
Annual Congress 2012

Abstract Number: 7070

Publication Number: P3767

Abstract Group: 3.3. Mechanisms of Lung Injury and Repair

Keyword 1: ALI (Acute Lung Injury) **Keyword 2:** Animal models **Keyword 3:** Inflammation

Title: The role of pre-receptor glucocorticoid metabolism in regulating the severity of ALI

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Body: Acute lung injury (ALI) is a major cause of respiratory failure in the critically ill patient. With a mortality rate of 40-60%, 50% of survivors left with pulmonary impairment and no current licenced treatment there is a need for novel therapies. Our current research suggests that local steroid metabolism by alveolar macrophages is defective in ALI patients. As a major function of these cells is phagocytosis of apoptotic neutrophils during resolution of inflammation, we sought to investigate the effect of pre-receptor glucocorticoid metabolism in a murine model of ALI. Using intra-tracheal instillations of LPS, we analysed the inflammatory response in wildtype mice compared to those deficient in 11β-hydroxysteroid dehydrogenase 1 (HSD1). These mice specifically lack the enzyme which converts inactive cortisone to active cortisol. Cell infiltrates and expression of several inflammatory markers within bronchial lavage fluid, as well as tissue permeability were examined to evaluate the immune response and lung damage. Here we report that in $HSD1^{-/-}$ mice, lung permeability increases ($6.1x10^{-3}$ $\pm0.9x10^{-3}$ v $10.7x10^{-3}$ $\pm2x10^{-3}$) 24hrs post-LPS. In addition, there was a build-up of apoptotic neutrophils ($20.3x10^{3}$ $\pm5.9x10^{3}$ v $39.2x10^{3}$ $\pm6.1x10^{3}$), with a significant increase in $CD11c^{+}CD11b^{+}$ monocytes recruited into the lung ($35.2x10^{3}$ $\pm5.7x10^{3}$ v $81.8x10^{3}$ $\pm1.4x10^{3}$) 72hrs post-LPS. Moreover, dys-regulation of IL6 was observed (1.5ng/ml ±0.62 versus 0.2ng/ml ±0.08) 72hrs post-LPS. Our data indicate that insufficient alveolar glucocorticoid metabolism augments lung injury and suggests that therapies targetting defective macrophage HSD-1 expression may have value in ALI.