European Respiratory Society
Annual Congress 2013

Abstract Number: 4749

Publication Number: 4846

Abstract Group: 10.1. Respiratory Infections

Keyword 1: Animal models **Keyword 2:** Infections **Keyword 3:** Idiopathic pulmonary fibrosis

Title: Influenza infection affects the degree of fibrosis and apoptosis in the bleomycin mouse model

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Body: Introduction: The bleomycin mouse mode can be used as a model of pulmonary fibrosis. The Influenza A virus can infects epithelial cells leading to cell death and injury. Acute exacerbations of Idiopathic Pulmonary Fibrosis (IPF) are characterised by epithelial cell apoptosis. with unknown cause. The role of infection in acute exacerbations of IPF is unclear. The aim of this study is to investigate the effect of influenza infection on bleomycin-induced pulmonary fibrosis. Materials and Methods: 60 U of bleomycin was instilled into lungs of 6-8 week old male C57Bl/6 mice. After 28 days mice were exposed intranasally with 10, 20 Units of influenza virus ‘x31’ or PBS, and lungs harvested 5 or 21 days later. Lung tissue harvested for mRNA analysis, histology and hydroxyproline levels. Animal studies were ethically reviewed and carried out in accordance with Animals (Scientific Procedures) Act 1986 and the GSK Policy on the Care, Welfare and Treatment of Animals. Results: Influenza infection increased in lung collagen levels: COL1 mRNA but not COL3 was increased. There was also an increase in matrix deposition on Masson’s trichrome staining. There were increased hydroxyproline levels in influenza infected mice with fibrotic lungs due to bleomycin administration, compared with mice exposed only to bleomycin. Non-fibrotic, influenza- infected mice showed apoptosis on histological TUNEL staining. CCNA2 mRNA in influenza infected mice with fibrotic lungs was increased compared to fibrotic mice alone indicating an increase in epithelial apoptosis. Conclusion: These data suggest that influenza infection may enhance the fibrotic response in the lung by promoting epithelial apoptosis and fibrogenesis.