Suppressing Severe Lung Inflammation to Ameliorate Influenza Related Morbidity and Mortality

A. Kurdowska¹, T. A. Tucker², J. Florence¹, A. Jeffers¹, W. Qin¹, S. Owens¹; ¹Univ At Texas Hlth Ctr At Tyler, Tyler, TX, United States, ²Univ of Texas Health Ctr At Tyler, Tyler, TX, United States.

Introduction: In the developed world, infection with influenza A virus (IAV) accounts for the majority of deaths associated with pneumonia. Severe infections with IAV can cause impaired gas exchange, bilateral pulmonary infiltrates, diffuse alveolar damage (DAD) and hypoxemia, which frequently accompany and are characteristic of acute respiratory distress syndrome (ARDS). In fact, respiratory failure related to ARDS is the main cause of death in patients infected with influenza virus. Importantly, our previous studies show that Bruton's tyrosine kinase (Btk) plays an important role in regulating alveolar inflammation during influenza infection and subsequent acute lung injury (ALI) / ARDS. Pulmonary edema is identified as a hallmark of ALI/ARDS. It is associated with an increased endothelial permeability and a disruption of the alveolar epithelial barrier. Proinflammatory signaling initiates epithelial cell dysfunction and apoptosis, and nuclear factor-κB (NF-κB) plays a central role in this process. NF-κB regulates transcription of many molecules that are involved in the inflammatory cascade, including activator protein 1 (AP-1). AP-1 family of proteins consists of Fos (c-Fos, Fos-B, FRA-1, and FRA-2) and Jun sub-families. In addition, previous studies from our laboratory revealed that epithelial cells from ALI/ARDS patients express significantly more activated FRA-1 when compared to normal tissues. Since epithelial cells express Btk, and there is persistent activation of FRA-1 in lungs of patients with ARDS (especially those with unfavorable prognoses) we tested the hypothesis that engagement of the Btk/FRA-1 pathway may contribute to epithelial injury.

Methods: We used the following techniques: immunofluorescence, western blotting, quantitative PCR, small molecule inhibition of cell signaling pathways, ELISA and other cell biology procedures. A mouse model of ALI associated with severe influenza virus infection was evaluated, and pulmonary function testing and CT scanning for lung volume analysis were employed.

Results and conclusions: Blocking of Btk with ibrutinib (Btk inhibitor) in a mouse model of ALI triggered by infection with influenza virus led to significant attenuation of FRA-1 expression in alveolar epithelial cells. Specifically, FRA-1 activation was decreased in ibrutinib treated animals, as evident from reduced translocation of FRA-1 to the nucleus. Our data also shows that Btk inhibition significantly attenuated TNF-α mediated expression of FRA-1 in epithelial cells. Based on our findings we hypothesize that the Btk/FRA-1 signaling cascade may promote loss of epithelial integrity, and that the high levels of activated FRA-1 detected in lungs of patients presenting with DAD (as seen in ARDS) may adversely impact epithelial barrier repair.

This abstract is funded by: NIH NHLBI (RO1 130133)

Am J Respir Crit Care Med 2020;201:A7427
Internet address: www.atsjournals.org