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Role of extracellular histones in acute lung injury during influenza pneumonia

Narasaraju Teluguakula[1], Harshini Ashar[1], Nathan Mueller[1], Tim Snider[1], Maram Prasanthi[1], Jennifer Rudd[1], Akhilesh Ramachandran[1], Vincent Chow T K[2] and **Esmon T Charles[3]**

[1]Oklahoma State University, USA
[2]National University of Singapore, Singapore
[3]Oklahoma Medical Research Foundation, USA

Objective: The prime complication characteristic to the influenza virus infection is viral pneumonia, which can then lead to acute respiratory distress syndrome (ARDS). Our previous studies have shown that excessive neutrophils and their generated neutrophil extracellular traps (NETs) contribute to lung tissue injury in severe influenza pneumonia. In the current study, we have evaluated the role of extracellular histones in tissue injury during influenza and tested therapeutic efficacy of anti-histone antibodies alone or in combination with an antiviral agent.

Materials & Methods: BALB/c Female mice were challenged with lethal influenza A/PR/8/34 (H1N1), 2500 pfu. Lung histopathology was analyzed. Bronchoalveolar lavage (BAL) was analyzed for vascular leakage, alveolar epithelial, endothelial damage and histones release. Histone-mediated cytotoxicity was measured by lactate dehydrogenase (LDH) release assay. Therapeutic efficacy of anti- histone antibodies (100ug/animal, subcutaneous) alone or in combination of oseltamivr (20 mg/kg) was evaluated.

Results: Influenza infected mice showed increased neutrophil influx, intra-alveolar hemorrhage, edema and macro- and microvascular thrombosis. Infection caused high extracellular histones release into the lung airspace. Released extracellular histones also showed high cytotoxicity in both alveolar epithelial and endothelial cells *in vitro*. Treatment with anti-histone antibody significantly reduced lung pathology, compared to oseltamivir treatment alone. Further combination of anti-histone antibodies together with oseltamivir resulted in 40% survival after lethal influenza challenge in mice.

Conclusions: These results demonstrate that the use of anti- histone antibodies in combination with a classical antiviral therapy can be a novel and effective treatment approach for severe influenza pneumonia.

Biography

Narasaraju Teluguakula has been working in the field of "Respiratory and infectious diseases" since he joined PhD program in 1995. He obtained Postdoctoral training in Lung Biology at Oklahoma State University, USA from 2001-2004 and in infectious diseases from 2005-2010 at National University of Singapore, Singapore. He has been a 'mentor' for many graduate and master students during his Postdoctoral research and also wrote two grants as a co-investigator. He has experience of working with infectious disease models and conceptual knowledge of lung physiology and pathology.

narasa@okstate.edu

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