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Targeting neutrophil-CXCR2 for the treatment of influenza pneumonia

Narasaraju Teluguakula[1], Harshini K Ashar[1], Jennifer M Rudd[1], Timothy A Snider[1], Mallika Achanta[1], Maram Prasanthi[1], Ramachandran Akhilesh[1], Jerry R Malayer[1], Jerry W Ritchey[1] and Vincent TK Chow[2]
[1]Oklahoma State University, USA
[2]National University of Singapore, Singapore

Complications of Acute Respiratory Distress Syndrome (ARDS), a severe form of acute lung injury, remain major cause of death in influenza pneumonia. Several recent studies have demonstrated that considerable lung damage is contributed by the host immune response in addition to the cytopathic effects of the influenza virus. Previously, we have demonstrated that excessive neutrophils recruitment and their generated Neutrophil Extracellular Traps (NETs) contribute to pathologic complications of ARDS in severe influenza pneumonia in mice. Neutrophils express predominantly CXC chemokine receptors including CXCR1 and CXCR2, which play key role in the recruitment and activation of neutrophils. This study was aimed to test the therapeutic potential of CXCR1/2 antagonism in severe influenza pneumonia. Our results have shown high increase in CXCR2 expression in both circulating and lung-recruited neutrophils. We used a selective CXCR1/2 antagonist, SCH527123 alone or in combination of an anti-vial agent, oseltamivir. BALB/c female mice were challenged with lethal influenza A/PR/8/34 (H_1N_1), 2500 pfu. Oseltamivir or SCH527123 were administered orally. Treatment with oseltamivir alone showed 15% survival, while all animals were died in SCH527123 alone treatment group. However the combined administration of these drugs resulted in 60% to 100% survival in mice after lethal influenza infection. The addition of SCH527123 to the combination therapy regime was also found to significantly alleviate lung pathology, compared to oseltamivir treatment alone. Lungs of infected animals following combination therapy showed decreased neutrophil influx, decreased release of extracellular histones, reduced vascular leakage, and reduced alveolar capillary damage. These results demonstrate that the use of CXCR1/2 antagonists in combination with a classical antiviral therapy can be a novel and effective treatment approach for severe influenza pneumonia.

narasa@okstate.edu