Role of Neutrophils in Influenza Virus Pathogenesis

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Abstract
Complications of acute respiratory distress syndrome (ARDS), a severe form of acute lung injury, remain major causes of death in influenza pneumonia. Our studies 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. We have identified chemokine receptor CXCR2 as the most induced among CC and CXC chemokine receptors in response to influenza and this study was aimed to test the therapeutic potential of CXCR2 antagonism against influenza. BALB/c Female mice were challenged with lethal influenza A/PR/8/34 (H1N1), 2500 TCID50. Oseltamivir or a CXCR2 antagonist, SCH527123 were administered orally alone or in combination. Lung histopathology, virus titer, vascular leak, extracellular histones and alveolar-capillary damage were assessed. Our results have shown significant increase in CXCR2 expression in both circulating and lung-recruited neutrophils. Treatment with oseltamivir alone showed 15% survival, while all animals in SCH527123 alone treatment group were succumbed to infection. However, the combined administration of these drugs resulted in 60% to 100% survival in mice after lethal influenza infection. The addition of SCH527123 to reduce lung pathology, neutrophil influx, vascular leakage and accumulation of extracellular histones compared to oseltamivir treatment alone. Histones are the major protein components in NETs and are known to have cytotoxic effects. We examined the role of extracellular histones in lung pathogenesis during influenza. BALB/c mice infected with influenza virus displayed high accumulation of extracellular histones, with widespread pulmonary microvascular thrombosis. Occluded pulmonary blood vessels with vascular thrombi often exhibited endothelial necrosis surrounded by hemorrhagic effusions and pulmonary edema. Histones released during influenza, induced cytotoxicity and showed strong binding to platelets within thrombi in infected mouse lungs. Nasal wash samples of influenza-infected patients also showed increased accumulation of extracellular histones, suggesting a possible clinical relevance of elevated histones in pulmonary injury. Blocking with anti-histone antibodies causes marked decrease in lung pathology in lethal influenza-challenged mice and improved protection when administered in combination with the antiviral agent oseltamivir. Currently we are testing these combination therapies in a swine-model of influenza pneumonia using 3-4 weeks’ old piglets.

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