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Angiopoietin-1 and keratinocyte growth factor restore the impaired alveolar fluid clearance induced by influenza H5N1 virus infection

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Background: Acute respiratory distress syndrome (ARDS) caused by high pathogenic avian influenza (HPAI) H5N1 virus infection has resulted in severe illness and high mortality rates among patients. Patients with ARDS are often characterized by impaired alveolar fluid clearance and alveolar edema. An understanding of the mechanism responsible for human alveolar edema will lead to the development of novel therapeutic treatments for ARDS patients. We hypothesized that the paracrine soluble factors angiopoietin-1 (Ang-1) and keratinocyte growth factor (KGF) can resolve alveolar fluid clearance by up-regulating the expression of major sodium and chloride transporters impaired by HPAI H5N1 virus infection. Materials and Methods: Human alveolar epithelial cells grown on transwell inserts were infected with HPAI H5N1 (A/HK/483/97) and low pathogenic avian influenza (LPAI) H1N1 (A/HK/54/98) viruses at MOI 0.1 or incubated with conditioned culture medium containing Ang-1 and/or KGF. At 24 and 48 h post-infection, the rate of alveolar fluid transport and protein permeability across the alveolar epithelium was measured. Protein expression of sodium and chloride transporters (Na-K-ATPase, CFTR, and epithelial sodium channel alpha subunit) was measured by qPCR, ELISA, and Western blot. Results: HPAI H5N1 (A/HK/483/97) virus infection significantly reduced net alveolar fluid transport and protein permeability when compared with H1N1 (A/HK/54/98) virus infection at 24 h post-infection and further reduced it at 48 h post-infection. This reduction in alveolar fluid clearance was associated with a substantial reduction in protein expression of Na-K-ATPase, CFTR, and epithelial sodium channel alpha subunit. The influenza virus–infected cells treated with Ang-1 and KGF restored the impaired alveolar edema fluid clearance and protein permeability after HPAI H5N1 virus infection. Furthermore, the paracrine soluble factors Ang-1 and KGF up-regulated the protein expression of the major sodium and chloride transporters resulting from the HPAI influenza virus infection. Conclusions: The paracrine soluble factors Ang-1 and KGF play an important role in maintaining human alveolar fluid clearance by up-regulating the sodium and chloride transporting systems in human alveolar epithelium. This study enriches the understanding of the development of ARDS in human H5N1 disease and may aid in the development of possible therapeutic applications.

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Immunomodulatory and anti-viral effects of statins in influenza H5N1 virus infection of human alveolar epithelial cells and peripheral blood–derived macrophages

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Background: Highly pathogenic avian influenza (HPAI) H5N1 virus panzootic in poultry continues to spread. It causes zoonotic human disease with a high (> 60%) fatality rate and continues to pose a pandemic threat. Based on clinical, animal, and in vitro cell studies, we and others have suggested that differences in viral replication competence, tissue tropism, and cytokine dysregulation between H5N1 and low pathogenic viruses may contribute to disease pathogenesis. Statins as HMG-CoA inhibitors act to reduce cholesterol and have been demonstrated to have anti-inflammatory and immune-modulatory activities. However, there is controversy about the benefits of statin use on influenza infection in mice and humans. In this study, we aimed to evaluate the effects of statin

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