S44-5 Pathogenesis of severe influenza and prevention and treatment of advanced disease

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Influenza A virus (IAV) is the most common infectious pathogen in humans, causing significant morbidity and mortality particularly in infants and the elderly. Multiple organ failure is observed during the advanced stage of influenza pneumonia, and influenza-associated encephalopathy (IAE) with severe edema. However, the relationship amongst factors that influence the progression of influenza with multiple-organ failure and lethal effects remains unclear.

There is a significant increase in proinflammatory cytokine levels ("cytokine storm"), including tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1ß, which affects host survival both positively and negatively. The inflammatory response affects cell adhesion, permeability, apoptosis, and increased mitochondrial permeability, potentially resulting in vascular dysfunction and multiple-organ failure. In this paper we reported that IAV infection upregulates several cellular proteases including ectopic trypsin and matrix metalloprotease (MMP)-9. Trypsin mediates the post-translational proteolytic cleavage of viral envelope glycoprotein, hemagglutinin, which is crucial for viral membrane fusion activity and viral entry and the subsequent tissue damage in various organs. Induction of both proteases synergistically degrades basement membrane proteins, potentially damaging the blood-brain barrier (BBB) and destroying endothelial cell tight junctions, followed by severe edema and multiple-organ failure.

In addition, we recently found that the majority of patients who died or were disabled by IAE, a transiently impaired energy metabolism, particularly carnitine palmitoyltransferase II disorder, was observed, despite the absence of symptomatic manifestations of energy metabolism disorder in daily life.

Based on these results, prevention and treatment of severe influenza will be discussed.