2. Abstract

Certain highly pathogenic avian influenza viruses have the capability to infect mammals and cause severe disease, often with fatal outcome. The natural reservoir of these viruses is migrating wild waterfowl, which usually show no clinical signs of disease. These characteristics of highly pathogenic avian influenza viruses may create opportunities for a pandemic virus to emerge, and it is therefore important to identify host and viral factors related to high virulence in humans and animals. To this end, we analyzed the interactions between different influenza A virus isolates and cells of the innate immune system of pig and man, including lung endothelial cells and bone marrow-derived dendritic cells. Endothelial cells and bone marrow-derived dendritic cells were susceptible to infection by human, avian and porcine influenza viruses based on intracellular nucleoprotein detection. However, the percentage of infected cells and expression levels of NP varied significantly between human and avian influenza A virus isolates, with certain of the latter usually showing higher infectivity. After infection, activation markers like major histocompatibility complex II for dendritic cells and E-selectin for endothelial were upregulated. Bone marrow-derived dendritic cells and endothelial cells secreted proinflammatory cytokines such as interleukin-6 following infection. Interestingly, H5N1 highly pathogenic avian influenza viruses were most efficient in infecting and activating the cells. This was also associated with a higher rate of cell death. For endothelial cells we could show by reverse genetics experiments that the viral hemagglutinin is responsible for the differences between human isolates and avian H5N1 influenza A viruses. Overall, our results indicate that avian H5N1 viruses differ in their receptor specificity and activation potential of cells of the reticuloendothelial system from human and porcine isolates, and these differences could explain the inefficient transmission of avian influenza viruses to humans, as well as aberrant innate immune responses found in man infected with such viruses. These have been proposed to be associated with the high fatality rate once an infection is established.