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Influenza virus and apoptosis
—the role of double-stranded RNA-activated protein kinase

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The influenza virus causes worldwide epidemics of acute upper respiratory inflammation and often complicates other conditions, particularly in the elderly. However, the mechanisms involved in the damage to host cells have not been clarified. We and others have reported that influenza virus infection induces apoptotic death of host cells both in vitro and in vivo. We also found that the virus infection augmented the expression of apoptotic receptor, Fas/Apo-1 (CD95). The virus elicited a transient but marked increase in Fas mRNA, followed by Fas expression on the cell surface. The virus infection stimulated the activity of Fas gene promoter, which contains 8 repeats of NF-IL6 binding motif. The DNA binding activity of NF-IL6 increased after the virus infection, whereas the amount of NF-IL6 unchanged, suggesting that the NF-IL6 activation is due to modification. We suggested that double-stranded RNA (dsRNA)-activated protein kinase (PKR) is involved in the induction of Fas by the virus infection, since a synthetic dsRNA, poly(I)-poly(C), similarly increased the amount of Fas mRNA which was inhibited by the potent PKR

inhibitor, 2-aminopurine. Moreover, the expression of a catalytically inactive PKR mutant having a point mutation in the catalytic domain at 296K to R in HeLa cells trans-dominantly suppressed the augmented expression of Fas by influenza virus infection. We speculate that the virus activated-PKR phosphorylates NF-IL6 which then stimulates Fas gene transcription. Recently, we observed that the Fas ligand was also expressed on the influenza virus-infected cells, and the virus-induced apoptosis was inhibited in the presence of an antagonistic antibody against Fas ligand. These results suggest that the virus-infected contact and kill each other by Fas and Fas-ligand interaction.

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