MORPHOLOGICAL STUDIES ON THE ENTRY PROCESS OF INFLUENZA VIRUS AND EFFECTS OF MONOCLONAL ANTIBODIES ON THE PROCESS

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The entry process of influhnza viruses, A/seal/Massachusetts/1/80 (H7N7) and A/Aichi/2/68(H3N2), into Madin-Darby canine kidney (MDCK) cells was morphologically examined. Viruses were seen bound to the cell surface at 0°C. After warming at 37°C, the viruses were endocytosed into the cell and then appeared in the smooth-surfaced vacuoles. In the vacuoles, fusion of the viral envelope with the membrane was observed. This is the first morphological evidence showing that the penetration of influenza virus genome into cytoplasm occurs by the mechanism of fusion from vacuoles.

Monoclonal antibodies to different antigenic sites on the hemagglutinin molecule of A/seal/Massachusetts/1/80 (H7N7) influenza virus were then studied for their effects on the entry process of viral infection. Monoclonal antibodies belonging to group I, which inhibited hemagglutination of the virus, blocked attachment of the virus to the cells. On the other hand, monoclonal antibodes belonging to grop IV, which failed to inhibit hemagglutination of the virus yet effectively neutralized viral infectivity, did not block the attachment of the virus to the cells. Virus particles, which were bound with the group IV antibodies, attached to cell surface, were endocytosed and then appeared in the smooth-surfaced vacuoles and lysosomes. No fusion of the viral envelope with the membrane was observed. These findings suggest that the neutralizing antibodies to the hemagglutinin, which failed to block attachment of the virus to the cells, inhibited the fusion step in intracellular vacuoles.

The present results, therefore, support the following hypothesis for the mechanism of neutralization of viral infectivity with non-hemagglutination-inhibiting antibodies : that is, interference with a low pH-induced conformational change in the hemagglutinin molecule by antibody-binding results in inhibtion of the fusion step in the viral replication process.