Control of Avian Influenza: Defense Strategies on Respiratory Bioterror Agent

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The H5N1 'avian flu' in Hong Kong in 1997 was the first documented incidence of human infection and death associated with avian influenza virus. The virulence was unusually severe with about 30% of fatality, a harbinger of incipient pandemic situation. The biological basis for the severity of human H5N1 disease has remained unclear. Although highly pathogenic avian influenza viruses have been identified before the 1997 outbreak, their devastating effects had been confined to poultry. With the Hong Kong outbreak, it became clear that the virulence potential of these viruses extends to humans (1, 2, 3). Now, the Biological Weapons Convention (BWC), in an effort for stipulating international law against weaponization of microorganisms, classifies the virus as potential means for bio-terroristic attack.

Moreover, conventional H3N1 and H1N1 type of Influenza virus remains an essentially uncontrolled infectious agent causing frequent outbreaks of epidemics and pandemics among humans. To better understand and curb the disease, a good experimental system has been in need for investigation of the parameters that control the pathogenicity of the virus. Reverse genetic methodology has been proven potentially very useful in introducing an "attenuation character" into the virus and should provide a precise means to develop a live influenza vaccine.

Current research interest centers around developing live influenza vaccine by both conventional serial passage method and newly developed reverse genetic technology (4, 5). These technologies are being applied to (i) identification of cis-acting signals involved in influenza gene replication, (ii) developing chimeric influenza viruses as expression vectors for foreign proteins as vaccine vectors for other infectious diseases, and (iii) development of genetically engineered influenza live vaccine from cold-adapted strain.

Recently, we discovered that the expression of the two surface antigens, haemagglutinin (HA) and neuraminidase (NA) could be modulated by a single promoter mutation (6). Since both HA and NA are involved in protective immunity of influenza infection, the ability to change the repertoire of the two surface antigens could be usefully applied to improve the immunogenicity of influenza vaccine. Through conventional repeated passage at low temperature, a master strain of live influenza vaccine was developed. It is possible to tranfer the cis-acting signal that controls the repertoire of surface

antigen unto the cold adapted master strain through transfection of influenza RNP complex. This genetically engineered influenza virus is expected to present higher amount of the HA protein on the attenuated virus, and will be an ideal candidate for an improved live vaccine against influenza infection. Based upon these technical platforms, strategies of utilizing influenza virus as vaccine carrier for other infectious diseases will also be developed.

Combining the reverse genetic technology with the live influenza vaccine would lead to development of new strategies to minimize potential morbidity and mortality of the misuse of the influenza virus.

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