Pandemic Preparedness: Immune Responses of Live Influenza Vaccine

Baik Lin Seong

Department of Biotechnology, College of Engineering, Yonsei University, 134 Shinchon-Dong, Seodaemun-Ku, Seoul 120-749, Korea

Influenza virus remains an essentially uncontrolled infectious agent causing frequent outbreaks of epidemics and pandemics. Influenza pandemics are caused by sudden emergence of a new influenza subtype in humans. New subtypes most probably derive from the vast animal influenza reservoir, where 15 different influenza A subtypes freely circulate including aquatic migratory birds. Only two subtypes (H3 and H1) are presently circulating in humans. However, if a subtype extends its host range to include humans, it would probably ignite the next pandemic. With the unprecedented outbreak of avian influenza in Asia (caused by H5N1), the world has come closer than ever to the first pandemic since 1968. Our previous experience suggests that vaccines would serve the best line of defense against the high morbidity and mortality invariably associated with influenza pandemic.

Although trivalent subunit vaccine has been available, the influenza vaccine has been under-utilized because of cumbersome route of vaccination and low level of protection. Therefore, there has always been a great need to develop live attenuated influenza vaccine which can be administered through nasal route and elicit better immunogenicity. Introduction of attenuation phenotype into the viral genome through conventional 'cold-adaptation' or reverse genetic methodology has been proven useful for the generation of live attenuated influenza vaccine.

In part of our efforts for developing live influenza virus vaccine, a live vaccine carrier was established through conventional repeated passage at low temperature. The virus was evaluated for several properties: *ca, ts, att* phenotype and protective immune responses. By reassortant formation between the 'cold-adapted' vaccine carrier and virulent strains, a prototype of trivalent live influenza vaccine is developed. This strain was evaluated for their ability to protect mice from challenge with same subtype and different subtype of influenza A virus. The vaccination of mice with live attenuated influenza virus provided complete protection against homologous and heterologous virus challenge.

Besides well known prophylactic effect, a desirable trait for live attenuated vaccine may include potential therapeutic effect by interfering with wild-type viruses. On the basis of the ability of the ca virus to suppress wt viral replication, we examined in mouse infection model if the X-31 *ca* virus could interfere with the virulent virus. Prior vaccination with the *ca* virus about 1-4 days before challenge with virulent virus or even simultaneous infection of vaccine virus and virulent virus resulted in marked improvement in clinical signs associated with influenza infection. The administration of this ca virus may confer immediate protection and block further spread of the virulent virus, and could be considered useful for minimizing morbidity and mortality associated with natural outbreak or intentional use of influenza virus.