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A Missing Link for the Global Pandemic Influenza Outbreak

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Influenza has been an important public health issue epidemiologically with worldwide impact. Three major public health problems of influenza are: (1) rapid changes of influenza viruses genetically and antigenically; (2) emergence of novel influenza viruses from genetic reassortant involving animal influenza viruses to human with insufficient herd immunity; and (3) incomplete coverage of epitopes on significant antigenic drifted influenza viruses by the World Health Organization (WHO) recommended influenza vaccine strains [1]. The vaccine-mismatched influenza viruses have caused increased mortalities in the elderly in Taiwan and globally [2]. On the other hand, the emergence of 2009 pandemic influenza A (H1N1) viruses (pH1N1) with high viral transmissibility has created public health threat, particularly in those areas with endemicity of avian influenza viruses A (H5N1). Recently, Kawaoka et al. reported the emergence of reassortants with even better growth kinetics after coinfection of pH1N1 and a contemporary H5N1 virus in human lung cell lines [3]. At present, the most endangered threat comes from the emerging reassortants between these H5N1 and pH1N1 that might result in public health disaster. Furthermore, numerous reports in the U. S. Midwest suggested that pigs and human farm workers with influenza-like illness (ILI) passed on viruses to others [4,5]. All these together have demonstrated that origin and mechanisms responsible for the emergence of pandemic influenza viruses and their associated epidemiological conditions are the most important public health questions.

The differences in inter-species transmission and pathogenesis of influenza viruses represent an interesting research topic. Previous studies showed that HA of AIV H5N1 binds perfectly to α-2,3-Galdisaccharide part of sialic acid on the natural host cell, whereas the human or mammalian influenza virus binds to α-2,6-Gal disaccharide. However, humans would be occasionally infected by avian influenza virus due to the α-2,3-linkage disaccharide residue distributed only on the lower respiratory tract surface cells [6,7]. Another studies presented that HA Receptor-Binding Domain (RBD) of AIV is usually conserved. However, if the E190D or G225D mutation existed in H1 of AIVs, the H1 virus could infect humans due to the stronger affinity towards the α-2,6-Gal disaccharide. Nevertheless, the Q226L mutation in H2 or H3 of AIVs could also facilitate the binding of α-2,6-Gal disaccharide [8]. Except for HA, other viral proteins also play important roles in zoonotic infection. For example, the residue 627 of the influenza virus polymerase PB2 subunit may alter the infectivity of zoonotic influenza virus for human host [9,10]. The NS1 protein, in different influenza virus serotypes or different strains also influence the expression of interferon-regulated genes [11]. Another study showed the evidence for cross-species influenza virus infection due to the mutation of influenza virus A matrix protein 1 (M1) [12]. All these above data support that pathogenesis of influenza viruses involve multiple molecular determinants in different segments of viral genes. Therefore, it is critical to monitor the changes of whole viral genome in influenza viruses and the epidemiological conditions, which facilitate the virus to transmit from avian to human or swine to swine or swine to human.

Global efforts are needed to determine the molecular, ecologic and/or environmental factors that may influence the evolutionary changes, emergence, interspecies transmission, adaptation to mammalian hosts/humans and subsequently large-scale human-to-human transmission, increasing epidemiologic/pandemic potential, and elevated pathogenicity of influenza viruses. In fact, the epidemiology of influenza and the pandemic potentials of novel influenza viruses have to be viewed from ecological perspective, involving both animal and human parts. Till now, there have been fewer studies to integrate research at both sides to answer the important epidemiological changes at population levels from different host species and even before the major changes (e.g., Before outbeaks/epidemics/pandemics). Therefore, the causal inference has remained an enigma. Two essential research tasks are needed including monitoring molecular changes of influenza viruses through an integrated influenza virological surveillance research at the inter-phases of the three important hosts – avian, swine and human and detail bioinformatics data analyses, and to elucidate the mechanism of protection by fully understanding antigenic cross-reactivity, cross-protection and herd immunity at both levels of individuals and populations, respectively.

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