News

China makes an impressive breakthrough in avian influenza virus research — Discovering the "heart" of avian influenza virus

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The successive appearance of strains of epizootic avian influenza A virus with the subtype H5N1 in China has attracted considerable concern from the public and Chinese authorities. According to the latest WHO estimates as of February 2, 2009, the number of H5N1 virus deaths in China totaled 25, second only to Indonesia and Viet Nam (*http://www.who.int/csr/disease/avian_influenza/country/cases_table_2009_02_02/en/index.html*).

The H5N1 virus is highly contagious among birds and is fatal when transmitted to humans, though the means by which this occurs is still unknown. Owing to the possible variation of the H5N1 prototype virus, together with the fact that it has the propensity to exchange genes with influenza viruses from other species, humans have no natural immunity to the virus. Despite years of efforts, the exact pathogenesis of H5N1 transmission to humans is still not completely clear, nor is potential human-to-human transmission as could lead to an epidemic or even worldwide pandemic (*Enserink M. Science. 2009; 323:324*). Unfortunately, current antiviral treatment and therapeutic measures cannot effectively overcome this virulent virus that causes highly pathogenic avian influenza (HPAI).

Researchers from around the world are working to study the virology of influenza viruses, including their methods of infiltration, replication, and transcription, to elucidate the mechanisms of unremitting viral infection in terms of aspects such as the virus, host, and environment. These researchers are also working to identify potential molecular targets related to H5N1 for anti-influenza drug intervention.

A recent H5N1-related study from China provides encouraging information. According to the People's Daily (*Renmin Ribao*), a newspaper out of Beijing, professor Liu Yingfang, academician Rao Zihe, and fellow researchers from more than 6 research centers, including the Institute of Biophysics Chinese Academy of Sciences, Nankai University, and Tsinghua University, have achieved exciting results in providing a detailed understanding of the mechanisms of action of the RNA polymerase PA subunit, the "heart" of the avian influenza virus, at the atomic level. They hope to provide clues to potential avian influenza therapy targets and a new platform for new drug discovery (*http://202.123.110.5/jrzg/2009-02/06/content_1222973.htm, available as of February 6, 2009*).

According to Liu *et al.*, influenza viruses are enveloped, negatively stranded RNA viruses with a segmented genome (consisting of 8 RNA segments) that can encode 11 kinds of viral proteins. Among these proteins, the complex of influenza polymerase, consisting of PB1, PB2, and PA subunits, is regarded to be what gives life to influenza viruses because of its essential catalytic role in viral RNA replication and mRNA transcription in the nucleus of infected cells. Notwithstanding earlier virology studies on the influenza virus that elucidated the functions of PB1 and PB2, the exact function of PA is still not completely clear.

The group resolved the crystal structure of the carboxyl-terminus of PA in complex with the amino-terminus of PB1 peptides for the first time. This structure mode provides details for the interactions of PA and PB1, as well as the binding sites of PA and RNA. Results of the research, entitled the "Crystal structure of the polymerase PA(c)-CPB1(N) complex from an avian influenza H5N1 virus," were published in the August 28th issue of the respected international scientific journal *Nature* (*He X, Zhou J, Bartlam M, et al. Nature. 2008; 454:1123-1126*).

Further efforts by the group served to indicate the fine three-dimensional structure of the *N*-terminal of PA protein. They revealed that the PA subunit holds an endonuclease active site and that it, rather than the PB1 subunit as was previously, plays a critical role in the endonuclease activity of influenza virus polymerase. In addition, PA's characteristics of being highly conserved and having little mutations make it an attractive target for anti-influenza therapeutics. Specifically, endonuclease can block the mRNA of host cells cached by the complex of polymerase, resulting in mRNA transcription.

Results of the group's most recent research have been published in a recent February 4th issue of *Nature* (*Yuan P, Bartlam M, Lou Z, et al. Nature. 2009; Epub ahead of print*).

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