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CASCIRE surveillance network and work on avian influenza viruses

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Studies on influenza virus by Chinese Academy of Sciences (CAS) could be traced back as early as 2005 by the CAS Key Laboratory of Pathogenic Microbiology and Immunology (CASPMI), who discovered that Qinghai-like Clade 2.2 H5N1 subtype highly pathogenic avian influenza virus (HPAIV) first caused severe outbreak in wild birds in Qinghai Lake (Liu et al., 2005).

Since then, to set the platform for further investigative work, CASPMI has worked continuously on the surveillance, genetic evolution, pathogenesis, cross-species infections to mammals and humans, antivirals, antibodies and vaccines against influenza virus, as well as other emerging infectious pathogens. In 2014, the CAS Center for Influenza Research and Early-warning (CASCIRE) (http://www.im.cas.cn/xwzx/jqyw/201412/t20141229_4283087.html) and the Network Surveillance Unit (NUS) of CASCIRE (Figure 1), as well as the joint-lab between CASCIRE and the regions of The Belt and Road (e.g. Russia) have been developing a coordinated emergency response and research capacity on emerging or re-emerging infectious diseases. In this article, the aims of CASCIRE and its work on influenza were summarized, with the aim of promoting collaborations between CASCIRE and other research groups for better prevention and control of emerging or re-emerging infectious diseases.

THE ROLES OF MIGRATORY BIRDS IN THE EVOLUTION AND TRANSMISSION OF HPAIVS

During our surveillance studies, the Qinghai-like Clade 2.2 H5N1 virus was identified again in 2006 at Qinghai Lake. While the virus possessed some differences in its genome compared to those isolated in 2005, and was more similar to those identified in Asia, Europe and Africa along the migratory flyways of wild birds. We then hypothesized that wild birds play important roles for the spread, transmission and evolution of HPAIVs worldwide through their migratory activities (Wang et al., 2008). Currently, the Qinghai-like Clade 2.2 H5N1 virus has evolved into different sub-clades in poultry, is dominant and occasionally causes sporadic human infections in Egypt (http://www.who.int/influenza/vaccines/virus/characteristics_virus_vaccines/en/).

Our hypothesis was further supported by the novel reassortant SMX-like Clade 2.3.2.1c H5N1 virus, which evolved from Clade 2.3.2 found in 2009 (Hu et al., 2011), in whooper swans and wild ducks in Sanmenxia city of the Yellow River Region in 2015 (Bi et al., 2015d). The biological characteristics, including drug sensitivity screening and pathogenicity in chickens and mice were studied in our laboratory, and three diseased whooper swans were treated with sensitive drugs and cured. Moreover, CASCIRE was able to warn about the spread of the SMX-like Clade 2.3.2.1c H5N1 based on the flyways of wild birds. Based on this early warning, the SMX-like viruses were quickly identified and treated in wild birds in Inner Mongolia and Qinghai Lake (Bi et al., 2016a) (http://www.im.cas.cn/xwzx/jqyw/201509/t20150902_4419497.html). Due to the typical genetic characteristics with Clade 2.3.2.1c HA and H9N2-derived PB2 gene, the SMX-like viruses were easy to be differentiated and were again identified in wild birds and poultry in other Asian and European regions along the flyways during 2014–2015. The viruses were found to possess mutations in its genome, indicating viral evolution (Bi et al., 2016a). Studies on SMX-like H5N1 virus further supported our viewpoints on the roles of migratory birds in the evolution and transmission of HPAIVs. As a result, our hypothesis proposing that HPAI spread is facilitated over long distances by migratory wild birds is now largely accepted by the scientific community, especially after the worldwide transmission of H5N8 HPAIVs (http://www.oie.int/en/animal-health-in-the-world/update-on-avian-influenza).

THE ROLES OF LIVE POULTRY MARKETS IN THE EVOLUTION AND TRANSMISSION OF NOVEL AIVS

The CASCIRE surveillance network monitors wildlife (e.g. wild birds), domestic animals (e.g. poultry), and includes sentinel hospitals for human cases, forming a complete circle for monitoring novel pathogens that pose potential risks to humans and animals alike. Human AIV infections may occasionally occur after exposure to the virus from live poultry or the environment, e.g. live poultry markets (LPMs) (http://www.who.int/influenza/human_animal_interface/HAI_Risk_Assessment/en/). A majority of viruses isolated from human cases possessed high genetic similarity to viruses from LPMs, such as H10N8 and H5N6 (Bi et al., 2015a; Bi et al., 2016b; Zhang et al., 2014). In addition, the novel AIVs, such as H7N9 and H5N6, are evolving, spreading and undergoing dynamic reassortment with low pathogenicity avian influenza viruses (LPAIVs) (e.g. H9N2) in LPMs (Bi et al., 2016b; Cui et al., 2014). Therefore, the LPMs were considered as “incubators” for the evolution and emergence of

Figure 1 The surveillance network of CASCIRE.

novel AIVs (Gao, 2014). Interestingly, the internal genes of novel, dominant H7N9, H10N8, and H5N6 AIVs were all found to originate from H9N2 LPAIVs (Bi et al., 2016b; Liu et al., 2013; Zhang et al., 2014). Novel AIVs carried by wild birds could be transmitted to domestic birds through direct or indirect contact, and then the HA and NA genes of the novel viruses were conserved and adapted to poultry by rapid reassortment with the internal genes of a poultry-adapted AIVs (e.g. H9N2), to help novel reassortants replicate and evolve in domestic poultry (Su et al., 2015). Thus, the poultry-adapted H9N2 may increase adaptation of aquatic bird origin HA and NA genes to domestic birds (Liu et al., 2014).

We also discovered that the H7N9 HPAIV variant in poultry from LPMs as early as July 2016 (Qi et al., 2017), and have subsequently identified several human cases (Zhang et al., 2017). Notably, we also found that H5N6 has gradually replaced H5N1 as a dominant subtype in poultry, especially in Southern China (Bi et al., 2016b). H5N6 has caused severe outbreaks amongst poultry in Southeast Asia and has also been found in wild birds in some regions of Asia and even in Europe after 2014 (Bi et al., 2016c) (http://www.oie.int/en/animal-health-in-the-world/update-on-avian-influenza). There is a real risk that H5N6 may also transmit globally, following the footsteps of H5N1 and H5N8.

THE MOLECULAR MECHANISM OF CROSS-SPECIES AIV INFECTION

There are at least two host barriers for AIVs to cross-infect mammalian cells. The first barrier is receptor binding, in which AIVs require the human-type (α2-6-SA) receptor binding ability to infect human cells. The second is that the viral ribonucleoprotein (vRNP) complex-polymerase of AIVs should function well in the new host cells for efficient virus replication. Our studies on the first barrier showed at the atomic level that the molecular mechanism of transmissibility of H5N1 viruses among ferrets caused by seven critical mutations in the HA protein (Lu et al., 2013; Zhang et al., 2013a). H1N1 viruses with the D225G mutation was found to have developed an ability to bind both human-type (α2-6-SA) and avian-type (α2-3-SA) receptors (Zhang et al., 2013b), thus elucidating the reason for severe lower respiratory disease in humans. Critical atoms associated to receptor binding were also identified in H4, H6 and H10-subtype influenza A, as well as influenza D viruses (Song et al., 2016; Song et al., 2017; Wang et al., 2015a; Wang et al., 2015b). We discovered that the novel H7N9 LPAIV with G226L mutation on HA possessed dual receptor binding properties (Shi et al., 2013), which explained why H7N9 was able to cross the first species barrier to infect humans. Stu-

dies on the second barrier showed that the PB2 gene was critical for H7N9 virus replication in human cells with high RNP activities, and was identified as an important determinant of virulence in mice (Bi et al., 2015c). Other genes, including HA and NA, also contributed to the infectivity of H7N9 in human cells. NA with a five-amino-deletion in the stalk region could not influence the virulence of H7N9 in mice, but a longer deletion in the NA stalk increased the pathogenicity of H7N9 in mice (Bi et al., 2015b). Uncontrolled cytokine release were identified in the infected hosts (Bi et al., 2015c; Bi et al., 2016d), and considered as an underlying reason for the high mortality caused by LPAIV H7N9 infections.

Several novel nuclear export signals (NES) identified in the NP, M1 and NS2, as well as phosphorylation sites in M1 and NS1, may work syngergistically for the nuclear export of vRNA, which is crucial for influenza A virus replication (Cao et al., 2012; Gao et al., 2014; Li et al., 2017; Wang et al., 2013; Yu et al., 2012; Zheng et al., 2017). The NES and nuclear localization signal (NLS) were also identified in M1 of influenza B virus (Cao et al., 2014).

HOST-VIRUS INTERACTION

The interactions between host factors and the virus are crucial for viral infectivity and host responses. Host factors were investigated by CASCIRE for the pathogenesis of influenza virus. For example, Cyclophilin A and NEDD8 (neural precursor cell expressed developmentally down-regulated 8) inhibited virus replication through interactions with M1 and PB2 of influenza virus, respectively (Liu et al., 2009; Liu et al., 2012). Cyclophilin A was also identified as a regulator controlling the severity of disease development caused by an uncontrolled immune response after infection (Li et al., 2016). Cyclin T1/CDK9 (cyclin-dependentkinases 9) was found to increase virus replication through up-regulating the transcription activity of vRNP (Zhang et al., 2010). microRNA-33a was found to disturb influenza A virus replication by targeting ARCN1 and inhibiting vRNP activity and virus replication (Hu et al., 2016).

Host factors involved with innate immunity during influenza virus infections were identified, such as Ndfip1, which was identified as an inhibitor of MAVS-mediated antiviral response (Wang et al., 2012). The antiviral effect of RIG-I-mediated IFN response was found to be regulated by T80 phosphorylation of the NS1 protein in influenza A viruses (Zheng et al., 2017). Interestingly, while influenza A virus NS1 protein interacts with RIG-I and TRIM25 to suppress the activation of RIG-I-mediated signaling, influenza B virus NS1 protein was unable to directly interact with RIG-I, but instead engages in the formation of a RIG-I/TRIM25/NS1-B ternary complex (Jiang et al., 2016). The non-coding RNAs were also discovered to modulate the antiviral interferon response against influenza A virus (Ma et al., 2016; Ouyang et al., 2014).

THE MOLECULAR MECHANISM OF DRUG RESISTANCE AND ANTIVIRAL MEASURES

Due to a broad M2-mediated inhibitor resistance to influenza A viruses (e.g. 2009 pandemic H1N1 and H7N9), neuraminidase inhibitors (NAIs) currently constitute the dominant class of anti-influenza drugs in clinics. However, NAIs (e.g. zanamivir) are more effective against group 1 than group 2 influenza A viruses, because of differences in the NA molecular structures (Li et al., 2010; Vavricka et al., 2011). In addition, NAI resistant strains were gradually identified in clinics during the NAI treatments. To address this, we explored the effect of older, general antiviral drugs, such as ribavirin, which worked as well as zanamivir against the H7N9 infections in mice (Bi et al., 2016e). We also developed and tested new compounds against NAI-resistant viruses based on the molecular mechanism of NAI-resistance, such as tetravalent zanamivir that presented outstanding activities against H7N9 and H3N2 infections (Fu et al., 2016; Wu et al., 2013). Studies on vaccine (http://www.im.cas.cn/xwzx/jqyw/201705/t20170527_4805236.html) and human antibody development against influenza viruses, as well as the emerging and re-emerging pathogens risk to China (Dai et al., 2016; Wang et al., 2016; Wu et al., 2015), were also performed by CASCIRE.

The ability to provide early-warning for outbreaks, thus leading to the development of antiviral measures (drugs, vaccines and human antibodies) for influenza viruses and other novel pathogens are the aims alongside elucidation of pathogenesis mechanisms. For One Health, CASCIRE hopes to establish future collaborations with worldwide research groups, expand surveillance efforts and promote the early-warning ability against emerging and re-remerging infectious diseases.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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