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Review Article

Progresses on Studies of Highly Pathogenic Avian Influenza H5N1 Cross-Species Infection and its Pathogenesis

Rongbao Gao*
Chinese National Influenza Center, National Institute for Viral Disease Control and Prevention, China

***Corresponding author:** Rongbao Gao, Chinese National Influenza Center, National Institute for Viral Disease Control and Prevention, CDC, 155 Changbai Rd, Changping District, Beijing 102206, China

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Abstract

The threat posed by highly pathogenic avian influenza A (H5N1) viruses to humans remains significant since the virus has caused sporadic human infections in 16 countries with a high case fatality rate (approximately 60%), circulated in poultry in several countries, and has the potential possibility to induce pandemic by mutation or/and reassortment with other influenza A subtypes. Although many studies showed that a number of amino acid mutations may contribute the adaption, transmissibility or the pathogenicity of avian influenza A H5N1 virus in mammals, the mechanism of the cross-species transmission is not clear so far. The current evidences indicated that both the virus and infected host itself played key role on viral infection and the pathogenesis. Therefore, in addition to monitoring the virus activity and molecular changes, discovery on the pathway of host regulation and control linked to viral infection factors would be also very helpful to control and prevent the disease.

Keywords: Highly pathogenic avian influenza virus H5N1; Cross-species infection Pathogenesis

Introduction

Highly Pathogenic Avian Influenza A Viruses (HPAIV) H5N1 have raised the global concerns due to high mortality and limited human-to-human transmission [1,2]. HPAIV H5N1 have spread and circulated in poultries in south east Asia, Europe and Africa since HPAIV H5N1 was first isolated from a farmed goose in Guangdong province of China in 1996 [3]. The virus caused first human infection in 1997 in Hongkong [4], reemerged in 2003, and had resulted into more than 650 human infections with almost 60% fatality in 16 countries since 2003 [5]. In addition, the virus showed to have potential droplet-transmissibility in humans by mutation or/and reassortment [6-9]. However, there is not a very effective therapy policy for the disease with clinical feature of quick deterioration so far. Therefore, the threat posed by HPAIV H5N1 to humans remains significant. Here, we reviewed the risk of HPAIV H5N1 cross-species infection and its pathogenesis.

Cross-spices transmission in mammals

The "host species barrier" existing between avian species and humans was generally considered to restrict cross-species transmission of influenza virus. The successful trans-species transmission of avian influenza viruses and the establishment of adaption in the human population required to cross several barriers from their natural reservoirs to humans. These barriers can be divided along three major steps defining cross-species transmission [10]: (1) animal-to-human transmission barriers; (2) virus-cell interaction barriers; and (3) human-to-human transmission barriers.

Influenza virus preference of Sialic Acid (SA) linked to Galactose (Gal) receptors binding has purposed to be a key factor of animal-to-human transmission barriers. In general, human influenza viruses bind preferentially to SA linked to Gal by α-2, 6 linkage (SA α-2, 6-Gal), whereas avian influenza viruses bind preferentially to SA α-2, 3-Gal linkages, and pig influenza viruses either attached to both α2,3-SA and α2,6-SA, or exclusively to α2,6-SA [11]. The restriction present that the virus binds only to a species-specific cell receptor, or an efficient virus replication subject to cellular factors is prevented [12]. This is the primary reason that the avian influenza A virus cannot infect humans easily. However, the HPAIV H5N1 viruses have transmitted to infect humans and various mammals from poultry [4,13]. Animal surveillance data showed that HPAIV H5N1 had been detected in pig, dog, cat, leopard and tiger (Table 1). Genomic analysis showed that some of current circulating H5N1 viruses have presented changes of receptor-binding features such as capacity of human-like receptor- or double receptor-binding [14,15] and have multiple cell tropism [16]. To be different with seasonal influenza virus, HPAIV H5N1 can replicate with high-level in infected cells *in vitro* under the condition of no trypcin adjunction, and caused death of chick embro in just cultured 48h. Animal model studies showed that a low titer of virus may result into death of ferrets after infection [17] and the virus can infect and kill mice without any adaption which need be consulted in human viruses [18]. The virus has obvious lethality to guinea pig as well [19]. These studies indicated that the HPAIV H5N1 have been undergoing steps of cross-species transmission. Furthermore, the H5N1 HA gene mutation studies show that efficient droplet transmission can be induced in ferret infected by the A/Indonesia/5/2005 (H5N1) virus with two amino acid changes (HA Q222L and G224S) on receptor binding sides and one mutation of HA T156A affecting on glycosylation N connection site [20] or virus with HA Q222L, N154D, T156A, T315I mutations of A/Vietnam/1203/2004 (H5N1) and remaining 7 H1N1pdm09 genes. These rescued viruses can bind both SA α-2,3 and α-2,6 Gal, and

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Table 1: The Cross-spices transmission of HPAIV H5N1in mammals.

Years	Country	Spices	Events	Isolates	Reference
2001, 2003	China	Pig	Two H5N1 viruses isolated from pigs.	A/swine/Fujian/1/01 and A/swine/Fujian/1/03	Zhu Q, et al. [24]
2003	Thailand	Tigers and leopards	Two tigers (Panthera tigris) and two leopards (P. pardus) at a zoo in Suphanburi, Thailand, showed clinical signs, including high fever and respiratory distress, and they died unexpectedly.	A/Leopard/Thailand/2004, A/Tiger/Thailand/2004	Keawcharoen, J. et al. [25]
2004	Thailand	Tiger	H5N1 avian influenza virus outbreak among zoo tigers in mid-October 2004, with 45 animals dead	A/Tiger/Thailand/CU-T3/04, A/Tiger/Thailand/CU-T7/04	Amonsin, A, et al. [26]
2004,	Thailand	Dog	HPAI H5N1 infection in a domestic dog following ingestion of the carcass of an infected duck.	A/Dog/Thailand/KU-08/04	Songserm, T. et al. [27]
2004	Thailand	Cat	H5N1 virus infection in a domestic cat infected by eating a pigeon carcass.	A/Cat/Thailand/KU-02/04	Songserm, T. et al. [28]
2005–2007	Indonesia	Pig	52 pigs in 4 provinces were infected, One isolate had acquired the ability to recognize a human-type receptor. No infected pig had influenza-like symptoms, indicating that influenza A (H5N1) viruses can replicate undetected for prolonged periods, facilitating avian virus adaptation to mammalian hosts.	A/swine/Banten/UT3081/2005, et al.	Nidom, C. A., et al. [29]
2006-2007	China	Pikas	To estimate the infection of wildlife with influenza A virus in a natural ecosystem, in China's Western Qinghai Province, from August 2006 to December 2007, Ochotona curzoniae (black-lipped) pikas were caught in the regions around Qinghai Lake	A/PK/QH/BI/0704/2007, et al.	Zhou, J. et al. [30]
2009	Egypt	Donkey.	H5N1 viruses were isolated from donkeys clinically affected with moderate respiratory distress including cough, fever and serous nasal discharge.	A/Equine/Egypt/av1/2009	Abdel-Moneim, A. S. et al. [31]

induced remarkable lung tissue damage and weight loss in ferrets [7]. These mutations in two (HA N154D/T156A) were common in H5N1 viruses circulating in poultry, indicating that it is possible to happen human-to-human transmission if these mutation or reassortments happened in nature. Fortunately, HPAIV H5N1 caused sporadic human infections only. Although the limited human-to-human transmission events have been reported in cluster cases from several countries [1, 21, 22] each reported cluster cases were from same family case yet. And no healthcare worker was transmitted to infect the virus so far [23].

The possible mechanism of cross-spices transmission

Infection of mammals by avian influenza viruses requires adaptive mutations to achieve high-level replication in the new host. However, the basic mechanism underlying this adaptation process is still unknown. Besides amino-acid changes in the HA gene, variant studies of animal model showed that many amino-acid changes in internal genes (PB2, PB1, PA, NP and NS) played roles on mammals adaption, virulence and/or replication efficiency (Table 2). For example, numbers of studies showed that the mutation of PB2 E627K or D701N altered polymerase activity, enhance virulence of virus in mice and induced mammalian host adaptation. And the mutation PB2 E627K, which is very common in H5N1 human isolates, improved viral replication capability under the condition of low temperature, enhanced polymerase protein to bind with NP, and enhanced viral replication in up respiratory tract and lung tissues as well [32, 33]. PB2 D701N mutation, an important determinant of HPAIV H5N1 cross-species transmission to mice [34], determined the transmissibility of H5N1 virus in guinea pig [35]. In addition, the genomic evolution data of human and mammalian H5N1 isolates indicated that M1 and PB2 present more diversity which may be associated with host adaption and transmissibility [36]. The recombination study on PB1, PB2 PA and NP genes from the HPAIV H5N1 and mammalian H1N1 virus showed the combination of mammalian H1N1 PB2 and HPAIV H5N1 PB1 genes present the highest polymerase activity in cells. And the rescued H5N1 virus with the both genes induced a significant response of proinflammatory cytokines in human macrophage, and caused severe pneumonia in mice besides the virus present much better adaptability in mouse under selective pressure [37]. Of note, the avian PB1 is the only gene reconstituted into the pandemic H2N2 and H3N2 virus so far, indicating that PB1 may play an important role on virus transmission. Similarly, studies have shown that NS protein plays a role in the virulence as well as in host adaptability of H5N1 virus. For example, NS2 M16I mutation of H5N1 virus was an adaptive mutation since it may help virus to escape restricted viral genome replication in mammalian cells [38]. Therefore, variant "specificity" site in multiple genes may relate to the mechanism of effective trans-spices infection of H5N1 viruses. These findings undoubtedly promoted the development of prevention and control strategies on the virus. However, it also formulated a challenge to the strategy as so many "determinants".

Pathogenesis of HPAIV H5N1

The clinical manifestations are fever with or without upper respiratory symptoms in the early stage HPAIV H5N1 infection, followed pneumonia with rapidly progressive aggravating, and developed into acute respiratory distress syndrome (ARDS) and multiple organ failures in most case finally [39]. The pathological features of HPAIV H5N1 infection were parenchymal lung involvement of the virus and diffuse alveolar damage [40,41]. Similar to the 1918 H1N1 Spanish flu, the most devastating infectious disease pandemic, HPAIV H5N1 infection present more serious in young adults than Children or elders [42,43]. Studies showed that, besides damage caused by excessive host immune response on the virus, bacterial co-infection contributed the disease and death in 1918 H1N1 infection [43,44]. To be different with 1918 H1N1 infection, bacterial co-infection was very rare in HPAIV H5N1 infection. Additionally, HPAIV H5N1 can infect beyond air-way tissue to extropulmonary

Table 2: The mutations affected adaption infection of HPAIV H5N1.

Protein	Amino acid position/motif	Phenotypic consequences	H5N1 consensus and/or background virus	Reference (PMID)
PB2	Asp256Gly	altered polymerase activity, mammalian host adaptation	A/chicken/Yamaguchi/7/2004	19052090
	Glu627Lys	altered polymerase activity and mammalian host adaptation	A/chicken/Yamaguchi/7/2004	19052090
		mammalian host adaptation	A/Vietnam/1203/2004, A/Vietnam/1204/2004, A/Vietnam/3030/04	19264775
		mammalian host adaptation, altered virulence in mice	A/chicken/Yamaguchi/7/2004	17098982
		mammalian host adaptation	A/swan/Germany/R65/2006	21849466
	Asp701Asn	mammalian host adaptation	A/Vietnam/1203/2004, A/Vietnam/1204/2004, A/Vietnam/3030/04	19264775
		mammalian host adaptation, altered virulence in mice	A/duck/Guangxi/22/2001, A/duck/Guangxi/352/2001	16140781
		altered replication efficiency, virulence and transmission in guinea pigs	A/Vietnam/1203/2004	19119420
PB1	Val3Ala, Arg207Lys, Asn328Lys, Asn375Ser	altered replication efficiency and virulence in ferrets	A/Vietnam/1203/2004, A/chicken/Vietnam/C58/2004	16533883
	Val473Leu, Pro598Leu	altered polymerase activity and replication efficiency	A/Cambodia/P0322095/2005	22090209
PB1-F2	Asn66Ser	altered virulence replication efficiency and antivirus response in mice	A/Vietnam/1203/2004	21852950
NP	Asn319Lys	altered replication efficiency	conserved in wild-type H5N1	18248089
NS2	Met16Ile	Enhanced polymerase activity in human cultured cells.	A/Thailand/1(KAN-1)/2004	22549831
PA	Ser149Pro, His266Arg, Ile357Lys, Ser515Thr	altered polymerase activity	A/duck/Fujian/01/2002, A/duck/Guangxi/53/2002	20211480

organs including brain and intestinal tissues [45-49]. These extrapulmonary infections may not induced significant pathology damage in local tissues but may induce systematic immune response associated with pathogenesis. Compared with seasonal influenza, the viral load was much higher in HPAIV H5N1 infection, and virus clearance was delayed [50]. Pathological studies showed that HPAIV H5N1 infected both type-I and -II pneumocytes in alveolar of patients, still can infect alveolar macrophages and Dendritic Cells (DC) and other innate immune cells [46,51,52]. Therefore, the virus is multicellular tropism *in vivo*. The virus can break the barrier between the organism infections in a variety of organ tissues.

Animal model and *in vitro* experiments suggested that the pathogenicity of HPAIV H5N1 was gene determinant. To be different with low pathogenic influenza virus, HPAIV has a motif of multiple basic amino acid (-RRRKR- or -RRRKKR (Arg, R; Lys, K)) in the HA cleavage site. Of note, the motif of high pathogenicity may be invalid on nonhuman primate animal [53]. The polymerase genes (PB2, PB1 and PA) are the important determinants of viral pathogenicity and host restriction as well. The interaction between polymerase gene RNA and host protein may play a decisive role in the virus life cycle [54]. In addition, NS protein is a factor in determining the virulence of H5N1. Most of HPAIV H5N1 possessed a 15-nucleotide (15-nt) deletion in position of NS 263-277. The deletion of the 15-nucleotide in NS gene enhanced virulence of H5N1 virus [55]. And some changes of amino acid in NS altered the virulence of H5N1 virus. For example, mutation of NS1 D92E enhanced viral pathogenicity in mice [55].

Besides the damage linked to viral replication, many studies have concluded that the severity of HPAIV H5N1 was related to the excessive host response. For example, H5N1 virus showed higher virulence in BALB/C mouse than in C57BL/6J mouse [56]. HPAIV H5N1 infection induced cytokines/chemokines storm and immune dysregulation which were showed to play roles in the pathogenesis of the infection in serials of clinic studies, animal model or *in vitro* experiments. The integration of the host innate immune response may contribute to virus spread in vivo. Compared to seasonal influenza viruses, H5N1 with the same dose of virus can induce much higher levels of inflammatory cytokines in macrophage. But the gene expression spectrum suggested that the host biological responses caused by either H5N1 or seasonal influenza virus were similar, and have consistent response pathway between the infections [57,58]. The stronger response of inflammatory cytokines induced by H5N1 included I-type IFN and TNF-α. Host response network analysis showed that the synergistic effect of IFN-β and TNF-αmay contribute to continuous high levels of inflammatory cytokines in early stage of infection. The high host response was related to disease [59]. Compared with wild mice, H5N1 virus spreads were limited in lung tissues of the mice with deficiency of INF-I receptor [60]. Autopsy studies indicated that excessive host immune response was related to pathogenesis of H5N1 infection as diffuse alveolar damage and infiltration of inflammatory cells in lung of patients. The conclusion was demonstrated or proved in animal models. For example, HPAIV H5N1 induced a continuously high expression of innate immunity genes, edge phenomenon of circulating T lymphocytes in early stage of infection, and significant apoptosis of activated DC cell in lung tissue in Macaca rhesus [61]. In addition, the CXCR3 gene appeared significantly increased in H5N1 infected ferret. And CXCR3 blockers AMG487 treatment can significantly reduce the symptoms of infection and delayed mortality [62]. And many susceptible or tolerable genes of host have been linked to H5N1 infection. The deletion of hemolytic complement gene Hc increased fatality of infected mice while those mice with high expression of Hc were survived [63].

In summary, HPAIV H5N1 circulating in poultry widely has cross species to infect humans and several other mammals. Although the cross-species infection still belongs to emerged accidents, the high mortality and limited human-to-human transmission induced by the virus have raised concern on the virus. In addition, although studies have showed variant gene determinants on the cross-species

transmission, the mechanism of the transmission is not clear so far. It is impossible to avoid that, with mutations or reassortments undergone in H5N1 virus, the effective human-to-human transmission would be possible to emerge. It is also a difficult issue for formulating prevention and control strategies for humans currently because many unconfirmed factors link to infection and transmission of the virus. The severe clinical symptoms in H5N1 patient were related to both the virus and excessively immune response of host. We may control the progression of the disease or relieve the disease through mediating the host response although host response is a perplexing network system. Therefore, to prevent and control the virus, in addition to the virus, research on host factors linked to viral infection would be one more important way.

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